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Complete List of Authors:	Fonvig, Christina; Odense University Hospital, Department of Orthopaedics and Traumatology; University of Southern Denmark, Department of Clinical Research Troelsen, Jens; University of Southern Denmark, Department of Sports Science and Clinical Biomechanics Dunkhase-Heinl, Ulrike; Lillebælt Hospital, Department of Paediatrics lauritsen, jens; Odense University Hospital, Department of Orthopaedics and Traumatology; University of Southern Denmark, Department of Clinical Research Holsgaard-Larsen, A. ; University of Southern Denmark, Department of Clinical Research; Odense University Hospital, Department of Orthopaedics and Traumatology
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Predictors of physical activity levels in children and adolescents with cerebral palsy: clinical cohort study protocol

Christina Esmann Fonvig, MSc.PT
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark &
OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark

Jens Troelsen, Professor, MSc, PhD, Head of Research for Active Living
Department of Sports Science and Clinical Biomechanics
University of Southern Denmark

Ulrike Dunkhase-Heinl, MD
Department of Paediatrics, Lillebaelt Hospital, Kolding

Jens Lauritsen, Professor
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark

Anders Holsgaard-Larsen, Associate Professor, MSc, PhD.
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark

Corresponding author:
Christina Esmann Fonvig, The Orthopaedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, J. B. Winsloews Vej 4, 5000 Odense C, Denmark.
E-mail: christina.esmann.fonvig@rsyd.dk

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Abstract

Introduction

Children and adolescents with cerebral palsy may be trapped in a vicious circle of low physical fitness, resulting in deconditioning that causes a further decrease in physical activity (PA), a lower quality of life, and an increased risk of developing non-communicable diseases (NCDs). Therefore, establishing a healthy and active lifestyle during childhood is even more important for individuals with a disability. However, the factors that influence habitual PA in children and adolescents with cerebral palsy remain unknown.

The present protocol outlines a prospective cohort study with the aim of investigating potential predictors of habitual PA in children and adolescents with cerebral palsy in order to provide evidence for optimizing PA levels and associated overall health.

Methods and analysis

This prospective cohort study will enroll participants with cerebral palsy between the ages of 8 and 15 years at Gross Motor Function Classification System (GMFCS) levels I–III. Using a modified version of the International Classification of Functioning, Disability and Health (ICF) model as a conceptual analytical framework, the analysis will be divided into six components and will provide predictors for habitual PA measured by accelerometry. The potential predictive variables are registry data on physical function (Danish Cerebral Palsy Follow Up Program [CPUP]); validated proxy-reported questionnaires on quality of life (Pediatric Quality of Life Inventory (PedsQL)), overall health, pain, and participation in daily activities (Pediatric Outcomes Data Collection Instrument (PODCI)); and supplementary questions regarding sleep, screen time, and socio-economic status.

Ethics and dissemination

The project is approved by the Danish Data Protection Agency (19/16396) and has been declared not notifiable by the Regional Committee on Health Research Ethics, cf. Committee Act Art. 14, paragraph 1 (S-20192000-23). The study results will be published in international peer-reviewed journals, presented at international conferences, and published in a PhD dissertation.

Trial registration

ClinicalTrials.org identifier: NCT04614207

Article Summary

Strength and limitations of this study

- The study will provide novel evidence that will aid identification of PA levels and patterns in children and adolescents with cerebral palsy for early intervention.
- The findings may be implemented in evidence-based PA guidelines, which currently are lacking for children and adolescents with cerebral palsy.
- Bootstrap validation will be performed to increase internal validation. Optimally, external validity of the findings should be verified in the future using an external cohort.

Introduction

Cerebral palsy

Cerebral palsy (CP) is a condition that describes a group of disorders (altered muscle tone, movement disorders, muscle weakness, ataxia, and rigidity) related to the development of movement and posture causing activity limitations and reduced quality of life(1). CP is a common impairment among children, with a prevalence of 2.1 per 1000 live births worldwide(2) and 2.4 per 1000 live births in Denmark(3). Cerebral palsy is attributed to non-progressive disturbances in the fetal central nervous system or in the developing infant within the first two years of life(1, 4). Although CP is a non-progressive diagnosis, it is a lifelong condition that requires attention through most of the person's life, as impairments are constantly evolving and inhibit performance of activities and participation in daily living(1, 5).

Physical activity

Low levels of PA are a worldwide threat to the health of children, including those with disabilities. For this reason, the World Health Organization recommends children to be moderate to vigorous physical active for at least 60 minutes per day, including muscle- and bone-strengthening activities at least three days per week(6). Although there are no specific evidence-based PA guidelines for children with cerebral palsy, it is clear that they have lower levels of PA and higher levels of time spent sedentary than their peers(7) and that their level of mobility limitation is negatively associated with their level of PA(8).

The long-term effects of reduced habitual PA and increased sedentary time include a greater risk of developing NCDs such as metabolic dysfunction, cardiovascular disease, and poor bone density. These problems can, in turn, result in poorer overall health, reduced life expectancy, and a greater

burden of disease in years of life lost to disability(9, 10). Ideally, childhood should be marked by high levels of intense play and habitual PA, which, in addition to providing protective physical benefits, also appear to improve mental health(11, 12).

Predictors of physical activity

In Scandinavia, healthcare professionals offer standardized clinical examinations throughout childhood using the Cerebral Palsy Follow-Up Program (CPUP), which was developed in Sweden more than 20 years ago(13) and was adopted in Denmark as a National Clinical Quality Database by the Danish Clinical Registries in 2015. CPUP is designed to support early detection of complications, such as hip dislocation, scoliosis, and muscle contracture, as well as to improve the quality of healthcare(13, 14). Danish Clinical Guidelines for physiotherapy and occupational therapy for children with CP emphasize that future research should focus on the short- and long-term effects of the interventions applied to improve the children's activities of daily living(15). Despite this recommendation, it has not been investigated whether the standardized examinations and accompanying variables of CPUP are associated with habitual PA. Thus, potential objective predictors of PA can be identified through this national clinical quality database, allowing early detection and potentially improved interventions.

To optimize activities of daily living and long-term health outcomes for the present population, a key objective is to encourage and facilitate an increase in habitual PA and reduce the amount of time spent sedentary(7). However, the current literature does not provide evidence for barriers to or motivators for PA in children and adolescents with cerebral palsy. Furthermore, no studies have examined the underlying reasons for altering habitual PA.

Aim and hypothesis

The aim of the present cohort-study is to identify and investigate potential predictors of habitual PA in children and adolescents with cerebral palsy, with the perspective of providing evidence to optimize PA levels and associated overall health.

We hypothesize that potential predictors of habitual PA can be identified through objective variables included in the CPUP database and in supplementary questionnaires on proxy-reported outcome measures, using a modified ICF model (Body Functions and Structures, Activities, Participation, Personal Factors, Environmental Factors, and Quality of Life) as a conceptual statistical framework.

Methods and analysis

Study design

A prospective clinical cohort study using historical registry data from CPUP and supplementary proxy-reported outcome measures will be conducted. The STROBE checklist for reporting cohort studies will be used to report the study findings(16).

Ethics and dissemination

The project has been approved by the Danish Data Protection Agency (19/16396) and has been declared not notifiable by the Regional Committee on Health Research Ethics, cf. Committee Act Art. 14, paragraph 1 (S-20192000-23). The Danish Clinical Registries granted access to the Cerebral Palsy Follow-Up Program (CPUP) database in June 2019. The study is pre-registered at ClinicalTrials.gov; identifier: NCT04614207.

The project will be conducted in accordance with the Helsinki Declaration II. Before participants (parents/guardians) give their informed written consent to take part in the study, they will receive written and oral information on the experimental procedure and potential risks. The families will be informed that they can withdraw from the study at any time. All subject data will be treated confidentially and in confidence according to the EU's General Data Protection Regulation.

The study results, whether positive, negative, or inconclusive, will be published in international peer-reviewed journals, presented at international conferences, and published in a PhD dissertation. The articles and presentation will not contain any information that could lead to identification of any participants.

Participants & study setting

Participants will be recruited from the five regions of Denmark. To increase the external validity and sample size of the present project, the inclusion criteria will be kept wide and will include children and adolescents between the ages of 8 and 15 (a biological age where gait and mobility are matured(17)) who are diagnosed with CP. The children/adolescents must be registered in the Danish CPUP and classified at Gross Motor Function Classification System (GMFCS) levels I–III, demonstrating an independent gait function with or without mobility devices. A flow diagram of participants through the study is illustrated in Figure 1. Parents/guardians must be able to read and understand Danish.

Figure 1. Flow diagram

Eligible participants will be identified through the Danish Health Data Authority, after which the parents/guardians will receive written information through secure digital post (e-Boks). If clarification is needed, the project manager can be contacted via telephone or e-mail. Interested

parents/guardians will consent electronically via personal link in e-Boks and will automatically be forwarded the questionnaires, which will be filled out electronically. For non-responders, an e-mail reminder will be sent out a total of three times. Habitual PA is to be measured using accelerometers (see below for further description). Participants will receive an accelerometer via postal mail, including a prepaid return envelope.

Data sources and measurements

Parents'/guardians' perceptions of their child's activity behavior, health status, socio-demographic background, sleep, and screen habits will be collected in an electronic questionnaire. Demographic characteristics (age, sex, CP type & subtype, GMFCS level) and detailed information on the participants' health and physical abilities, as evaluated by healthcare professionals, will be collected through CPUP (see below for further description of collected variables).

The patient-reported outcome measures will be entered directly into a secure web database, REDCap, under Open Patient data Explorative Network (OPEN), Odense University Hospital, Region of Southern Denmark(18), by the parents/guardians using a web link sent via secure digital post (e-Boks). Legal values have been set where possible, to validate the entered values. All collected data will be stored in OPEN Storage, merged, and analyzed at the Danish Health Data Authority Research Engine.

Quantitative variables

Accelerometry

Habitual PA will be assessed using the Axivity AX3 accelerometer. The use of an accelerometer is a common method for objectively measuring PA(19), and is considered a feasible and validated measure for ambulatory children and adolescents with CP(20).

The accelerometer is to be worn in a snug-fitting pouch in an elastic belt, strapped around the hip, with the device placed on the midaxillary line at the level of the iliac crest on the child's right side(19, 21). The accelerometer device is to be worn for seven successive days; five school days and a weekend(22). A valid wear day will be defined as a day where the accelerometer is worn for at least 8 hours between 6 a.m. and 10 p.m. on a weekday or for at least 10 hours on a weekend day. The minimum number of valid wear days will be four, including one weekend day(23). Non-valid data will be excluded for further analysis. Parents will be asked to keep a diary recording the wear time of the accelerometers. Non-wear time will be defined as time where the accelerometer is not worn (e.g., when showering). Total wear time and activity counts will be processed using the open source software GGIR(24). The GGIR default setting for non-wear time will be utilized. To encourage wear time, parents will be encouraged to sign up for daily SMS messages about reminding the child to put on the accelerometer.

The Axivity AX3 detects movement in three directions: vertical (X), anteroposterior (Y), and mediolateral (Z). The combination of these three axes allows for movement to be calculated into vector magnitude (VM), with $VM = \sqrt{(X^2 + Y^2 + Z^2)}$. Vector magnitude will be calculated per epoch of time in activity counts (counts per epoch of time). Sampling frequency will be set at 50 Hz with a dynamic range of ±8g. The collected raw data will provide information on the wearer's habitual PA behavior regarding acceleration of bodily movement.

The OMGUI v43 software will be used to set up and configure the accelerometers. The Axivity AX3 raw acceleration data will be converted to ActiGraph counts using GGIR(24). The overall level of PA will be expressed as average counts per day. Converting Axivity raw data to ActiGraph counts will allow for comparability with typically developed children and for sub-analysis using CP-specific cut-points for estimation of time spent in sedentary, light, or moderate-to-vigorous intensity across the different gross motor function levels(21).

Cerebral Palsy Follow-Up Program (CPUP)

Retrospective variables collected from the CPUP physiotherapy protocol, patient protocol, neuropediatric protocol, and orthopedic protocol will be used to predict the level of habitual PA. Physiotherapy assessments are reported to the database yearly for persons at GMFCS levels II and III, and biennially for persons at GMFCS level I. Assessments from the pediatricians and the orthopedic surgeons are collected respectively once before the age of 5 years and based on the child's age and gross motor function(13). Consequently, the retrospective CPUP data has been collected within the 38 months prior to assessment of PA level (see timeline, Figure 2).

Pediatric Quality of Life Inventory (PedsQL)

To evaluate health-related quality of life, a linguistically validated Danish version of the Pediatric Quality of Life Inventory (PedsQL) Cerebral Palsy Module, which is specifically designed for children with CP, will be used(25). It is based upon the parents' reports and measures physical, emotional, social, and school functioning. The construct and discriminant validity of the original version have been supported by comparing the scores from children with CP with a generic measure of the same construct from children without disability(26). Satisfactory internal consistency reliability coefficients of 0.87–0.97 have been demonstrated for the PedsQL parent proxy-report for children ages 8–18(27).

The Pediatric Outcomes Data Collection Instrument (PODCI)

Overall health, pain, and participation in normal daily activities will be assessed by a Danish version of the Pediatric Outcomes Data Collection Instrument (PODCI). Concurrent and discriminant validity have been assessed by comparing the Pediatric Outcomes Data Collection Instrument with other measures of health and well-being, gross motor function, and diagnostic subgroups in children with CP(28). Moderate to good test-retest reliability with ICC values of 0.71–0.97 have been reported in children with orthopedic or musculoskeletal disorders(29).

Supplementary questions

Information regarding sleep, screen time, self-reported range of motion in the lower extremities, means of transportation to and from school, and assessment of mobility through the Functional Mobility Scale (FMS)(30) will be collected by means of a supplementary parent-reported questionnaire.

Danish National Patient Register

For recruitment purposes, parents'/guardians' national security numbers will be applied for at the Danish National Patient Register, as will registry data on relevant hospital operations and procedures for the children/adolescents.

Study size

The eligible national cohort comprises a total of approximately 1100 children and adolescents in Denmark in the age group of 8–15 years. Based on previous experience of participation in studies by this patient group we expect an inclusion of 300-400 children.

Statistical methods

The World Health Organization (WHO) introduced the International Classification of Functioning, Disability and Health (ICF) in 2007 as a framework for discussing health and disability from a biopsychosocial perspective through the interaction of five components (i.e., Body Functions and Structures, Activity, Participation, Personal Factors, and Environmental Factors)(31). In 2010, Quality of Life (QoL) was integrated in a modified ICF model(32), which will be used in the current study as a statistical framework. This allows separate and combined analyses for each of the six components on the prediction of habitual PA, as measured by accelerometer, and will consequently provide data-driven knowledge about using the modified ICF model as a context for habitual PA for children and adolescents with CP.

The following figure operationalizes the statistical framework by sorting included outcome variables according to components in the modified ICF model.

Figure 2: Included predictive variables sorted into components according to the modified ICF model, including data collection timeline in months.

Analysis

The identification of predictive factors of habitual PA in children and adolescents with cerebral palsy between the ages of 8 and 15 years, will, as described above, be operationalized though a statistical analysis plan using the modified ICF model as a conceptual framework (Figure 2). Using a predictive model, the study aims to determine the associations between the response variable and the predictive variables, with the purpose of predicting the output value for new observations given their input values(33). The variable that is to be predicted (the response variable) is habitual PA, represented by accelerometer counts. Regardless of the collection time of the data, all other variables (Table 1) are considered prediction variables(33).

Table 1: Predictive variables

ICF component	CPUP variables		Questionnaire variables	
	Continuous	*Categorical*	*Continuous*	*Categorical*
Body Function & Structure				
Range of motion in the lower extremities	Variable most associated with habitual physical activity from the following measurements (on the most affected side): HIP · Abduction · Flexion · Internal rotation · External rotation · Elys test · Extension KNEE · extension (hip 90° flexion) · extension (hip 0°) ANKEL · Dorsal flexion with flexed knee · Dorsal flexion with extended knee	-	-	Visual evaluation of range of motion for most affected side ('more' or 'less' than the depicted picture): · HIP flexion · KNEE extension with opposite leg extended · KNEE extension with opposite leg flexed · ANKEL flexion with extended knee · ANKEL flexion with flexed knee: a. Decreased range of motion b. Full range of motion
Number of hours of sleep per night	-	-	1. Time in hours per day on school days. 2. Time in hours per day in the weekend	-
Pain	-	Y/N	-	-
Muscle tone (Modified Ashworth Scale)	-	The absence or presence of increased muscle tone in the most affected side of the lower extremity as evaluated on the Modified Ashworth scale.	-	-
BMI (body mass index)	Weight in kg / [Height (m)]^2		-	-
GMFCS level	-	· I · II · III	-	· I · II · III

Activities				
The Functional Mobility Score	-	FMS score (1-6) for: · 5 meter · 50 meter · 500 meter	-	FMS score (1-6) for: · 5 meter · 50 meter · 500 meter
GMFM-66 Score	0-100	-	-	-
Means of transport to and from school	-	-	-	· Walks · Bikes · Transported (e.g. by car, bus, cargo bike) · Other
Hours of screen time	-	-	1. Time in hours per day on school days. 2. Time in hours per day in the weekend	-
Ability to climb stairs	-	1. Climbs up stairs independently (Y/N) 2. Climbs down stairs independently (Y/N)	-	-
Bikes (bicycle, tricycle, running bike etc.)	-	· Often (daily) · Sometimes (a couple of times a week) · Rarely (a couple of times a month) · Never	-	-
Participation				
PODCI	-	-	0-100	-
Participation in physical training at school	-	Y/N	-	Y/N
Participation in recreational activities	-	Y/N	-	· Swimming · Horseback riding · Soccer · Handball · Dance · Strength training · Gymnastics · Basketball · Floorball · RaceRunning · Nothing · Other

Personal Factors				
Age	8-15 years	-	8-15 years	-
Sex	-	Boy/girl	-	Boy/girl
CP classification	-	· Spastic · Dyskinetic · Ataxic · Not classified/mixed form	-	-
Parents educational level	-	-	-	· Primary school up to and including 6th grade · Primary school 7th – 10th grade · High school education (e.g. HTX, STX, HHX) · Vocational education (e.g. office and shop assistant, etc.) · Short higher education (e.g. market economist, police officer, etc.) · Medium-term higher education (e.g. teacher, educator, nurse, bachelor of political science, etc.) · Long higher education (e.g. master degree) · PhD or research training · Other education · Do not know
Environmental Factors				
Residence region	-	5 possible regions: · Southern · Northern · Central · Zealand · Capital	-	-
Use of orthosis	-	Y/N	-	
Wheelchair use	-	· Does not use · Is assisted · Operates independently	-	-
Quality of Life				
PedsQL	-	-	0-100	-

To determine which variables predict the child's level of PA, multiple linear regression analysis will be performed according to the following models:

Primary analysis

Model 1) Multiple linear regression analysis between accelerometer counts (response variable) and all CPUP variables within each ICF component (predictive variables).

Secondary analysis

Model 2a) Backward stepwise regression with accelerometer counts as the response variable and all included CPUP variables as predictive variables. The Akaike information criterion (AIC) will be used to determine which variables to retain in the model. Resampling, as described below, will be used to address potential overfitting and to summarize the variability of selected variables(34).

Model 2b) Multiple linear regression analysis between accelerometer counts (response variable) and all included variables as predictive variables. This model will assess the degree of predictive strength that the questionnaire variables adds to model 1.

The coefficient of determination, adjusted R-squared, will illustrate the percentage of variance in PA that is explained by the predictive variables. The higher the coefficient, the stronger the relationship. The Root Mean Squared Error of the estimate will indicate the accuracy of the predictions. Results will be presented with an alpha of 0.05 and a 95% confidence interval.

Models will be checked using graphic inspection. Splines will be used to account for non-linear effects, and interactions will be included in the model based on relevant subject-matter knowledge. These will be specified in detail in the statistical analysis plan.

Bootstrapping will be performed to reduce the risk of overfitting the prediction model and will thus increase internal validation(35). Missing data will be addressed using multiple imputation applied to

each of the bootstrapped datasets(36). External validation can be verified using the Swedish CPUP registry data; however, this will not be performed in the present study.

To evaluate the significance of CPUP data collection periods relative to the time in months from the measure of PA, the model will test for differences in prediction analyses between the following time periods: 0 ≤ 12 months, 13 ≤ 24 months, and 25+ months (Figure 2).

Analysis of non-responders and excluded participants will be performed to disclose potential selection bias.

Statistical analyses will be performed using Stata.

Additional analyses

Several other related analyses will be reported separately. One further study will be on a sub-group of any children or adolescents who are referred for three-dimensional gait analyses as part of their individualized clinical treatment plan. Another analysis will use cut-points for sedentary, light, moderate, and vigorous activity for each of the three separate GMFCS levels(21) and then compare sedentary behavior and PA levels of children and adolescents with CP with those of typically developed children and adolescents. Finally, a qualitative study will be performed to explore the daily life challenges that parents describe facing in their pursuit of helping their children with CP live a physically active lifestyle.

Adverse events

Measuring habitual PA by accelerometry is a non-invasive method commonly used in research and has no known risks or side effects, including pain or discomfort.

Patient and public involvement statement

A pilot study was conducted during the fall of 2019 in which five families were invited to participate and then give feedback on the questionnaires, the use of the accelerometer, and the overall burden of participation. Feedback from the children and adolescents, as well as from their parents, led to minor alterations of the study design, such as the questionnaire setup, the use of a different type of elastic belt as well as eliminating the use of an additional accelerometer worn on the thigh.

Patient user groups contributed to the assessment of the project prior to funding being granted by the Elsass Foundation and the Region of Southern Denmark.

Study results are expected to be disseminated though a national interest organization for persons with cerebral palsy (e.g., articles on website, oral presentation), ensuring study results are communicated to the participants and also to a general wider patient community.

Discussion

The present study will provide novel evidence for how to optimize PA for children and adolescents with CP. Recruitment via secure digital post should increase recruitment efficiency, as eligible parties are invited to participate without dependency on health care attendances. Due to the wide inclusion criteria, results of this study are expected to have a high level of external validity and be generalizable to other children and adolescents with CP. To ensure the internal validity of the study, selection bias will be investigated through a non-responder analysis. A high acceptance by the treating health professionals is expected, as the majority of variables of interest are already implemented in CPUP.

The study findings may be implemented in evidence-based PA guidelines, which are currently lacking for children with cerebral palsy, thus providing health professionals with a clinical tool for treatment of cerebral palsy.

Limitations

This cohort study will be subject to some methodological limitations. Primarily, the current predictive regression analysis cannot determine causality between the predictive variables and the level of PA endured. Thus, the findings should optimally be validated in an external cohort and/or verified in randomized controlled trails. External validation of the prediction model may be achieved, for example, by using the Swedish CPUP registry data; however, this validation is not a part of the current protocol. Nevertheless, bootstrap validation will be performed to increase internal validation(35).

Using registry data ensures clinically relevant data on all persons in the target group; however, it also poses a risk of having data that is missing for unidentifiable reasons, which complicates the handling of missing data. In this study, missing data will be addressed using imputation of the missing values with the sample mean of the observed cases, which could result in biased estimates because the variance of the variable may be underestimated.

While the WHO definition of QOL is based on an individual's perception, proxy report by parents or caregivers is often necessary in the pediatric care setting due to a child's young age and/or limited ability to self-report(37). Although studies have shown that children and adolescents above the age of five are capable of self-reporting perceived quality of life independently(38), this study will use proxy evaluation due to the diverse cognitive abilities in the target group. Allowing for differentiated evaluation (proxy-reported or self-reported) would complicate comparability.

Using tape as a means of mounting the accelerometers could potentially ensure slightly better data quality and possibly better wear compliance compared to using elastic bands(39). However, placement of the accelerometer with tape requires professional assistance, thus making the use of elastic belts a far more feasible solution. Additionally, elastic belts have been reported to be more comfortable for the user.

Using only one accelerometer instead of two limits the possibility of differentiating activity types(40). However, this study will only be using one accelerometer to ensure better wear compliance among the children and adolescents.

Recruitment of participants for this study will take place during the COVID-19 pandemic. To account for the possible impact this may have on the study, parents will be asked to evaluate the degree to which their child's physical activity level is affected by COVID-19 on a 5-point Likert scale ranging from "He/she is a lot less physically active now than before COVID-19" to "He/she is a lot more physically active now than before COVID-19." Furthermore, accelerometer data is only to be collected on days that represent everyday life, i.e., not quarantine days, holidays, or sick days.

Conclusion

The present protocol outlines a research project that will investigate predictors of habitual PA in children and adolescents with cerebral palsy with the perspective of optimizing PA levels and associated overall health, activities of daily living, and quality of life.

Authors' contributions

Conceptualization and design of the study: AHL, JT, JL & CEF. First draft of manuscript: CEF. Critical revision of manuscript for important intellectual content and approval of final version: all authors.

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Competing interests statement

The authors declare that they have no competing interests.

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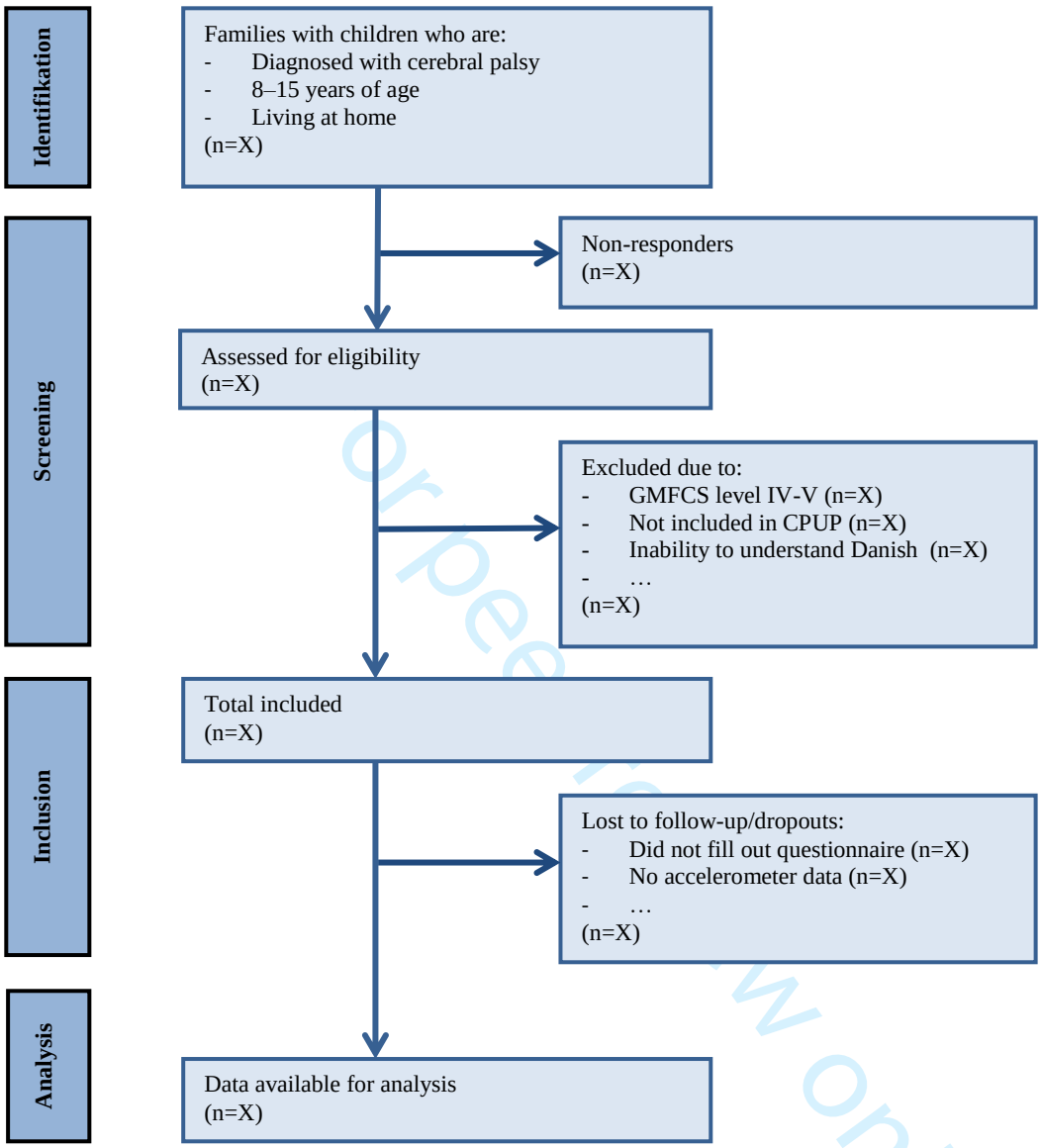
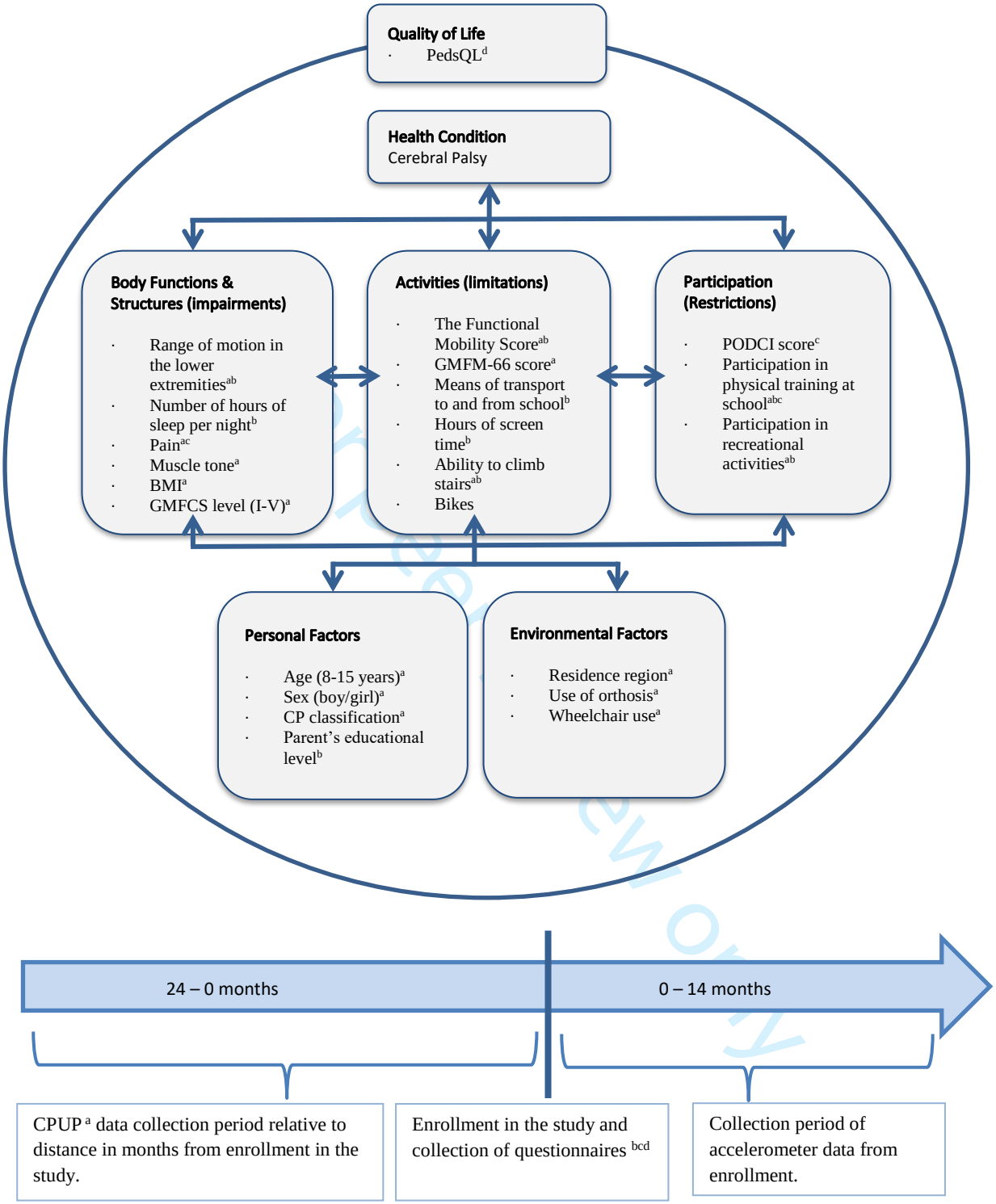
Captions for figures

Figure 1. Flow diagram

Figure 2: Included predictive variables sorted into components according to the modified ICF model, including data collection timeline in months





Variables derived from the following: [a]CPUP registry, [b]Parent reported questionnaire, [c]PODCI questionnaire, [d]PedsQl questionnaire

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	17-19
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12, 16-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12, 16-17
		(*b*) Describe any methods used to examine subgroups and interactions	17
		(*c*) Explain how missing data were addressed	16-17
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	Fig 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	-

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	-
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Predictors of physical activity levels in children and adolescents with cerebral palsy: clinical cohort study protocol

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PROTOCOL MANUSCRIPT

Predictors of physical activity levels in children and adolescents with cerebral palsy: clinical cohort study protocol

Christina Esmann Fonvig, MSc.PT
Orthopaedic Research Unit,
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark
OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark

Jens Troelsen, Professor, MSc, PhD, Head of Department
Department of Sports Science and Clinical Biomechanics
University of Southern Denmark

Ulrike Dunkhase-Heinl, MD
Department of Paediatrics, Lillebaelt Hospital, Kolding

Jens Lauritsen, Professor
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark

Anders Holsgaard-Larsen, Professor, MSc, PhD.
Department of Orthopaedics and Traumatology, Odense University Hospital &
Department of Clinical Research, University of Southern Denmark

Corresponding author:
Christina Esmann Fonvig, The Orthopaedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, J. B. Winsloews Vej 4, 5000 Odense C, Denmark.
E-mail: christina.esmann.fonvig@rsyd.dk

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Abstract

Introduction

Children and adolescents with cerebral palsy may be trapped in a vicious circle of low physical fitness, resulting in deconditioning that causes a further decrease in physical activity (PA), a lower quality of life, and an increased risk of developing non-communicable diseases (NCDs). Therefore, establishing a healthy and active lifestyle during childhood is even more important for individuals with a disability. However, the factors that influence habitual PA in children and adolescents with cerebral palsy remain unknown.

The present protocol outlines a prospective cohort study with the aim of investigating potential predictors of habitual PA in children and adolescents with cerebral palsy in order to provide evidence for optimizing PA levels and associated overall health.

Methods and analysis

This prospective cohort study will enroll participants with cerebral palsy between the ages of 8 and 15 years at Gross Motor Function Classification System (GMFCS) levels I–III. Using a modified version of the International Classification of Functioning, Disability and Health (ICF) model as a conceptual analytical framework, the analysis will be divided into six components and will provide predictors for habitual PA measured by accelerometry. The potential predictive variables are registry data on physical function (Danish Cerebral Palsy Follow Up Program [CPUP]); validated proxy-reported questionnaires on quality of life (Pediatric Quality of Life Inventory (PedsQL)), overall health, pain, and participation in daily activities (Pediatric Outcomes Data Collection Instrument (PODCI)); and supplementary questions regarding sleep, screen time, and socio-economic status.

Ethics and dissemination

The project is approved by the Danish Data Protection Agency (19/16396) and has been declared not notifiable by the Regional Committee on Health Research Ethics, cf. Committee Act Art. 14, paragraph 1 (S-20192000-23). The study results will be published in international peer-reviewed journals, presented at international conferences, and published in a PhD dissertation.

Trial registration

ClinicalTrials.org identifier: NCT04614207

Article Summary

Strength and limitations of this study

- The study will provide novel evidence that will aid identification of PA levels and patterns in children and adolescents with cerebral palsy for early intervention.
- The findings may be implemented in evidence-based PA guidelines, which currently are lacking for children and adolescents with cerebral palsy.
- Bootstrap validation will be performed to increase internal validation. Optimally, external validity of the findings should be verified in the future using an external cohort.

Introduction

Cerebral palsy

Cerebral palsy (CP) is a condition that describes a group of disorders (altered muscle tone, movement disorders, muscle weakness, ataxia, and rigidity) related to the development of movement and posture causing activity limitations and reduced quality of life(1). CP is a common impairment among children, with a prevalence of 2.1 per 1000 live births worldwide(2) and 2.4 per 1000 live births in Denmark(3). Cerebral palsy is attributed to non-progressive disturbances in the fetal central nervous system or in the developing infant within the first two years of life(1, 4). Although CP is a non-progressive diagnosis, it is a lifelong condition that requires attention through most of the person's life, as impairments are constantly evolving and inhibit performance of activities and participation in daily living(1, 5).

Physical activity

Low levels of physical activity (PA) are a worldwide threat to the health of children, including those with disabilities. For this reason, the World Health Organization recommends children to be moderate to vigorous physical active for at least 60 minutes per day, including muscle- and bone-strengthening activities at least three days per week(6). Although there are no specific evidence-based PA guidelines for children with cerebral palsy, it is clear that they have lower levels of PA and higher levels of time spent sedentary than their peers(7) and that their level of mobility limitation is negatively associated with their level of PA(8).

The long-term effects of reduced habitual PA and increased sedentary time include a greater risk of developing non-communicable diseases (NCDs) such as metabolic dysfunction, cardiovascular disease, and poor bone density. These problems can, in turn, result in poorer overall health, reduced

life expectancy, and a greater burden of disease in years of life lost to disability(9, 10). Furthermore, evidence suggests that more than 25% of adults with CP experience mobility decline, for some resulting in persistent loss of independent gait function, thus, emphasizing the importance of maintaining a physical active lifestyle throughout childhood and adolescence(11). Ideally, childhood should be marked by high levels of intense play and habitual PA, which, in addition to providing protective physical benefits, also appears to improve mental health(12, 13).

Predictors of physical activity

In Scandinavia, healthcare professionals offer standardized clinical examinations throughout childhood using the Cerebral Palsy Follow-Up Program (CPUP), which was developed in Sweden more than 20 years ago(14) and was adopted in Denmark as a National Clinical Quality Database by the Danish Clinical Registries in 2015. CPUP is designed to support early detection of complications, such as hip dislocation, scoliosis, and muscle contracture, as well as to improve the quality of healthcare(14, 15). Danish Clinical Guidelines for physiotherapy and occupational therapy for children with CP emphasize that future research should focus on the short- and long-term effects of the interventions applied to improve the children's activities of daily living(16). Despite this recommendation, it has not been investigated whether the standardized examinations and accompanying variables of CPUP are associated with habitual PA. Thus, potential objective predictors of PA can be identified through this national clinical quality database, allowing early detection and potentially improved interventions.

To optimize activities of daily living and long-term health outcomes for the present population, a key objective is to encourage and facilitate an increase in habitual PA and reduce the amount of time spent sedentary(7). However, the current literature does not provide evidence for barriers to or

motivators for PA in children and adolescents with cerebral palsy. Furthermore, no studies have examined the underlying reasons for altering habitual PA.

Aim and hypothesis

The aim of the present cohort-study is to identify and investigate potential predictors of habitual PA in children and adolescents with cerebral palsy, with the perspective of providing evidence to optimize PA levels and associated overall health.

We hypothesize that potential predictors of habitual PA can be identified through objective variables included in the CPUP database and in supplementary questionnaires on proxy-reported outcome measures, using a modified ICF model (Body Functions and Structures, Activities, Participation, Personal Factors, Environmental Factors, and Quality of Life) as a conceptual statistical framework.

Methods and analysis

Study design

A prospective clinical cohort study using historical registry data from CPUP and supplementary proxy-reported outcome measures will be conducted. The STROBE checklist for reporting cohort studies will be used to report the study findings(17). Enrollment commenced November 3rd 2020 and is expected to end by December 2021.

Ethics and dissemination

The project has been approved by the Danish Data Protection Agency (19/16396) and has been declared not notifiable by the Regional Committee on Health Research Ethics, cf. Committee Act Art. 14, paragraph 1 (S-20192000-23). The Danish Clinical Registries granted access to the

Cerebral Palsy Follow-Up Program (CPUP) database in June 2019. The study is pre-registered at ClinicalTrials.gov; identifier: NCT04614207.

The project will be conducted in accordance with the Helsinki Declaration II. Before participants (parents/guardians) give their informed written consent to take part in the study, they will receive written and oral information on the experimental procedure and potential risks. The families will be informed that they can withdraw from the study at any time. All subject data will be treated confidentially and in confidence according to the EU's General Data Protection Regulation.

The study results, whether positive, negative, or inconclusive, will be published in international peer-reviewed journals, presented at international conferences, and published in a PhD dissertation. The articles and presentation will not contain any information that could lead to identification of any participants.

Participants & study setting

Participants will be recruited from the five regions of Denmark.

To increase the external validity and sample size of the present project, the inclusion criteria will include children and adolescents of 8-15 years (born between 01.01.2003 - 31.12.2013) who are diagnosed with CP. Inclusion via invitation commenced November 3rd 2020.

. The children/adolescents must be registered in the Danish CPUP and classified at Gross Motor Function Classification System (GMFCS) levels I–III, demonstrating an independent gait function with or without mobility devices. A flow diagram of participants through the study is illustrated in Figure 1. Parents/guardians must be able to read and understand Danish.

Figure 1. Flow diagram

Eligible participants will be identified through the Danish Health Data Authority, after which the parents/guardians will receive written information through secure digital post (e-Boks). If clarification is needed, the project manager can be contacted via telephone or e-mail. Interested parents/guardians will consent electronically via personal link in e-Boks and will automatically be forwarded the questionnaires, which will be filled out electronically. For non-responders, an e-mail reminder will be sent out a total of three times. Habitual PA is to be measured using accelerometers (see below for further description). Participants will receive an accelerometer via postal mail, including a prepaid return envelope.

Data sources and measurements

Parents'/guardians' perceptions of their child's activity behavior, health status, socio-demographic background, sleep, and screen habits will be collected in an electronic questionnaire. Demographic characteristics (age, sex, CP type & subtype, GMFCS level) and detailed information on the participants' health and physical abilities, as evaluated by healthcare professionals, will be collected through CPUP (see below for further description of collected variables).

The patient-reported outcome measures will be entered directly into a secure web database, REDCap, under Open Patient data Explorative Network (OPEN), Odense University Hospital, Region of Southern Denmark(18), by the parents/guardians using a web link sent via secure digital post (e-Boks). Legal values have been set where possible, to validate the entered values. All collected data will be stored in OPEN Storage, merged, and analyzed at the Danish Health Data Authority Research Engine.

Quantitative variables

Accelerometry

Habitual PA will be assessed using the Axivity AX3 accelerometer. The use of an accelerometer is a common method for objectively measuring PA(19), and is considered a feasible and validated measure for ambulatory children and adolescents with CP(20).

The Axivity AX3 detects movement in three directions: vertical (X), anteroposterior (Y), and mediolateral (Z). The combination of these three axes allows for movement to be calculated into vector magnitude (VM), with $VM = \sqrt{(X^2 + Y^2 + Z^2)}$. Vector magnitude will be calculated per epoch of time in activity counts (counts per epoch of time). Sampling frequency will be set at 50 Hz with a dynamic range of ±8g(21). The collected raw data will provide information on the wearer's habitual PA behavior regarding acceleration of bodily movement.

The accelerometer is to be worn in a snug-fitting pouch in an elastic belt, strapped around the hip, with the device placed on the midaxillary line at the level of the iliac crest on the child's right side(19, 22). The accelerometer device is to be worn for seven successive days; five school days and a weekend(23). A valid wear day will be defined as a day where the accelerometer is worn for at least 10 hours out of the expected awake time (defined as hours between 6 a.m. and 10 p.m. on weekdays, and 7 a.m. and 11:59 p.m. om weekend days). A similar method has been used in the study by Rasmussen et al. (2020) to assess non-sedentary time with screen time use(21). The minimum number of valid wear days will be four, including one weekend day(24). According to procedures used in previous studies(21) non-wear periods are identified and registered as missing data by evaluating three signal features generated from acceleration in combination with temperature and predefined expected awake time. Periods of no movement (acceleration below 20 mg) will be identified as non-wear depending on the timespan; 1) periods longer than 120 min

will always be identified as non-wear, 2) periods from 45 to 120 min are identified as non-wear if the average temperature is below an individually estimated non-moving temperature (NMT) threshold, 3) periods of 10 to 45 min with no movement are only identified as non-wear if the average temperature is below the NMT threshold and if the end of the period is within the expected awake time. Device transportation (registration of movement when the device is not worn by the child) is identified as non-wear if the average temperature of the period is below the NMT threshold(21). Non-valid data will be excluded for further analysis.

Total wear time and activity counts will be processed using Matlab (Mathworks Inc., Natick, Massachusetts, US). To optimize wear time, parents will be offered a daily SMS message encouraging the child to wear the accelerometer.

The OMGUI v43 software will be used to set up and configure the accelerometers. The Axivity AX3 raw acceleration data will be converted to ActiGraph counts using the methods described by Brønd et al. (25). The overall level of PA will be expressed as average counts per day. Converting Axivity raw data to ActiGraph counts will allow for comparability with typically developed children and for sub-analysis using CP-specific cut-points for estimation of time spent in sedentary, light, or moderate-to-vigorous intensity across the different gross motor function levels(22).

Cerebral Palsy Follow-Up Program (CPUP)

Retrospective variables collected from the CPUP physiotherapy protocol, patient protocol, neuropediatric protocol, and orthopedic protocol will be used to predict the level of habitual PA. Physiotherapy assessments are reported to the database yearly for persons at GMFCS levels II and III, and biennially for persons at GMFCS level I. Assessments from the pediatricians and the orthopedic surgeons are collected respectively once before the age of 5 years and based on the

child's age and gross motor function(14). Consequently, the retrospective CPUP data has been collected within the 38 months prior to assessment of PA level (see timeline, Figure 2).

Pediatric Quality of Life Inventory (PedsQL)

To evaluate health-related quality of life, a linguistically validated Danish version of the Pediatric Quality of Life Inventory (PedsQL) Cerebral Palsy Module, which is specifically designed for children with CP, will be used(26). It is based upon the parents' reports and measures physical, emotional, social, and school functioning. The construct and discriminant validity of the original version have been supported by comparing the scores from children with CP with a generic measure of the same construct from children without disability(27). Satisfactory internal consistency reliability coefficients of 0.87–0.97 have been demonstrated for the PedsQL parent proxy-report for children ages 8–18(28).

The Pediatric Outcomes Data Collection Instrument (PODCI)

Overall health, pain, and participation in normal daily activities will be assessed by a Danish version of the Pediatric Outcomes Data Collection Instrument (PODCI). Concurrent and discriminant validity have been assessed by comparing the Pediatric Outcomes Data Collection Instrument with other measures of health and well-being, gross motor function, and diagnostic subgroups in children with CP(29). Moderate to good test-retest reliability with ICC values of 0.71–0.97 have been reported in children with orthopedic or musculoskeletal disorders(30).

Supplementary questions

The following assessment will be evaluated by means of a supplementary parent-reported questionnaire: The child's average sleep and screen time on a typical weekday and weekend-day, and parent's socio-economic status as determined by the parent (based on questionnaires used in the PHASER study)(31). Visual evaluation of range of motion for the joint on the most affected side;

the parent is shown a picture of a joint movement (positioned in the minimum range of motion considered acceptable according to the CPUP's physiotherapy protocol) (32), and is asked to evaluate whether the child's joint is capable of 'more' or 'less' movement than the depicted picture (see Appendix – Parent-evaluated range of motion in the lower extremity). Furthermore, assessment of mobility through the Functional Mobility Scale (FMS)(33) (for more detail see Table 1).

All data from the PedsQL, PODCI and supplementary questionnaires are proxy-reported by a parent or caregiver.

Danish National Patient Register

For recruitment purposes, parents'/guardians' national security numbers will be applied for at the Danish National Patient Register, as will registry data on relevant hospital operations and procedures for the children/adolescents.

Study size

The eligible national cohort comprises a total of approximately 1100 children and adolescents in Denmark in the age group of 8–15 years. Based on previous experience of participation in studies by this patient group we expect an inclusion of 300-400 children.

Statistical methods

The World Health Organization (WHO) introduced the International Classification of Functioning, Disability and Health (ICF) in 2007 as a framework for discussing health and disability from a biopsychosocial perspective through the interaction of five components (i.e., Body Functions and Structures, Activity, Participation, Personal Factors, and Environmental Factors)(34). In 2010, Quality of Life (QoL) was integrated in a modified ICF model(35), which will be used in the current study as a statistical framework. This allows separate and combined analyses for each of the six components on the prediction of habitual PA, as measured by accelerometer, and will

consequently provide data-driven knowledge about using the modified ICF model as a context for habitual PA for children and adolescents with CP.

The following figure operationalizes the statistical framework by sorting included outcome variables according to components in the modified ICF model.

Figure 2: Included predictive variables sorted into components according to the modified ICF model, including data collection timeline in months.

Analysis

The identification of predictive factors of habitual PA in children and adolescents with cerebral palsy between the ages of 8 and 15 years, will, as described above, be operationalized though a statistical analysis plan using the modified ICF model as a conceptual framework (Figure 2). Using a predictive model, the study aims to determine the associations between the response variable and the predictive variables, with the purpose of predicting the output value for new observations given their input values(36). The variable that is to be predicted (the response variable) is habitual PA, represented by accelerometer counts. Regardless of the collection time of the data, all other variables (Table 1) are considered prediction variables(36).

PROTOCOL MANUSCRIPT

Table 1: Predictive variables

ICF component		CPUP variables	Questionnaire variables
Body Function & Structure	Range of motion in the lower extremities	*Continuous value:* Variable most associated with habitual physical activity from the following measurements (on the most affected side) measured in degrees: HIP · Abduction · Flexion · Internal rotation · External rotation · Ely's test · Extension KNEE · extension (hip 90° flexion) · extension (hip 0°) ANKLE · Dorsal flexion with flexed knee Dorsal flexion with extended knee	Visual evaluation of range of motion for most affected side. *Categorical values:* 'more' or 'less' than the depicted picture of the following joints (see appendix for illustrations): · HIP flexion · KNEE extension with opposite leg extended · KNEE extension with opposite leg flexed · ANKLE flexion with extended knee · ANKLE flexion with flexed knee: a. Decreased range of motion b. Full range of motion
	Number of hours of sleep per night		*Continuous value:* 1. Time in hours per day on school days. 2. Time in hours per day in the weekend
	Pain	*Categorical values:* Yes/No	
	Muscle tone (Modified Ashworth Scale)	*Categorical value*: The absence or presence of increased muscle tone in the most affected side of the lower extremity as evaluated on the Modified Ashworth scale.	
	BMI (body mass index)	*Continuous value:* Weight in kg / [Height (m)]^2	
	GMFCS level	*Categorical values:* I-III	*Categorical values:* I-III
Activities	The Functional Mobility Score	*Categorical values:* FMS score (1-6) for: · 5 meter · 50 meter · 500 meter	*Categorical values* FMS score (1-6) for: · 5 meter · 50 meter · 500 meter
	GMFM-66 Score	*Continuous score:* 0-100	
	Means of transport to and from school		*Categorical values:* · Walks · Bikes · Transported (e.g. by car, bus, cargo bike) · Other
	Hours of screen time		*Continuous value:* 1. Time in hours per day on school days. 2. Time in hours per day in the weekend
	Ability to climb stairs	*Categorical values:* 1. Climbs up stairs independently (Yes/No) 2. Climbs down stairs independently (Yes/No)	
	Bikes (bicycle, tricycle, running bike etc.)	*Categorical values:* · Often (daily) · Sometimes (a couple of times a week)	

		· Rarely (a couple of times a month) · Never	
Participation	PODCI		*Continuous score:* 0-100
	Participation in physical training at school	*Categorical values:* Yes/No	*Categorical values:* Yes/No
	Participation in recreational activities	*Categorical values:* Yes/No	*Categorical values:* · Swimming · Horseback riding · Soccer · Handball · Dance · Strength training · Gymnastics · Basketball · Floorball · RaceRunning · Nothing · Other
Personal Factors	Age	Age in years	Age in years
	Sex	*Categorical values:* Male/Female	*Categorical values:* Male/Female
	CP classification	*Categorical values:* · Spastic · Dyskinetic · Ataxic · Not classified/mixed form	
	Parents educational level		*Categorical values:* · Primary school up to and including 6th grade · Primary school 7th – 10th grade · High school education (e.g. HTX, STX, HHX) · Vocational education (e.g. office and shop assistant, etc.) · Short higher education (e.g. market economist, police officer, etc.) · Medium-term higher education (e.g. teacher, educator, nurse, bachelor of political science, etc.) · Long higher education (e.g. master degree) · PhD or research training · Other education · Do not know
Environmental Factors	Residence region	*Categorical values:* · Region of Southern Denmark · Region of Northern Denmark · Central Denmark Region · Region Zealand · Capital Region of Denmark	
	Use of orthosis	*Categorical* values: Yes/No	
	Wheelchair use	*Categorical values:* · Does not use · Is assisted · Operates independently	
Quality of Life	PedsQL		*Continuous score:* 0-100

To determine which variables predict the child's level of PA, multiple linear regression analysis will be performed according to the following models:

Primary analysis

Model 1) Multiple linear regression analysis between accelerometer counts (response variable) and all CPUP variables within each ICF component (predictive variables).

Secondary analysis

Model 2a) Backward stepwise regression with accelerometer counts as the response variable and all included CPUP variables as predictive variables. The Akaike information criterion (AIC) will be used to determine which variables to retain in the model. Resampling, as described below, will be used to address potential overfitting and to summarize the variability of selected variables(37).

Model 2b) Multiple linear regression analysis between accelerometer counts (response variable) and all included variables as predictive variables. This model will assess the degree of predictive strength that the questionnaire variables adds to model 1.

The coefficient of determination, adjusted R-squared, will illustrate the percentage of variance in PA that is explained by the predictive variables. The higher the coefficient, the stronger the relationship. The Root Mean Squared Error of the estimate will indicate the accuracy of the predictions. Results will be presented with an alpha of 0.05 and a 95% confidence interval.

Models will be checked using graphic inspection. Splines will be used to account for non-linear effects, and interactions will be included in the model based on relevant subject-matter knowledge. These will be specified in detail in the statistical analysis plan.

Bootstrapping will be performed to reduce the risk of overfitting the prediction model and will thus increase internal validation(38). Missing data will be addressed using multiple imputation applied to

each of the bootstrapped datasets(39). External validation can be verified using the Swedish CPUP registry data; however, this will not be performed in the present study.

To evaluate the significance of CPUP data collection periods relative to the time in months from the measure of PA, the model will test for differences in prediction analyses between the following time periods: 0 ≤ 12 months, 13 ≤ 24 months, and 25+ months (Figure 2).

Analysis of non-responders and excluded participants will be performed to disclose potential selection bias.

Statistical analyses will be performed using Stata.

Additional analyses

Several other related analyses will be reported separately. One further study will be on a sub-group of any children or adolescents who are referred for three-dimensional gait analyses as part of their individualized clinical treatment plan. Another analysis will use cut-points for sedentary, light, moderate, and vigorous activity for each of the three separate GMFCS levels(22) and then compare sedentary behavior and PA levels of children and adolescents with CP with those of typically developed children and adolescents. Finally, a qualitative study will be performed to explore the daily life challenges that parents describe facing in their pursuit of helping their children with CP live a physically active lifestyle. The methods and findings of this study will be reported elsewhere.

Adverse events

Measuring habitual PA by accelerometry is a non-invasive method commonly used in research and has no known risks or side effects, including pain or discomfort.

Patient and public involvement statement

A pilot study was conducted during the fall of 2019 in which five families were invited to participate and then give feedback on the questionnaires, the use of the accelerometer, and the overall burden of participation. Feedback from the children and adolescents, as well as from their parents, led to minor alterations of the study design, such as the questionnaire setup, the use of a different type of elastic belt as well as eliminating the use of an additional accelerometer worn on the thigh.

Patient user groups contributed to the assessment of the project prior to funding being granted by the Elsass Foundation and the Region of Southern Denmark.

Study results are expected to be disseminated through a national interest organization for persons with cerebral palsy (e.g., articles on website, oral presentation), ensuring study results are communicated to the participants and also to a general wider patient community.

Discussion

The present study will provide novel evidence of predictors of PA for children and adolescents with CP. Recruitment via secure digital post should increase recruitment efficiency, as eligible parties are invited to participate without dependency on health care attendances. Due to the wide inclusion criteria, results of this study are expected to have a high level of external validity and be generalizable to other children and adolescents with CP. To ensure the internal validity of the study, selection bias will be investigated through a non-responder analysis. A high acceptance by the treating health professionals is expected, as the majority of variables of interest are already implemented in CPUP.

The study findings may be implemented in evidence-based PA guidelines, which are currently lacking for children with cerebral palsy, thus providing health professionals with a clinical instrument to help increase PA levels in children and adolescents with cerebral palsy.

Limitations

This cohort study will be subject to some methodological limitations. Primarily, the current predictive regression analysis cannot determine causality between the predictive variables and the level of PA endured. Thus, the findings should optimally be validated in an external cohort and/or verified in randomized controlled trails. External validation of the prediction model may be achieved, for example, by using the Swedish CPUP registry data; however, this validation is not a part of the current protocol. Nevertheless, bootstrap validation will be performed to increase internal validation(38).

Using registry data supports clinically relevant data on all persons in the target group; however, it also poses a risk of having data that is missing for unidentifiable reasons, which complicates the handling of missing data. In this study, missing data will be addressed using imputation of the missing values with the sample mean of the observed cases, resulting in a potential risk of biased estimates due to variance of the variable may be underestimated.

A possible 0-38 month time lag between variables collected via CPUP and the accelerometer data is a methodology limitation. As the participants are at a developmental age where physical change can be monumental, sensitivity analysis will be performed to evaluate the potential significance of the time lag.

To allow for comparability, data on sleep time, screen time and socio-economic status were assessed using a questionnaire developed for assessment of typically developed children and

adolescents in Denmark(31). Data could have been strengthened by the use of validated questionnaires.

While the WHO definition of QOL is based on an individual's perception, proxy report by parents or caregivers is often necessary in the pediatric care setting due to a child's young age and/or limited ability to self-report(40). Although studies have shown that children and adolescents above the age of five are capable of self-reporting perceived quality of life independently(41), this study will use proxy evaluation due to the diverse cognitive abilities in the target group. Allowing for differentiated evaluation (proxy-reported or self-reported) would complicate comparability.

Although the study aims to cover a broad aspect of ICF components, important personal and environmental factors such as self-efficacy, social support, motivation, and physical access are not included in the analysis.

While children at GMFCS IV may walk assisted as a means of ambulation over short distances, or participate in active propulsion, neither level IV or V are included in this study as the use of wheelchairs complicate valid measurement of physical activity using accelerometer. Consequently, results of this study will not be applicable to children at a GMFCS level IV-V and thus hinders external validity.

Using tape as a means of mounting the accelerometers could potentially ensure slightly better data quality and possibly better wear compliance compared to using elastic bands(42). However, placement of the accelerometer with tape requires professional assistance, thus making the use of elastic belts a far more feasible solution. Additionally, elastic belts have been reported to be more comfortable for the user.

Using only one accelerometer instead of two limits the possibility of differentiating activity types(43). Furthermore, a hip worn accelerometer may exclude capturing upper-limb activities,

possibly resulting in an underestimation of physical activity levels. However, this study will only be using one accelerometer to ensure better wear compliance among the children and adolescents.

Recruitment of participants for this study will take place during the COVID-19 pandemic. To account for the possible impact this may have on the study, parents will be asked to evaluate the degree to which their child's physical activity level is affected by COVID-19 on a 5-point Likert scale ranging from "He/she is a lot less physically active now than before COVID-19" to "He/she is a lot more physically active now than before COVID-19." Furthermore, accelerometer data is only to be collected on days that represent everyday life, i.e., not quarantine days, holidays, or sick days.

Conclusion

The present protocol outlines a research project that will investigate predictors of habitual PA in children and adolescents with cerebral palsy with the perspective of optimizing PA levels and associated overall health, activities of daily living, and quality of life.

Authors' contributions

Conceptualization and design of the study: AHL, JT, JL, UDH & CEF. First draft of manuscript: CEF. Critical revision of manuscript for important intellectual content and approval of final version: all authors.

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Competing interests' statement

The authors declare that they have no competing interests.

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Data availability statement

Due to ethical and legal considerations, our data cannot be shared publicly. This is due to the restrictions from the Regional and the National Committee on Health Research Ethics and the General Data Protection Regulation (EU) 2016/679, since the data contains person-specific information on sex, birth date, and cerebral palsy classification among other.

Data are available for researchers who meet the criteria for access to confidential data. Access may be acquired through contact to the research group.

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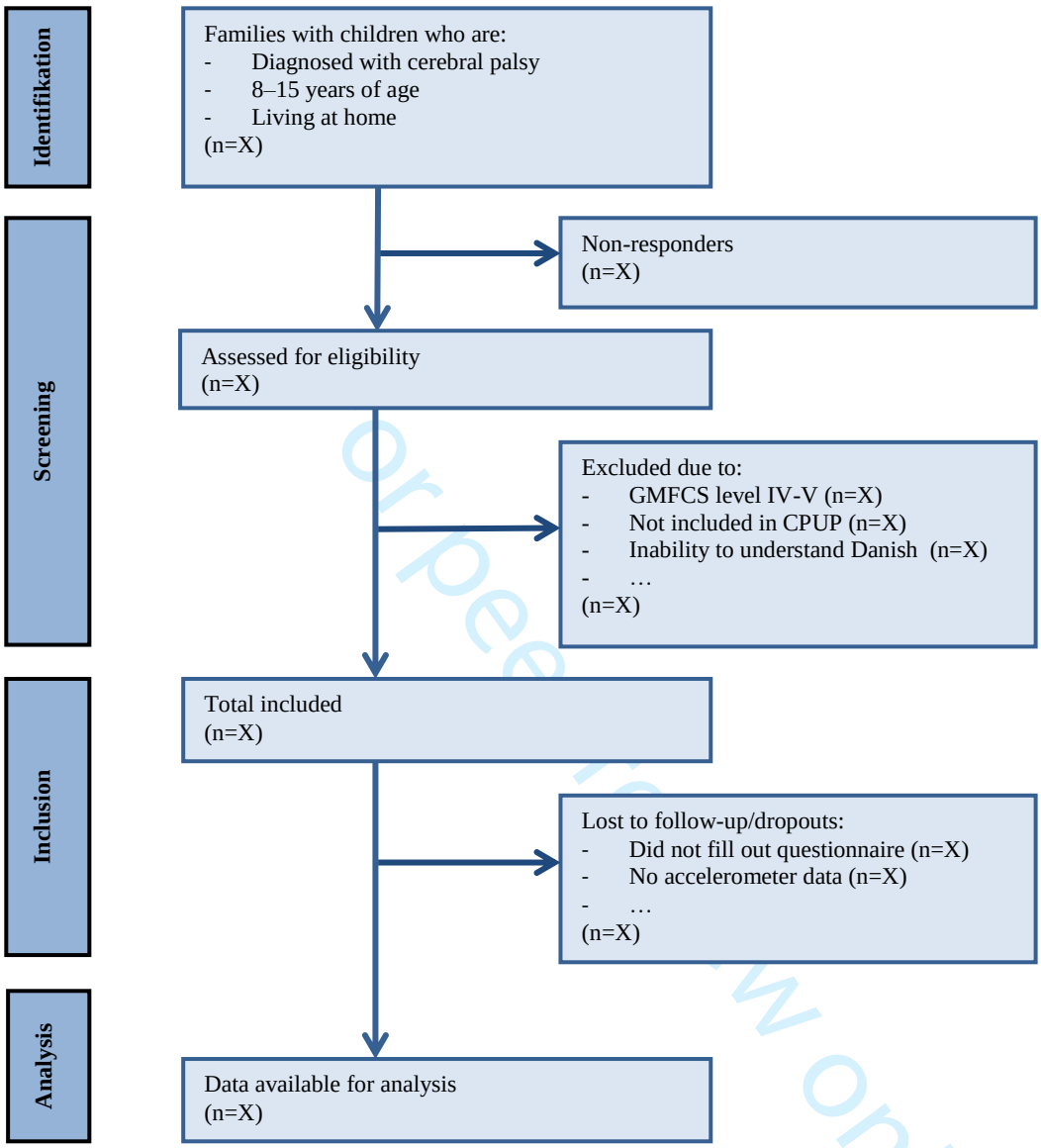
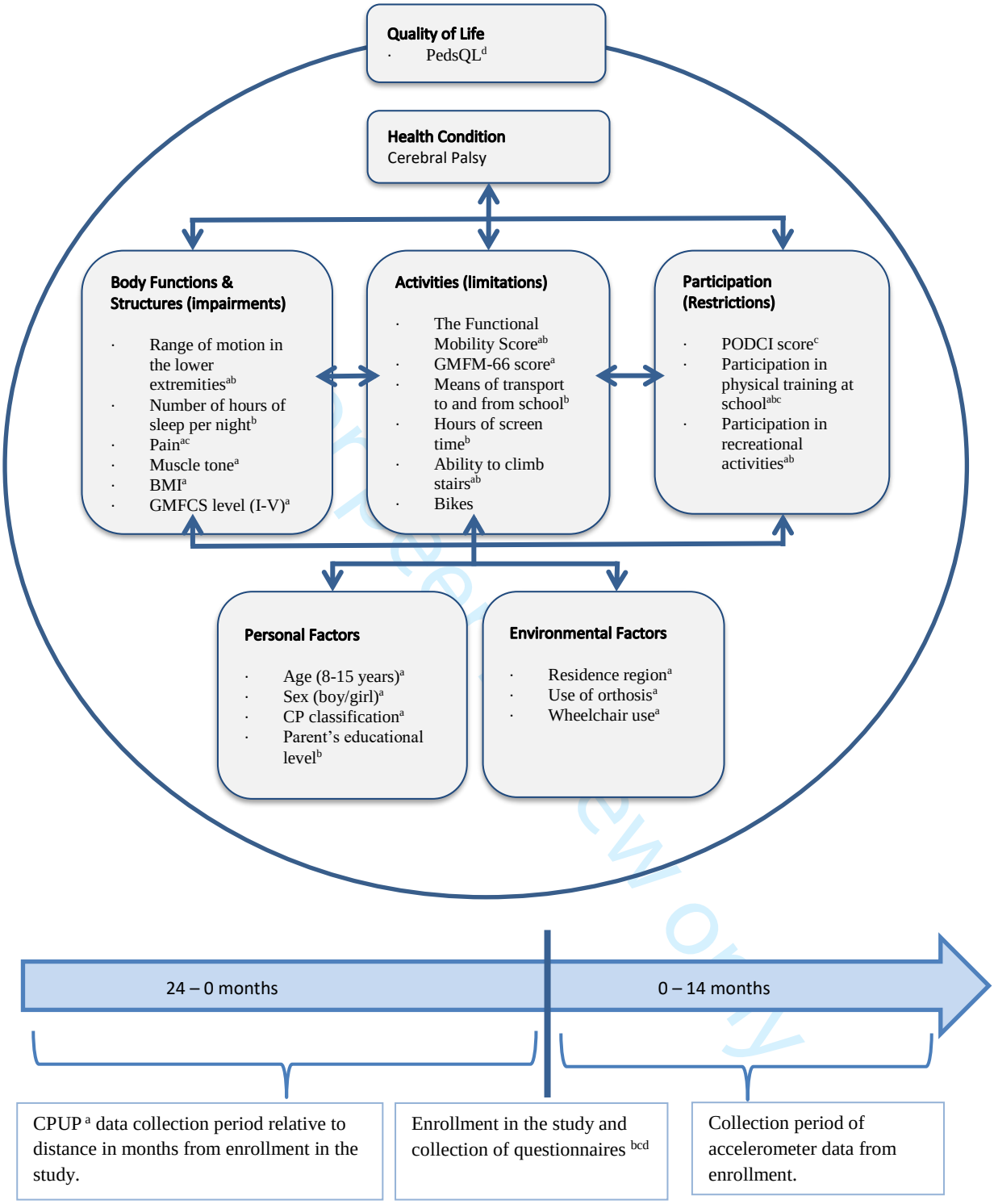




Variables derived from the following: [a]CPUP registry, [b]Parent reported questionnaire, [c]PODCI questionnaire, [d]PedsQl questionnaire

Appendix – Parent-evaluated range of motion in the lower extremity

The appendix is an English version of the parent-evaluated range of motion assessment for the lower extremity with the purpose of evaluating whether parent-reported range of motion is an operational method of assessment. The parent-reported assessments are not intended to replace the CPUP range of motion values.

The parent is asked to evaluate range of motion on the most affected side, by stating whether the child's joint is capable of 'more' og 'less' movement than the depicted picture. The joint angle in the picture is the minimum range of motion considered acceptable according to the CPUP's physiotherapy protocol (1).

The following pictures depict movement in different lower extremity joints. Please only assess range of motion in the most affected limb (the limb with the greatest movement limitation)

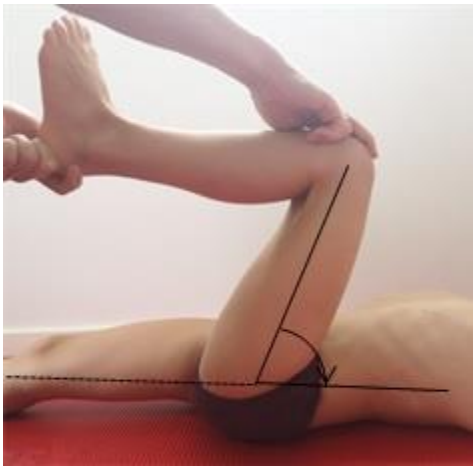
Please note which leg is assessed: ○ RIGHT ○ LEFT

Each movement is illustrated with one picture. Based on the picture, please evaluate whether your child's joint is capable of 'more' or 'less' than depicted.

Hip flexion – the child is lying flat on his/her back, with the opposite leg stretched out on the floor. When you gently press the child's knee towards the stomach/chest, then

○ The hip CANNOT reach the position in the picture before meeting resistance

○ The hip can flex further (the knee is moved closer to the stomach/chest) than depicted.

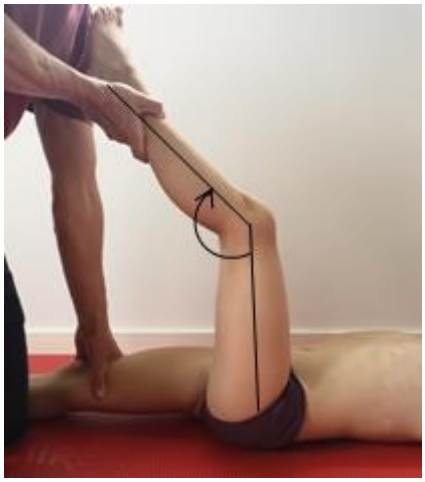


Knee extension – the child is lying flat on their back, with both legs stretched out. When you gently lift the child's foot from the surface, then

- The knee CANNOT reach the position in the picture
- The knee can reach the position in the picture, or may even bend backward (hyperextend)

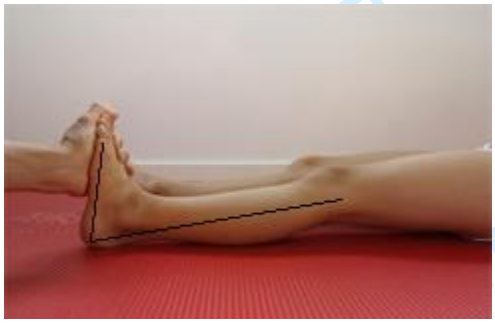
Popliteal angle – have the child lay on his/her back on the floor with the opposite leg stretched out. Hold the leg to be assessed so that the thigh is pointing straight up towards the ceiling. In this position, extend the knee as much as possible before meeting resistance.

- The knee CANNOT be extended as much as depicted
- The knee can be extended just as much, or more, than depicted



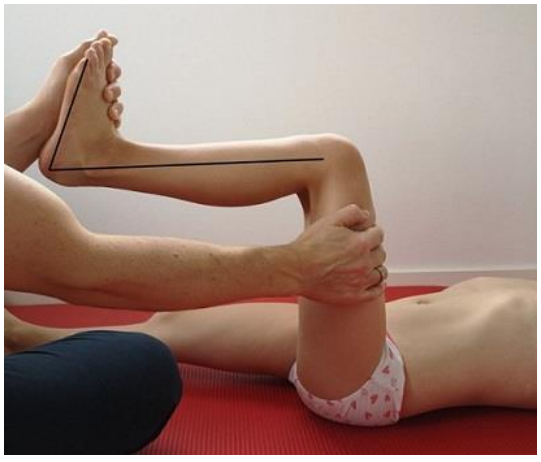
Flexion of the ankle with an extended knee – have the child lay flat on his/her back with the opposite leg stretched out. Press against the sole of the foot with one hand

- The foot CANNOT be pressed towards the shin as depicted
- The foot can be pressed towards the shin as depicted, or further.



Flexion of the ankle with a flexed knee – have the child lay flat on his/her back with the opposite leg extended. The test leg flexed 90 degrees in the hip and in the knee (see picture). Press against the sole of the foot with one hand, and hold back on the child's thigh with the other hand.

- The foot CANNOT be pressed towards the shin as depicted
- The foot can be pressed towards the shin as depicted, or further.



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	17-19
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13, 17-18
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13, 17-18
		(*b*) Describe any methods used to examine subgroups and interactions	17-18
		(*c*) Explain how missing data were addressed	17-18
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	-
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	Fig 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	-

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	-
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.