JOYCE BENNER

CONSEQUENCES OF AGING WITH CEREBRAL PALSY

Core outcomes of health, activities and participation

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Consequences of Aging with Cerebral Palsy
Core outcomes of health, activities and participation

Gevolgen van ouder worden met cerebrale parese
Belangrijke uitkomsten in gezondheid, activiteiten en participatie

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1

INTRODUCTION

Advancements of medical care and rehabilitation in the past decades have contributed to longer life expectancies for people with cerebral palsy (CP). Adults with CP may experience health problems and functional limitations such as chronic pain or fatigue, a low level of physical fitness, difficulty in walking, dependency in self-care, and early onset of chronic diseases. A substantial proportion of adults with CP have low levels of physical activity and seem restricted in their participation, for example in paid employment. Additionally, their functioning, disability, and health changes across the lifespan in response to aging. Because of increasing physical disability with increasing age, people with CP are suggested to experience accelerated aging. Systematic follow-up of the core outcomes that reflect the most important health issues, activities and participation of adults with CP would allow us to design appropriate rehabilitation interventions and prevention strategies for this population.

This thesis describes the level and long-term course of functioning, disability, and health in adults with CP, and the core outcomes for this population based on current literature. In addition, it describes how a core outcome measurement set for adults with CP is developed, focusing on chronic disease risk.

CEREBRAL PALSY

Cerebral palsy (CP) is the most common cause of physical disability in childhood, with a prevalence ranging from 1.7 to 3 per 1,000 live births.[1] According to its definition, CP describes a group of permanent movement and posture disorders that result from non-progressive disturbances to the developing fetal or infant brain. Impairments commonly associated with the condition are included in the definition because of their substantial impact on the individual. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behavior, by epilepsy, and by secondary musculoskeletal problems.[2] Almost half of the population has a moderate to severe intellectual disability.[3]

The existence of different typologies refers to the complexity of CP. Clinical signs and symptoms, topographical involvement of extremities, and the severity of the motor disorders may differ largely between each individual with CP. The three main types of clinical symptoms and signs (spasticity, dyskinesia, or ataxia) can manifest in either all four limbs (quadriplegia), primarily on one side of the body including one upper and lower extremity (hemiplegia), or primarily in the lower extremities (diplegia).[4, 5] The Surveillance of Cerebral Palsy in Europe (SCPE) agreed on distinguishing four main types of CP: unilateral spastic, bilateral spastic, dyskinetic, and ataxic.[6] The severity of motor disorders can be classified by the Gross Motor Function Classification System (GMFCS)[7]. In this system,

distinction between five levels of gross motor functioning is based on ambulatory and postural abilities, the need for assistive technology, and – to a much lesser extent – quality of movement. Individuals with GMFCS level I generally walk without restrictions, but speed, balance, and coordination may be limited. At the other end of the spectrum, individuals with GMFCS level V are dependent on extensive assistive technology and physical assistance.[7] Approximately 60% of the population is classified as GMFCS level I-II and thus has a mild motor impairment.[8]

Lifelong condition

Due to several advances in healthcare resulting in increased survival, nowadays most individuals with CP have a nearly normal lifespan.[9] If ambulatory, manual, mental, and visual impairments are not severe, life expectancy is close to that of the general population.[9, 10] Adults with CP represent a growing population and now outnumber children and youth with CP by approximately 3:1.[11] Consequently, clinicians and researchers are changing their perspectives towards considering CP as a lifelong condition.

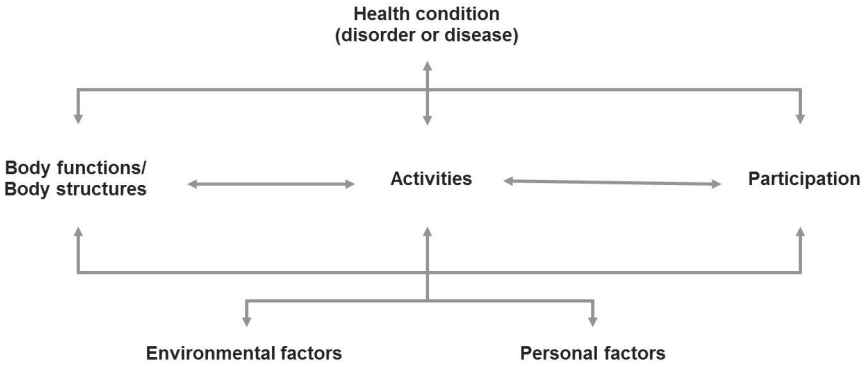
Aging with CP demands a lot from the individual's body and its available capacity. Over time, neuromuscular and skeletal changes occur that can lead to secondary health issues: additional health problems that occur as a result of having a primary disability.[12, 13] Common examples in CP are pain, fatigue, or depression.[14] Furthermore, adults with CP often acquire chronic diseases like cardiovascular disease, diabetes, or chronic lung disease, at a younger age compared to the general population.[15, 16] These additional health conditions (i.e. comorbidities) can develop independently of the primary disability. Aging with CP therefore presents itself in three different forms: (1) normal aging as it affects everyone, where body functions become less vital and deteriorate; (2) increasing secondary health issues that are influenced by the primary disability (e.g. pain resulting from spasticity); and (3) early onset of comorbid, chronic diseases (e.g. cardiometabolic disease).

CONSEQUENCES OF CEREBRAL PALSY

The primary movement and posture disorders, secondary health issues, and comorbid chronic diseases that may occur in people with CP, have lifelong consequences for their level of functioning. Outcomes of functioning are often described by the International Classification of Functioning, Disability and Health (ICF).[17] This conceptual framework can be used to describe the consequences of a health condition, like CP, in a broader biopsychosocial context. The ICF distinguishes the components of body functions and structures, activities and participation, and elaborates on their interactions. Importantly, the framework also incorporates the notion that personal and environmental factors

can facilitate or hinder successful functioning (Figure 1). In the ICF, the term *functioning* refers to all body functions and structures, activities and participation, while *disability* is the parallel term for body impairments, activity limitations and participation restrictions. For healthcare providers, the ICF provides a basis to guide goal setting and intervention planning, and assists them to look beyond their own areas of practice and communicate across disciplines.[18] On a population level, the ICF allows for understanding and studying functioning, disability and health, and for describing outcomes and its determinants.

Figure 1.1 The International Classification of Functioning, Disability and Health (ICF) framework.[17]



Body functions and health issues

Body functions refer to physiological functions of the body, such as neuromotor functions related to joints, muscles, and movement. Impaired neuromuscular functions are hallmark for CP and present symptoms such as spasticity, hypertonia, muscle weakness, or lack of selective motor control.[19] These body impairments can lead to a variety of health issues. For example, spasticity and hypertonia may result in musculoskeletal problems (e.g. muscle contractures, joint dislocation)[20] that often result in or are accompanied by pain and/or fatigue.[14, 21-23] Both pain and fatigue are more frequently reported by people with CP compared to the general population.[22, 24] Impairments can also occur in functions of ingestion (e.g. difficulties in swallowing), digestion, voice, or speech.[25] Other common health issues in CP include epilepsy, disturbed bowel and bladder function, respiratory problems, and sensory problems such as seeing or hearing impairments.[25, 26] These health issues, in conjunction with musculoskeletal problems, may also result in sleep disorders.[27]

Health-related physical fitness

People with CP demonstrate low levels of health-related fitness, including poor cardiorespiratory endurance, unfavorable body composition, and low muscular strength.[28] Studies consistently report low levels of cardiorespiratory endurance for children,

adolescents, and adults with CP.[28-30] Overweight and obesity are common, but literature is inconsistent regarding differences between people with CP and the general population.[28, 31] Reduced levels of health-related fitness may contribute to the worsening of health issues and development of chronic diseases. Recent reports have demonstrated that adults with CP are at heightened risk of multimorbidity,[32-34] the presence of multiple (comorbid) chronic diseases.

Activities

Activity refers to the execution of a task or action, like activities of self-care and mobility in which people with CP may experience limitations. Self-care encompasses general daily activities like washing, toileting, dressing, eating and drinking.[17] Limitations herein may primarily be the result of impaired body functions. Although many adults with CP indicate independency in performing self-care activities, the level of need of help may increase over time.[35] This increase in need for help is even more marked in activities of mobility like walking or moving around in a wheelchair.[35]

Physical behavior

Physical behavior refers to an individuals' behavior in terms of body postures, movements, and/or daily activities, and encompasses both physical activity and sedentary behavior.[36] Physical activity is recognized as important health-promoting behavior throughout the lifespan of every individual. However, due to the health issues associated with the condition, participating in physical activity is often challenging for people with CP. Indeed, physical activity levels are low and sedentary behavior is high in those with CP.[27, 29, 37, 38] Interventions to improve this physical behavior are moderately effective,[39, 40] which is alarming considering its concomitant risk of (early onset of) chronic disease and multimorbidity.

Participation

Participation is defined as involvement in life situations and includes domestic life, interpersonal relationships, employment, community life and recreation and leisure.[17] Despite relatively high participation levels in young adults with CP, most of them experience difficulties in participation.[41] Restrictions in participation are also seen in middle-aged adults with CP; fewer individuals are employed compared to the general population.[42]

OUTCOME MEASUREMENT

Outcome measurement, typically referring to the measurement of health-related outcomes, is essential in clinical practice and health research. An outcome is defined as the construct or aspect of interest, or the *what* to measure. An outcome measurement instrument is the means used to quantify this outcome, or the *how* to measure (e.g., examinations by health

professionals, biomarkers, patient-reported questionnaires, or performance-based tests). Results of these measurements can be used as a basis for clinical management.

As the number of potential outcomes and available outcome measurement instruments has increased dramatically over the past decades, the choice of which outcome measurement instrument to use for a given outcome has become more difficult. Often multiple outcome measurement instruments can assess the same outcome in a specific population. This leads to inconsistency in reporting outcomes, making it difficult to compare findings across different clinical studies or institutions. Consequently, research or intervention evaluations become less informative for clinical practice. A solution to this problem is to standardize outcome measurement by determining core outcomes and core outcome measurement instruments.[43]

Core outcomes

Core outcomes are recommendations of *what* should be measured and reported in clinical practice and health research in a specific population. For adults with CP, a large number of potential outcomes can be measured, which is clearly reflected in the current literature on this population. Inconsistency in the currently reported outcomes for adults with CP can be overcome by describing these outcomes in the ICF framework. Core outcomes can also be targeted to a specific area within a specific population, for example, risk of chronic diseases and multimorbidity in adults with CP.

Core outcome measurement instruments

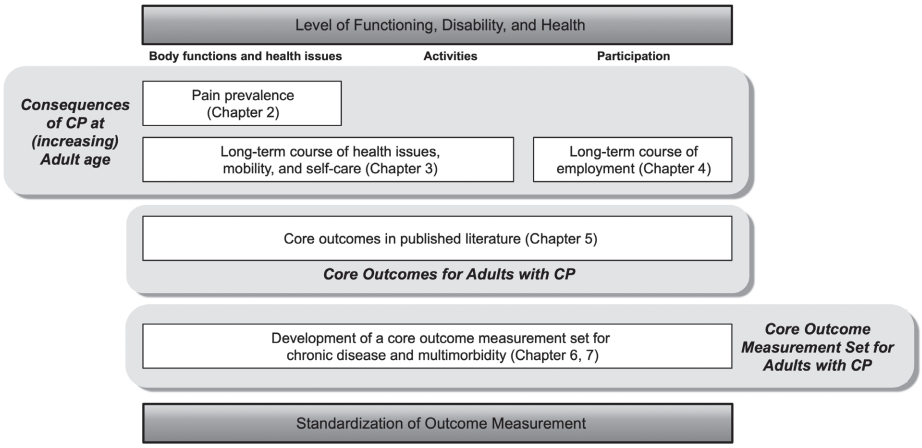
Once an initial list of core outcomes –in a specific population or area– is identified, it should be determined *how* these outcomes can be measured and reported.[43] To this end, core sets of outcome measurement instruments are developed, including recommendations and details on the instruments to use that measure the core outcomes. The development of a core set generally includes stakeholders representing all perspectives, including those from clinicians, researchers, and from the target population. After development, such a core set can be implemented in clinical practice and health research for the standardization of outcome measurement in a specific population or area.

AIMS AND OUTLINE OF THIS THESIS

Despite an increasing number of studies providing insight into the consequences of CP at adult age, current knowledge is limited by a lack of longitudinal studies. As such, there is a need for evidence describing the consequences of aging with CP. Furthermore, core outcomes for adults with CP are lacking, and to date no attempt has been made to standardize outcome measurement for (consequences of) CP in adulthood. The first aim

of this thesis was to improve our knowledge on the *consequences of CP at (increasing) adult age*. Secondly, it aimed to identify *core outcomes for adults with CP*, using the ICF framework as a reference. The third aim was to develop a *core outcome measurement set* for individuals with CP, focusing on chronic disease risk and multimorbidity. Figure 1.2 presents an outline of the aims and chapters of this thesis and their overlying concepts.

Figure 1.2 Outline of the content of this thesis.



The first part of this thesis describes the level and long-term course of outcomes across the ICF framework. In ***Chapter 2***, we studied pain and its characteristics and determinants in adults with CP by means of a meta-analysis of individual participant data. ***Chapter 3*** describes a prospective cohort study exploring the long-term course of perceived health, health issues, self-care, and mobility in adults with CP. The long-term course of employment was explored for this cohort in ***Chapter 4***, were we identified subgroups at risk for unemployment. Then, in ***Chapter 5*** we broadened our scope with a systematic literature review that explored the core outcomes in published literature on adults with CP, again across the ICF. In the last part, the development of a core outcome measurement set to monitor risk factors of chronic diseases and multimorbidity is described. ***Chapter 6*** presents the study protocol of the development of this core set, targeting the following outcomes: cardiorespiratory endurance, body composition, physical behavior, sleep, nutrition, blood pressure, and blood lipids and glucose. In ***Chapter 7***, the selection of outcome measurement instruments into a preliminary core set, by means of a literature review and Delphi procedure with clinical and research experts, is explained. Finally, ***Chapter 8*** discusses the main results of this thesis. Strengths and limitations of the studies described above, and clinical implications and suggestions for future research are discussed.

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3

Long-term deterioration of perceived health and functioning in adults with cerebral palsy

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ABSTRACT

Objective: To describe longitudinal change in perceived health, presence of health issues and functional level in adults with cerebral palsy (CP).

Design: Prospective cohort study.

Setting: Participants' daily environment.

Participants: Adults (n=49) with CP (age range, 35-45y; 27 (55%) men; 36 (75%) spastic) formerly known in pediatric rehabilitation care participated.

Interventions: Not applicable.

Main Outcome Measures: Postal questionnaires were completed by the adults or their proxies (n=9). Health outcomes included perceived health (adapted from the 36-Item Short Form Health Survey) and presence of health issues such as pain, severe fatigue (dichotomized), and functional level (Barthel Index; walking performance).

Results: Over a 10-year period, the percentage of adults with CP worrying about their health increased (29%-54%, p=0.008) and those indicating that health problems limit their activities increased (19%-45%, p=0.002). In the same period, most adults continued to report good general health (93%-86%, p=0.148). Presence of some health issues increased over time, such as pain; severe fatigue was a common health issue at follow-up (32%). Over a 14-year period, mobility and self-care deteriorated (Barthel Index, 17.1 [SD 4.8] to 16.3 [SD 5.6], p=0.007). Walking performance, specifically indoors, declined (83%-71%, p=0.010).

Conclusions: Adults with CP experienced deterioration in health outcomes in the long term. Most notably, perceived health and functional level decreased. Pain and severe fatigue were the most common health issues in adult CP. More research is required to explore the mechanisms at work in the process of aging in persons with CP. Systematic follow-up of adults with CP appears necessary to timely detect and intervene in health problems. and functional decline

INTRODUCTION

Cerebral Palsy (CP) describes a group of permanent disorders of movement and posture causing activity limitation, attributed to nonprogressive disturbances in the developing fetal or infant brain.[1] CP affects approximately 2 in 1000 live births.[2,3] Based on increases in survival rate and longevity of individuals with CP, currently most persons with CP are adults.[4] Bearing in mind this demographic age distribution, it is essential to use a life span perspective with regard to health care services.[5-7]

In cross-sectional studies in adults with CP, pain and fatigue are frequently reported with a high prevalence and co-occurrence.[8-11] Musculoskeletal problems (such as joint deformities) are reported in 15% to 57% of younger adults.[5] Other health problems include bowel and bladder incontinence, feeding problems, epilepsy, depressive symptoms, and sensory impairments.[5,12] Moreover, adults with CP experience deterioration of walking.[12-15] For example, 52% of the adults with CP retrospectively reported walking deterioration over a 7-year period.[14] Deteriorated walking was associated with bilateral CP, greater pain, and greater effect of pain on activities of daily living. The prevalence of daily pain increased over a 7-year period, whereas fatigue did not.[14] Loss of self-care skills (e.g., eating, bathing, and dressing) has also been reported.[16] However, in the latter studies, adults with intellectual impairments were excluded. Data on the course of other health problems are largely lacking.

Cieza et al.[17] indicated that in several clinical populations, mobility, self-care, and pain were among the explanatory factors for perceived general health. For adults with CP, it remains unknown whether similar factors explain their perceived health. Knowledge of determinants of perceived health and insight into the longitudinal change of health and functioning is necessary to improve health care for adults with CP. Therefore, the present study aims to prospectively assess perceived health, self-reported health issues, and functional level of adults with CP and investigate the longitudinal change over 10 or 14 years. In addition, associations with perceived health are explored.

METHODS

A representative Dutch cohort of adults with CP, formerly treated in pediatric rehabilitation, was prospectively followed since 1996. At baseline, the following inclusion criteria were applied: (1) diagnosis of CP; (2) born between 1965 and 1974; and (3) known to the rehabilitation center in The Hague, a center with a regional adherence area.[18] Participants were assessed at baseline (n=80), 4-year follow-up (n=54),[5] and 14-year follow-up (n=49). The total cohort comprised 88 adults, because 8 adults were enrolled at 4-year follow-

up. The present study focuses on the results of 49 participants for whom longitudinal data were available over a 10- or 14-year period. The study was approved by the Medical Ethics Committee of Reinier de Graaf Medical Center (Delft, ME 00-14). All participants provided informed consent.

Measurements

Fourteen-year follow-up was conducted through postal questionnaires. Participants were requested to self-report, with (physical) assistance if required; for another 9 persons their primary caregiver completed the questionnaire because of intellectual impairment. This enabled those with severe physical disability or intellectual impairment to participate and was consistent with baseline and 4-year follow-up data (methods described elsewhere).[5,18] Demographic and clinical characteristics were measured at baseline, 4-year follow-up, and 14-year follow-up unless otherwise stated. Perceived health and health issues were measured at 4- and 14-year follow-up; functional level at baseline and 14-year follow-up.

Demographic and clinical characteristics

The following characteristics were recorded: age, sex, marital status, having children, level of education, type and laterality of CP, and gross motor function. Type of education, assessed at inclusion, was used as an indicator for intellectual impairment: adults who either had no primary education or attended day centers or special education for children with severe learning difficulties were classified as having an intellectual impairment.[19] Level of education was categorized as low (prevocational practical education or lower, including intellectual impairment), medium (prevocational theoretical education and upper secondary vocational education), or high (secondary education, higher education, and university).[20] The subtype of CP (spastic or nonspastic) and its laterality (unilateral or bilateral) were collected from the medical files at inclusion. The level of gross motor function was classified at the 4-year follow-up according to the Gross Motor Function Classification System (GMFCS).[21] For those not participating in 4-year follow-up, the GMFCS level was determined post hoc using baseline information on walking function, climbing stairs, and use of assistive mobility devices; these scores were dichotomized (level I-III vs level IV-V).

Perceived health

Perceived health was assessed by 3 questions similar to the 36-Item Short Form Health Survey items that address personal evaluation of health and role limitations, including current health, health outlook or worry, and interference of health with daily activities.[22] Questions were as follows: "Do you usually feel healthy?" "Do you worry about your health?" and "Do problems with your health limit your activities?" and these were answered either yes (1) or no (0).[5]

Health issues

Three components of the McGill Pain Questionnaire (MPQ)[23] were assessed: (1) presence of pain; (2) pain intensity; and (3) pain effect. Presence of pain was scored either yes or no; least and worst pain intensity were scored on a horizontal 100-mm visual analogue scale; and pain effect was assessed by the McGill Pain Questionnaire- Quality of Life Index (MPQ-QLI) (range, 0-27), with higher scores indicating a higher effect.[23] Medication use in the past 2 years defined whether experiencing epilepsy, respiratory, and gastrointestinal problems. Participants were asked whether they had regular constipation or problems with swallowing. Bowel and bladder incontinence were derived from the scores on the corresponding items of the Barthel Index.[24,25] At 4-year follow-up, these two items were derived from the Functional Independence Measure and converted to Barthel scores.[5,26] Severity of fatigue was assessed with the Fatigue Severity Scale,[27] consisting of 9 statements concerning severity and effect on a 7-point Likert scale. Based on the mean score, severe fatigue (Fatigue Severity Scale, ≥5.1) was assessed.[28] Limitations in vision and hearing were assessed by 4 questions derived from the physical limitations indicator developed by the Organization for Economic Cooperation and Development.[29] Speech problems addressed speech intelligibility and were assessed by asking participants whether their speech was comprehensible over the telephone. Presence of the above health issues were coded either yes (1) or no (0). At 4-year follow-up, severe fatigue was not assessed and methods to assess swallowing, speech, vision, and hearing problems deviated from 14-year follow-up.[5] Hence, only data at 14-year follow-up were available for these health issues.

Functional level

Functional level addressed both mobility and self-care (Barthel Index) as well as walking performance. The Barthel Index[24,25] measures independence in performance of mobility and self-care activities, resulting in a sum score (range, 0-20), with higher scores indicating more independence. Two domain scores differentiated between mobility and self-care items. The mobility domain (range, 0-8) includes transfer, mobility and stairs. The self-care domain (range, 0-8) includes dressing, bathing, grooming, feeding, and toileting.[30] We assessed walking performance (1=walking, if required with assistive devices; 0=not walking) for 3 distances: <10m (indoors), 10-100m (short distances outdoors), and >100m (long distances outdoors).

Statistical analyses

Descriptive statistics were used to present sample characteristics and outcomes. Logistic regression analysis explored loss to follow-up. To explore longitudinal change in perceived health, health issues, and functional level, we performed generalized estimated equation analyses with exchangeable correlation structures.[31] Time was entered as predictor of the outcomes in each model; parameter estimates (B) with 95% confidence intervals (CIs) were

determined for both dichotomous and continuous outcome variables. Complementary to generalized estimated equation models for dichotomous variables, proportions of change (increase and decrease) between the 2 relevant time points were calculated and tested for significance by the 95% CI.[31] We chose this method over the McNemar test because we were interested in proportions of participants changing in a specific direction. The results of longitudinal data analyses were validated for robustness by performing the analyses excluding those participants using proxy reports.

At 14-year follow-up, associations with perceived health were explored cross-sectionally by logistic regression analyses performed in 2 steps. First, univariate models tested associations for participants' characteristics, health issues, and functional level. Second, multivariate models were performed entering a significant (p<0.05) factor from the first step, with adjustment for intellectual impairment and GMFCS level. To accommodate the sample size, separate models were tested for each factor one at a time. Data were analyzed using SPSS version 21.0 (IBM SPSS Statistics, Armonk, NY, USA).

Table 3.1. Characteristics of participants at 14-year follow-up (n=49).

Characteristics	Participants (n=49)
Males/females, n	27/22
Age, mean (SD)	39.8 (3.0)
Age, range	35-45y
Respondent, n (%)	
Self-report	30 (61)
Assisted self-report	10 (21)
Proxy	9 (18)
CP subtype,[a] n (%)	
Spastic	36 (75)
Unilateral	18 (38)
Bilateral	18 (38)
Non-spastic	12 (25)
GMFCS, n (%)	
Level I-III	39 (80)
Level IV-V	10 (20)
Intellectual impairment, n (%)	11 (22)
Education level, n (%)	
Low	31 (63)
Medium	11 (22)
High	7 (14)
Marital status,[a] n (%)	
Single	32 (67)
Married/cohabitating	16 (33)
Having children, n (%)	10 (21)

[a] Missing data for CP subtype (n=1) and marital status (n=1). GMFCS, Gross Motor Function Classification System.

RESULTS

Of the 88 adults invited for 14-year follow-up, 64 were reached (23 unknown addresses, 1 deceased). Six returned blank questionnaires, and 9 did not respond for unknown reasons. In total, 49 adults (56% of cohort; 77% of eligible persons) consented to participate and completed the questionnaire, of whom 10 with assistance and 9 proxies. There were no differences between respondents and nonrespondents with regard to age, sex, laterality, GMFCS level, or intellectual impairment ($\chi^2(1)=1.86$, $p=0.17$). Of these 49, 18 had not participated in 4-year follow-up, therefore, longitudinal data of perceived health and health issues were available for a subsample of 31 (6 proxy). One participant had no baseline data; therefore, longitudinal data of functional level were available for 48 (8 proxy). Characteristics of the study sample are summarized in Table 3.1.

Perceived health, health issues and functional level

Table 3.2 presents the longitudinal change for perceived health and health issues (10-year period) and functional level (14-year period). Percentages and mean scores at 2 time points are shown in Figure 3.1, including health issues with data only at 14-year follow-up. Over a 10-year period, there was an increase in worrying about health (29% increase, $p=0.008$) (see Figure 3.1A) and being limited in activities because of health problems (26% increase, $p=0.002$). Most adults continued to report good general health.

Over a 10-year period, the percentage of adults reporting pain increased to 71% (16% increase, significant proportion of change) (see Figure 3.1B). The level of least pain intensity increased (4.2 [SD 9.5] to 15.1 [SD 17.0], $p=0.006$); the worst experienced pain did not change (68.5 [SD 29.4] to 74.9 [SD 19.3], $p=0.470$). The effect of pain on daily life remained stable (MPQ-QLI 3.0 [SD 4.4] to 5.3 [SD 5.6], $p=0.138$). The increase in gastrointestinal problems was significant in the complementary analysis (17% increase). Presence of epilepsy, respiratory problems and constipation, and bowel and bladder incontinence were unchanged. At the 14-year follow-up, 32% was severely fatigued (see Figure 3.1B). All adults with severe fatigue also reported pain; among the 22 adults with pain, severe fatigue was prevalent in 46%.

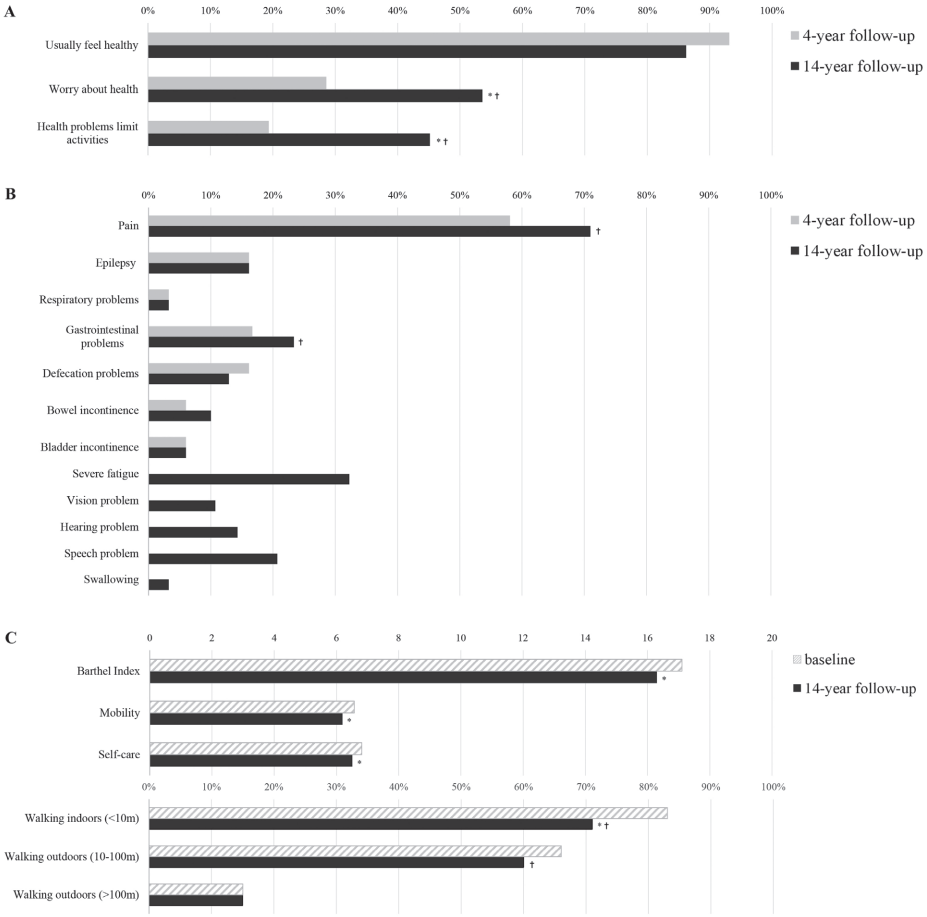
Over a 14-year period, the Barthel Index decreased (17.1 [SD 4.8] to 16.3 [SD 5.6], $p=0.007$) (see Figure 3.1C); 13 adults (28%) declined at least two points on the 0 to 20 scale. Scores of both the mobility and the self-care domains decreased (6.8 [SD 2.4] to 6.5 [SD 2.7], $p=0.048$ and 6.6 [SD 2.1] to 6.2 [SD 2.4], $p=0.013$, respectively). The percentage of adults walking indoors decreased (12% decrease, $p=0.010$); also, the percentage walking short distances outdoors decreased (13% decrease, significant proportion of change). The percentage walking long distances outdoors remained stable (see Figure 3.1C).

Table 3.2. Longitudinal change in perceived health, health issues, and functional level.

	GEE Model*			Complementary Method	
Outcome	B	95% CI	*p*	Proportions of change† (%)	95% CI
Perceived health (n=31)					
Usually feel healthy	-0.80	-1.89, 0.29	0.148	- 7 0	-0.02, 0.16 NA
Worry about health	1.14‡	0.30, 1.98	0.008	- 4 + 29§	-0.03, 0.10 0.12, 0.45
Health problems limit activities	1.23‡	0.45, 2.02	0.002	0 + 26§	NA 0.10, 0.41
Health issues (n=31)					
Pain	0.57	-0.09, 1.23	0.092	- 3 + 16§	-0.03, 0.09 0.03, 0.29
Least intensity	9.43‡	2.72, 16.14	0.006	NA	
Worst intensity	6.20	-10.62, 23.02	0.470	NA	
Impact (MPQ-QOL)	1.91	-0.61, 4.43	0.138	NA	
Epilepsy	0	NA	NA	0 0	NA NA
Respiratory problems	0	NA	NA	- 3 + 3	-0.03, 0.09 -0.03, 0.09
Gastrointestinal problems	0.45	-0.72, 1.62	0.446	- 10 + 17§	-0.01, 0.21 0.03, 0.30
Constipation	-0.26	-1.14, 0.62	0.563	- 7 + 3	-0.02, 0.15 -0.03, 0.09
Bowel incontinence	0.44	-0.42, 1.30	0.313	0 + 3	NA -0.03, 0.09
Bladder incontinence	0	NA	NA	- 3 + 3	-0.03, 0.09 -0.03, 0.09
Functional level (n=48)					
Barthel Index	-0.81‡	-1.40, -0.22	0.007	NA	
Mobility	-0.39‡	-0.77, -0.01	0.046	NA	
Self-care	-0.30‡	-0.53, -0.06	0.013	NA	
Walking indoors (<10m)	-0.72‡	-1.27, -0.17	0.010	0 - 12§	NA 0.03, 0.22
Walking outdoors (10-100m)	-0.28	-0.82, 0.26	0.313	+ 6 - 13§	-0.01, 0.13 0.03, 0.22
Walking outdoors (>100m)	0	NA	NA	+ 8 - 8	0.01, 0.16 0.01, 0.16

Perceived health, health issues over a 10-year period (n=31), functional level over a 14-year period (n=48); parameter estimates (B) are unstandardized. * Logistic GEE models for dichotomous outcome variables (health issues, walking performance; yes=1, no=0); linear GEE models for continuous outcome variables (pain intensity and effect, Barthel Index). † Proportions of decrease (-) and increase (+) for dichotomous outcomes. When the proportion equaled zero, the 95% CI could not be determined. ‡ $p<.05$. § Significant by means of 95% CI. GEE, generalized estimating equation; NA, not applicable.

Figure 3.1. Perceived health, health issues and functional level over time.



(A) Perceived health over a 10-year period (n=31). (B) Health issues over a 10-year period (n=31). (C) Functional level over a 14-year period (n=48). * Significant change in generalized estimating equation analysis (p<.05). † Significant proportion of change (increase or decrease).

Robustness

Additional analyses excluding those participants using proxy reports showed similar results, except for a trend for longitudinal change in the Barthel Index (17.7 [SD 4.3] to 17.1 [SD 4.9]; B= -0.55, 95% CI -1.15 to 0.05, p=0.07) and no significant change in the mobility domain (6.7 [SD 2.1] to 6.5 [SD 2.3]; B= -0.23, 95% CI -0.62 to 0.17, p=0.26).

Determinants of perceived health

At 14-year follow-up, being worried about health was significantly associated with presence of pain and severe fatigue and a higher functional level (Barthel Index and walking performance on short distances) in the univariate models (Table 3.3). Adults with intellectual impairment were less likely to be worried. In the models adjusted for intellectual impairment and GMFCS level, only pain and severe fatigue remained significant. Similarly, pain and severe fatigue were associated with health problems limiting activities. Associations with usually feeling healthy were not explored because of skewed distribution.

DISCUSSION

In this adult study population, perceived health decreased considerably, presence of some health issues increased, and functional level deteriorated slightly. Although most adults continued to report good general health, adults with CP became increasingly more worried about their health and perceived more effect of their health problems on activities of daily living. Pain and severe fatigue were the most common health issues and were associated with perceived poor health.

Thus, at adult age, persons with CP are facing new or increasing health problems, which may lead to reduced functional independence and decreased quality of life in persons aging with CP.[32] In the general population, neither of these changes seem to occur before middle age.[33] This suggests that people with CP may experience accelerated aging. However, it is yet unknown to what extent this is directly related to CP itself.

Pain was reported in 71%, which is in accordance with reported pain prevalences in adults with CP of 62% to 83%.[11,14,34-36] In line with Opheim et al.,[14] who surveyed adults with CP without intellectual impairment, pain prevalence increased over time. Those authors found no change in pain intensity, whereas we observed an increase of the least pain intensity. Moreover, they found an increasing impact of pain on daily activities,[14] whereas we did not. This may be explained by a difference in scales used. Prevalence and co-occurrence of pain and severe fatigue were comparable to those in adults with spastic bilateral CP,[11] thus adding to the evidence of a pain/fatigue complex in adults with CP. Associations between fatigue and pain, as well as exertion as cause of increased pain, have been reported in adults with CP.[36,37] Our results support this, since all severely fatigued adults also reported pain.

Independence in mobility and self-care decreased over time. Although the changes were small, such decrease has previously been reported.[16] This is consistent with our clinical experience that at increasing age, adults with CP may have a greater need for assistance in these activities.

Table 3.3. Factors associated with perceived health (n=49).

	Worry About Health						Health Problems Limit Activities					
		Univariate Model		Adjusted Model*				Univariate Model		Adjusted Model*		
Factor Level	Yes (%)	OR	95% CI	aOR	95% CI	R^2	Yes (%)	OR	95% CI	aOR	95% CI	R^2
Characteristics												
Age (per year)	NA	1.10	0.90, 1.34	NT	NT	NT	NA	0.96	0.79, 1.17	NT	NT	NT
Sex												
Male	50	NA	NA	NT	NT	NT	35	NA	NA	NT	NT	NT
Female	57	1.33	0.41, 4.33	NT	NT	NT	59	2.73	0.85, 8.81	NT	NT	NT
Laterality												
Unilateral	60	NA	NA	NT	NT	NT	45	NA	NA	NT	NT	NT
Bilateral	46	0.56	0.17, 1.88	NT	NT	NT	48	1.14	0.36, 3.62	NT	NT	NT
GMFCS												
Level I-III	61	NA	NA	Included in each separate			53	NA	NA	Included in each separate		
Level IV-V	22	0.18	0.03, 1.00	adjusted model			20	0.23	0.04, 1.20	adjusted model		
Intellectual impairment												
No impairment	63	NA	NA	Included in each separate			49	NA	NA	Included in each separate		
Impairment	20	0.15†	0.03, 0.80	adjusted model			36	0.60	0.15, 2.42	adjusted model		
Health issues												
Pain												
No	27	NA	NA	NA	NA	NA	19	NA	NA	NA	NA	NA
Yes	67	5.50†	1.39, 21.72	4.90†	1.11, 21.60	0.33	59	6.33†	1.50, 26.73	5.25†	1.20, 22.96	0.23
Epilepsy												
No	56	NA	NA	NT	NT	NT	42	NA	NA	NT	NT	NT
Yes	33	0.39	0.06, 2.36	NT	NT	NT	71	3.53	0.61, 20.38	NT	NT	NT
Respiratory problems												
No	53	NA	NA	NT	NT	NT	45	NA	NA	NT	NT	NT
Yes	100	NA	NA	NT	NT	NT	100	NA	NA	NT	NT	NT
Gastrointestinal problems												
No	46	NA	NA	NT	NT	NT	42	NA	NA	NT	NT	NT
Yes	73	3.20	0.72, 14.25	NT	NT	NT	55	1.68	0.43, 6.54	NT	NT	NT

Table 3.3. Continued

	Worry About Health						Health Problems Limit Activities					
		Univariate Model		Adjusted Model*				Univariate Model		Adjusted Model*		
Factor Level	Yes (%)	OR	95% CI	aOR	95% CI	R^2	Yes (%)	OR	95% CI	aOR	95% CI	R^2
Constipation												
No	52	NA	NA	NT	NT	NT	41	NA	NA	NT	NT	NT
Yes	67	1.82	0.15, 21.62	NT	NT	NT	100	NA	NA	NT	NT	NT
Bowel incontinence												
No	60	NA	NA	NT	NT	NT	47	NA	NA	NT	NT	NT
Yes	0	NA	NA	NT	NT	NT	25	0.38	0.04, 3.98	NT	NT	NT
Bladder incontinence												
No	57	NA	NA	NT	NT	NT	47	NA	NA	NT	NT	NT
Yes	0	NA	NA	NT	NT	NT	0	NA	NA	NT	NT	NT
Severe fatigue												
No	44	NA	NA	NA	NA	NA	35	NA	NA	NA	NA	NA
Yes	83	6.43†	1.21, 34.19	12.15†	1.20, 122.60	0.39	77	6.11†	1.41, 26.57	5.97†	1.22, 29.10	0.25
Vision problem												
No	51	NA	NA	NT	NT	NT	45	NA	NA	NT	NT	NT
Yes	60	1.43	0.21, 9.49	NT	NT	NT	40	0.82	0.12, 5.42	NT	NT	NT
Hearing problem												
No	56	NA	NA	NT	NT	NT	44	NA	NA	NT	NT	NT
Yes	33	0.39	0.06, 2.36	NT	NT	NT	50	1.29	0.23, 7.23	NT	NT	NT
Speech problem												
No	65	NA	NA	NT	NT	NT	49	NA	NA	NT	NT	NT
Yes	0	NA	NA	NT	NT	NT	33	0.53	0.11, 2.43	NT	NT	NT
Swallowing												
No	54	NA	NA	NT	NT	NT	46	NA	NA	NT	NT	NT
Yes	50	0.86	0.11, 6.73	NT	NT	NT	50	1.20	0.16, 9.30	NT	NT	NT

Table 3.3. Continued

	Worry About Health						Health Problems Limit Activities					
		Univariate Model		Adjusted Model*				Univariate Model		Adjusted Model*		
Factor Level	Yes (%)	OR	95% CI	aOR	95% CI	R^2	Yes (%)	OR	95% CI	aOR	95% CI	R^2
Functional level												
Barthel Index (per point)	NA	1.20†	1.04, 1.39	1.23	0.92, 1.63	0.29	NA	1.04	0.94, 1.16	NT	NT	NT
Mobility (per point)	NA	1.43†	1.08, 1.90	1.45	0.83, 2.52	0.28	NA	1.11	0.88-1.39	NT	NT	NT
Self-care (per point)	NA	1.50‡	1.10, 2.05	1.42	0.83, 2.44	0.28	NA	1.04	0.84, 1.28	NT	NT	NT
Walking indoors (<10m)												
Yes	68	NA	NA	NA	NA	NA	52	NA	NA	NT	NT	NT
No	21	0.13‡	0.03, 0.57	0.12	0.01, 1.24	0.31	33	0.47	0.13, 1.68	NT	NT	NT
Walking outdoors (10-100m)												
Yes	67	NA	NA	NA	NA	NA	44	NA	NA	NT	NT	NT
No	35	0.27†	0.08, 0.98	0.49	0.10, 2.53	0.22	45	1.02	0.32, 3.27	NT	NT	NT
Walking outdoors (>100m)												
Yes	33	NA	NA	NT	NT	NT	17	NA	NA	NT	NT	NT
No	56	2.59	0.42, 15.84	NT	NT	NT	50	5.00	0.54, 46.53	NT	NT	NT

Note. In dichotomous factors, the first mentioned level was the reference category. aOR, adjusted odds ratio; NA, not applicable; NT, not tested; OR, odds ratio; *R2*, Nagelkerke *R* square explained variance. * Each significant ($p<.05$) factor in the univariate models was included one at a time in a separate model with adjustment for intellectual impairment and GMFCS level. † $p<.05$. ‡ $p<.01$.

Furthermore, we observed a significant proportion of adults who deteriorated in their walking performance at short distances. A recent systematic review showed that in 25% or more of persons with CP, walking decline occurs in early adulthood and is related to increasing age.[15] However, where the review referred to walking decline in several circumstances, the present study specifically demonstrated a walking decline at short distances. For most participants, overall walking performance at long distances remained limited, indicating that from young adulthood many preferred other mobility modes over walking.

The present results indicate that most adults with CP continue to experience good general health, notwithstanding the increasing consequences of their disability and worries about their health. The items we used to assess perceived health were broad, and, in addition to the commonly used single item of perceived general health,[17,38] we also focused more specifically on the perceived health concerns and interference with activities of daily living. The above disparity between both evaluations can possibly be understood similar to the disability paradox: many people with chronic disabilities are known to report good general quality of life (in this study: general health), despite the specific consequences of their disability and health problems.[39,40] We found that presence of pain and severe fatigue, adjusted for intellectual impairment and GMFCS level, were associated with perceived poor health. Also mobility, self-care, and walking performance were univariately associated with being worried about health. Similar associations seem evident in other clinical populations, such as stroke or spinal cord injury, and in the general population.[17]

Although health issues and functional decline among adults with CP have been addressed more frequently in the past decade,[11-16,38] future longitudinal studies are required to further evaluate deterioration of health and functioning in the long term. Current research-focused and population-based surveillance programs for CP are being continued into adulthood.[41,42] The present study underlines the need for such regular patient monitoring, as targets for prevention and treatment can be explored. Moreover, translational research appears necessary to understand the mechanisms at work in the process of aging and to what extent it may be related to CP or its accompanying secondary consequences. Several concepts are conceivable. For example, increasing secondary consequences may be caused by worsening primary impairments or by an increasing load of these primary impairments over decades. Alternatively, changes that affect the aging population in general may be accelerated or the effect of these changes may be greater in aging persons with CP.

Study Limitations

First, results are based on a small sample, limiting statistical power. This was a prospective cohort study, so invitations for 14-year follow-up were limited to those in the cohort. Also,

perceived health and health issues were not assessed at baseline, reducing the number of longitudinal data for these outcomes. Nevertheless, the response rate was relatively high. Given that there was no selective loss to follow-up and that the distribution of clinical characteristics was similar to large population studies,[43] the present sample appears representative. Second, the pooling of self-reports and proxy reports in the data analyses may have biased the results. However, results seemed robust as verified by the additional analyses excluding those with proxy reports. Proxy reports are assumed to be the best alternative to self-reports in persons with intellectual impairment,[44,45] although the direction of its potential bias may comprise both under- and overestimation.[38,46,47] Third, because the present follow-up was performed in adults aged 35 to 45 years, long-term problems in older adults are outside the scope of the present study. Fourth, subgroups at increased risk for early deterioration could not be explored because of the sample size. The cross-sectional analyses, however, demonstrated some indicators for increased risk of perceived poor health, namely, no intellectual impairment, and presence of pain and severe fatigue.

CONCLUSION

This study provides insight into the longitudinal change of perceived health, health issues, and functional level of adults with CP over a 10- to 14-year period. In the long term, adults with CP experienced deterioration of these health outcomes. Possibly, persons with CP experience an accelerated aging process, whether or not directly related to CP. Pain and severe fatigue are the most common health issues in adult CP and are explanatory for perceived poor health. Although most adults with CP remain largely independent in their activities of daily living, the need for personal assistance in mobility and self-care increases over time. Moreover, adults with CP demonstrate walking decline on short distances. Systematic follow-up of adults with CP is required to timely detect and intervene in health problems and functional deterioration. The present findings reaffirm the importance of lifespan care for persons living with CP.

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4

Course of employment in adults with cerebral palsy over a 14-year period

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ABSTRACT

Aim: To explore the course of employment in adults with cerebral palsy (CP) over 14 years, and to identify subgroups at risk for unemployment.

Method: Sixty-five adults with CP (33 (52%) men, 31 (48%) women; baseline age, 25.7 [SD 3.16]; intellectual impairment 25%; bilateral CP 65%) participated in a prospective cohort study. Self-reports of employment and work hours per week in 1996, 2000 and 2010 were documented. The course of employment (including sheltered work) and work hours per week were analyzed, using generalized estimating equations (GEE).

Results: Overall, employment rate was stable over time (38%-45%, p=0.413), but lower than in the general population (75%-86%, p<0.001). Employment rates were specifically low in adults with intellectual impairment, bilateral CP, and in adults with Gross Motor Function Classification System (GMFCS) levels IV and V. Work hours per week declined (35.0 [SD 7.9] to 31.2 [SD 10.3], p=0.033), especially among females (32.3 [SD 6.4] to 23.4 [SD 7.4], p<0.001). Similar to the general population, females often worked part-time.

Interpretation: Employment was low compared with the general population, but remained stable in the long term; however, work hours per week decreased. Adults with intellectual impairment, bilateral CP, and GMFCS levels IV and V are subgroups at risk for unemployment.

INTRODUCTION

Cerebral Palsy (CP) describes a group of permanent disorders of movement and posture causing activity limitation, attributed to non-progressive disturbances in the developing fetal or infant brain.[1] Based on increased survival rates and longevity of persons with CP, currently the majority are adults.[2] As a result, a lifespan perspective for persons with CP is required to provide them with appropriate support.[3-5]

Employment is one of the life areas in which adults with CP experience restrictions in participation.[3,6] Employment rates of adults with CP vary between 29% to 53%, which is lower than those of the general population in Western countries.[3,6-10] Among persons with CP, those with intellectual and severe physical disability, epilepsy and lower levels of education are at increased risk for being unemployed.[3,7,8] In the Netherlands, employment rates of the working-age population with chronic conditions or physical disabilities are 23% to 33%, compared to 67% of the general population.[11] In addition, persons in this population work fewer hours per week, 24.6 hours, compared to 30.3 hours per week in the general population. Furthermore, both employment rates and work hours seem to decline from the age of 40 years onwards.[11]

For adults with CP, little is known about the course of employment in the long term. In a 7-year follow-up study in Norway,[12] the employment rate appeared stable (39%-43%), while in Sweden decreasing participation in inclusive employment (83%-64%) was reported in a 12-year follow-up study.[13] In previous studies, information on work hours a week was limited. Moreover, subgroups of adults with CP who are at increased risk for unemployment have not yet been studied in a longitudinal design.

The primary aims were to investigate, over a 14-year period, the course of employment status and work hours per week in adults with CP, including persons with intellectual impairment, and to explore whether courses differ between subgroups. Secondary aims were to identify subgroups at risk for unemployment and to investigate whether specific subgroups work relatively few hours, by exploring associated factors with employment status and work hours per week.

METHODS

Participants and measurements

A representative cohort of Dutch adults with CP was prospectively followed since 1996. Adults were recruited from the rehabilitation center in The Hague, a center with a regional

function. Inclusion criteria were (1) a diagnosis of CP, (2) born between 1965 and 1974, and (3) known to the rehabilitation center.[14] Participants were assessed at baseline,[14] at 4-year follow-up,[4] and at 14-year follow-up. Data were collected using self-report questionnaires (baseline and 14-year follow-up) or semi-structured interviews (4-year follow-up). The study was approved by the Medical Ethics Committee of Reinier de Graaf Medical Center (Delft, ME 00-14). All participants provided informed consent.

Sociodemographic and clinical characteristics

We collected the following socio-demographic and clinical characteristics: sex, age, level of education, laterality of CP, gross motor function, marital status, living status and having children. Level of education was used as an indicator for intellectual impairment: adults who either had no primary education or attended day centers or special education for children with severe learning difficulties were classified as having an intellectual impairment, all others were classified as average intelligence or higher.[15] Level of education was categorized as low (prevocational practical education or lower, including intellectual impairment), medium (prevocational theoretical education and upper secondary vocational education) or high (secondary education, higher education and university).[15] Data on laterality of CP (bilateral/unilateral) were collected from the medical files at baseline and checked at 4-year follow-up.[4,14] The level of gross motor function was classified according to the Gross Motor Function Classification System (GMFCS)[16] at 4-year follow-up.[4] For those who not participated at 4-year follow-up, GMFCS level was determined post hoc based on baseline information on walking function, climbing stairs and use of assistive mobility devices. For analyses, education level (low vs medium/high), and GMFCS level (IV and V vs I to III) were dichotomized. Marital status was dichotomized as single versus married or cohabitating. Living status was dichotomized as living with parents, in a sheltered home or institution versus living alone or with a partner. Participants indicated whether they had children (yes/no).

Employment

Employment was assessed by questions addressing daily occupation and employment situation (type of market, work hours). Being employed – either on the open labor market (competitive) or sheltered – was defined as performing paid work for 12 or more hours per week.[17] For those employed, we assessed work hours per week. Adults with CP were compared with reference values of the age-matched Dutch general population: the proportion employed in the Dutch working-age population, and work hours per week were derived from Statistics Netherlands for 1996 (20-30y), 2000 (25-35y), and 2010 (35-45y).[17]

Statistical analysis

Descriptive statistics were used to describe sample characteristics and outcomes; logistic regression analysis explored loss to follow-up. To study course of outcomes over time, we performed generalized estimating equations (GEE) analyses with exchangeable correlation structures, an appropriate method for handling missing data. Outcomes were employment status (no=0, yes=1), and – for those employed – work hours per week. Hence, both logistic and linear models were used. First, we entered time as sole factor in each model to explore course over time. Secondly, we added one subgroup factor and its interaction (time´subgroup) to compare course over time between specific subgroups. Subgroup comparisons were made, one at a time, for sex, education level, intelligence, laterality and GMFCS level. When course over time differed between subgroups (i.e. the interaction was significant), we also presented within-group estimates. Estimates of the interactions thus represent between-group differences in course over time, whereas estimates for specific subgroups represent course over time within that subgroup. Furthermore, we were interested in overall associations of factors with employment status and work hours per week. Therefore, models with specific subgroups as sole factor explored associations with these outcomes; female, low education level, intellectual impairment, bilateral CP and GMFCS levels IV and V were the reference categories. For all GEE analyses, we additionally re-estimated models for education level and GMFCS level by excluding or correcting for participants with intellectual impairment. Finally, employment status and work hours were compared with the age-matched Dutch general population, using one-sample binomial tests (for proportions) and one-sample *t*-tests (for means). All analyses were performed using SPSS version 21.0 (IBM SPSS Statistics, Armonk, NY, USA); the level of significance was $p<0.05$ (two-tailed).

RESULTS

A total of 80 adults with CP were enrolled at baseline, eight additional adults were enrolled in the cohort at 4-year follow-up. Of these 88 adults, 65 had employment data on at least 2 assessments: 64 at baseline (98%), 47 at 4-year follow-up (72%), and 49 at 14-year follow-up (75%). Accordingly, one participant was enrolled at 4-year follow-up, 18 had intermittent missing data and 16 were lost to 14-year follow-up. Missing data were not selective to age, sex, level of intelligence, laterality or GMFCS level ($\chi^2=3.26$, df=1, $p=0.071$, Nagelkerke $R^2=0.06$). Characteristics of the participants at the three time points are presented in Table 4.1.

Table 4.1. Characteristics of participants (n=65).

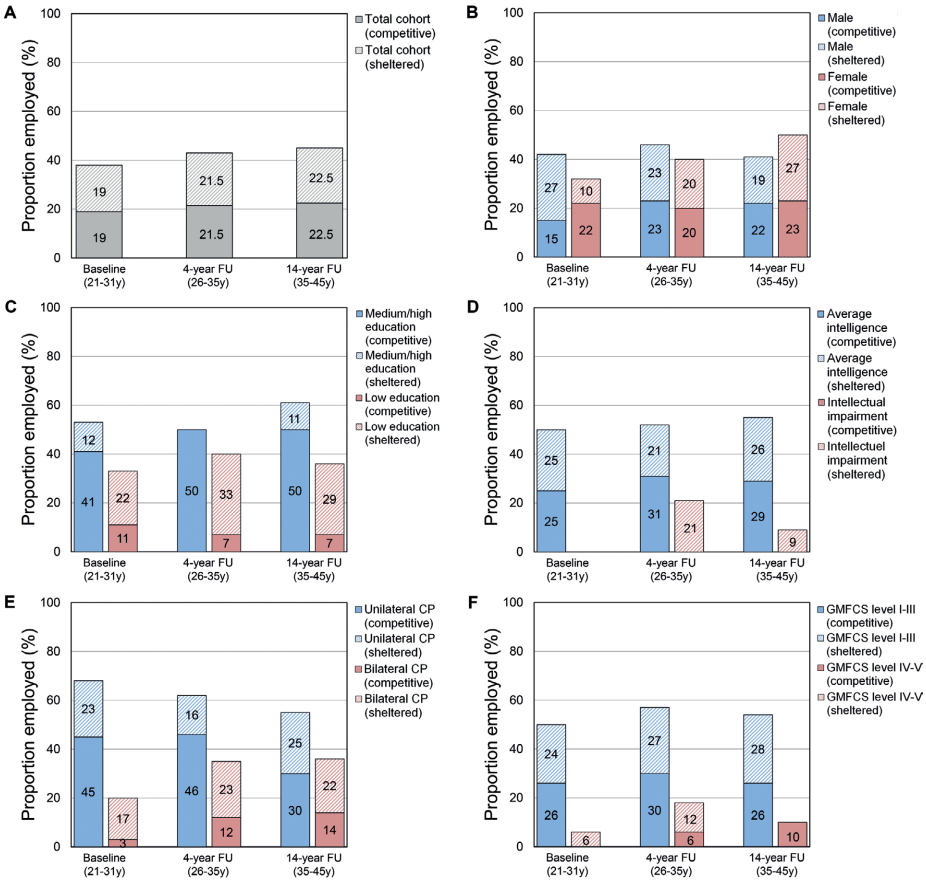
Characteristics	Baseline, 1996 (n=64)	4y follow-up, 2000 (n=47)	14y follow-up, 2010 (n=49)
Males/females, n	33/31	22/25	27/22
Age, mean (SD)	25.7 (3.2)	30.2 (3.4)	39.8 (3.0)
Age, range	21-31y	25-36y	35-45y
Education level,[a] n (%)			
Low	45 (73)	30 (65)	31 (63)
Medium	12 (19)	8 (17)	11 (22)
High	5 (8)	8 (17)	7 (14)
Intelligence,[b] n (%)			
Intellectual impairment	16 (25)	14 (30)	11 (22)
Average intelligence	48 (75)	33 (70)	38 (78)
Laterality of CP,[a] n (%)			
Bilateral	41 (65)	34 (72)	28 (58)
Unilateral	22 (35)	13 (28)	20 (42)
GMFCS, n (%)			
Level IV-V	18 (28)	17 (36)	10 (20)
Level I-III	46 (72)	30 (64)	39 (80)
Marital status,[a] n (%)			
Single	56 (88)	38 (81)	32 (67)
Married/cohabitating	8 (12)	9 (19)	16 (33)
Living status,[a] n (%)			
Living with parents/in a sheltered home/institution	39 (61)	28 (60)	21 (44)
Living alone/with partner	25 (39)	19 (40)	27 (56)
Having children, n (%)	4 (6)	5 (11)	10 (21)

[a] Missing data for education level (baseline n=2, 4y follow up n=1), laterality of CP (baseline n=1, 14y follow-up n=1), marital status (14y follow-up n=1) and living status (14y follow-up n=1). [b] Intellectual impairment was estimated from their level of education: adults who either had no primary education or attended day centers or special education for children with severe learning difficulties were classified as having an intellectual impairment. GMFCS, Gross Motor Function Classification System.

Course of employment over time

Table 4.2 presents the results for employment status and work hours per week over time in adults with CP (upper part). Proportions of persons employed (competitive or sheltered) are depicted in Figure 4.1. Modelled data are presented in Table 4.3. For the total cohort, employment was stable over time. There was, however, difference in course over time between subgroups of intelligence and laterality. Employment remained stable in adults with average intelligence or higher, while adults with intellectual impairment had increased odds on employment over time. Adults with unilateral CP had non-significant decreased odds on employment over time (p=0.070), whereas adults with bilateral CP had increased odds. All other subgroups remained stable, including both levels of education when participants with intellectual impairment were excluded (between-group difference education level: odds ratio (OR) 1.13, 95% confidence interval [CI] 0.68-1.87, p=0.637).

Figure 4.1. Proportions of adults with cerebral palsy (CP) employed over time for the total cohort, and specified per subgroup.



Proportions of adults with CP employed are presented for the total cohort (a), and for the subgroups sex (b), education level (c), intelligence (d), laterality (e), and Gross Motor Function Classification System (GMFCS) (f). Bars further indicate job type; the solid stacks represent competitive employment, and the striped stacks represent sheltered employment.

Among those employed, work hours significantly declined over time. This decline was different between subgroups of sex: work hours remained stable for males, whereas females declined. Work hours also declined in adults with GMFCS levels I to III, and adults with average intelligence or higher had a non-significant decline in work hours (p=0.050). Estimates of interactions for intelligence and GMFCS level were not conclusive as distributions of subgroups were skewed; within-group estimates are not presented for intellectual impairment and GMFCS levels IV and V due to too small subgroups (n≤5; Table 4.3).

Table 4.2. Employment and work hours over time in adults with cerebral palsy (CP) and Dutch age-matched population.

	Employed n (%)			Work hours per week[a] mean (SD)		
Adults with CP	Baseline (n=64)	4y follow-up (n=47)	14y follow-up (n=49)	Baseline	4y follow-up	14y follow-up
Total cohort	24 (38%)	20 (43%)	22 (45%)	35.0 (7.9)	32.5 (9.3)	31.2 (10.3)
Sex						
Female	10 (32%)	10 (40%)	11 (50%)	32.3 (6.4)	29.8 (8.7)	23.4 (7.4)
Male	14 (42%)	10 (46%)	11 (41%)	36.7 (8.5)	35.3 (9.5)	39.1 (5.8)
Education level[b]						
Low	15 (33%)	12 (40%)	11 (36%)	33.3 (8.6)	32.1 (9.5)	30.3 (8.9)
Medium/high	9 (53%)	8 (50%)	11 (61%)	37.2 (6.7)	33.3 (9.6)	32.2 (12.0)
Intelligence						
Intellectual impairment	0 (0%)	3 (21%)	1 (9%)	NA	NA	NA
Average intelligence	24 (50%)	17 (52%)	21 (55%)	35.0 (7.9)	33.6 (9.1)	32.0 (10.0)
Laterality[b]						
Bilateral CP	8 (20%)	12 (35%)	10 (36%)	31.0 (9.8)	31.5 (10.4)	28.0 (12.0)
Unilateral CP	15 (68%)	8 (62%)	11 (55%)	36.8 (6.4)	34.1 (7.6)	33.4 (8.5)
GMFCS						
Level IV-V	1 (6%)	3 (18%)	1 (10%)	NA	NA	NA
Level I-III	23 (50%)	17 (57%)	21 (54%)	34.8 (8.0)	32.6 (9.0)	30.6 (10.2)
Dutch general population	1996 (20-30y)	2000 (25-35y)	2010 (35-45y)	1996 (20-30y)	2000 (25-35y)	2010 (35-45y)
Total population[c]	69%[e]	82%[e]	83%[e]	33.4	35.3	33.8
Female	64%[e]	71%[e]	74%[d]	30.4	29.4	26.2
Male	74%[e]	92%[e]	91%[e]	36.0	40.0	40.5

[a] Work hours per week are described only for those employed. [b] Missing data for education level (baseline n=2, 4y follow up n=1) and laterality (baseline n=1, 14y follow-up n=1). [c] Total working-age population. [d] $p<0.05$. [e] $p<0.01$. GMFCS, Gross Motor Function Classification System; NA, not applicable (because of a small subgroup).

Employment and associated factors

Employment status was significantly associated with intelligence, laterality, and GMFCS level. Adults with average intelligence or higher (OR 9.40, 95% CI 2.64-33.46, p=0.001), unilateral CP (OR 4.12, 95% CI 1.56-10.91, p=0.004) and GMFCS level I to III (OR 9.02, 95% CI 2.31-35.13, p=0.002) had consistently higher employment rates compared with their counters (Table 4.2, Figure 4.1); the latter also when corrected for intellectual impairment (OR 6.01, 95% CI 1.39-35.13, p=0.016). No associations were found with sex, nor with education level, nor if excluding participants with intellectual impairment.

Among those employed, work hours were associated with sex (b 8.09, 95% CI 3.06-13.13, p=0.002). There was a non-significant trend for an association with laterality (b 5.32, 95% CI -0.43 to 11.07, p=0.070). Associations with intelligence and GMFCS level were not analyzed because of too small subsamples of persons employed (n≤5).

Employment compared with the general population

Proportions employed in the age-matched Dutch general population, both total as well as specified for sex are presented in Table 4.2 (lower part). Significant differences between adults with CP and the general population are indicated. Employment was consistently lower in the CP cohort compared with the general population. This was also true when females and males were compared separately. Work hours per week were comparable: the mean differences between adults with CP and the general population were +1.6, -2.8 and -2.6 hours per week for the studied time points. Also, no differences in work hours were found for females and males separately.

DISCUSSION

This is the first prospective cohort study to investigate employment in adults with CP over a long period of time. The follow-up period comprised the age range of 21 to 45 years, regarding a period in which employment plays a central role in life. The major finding was that overall the employment rate of adults with CP was stable over 14 years. However, work hours seemed to decline over time from a young age onwards, specifically in females with CP. The results confirm that overall employment rates were consistently lower compared with the general population. Employment rates were particularly low among adults with more severe intellectual and physical impairments.

Table 4.3. Course over time for the total cohort, between-group differences (interaction), and course over time within subgroups.

Employed	**N[a]**	**OR**	**95% CI**	**p**		**n[b]**	**OR**	**95% CI**	**p**
Course over time									
Total cohort	160	1.10	0.88, 1.36	0.413					
Between-group differences (interaction)					*Within-group course over time*				
Sex	160	0.71	0.45, 1.11	0.131					
Education level	157	0.98	0.60, 1.59	0.920					
Intelligence	160	0.44	0.29, 0.65	<0.001	Intellectual impairment	41	2.36	1.74, 3.20	<0.001
					Average intelligence	119	1.03	0.80, 1.31	0.829
Laterality	158	0.49	0.31, 0.79	0.003	Bilateral CP	103	1.49	1.08, 2.07	0.016
					Unilateral CP	55	0.74	0.53, 1.03	0.070
GMFCS	160	0.71	0.40, 1.27	0.251					
Work hours per week[c]	**N[a]**	**b**	**95% CI**	**p**		**n[b]**	**b**	**95% CI**	**p**
Course over time									
Total employed	63	-1.78	-3.42, -0.15	0.033					
Between-group differences (interaction)					*Within-group course over time*				
Sex	63	5.48	2.73, 8.24	<0.001	Female	29	-4.78	-7.21, -2.35	<0.001
					Male	34	0.70	-0.60, 1.99	0.290
Education level	63	-0.02	-3.43, 3.40	0.993					
Intelligence[d]	63	7.68	5.08, 10.27	<0.001	Intellectual impairment	4	NA	NA	NA
					Average intelligence	59	-1.64	-3.29, 0.002	0.050
Laterality	61	1.54	-2.32, 5.40	0.434					
GMFCS[d]	63	-4.01	-5.69, -2.34	<0.001	Level IV-V	5	NA	NA	NA
					Level I-III	58	-2.01	-3.69, -0.34	0.018

[a] *N* represents the total number of observations in the models. [b] *n* represents the total number of observations for the specific subgroups (within-group course over time). [c] Work hours per week were analyzed only for those employed. [d] For work hours per week, estimates of interactions for intelligence and GMFCS are not conclusive as distributions of subgroups were skewed.

OR, odds ratio; CI, confidence interval; GMFCS, Gross Motor Function Classification System; NA, not applicable (because of a small subgroup).

Only some other studies focused on the long-term course of employment in individuals with CP. Over a 12-year period, Törnbom et al.[13] identified a decreased employment rate in middle-aged adults with physical disability (mainly CP) and average intelligence. In a 7-year follow-up, Opheim et al.[12] presented employment rates similar to baseline in a broad age range. Thus, results appeared inconsistent. In our research group, over a 4-year period, Verhoef et al.[10] reported increasing employment in emerging adults with CP entering the labor market. Although a moderate part was still studying, in the same period unemployment in CP also increased, indicating that persons with CP are already at risk for unemployment from young adulthood onwards. Verhoef et al.[10] expected a further increase in employment after the age of 20 to 24 years, since at that age range a proportion was still studying. However, based on the present results, employment rates of adults with CP seem to stabilize between 21 to 45 years. This is in accordance with Mitchell et al.,[9] who found in a cross-sectional study the highest employment rates for individuals with disabilities (including CP) in their twenties and thirties (56% and 60% respectively) while from their forties onwards, employment showed a decline (42%-28%). Moreover, individuals with disability seem more engaged in part-time work than their non-disabled peers.[18] Our longitudinal study was confined to the age of 45 years, thus a further course of employment in adults with CP remains unclear. However, we already demonstrated a decline in work hours before the age of 45.

The observed decline in work hours might be linked to worsening health problems and mobility decline,[19] likely reflecting a reduced work capacity in adults living with CP. Moreover, we observed a strong decline in work hours among females with CP. A similar pattern of growing part-time employment was observed among females of the Dutch general population,[11,20] likely explained by a cultural feature of females in a dual role as worker and primary caregiver. Females that become mothers often follow a course of intermittent work across the lifespan.[20] Additional analyses showed that, in our study, females that became mothers decreased their work hours. This dual role seems to apply to females with CP as well.

In contrast to some earlier findings, we found no association between employment and education level. A high education level has found to be significant for achieving competitive employment in adults with CP.[7,21] In our analyses, we did not differentiate competitive from sheltered employment, which may have precluded such an association. However, the figure shows that the most substantial contrast between competitive and sheltered employment lies between subgroups with different education levels. At the time of study, there was a relatively high density of sheltered employment and financial resources in the Netherlands

compared with other European countries.[22] Present results seem to reflect this, since a fair proportion of employed adults with CP had sheltered employment.

Notwithstanding the above, adults with intellectual impairment or with severe gross motor problems were often unemployed. The subgroup GMFCS level IV and V reflects a group of individuals with severe activity limitations, and half of them had intellectual impairment (10 out of 19). Of these 10 adults, only two were employed at one point in time. This confirms that having both a physical disability and intellectual impairment represents 'double jeopardy' in terms of employment.[23] In the present study, adults with unilateral CP were more often employed, and tended to work more hours per week than those with bilateral CP. Previous studies reported that adults with unilateral CP were often competitively employed, whereas in bilateral CP, sheltered employment was more common.[3,6] Our results seem to confirm this (Figure 4.1). At the same time, we demonstrated that employment rates in adults with bilateral CP showed a positive course and stabilization, whereas in unilateral CP a decrease may appear over time. It seems that persons with unilateral CP gradually no longer succeed in maintaining their functional level, which is in line with our clinical experience. Alternatively, part-time work could be beneficial, as it provides good balance between personal or health needs and working life.[18] Nowadays, employers are obliged to help individuals with disability, which provides the opportunity to remain employed by means of part-time employment. Moreover, reintegration and health care services may support adults with CP by vocational interventions aiming at balancing personal capabilities, helping with an ergonomic workplace, and other environmental support.

A limitation of our study is the relatively small sample size, although partly met by the repeated measurements. Response rates at the follow-up assessments were quite high (72% and 75% respectively) and there was no selective loss to follow-up. Moreover, given that the distribution of clinical characteristics was similar to those reported in large population studies,[24] we assumed that the present cohort was representative for the population of adults with CP. For smaller subgroups (intellectual impairment and GMFCS level IV and V), results should be interpreted with care. Furthermore, we had no documented data on employment in the periods between follow-up, during which participants may have entered or exited their jobs. Although the follow-up period enabled us to describe the course of employment up to the age of 45, the further course of employment for persons aging with CP remains unclear. Nonetheless, this was the first long prospective cohort study to investigate employment in adults with CP and results significantly add to our knowledge on employment in the long term. In future longitudinal research, these limitations could be addressed by studying different age cohorts, and conducting follow-up assessments at shorter intervals.

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5

Outcomes in adults with cerebral palsy: Systematic review using the International Classification of Functioning, Disability and Health

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ABSTRACT

Aim: In the context of the development of an International Classification of Functioning, Disability and Health (ICF) Core Set for adults with cerebral palsy (CP), this systematic review sought to identify the outcome measures used in studies on adults with CP, to examine their content using the ICF as a reference, and to demonstrate the most studied areas in this population.

Method: Embase, MEDLINE, Web of Science, PsycINFO, CINAHL, Cochrane, and Google Scholar were searched for studies on adults with CP published between 2000 and 2017. Meaningful concepts of commonly used outcome measures were linked to the ICF, and frequencies of resultant ICF categories were explored.

Results: In 274 included articles, 332 outcome measures were identified of which 155 were commonly used. In total, 4409 meaningful concepts were linked to the ICF. The component 'Activities and participation' included the most frequent categories, followed by 'Body functions'. The most frequent categories were b280 'Sensation of pain' (37.6%), d450 'Walking' (33.3%), and d850 'Remunerative employment' (27.5%).

Interpretation: The broad range of ICF categories identified in this systematic review emphasizes the heterogeneity of functioning and disability in adults with CP. The current results specifically reflect the researchers' perspective and will serve as candidate categories to consider in the development of an ICF Core Set for adults with CP.

INTRODUCTION

Cerebral palsy (CP) describes a group of permanent disorders of movement and posture causing activity limitations,[1] and is the most common cause of physical disability in childhood.[2] CP is caused by non-progressive disturbances in the developing fetal or infant brain, resulting in a motor disorder that is often accompanied by secondary impairments, for example cognitive or sensory impairments or communication impairments.[1] In developed countries, CP affects 2 to 2.5 per 1000 live births.[3-5] Much research in CP has focused on children. However, given the increasing survival rates and longevity of individuals with CP, with the majority experiencing adulthood,[6,7] research in the past two decades has increasingly focused on the impact of CP throughout the lifespan.

Research on health-related status of adults with CP describes a broad range of outcomes.[8] Physical and cognitive impairments, activity limitations, and participation restrictions are well recognized as disabling consequences in adults with CP. The extent of these consequences often depends on the type and severity of the health condition, but also on various contextual factors. Given the wide variety of descriptors of outcomes and related factors found in the literature, a uniform language to describe the impact of CP in adulthood is desirable. In 2001, the World Health Organization (WHO) launched the International Classification of Functioning, Disability and Health (ICF),[9] now an internationally accepted standard for describing functioning and disability. In the ICF, functioning and disability are seen as the universal human experience of the complex interaction between a person's health condition and contextual factors. Whereas functioning is described by what the body does (i.e. body functions), body structures, tasks or actions an individual performs, and involvement in major life activities (i.e. activities and participation), disability is an umbrella term referring to body impairments, activity limitations, and participation restrictions. Contextual factors encompass environmental factors, describing the physical, social, and attitudinal environment in which people live, and personal factors, comprising features of an individual that are not part of the health condition such as age, sex, or coping style.[9]

Systematic assessment of physical and cognitive impairments, and activity limitations and participation restrictions in relevant life areas, is essential in health care settings to identify problems in health and functioning, and to plan effective interventions.[10] Several outcome measures have been used to evaluate different areas of functioning and disability in adults with CP. However, there is no consensus on the most important areas to assess in these adults, nor is it clear how to select the most appropriate outcome measures. For clinicians and researchers to develop and provide optimal care for adults with CP, it is vital to have consensus on the outcomes to assess and on a universal language that describes those

outcomes. The ICF is suitable for this purpose; however, with more than 1400 categories describing all areas of functioning, its applicability for everyday use in clinical settings is challenging. To address this challenge, WHO and the ICF Research Branch created a methodology for developing Core Sets of ICF categories.[11] An ICF Core Set can facilitate the description of the functioning of individuals with a specific health condition in everyday practice by providing a limited list of essential categories selected from the entire ICF. It can provide guidance for clinical assessments, planning of interventions, and selecting measures for evaluation. Moreover, ICF Core Sets offer the possibility to compare clinical data between patients, institutions, and countries, and may serve as a basis to improve communication between professionals and settings on an international level.[12]

So far, ICF Core Sets have been developed for various health conditions.[13] Among the 35 ICF Core Sets is one for children and young people with CP.[14-18] Since life experiences of individuals with CP naturally changes from childhood to adulthood,[19] and since health issues seem to deteriorate throughout the lifespan,[20] the ICF Core Set for children and young people with CP is considered insufficiently applicable to adults with CP. To address this issue, our research group initiated a project to develop an ICF Core Set for adults with CP across different types and severity levels.

ICF Core Sets are developed by means of a three-phase, multi-method scientific process.[11] The first phase is designed to collect current evidence, which involves four preparatory studies: a systematic literature review, a qualitative study, a multicentre cross-sectional study in a clinical setting, and a global expert survey. These are meant to consider the perspectives of researchers, patients, and clinicians, and to capture their views on relevant aspects of health and functioning. The second phase comprises an international consensus conference with experts and health care professionals. The final phase involves validating and implementing the first version of the ICF Core Set.[11] In the present article, we report on the systematic literature review, capturing the perspective of researchers on CP in adulthood by identifying a list of ICF categories that are most commonly addressed in the literature on adults with CP.[21] These categories will serve as candidate categories for the international consensus conference, during which the first version of the ICF Core Set for adults with CP will be finalized.

The objective of this systematic literature review was to identify this list of candidate categories. Specific aims were to: (1) identify all outcome measures used in published studies on adults with CP over the past decades, (2) uncover the functioning content of those measures using the ICF, and (3) pinpoint the most frequently addressed areas of functioning and contextual factors in adults with CP using the ICF.

METHODS

Search strategy and eligibility criteria

Seven electronic databases (Embase, MEDLINE, Web of Science, PsycINFO, CINAHL, Cochrane, Google Scholar) were searched for literature published between January 2000 and January 2017. The search strategy was developed in consultation with an information specialist and included three major themes: 'cerebral palsy', 'adult', and 'outcome assessment'. Key terms were mapped to controlled headings and expanded to include free-text terms, as appropriate for the specific database.

Results from the searches were gathered in EndNote and duplicates were removed. In a first round, titles and abstracts were screened for eligibility. Subsequently, full-text articles of the included abstracts were retrieved and screened for eligibility. Studies were included according to the following five criteria: (1) Observational and experimental study designs, and excluding meta-analyses, reviews, case studies, qualitative studies, comments, and study protocols; (2) Describing individuals with CP only, or in case–control design; (3) Describing more than 10 adults who were at least 18 years of age at time of the first measurement or at follow-up. Studies describing both children and adults with CP were included when at least 50% (and at least 10 participants) of the sample were adults, or in case this was unclear, the mean sample age was at least 18 years; (4) Reporting on outcomes of functioning, and excluding studies reporting on evaluations of services; for example evaluation of transition services, or complications and adverse events of surgery; and (5) Inclusions were limited to full-paper peer-reviewed journal articles written in English. Multiple publications on the same study sample, including follow-up studies, were combined and counted as one study ('unique study') to avoid duplication of outcome measures. Publications of a study on a specific subset of a larger sample, using clearly distinct outcome measures, were not combined.

The first two authors (JB, SN) independently performed title/abstract and full-text screening. Disagreement about inclusion was discussed and resolved between the two reviewers. Any discrepancies were discussed with a third reviewer (RBE) until consensus was reached.

Data extraction

From each included study we extracted information on country, study design, and participant characteristics, using a standardized electronic data record sheet. The country where the study was conducted was allocated to one of the six WHO regions, whereby we further distinguished between North and South America.[9] Design of the study was

recorded according to the Cochrane Consumers and Communication Review Group Study Design Guide,[22] and grouped into observational or experimental designs. Participant characteristics included sample size, age, sex, CP subtype, and level of gross motor functioning. The subtype of CP was classified according to the diagnostic classification system of the Surveillance of Cerebral Palsy in Europe,[23] and for movement and posture abnormality: spastic, dyskinetic, ataxic, or mixed. Spastic CP was further distinguished for limb distribution if applicable, namely unilateral or bilateral spastic CP. Gross motor functioning was classified according to the Gross Motor Function Classification System (GMFCS).[24,25] For studies with multiple publications, participant characteristics were extracted from the largest (often baseline) sample.

All outcome measures used in the included studies were recorded, and the number of studies in which the individual measures were used was documented. For studies with multiple publications, the outcome measures used were counted only once. We identified single-item and multiple-item measures. A single-item measure, for example, is the Modified Ashworth Scale, a clinical assessment. A multiple-item measure, for example, is the Short Form Health Survey, a patient-oriented measure containing 36 individual items. Outcome measures comprised patient-oriented measures (i.e. self- or proxy-report questionnaires), clinical assessments (including those requiring specialized equipment), and non-tool measures (often single-patient-oriented questions) mentioned in the text of publications. From the outcome measures that were used in at least two studies ('common measures'), we extracted all individual items before linking each item to the ICF.

Linking to the ICF

Before starting the linking process, three reviewers (JB, SN, and CL) acquired thorough knowledge of the refined ICF linking rules by consulting the eLearning tool,[26] and during practice sessions including a tutorial with an expert (MS) from the ICF Research Branch. On the basis of experience gathered over several years for various projects by many clinicians and researchers around the world, refinements were made to the original linking rules,[27,28] addressing linking of all concepts within an item instead of only the most relevant one, linking to the most precise ICF category, and the use of the 'other specified' and 'unspecified' categories.[21]

For each item extracted from the common measures, we identified the meaningful concepts. A concept was defined as one separate meaningful entity; one or more concepts could be identified from a single item. For example, the item 'during the past 4 weeks, how much did pain interfere with your normal work' from the Short Form Health Survey contains two meaningful concepts: 'pain' and 'work'. The meaningful concepts were then

linked to the most precise ICF category in the components of 'Body functions' (denoted by the letter 'b'), 'Body structures' (s), 'Activities and participation' (d), and 'Environmental factors' (e).[21] Concepts were also linked to 'Personal factors' (pf) although these are not yet classified in the ICF. An ICF code starts with the letters b, s, d, or e, followed by a numeric code. The ICF is organized hierarchically: the first level is made up of chapters (first digit of the numeric code), and each chapter consists of second-level categories (second and third digit), followed by more detailed third-level and, for some cases, fourth-level categories (subsequent digits), as can be seen in the following example from the component 'Body functions': (1) first-level chapter: b2, 'Sensory functions and pain'; (2) second-level category: b280, 'Sensation of pain'; (3) third-level category: b2801 'Pain in body part'; (4) fourth-level category: b28013, 'Pain in back'. Some concepts were assigned the code nd (not definable), for example for 'general health' (code nd-gh) as this is too general to link to an ICF category. Finally, a few concepts could not be linked since the information was beyond the scope of the ICF. In that case, the code nc (not covered) was used, for example for 'quality of life' (code nc-qol).

Since some of the identified measures were previously linked in other projects,[21] existing linking results were obtained from the ICF Research Branch and independently checked by two reviewers (JB, SN). Concepts identified in clinical assessments were pre-linked by a third reviewer (CL), a physician in physical medicine and rehabilitation. The first two reviewers independently checked the pre-linked ICF categories.

The linking process was performed independently by the same two reviewers (JB, SN). Results were compared, and disagreement was resolved by discussion. A minority of the discrepancies were discussed with a third reviewer (CL) until final agreement was reached. Initial interrater agreement of the independent linking conducted before consensus or consultation with the third linker in case of disagreement was determined for second-level categories (see data analysis below) by calculating Cohen's κ.[29]

Data analysis

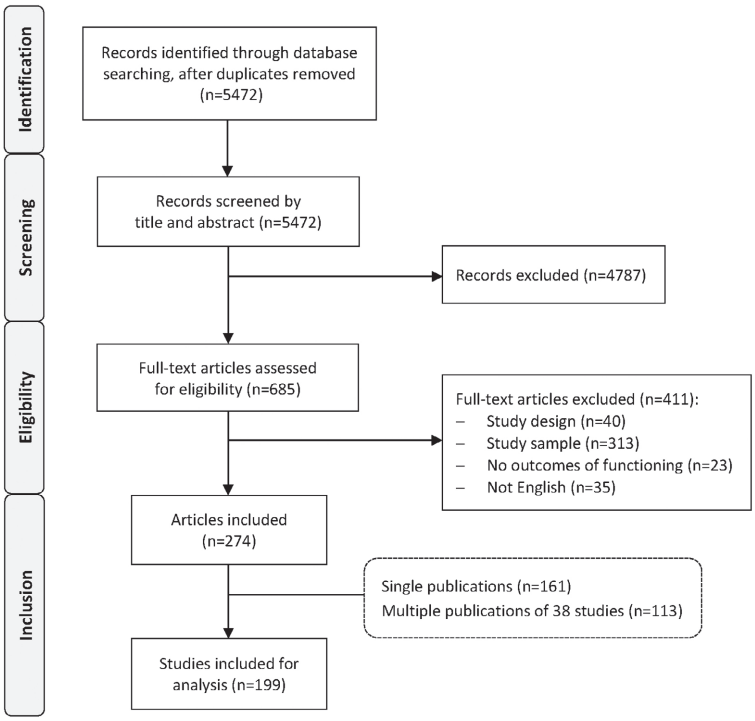
Frequency analysis was used to examine the total number of outcome measures and linked ICF categories that the common measures contained, along with corresponding percentages relative to the number of studies in which they were used. If an ICF category was repeatedly assigned within one multiple-item measure, or within one study, it was counted only once. ICF categories found in at least 5% of the studies were included in the list of candidate categories.[11] To be consistent with previous ICF Core Set studies, we only report the second-level categories; concepts linked to a more specific third- or fourth-level category were reported at their corresponding second-level category.

RESULTS

Study selection and characteristics

The initial search yielded 5472 records (Figure 5.1). After title and abstract screening, full-text articles of 685 records could be retrieved and were reviewed. A total of 274 articles (5.0%) finally met the eligibility criteria. Of these, 113 eligible articles included multiple publications of 38 unique studies and 161 were single publications. Therefore, 199 unique studies were finally included for further review.

Figure 5.1. Flow diagram of article selection process.



Over half of the studies were published in the previous 6 years (Table 5.1). The 199 studies included 176 with an observational design and 23 experimental studies. Most studies were conducted in Europe (39.7%), Northern America (27.1%), and the Western Pacific (25.6%). Sample sizes ranged from 11 to 14806 (median 33, interquartile range 20–69). Overall, 55.2% of the participants were male, and the mean age was 31 years, indicating that mainly younger adults were studied. A total of 139 studies (69.8%) reported participants' CP subtype and 91 studies (45.7%) used the GMFCS to classify their participants (see Tables 5.1 and 5.2 for all study and participant characteristics).

Table 5.1. Characteristics of included studies (*n*=199).

Study characteristics	n	%
Publication year		
2000–2010	94	47.2
2011–2016	105	52.8
World Health Organization regions		
Europe	79	39.7
North America	54	27.1
Western Pacific	51	25.6
South America	11	5.5
Africa	2	1.0
Eastern Mediterranean	2	1.0
Study design		
Observational	176	88.5
Case series	30	15.1
Cross-sectional	103	51.8
Cohort	16	8.0
Case–control	27	13.6
Experimental	23	11.6
Randomized controlled trial	10	5.0
Others	13	6.6
Sample sizes		
10–20	58	29.1
21–50	74	37.2
51–100	34	17.1
101–500	27	13.6
501–1000	2	1.0
>1000	4	2.0

Outcome measures

The studies used a total of 332 outcome measures, including 204 single-item and 128 multiple-item measures. Table 5.3 presents the single- and multiple-item outcome measures most often used in the 199 studies. Single-item measures included single (172) and multiple (32) types of measurement. For example, walking included multiple types of measurement as it was clinically assessed by the Six Minute Walk Test and self-reported on the Wilson Mobility Scale. A total of 242 types of single-item measure were identified; 20 (8.3%) were patient-oriented, 94 (38.8%) were clinical assessments, and 128 (52.9%) were non-tool measures. Multiple-item measures included 92 (71.9%) patient-oriented measures and 36 (28.1%) clinical assessments.

Table 5.2. Participant characteristics (*n*=32 933).

Participant characteristics	n	%
Age (*n*=10 841, 32.9%)	Mean age, y	Range, y
Mean age of samples	31.0	18–58
Minimum age of samples	18.5	5–57
Maximum age of samples	51.1	20–84
Sex (*n*=32 443, 98.5%)		
Male	17 916	55.2
Female	14 527	44.8
Cerebral palsy subtype (*n*=8 236, 25.0%)		
Spastic	6413	77.9
Unilateral spastic	1367	16.6
Bilateral spastic	3748	45.5
Unspecified	1298	15.8
Dyskinetic	1028	12.5
Ataxic	100	1.2
Mixed types	330	4.0
Unknown	365	4.4
GMFCS level (*n*=4 337, 34.5%)[a]		
Level I	758	17.5
Level II	905	20.9
Level III	697	16.1
Combined levels I–III	260	6.0
Level IV	712	16.4
Level V	748	17.2
Combined levels IV–V	221	5.1
Unknown	36	0.8

Data are n (%) unless otherwise stated. [a] One study was deliberately not included here, because its large sample only of persons classified in Gross Motor Function Classification System (GMFCS) level V (*n*=747) affected the distribution of the GMFCS.

In the single-item measures, assessment of pain was most frequent, measured by patient-oriented (52.5%) and non-tool measures (47.5%). Mobility of joints and spasticity were also frequently addressed, often measured by clinical assessments (86.2% and 82.8%, respectively). Also, walking, muscle power, gross motor function, and hip displacement were used in more than 10% of the studies. In the multiple-item measures, the Short Form Health Survey (5.5%) was the most frequently used patient-oriented measure, followed by the Barthel Index (4.0%), Assessment of Life Habits (2.5%), and the Fatigue Severity Scale (2.5%). The most common clinical measures among multi-item measures were the Functional Independence Measure (4.0%), Gross Motor Function Measure (3.5%), the Functional Mobility Scale (3.0%), and Japanese Orthopaedic Association score (3.0%).

A total of 156 out of 332 outcome measures were identified in at least two studies; these common measures were reported in 189 (95.0%) of the included studies. One multiple-item measure could not be retrieved in English. In the end, 114 single-item measures and 1044 items from 41 multiple-item measures (total of 1158 items) were linked to the ICF.

Table 5.3. Most frequent single- and multiple-item outcome measures used in studies (*n*=199) on adults with cerebral palsy.

Outcome measure	Type	Items in measure	Used in number of studies, n (%)
Single-item measures			
Pain	Patient-oriented, non-tool	1	40 (20.1)
Mobility of joints	Clinical, non-tool	1	29 (14.6)
Spasticity	Clinical, non-tool	1	
Walking	Patient-oriented, clinical, non-tool	1	27 (13.6)
Muscle power	Clinical, non-tool	1	25 (12.6)
Gross motor function	Patient-oriented	1	22 (11.1)
Hip displacement	Patient-oriented, clinical, non-tool	1	
Multiple-item measures			
Short-Form Health Survey	Patient-oriented	36	11 (5.5)
Barthel Index	Patient-oriented	10	8 (4.0)
Functional Independence Measure	Clinical	18	
Gross Motor Function Measure	Clinical	88	7 (3.5)
Functional Mobility Scale	Clinical	3	6 (3.0)
Japanese Orthopaedic Association Score	Clinical	4	
Assessment of Life Habits	Patient-oriented	80	5 (2.5)
Fatigue Severity Scale	Patient-oriented	9	

Representation of the most frequent single- and multiple-item outcome measures obtained from 199 studies.

ICF categories

The 1158 items of the common measures revealed a total of 4409 meaningful concepts that were linked to the ICF. Overall, 24 concepts (0.5%) were linked to an ICF component, 106 concepts (2.4%) to first-level ICF categories (chapters), and 3956 concepts (89.7%) to second-, third-, or fourth-level ICF categories. The other 323 concepts were regarded as personal factors (74, 1.7%), not covered (131, 3.0%), or not defined (118, 2.7%). The Cohen's κ of 0.61 (95% confidence interval 0.59–0.63) indicated moderate interrater agreement between the independent linkers.

Table 5.4. Relative frequency of first-level categories (chapters) identified in studies using common measures (*n*=189).

ICF code	Chapter	Used in number of studies, *n* (%)
b	***Body functions***	
b1	Mental functions	52 (27.5)
b2	Sensory functions and pain	85 (45.0)
b3	Voice and speech functions	17 (9.0)
b4	Functions of the cardiovascular, haematological, immunological and respiratory systems	35 (18.5)
b5	Functions of the digestive, metabolic and endocrine systems	37 (19.6)
b6	Genitourinary and reproductive functions	31 (16.4)
b7	Neuromusculoskeletal and movement-related functions	83 (43.9)
s	***Body structures***	
s7	Structures related to movement	60 (31.7)
d	***Activities and participation***	
d1	Learning and applying knowledge	28 (14.8)
d2	General tasks and demands	22 (11.6)
d3	Communication	26 (13.8)
d4	Mobility	105 (55.6)
d5	Self-care	66 (34.9)
d6	Domestic life	34 (18.0)
d7	Interpersonal interactions and relationships	39 (20.6)
d8	Major life areas	52 (27.5)
d9	Community, social and civic life	38 (20.1)
e	***Environmental factors***	
e1	Products and technology	50 (26.5)
e3	Support and relationships	25 (13.2)
e5	Services, systems and policies	23 (12.2)
pf	***Personal factors***	37 (19.6)
nc	***Not covered***	51 (27.0)
nd	***Not defined***	33 (17.5)

Only International Classification of Functioning, Disability and Health categories measured in [3]5% of all studies applying common measures are presented. Categories are ordered numerically within each component.

Tables 5.4 and 5.5 show the chapters and second-level categories respectively, identified in at least 5% of the studies using common measures. Second-level ICF categories present in at least 15% of the studies are depicted in the ICF model in Figure 5.2. 'Body functions' included seven chapters, of which b2 'Sensory functions and pain' (45.0%) and b7 'Neuromusculoskeletal and movement-related functions' (43.9%) were the most frequent (Table 5.4). More specifically, b280 'Sensation of pain' (37.6%) and b710 'Mobility of joint functions' (19.0%) were the most frequent second-level categories (Table 5.5). In 'Body structures', only chapter s7 'Structures related to movement' was identified; herein s750 'Structure of lower

extremity' (21.7%) was most frequently measured. 'Activities and participation' was the most covered component overall, including nine chapters and 43 second-level categories. Among these, chapters d4 'Mobility' (55.6%), and d5 'Self-care' (34.9%) were the most frequent, and d450 'Walking' (33.3%) and d850 'Remunerative employment' (27.5%) were the most frequent second-level categories. Four chapters were identified in 'Environmental factors', of which e1 'Products and technology' (26.5%) was the most frequent. More specifically, e120 'Products and technology for personal indoor and outdoor mobility and transportation' (16.9%) was most frequent. In 'Personal factors', sociodemographic concepts were common (15.9%). Frequently used concepts that were not covered or not defined by the ICF included those related to body composition (10.1%) and general health (9.5%).

DISCUSSION

This systematic review identified and quantified the most studied areas of functioning and disability reported in an extensive number of published studies on adults with CP using the ICF as a reference.[21] Most of the items of common outcome measures could be translated into the universal language of the ICF. The results summarize the functioning concepts addressed in studies pertaining to adults with CP so far. Accordingly, the results represent the researchers' perspective in the development of an ICF Core Set for adults with CP.

In line with the definition of CP,[1] ICF categories referring to mobility and movement-related functions were among the most frequently studied at adult age. 'Mobility' (d4) was the most frequently addressed ICF chapter—a chapter that includes 'Walking' (d450), 'Moving around' (d455), and 'Changing and maintaining body positions' (d410 and d415); these activities are all reflected in the GMFCS.[24] 'Sensory functions and pain' (b2) was the second most frequent chapter, almost completely represented by the overall most frequent second-level category of 'Sensation of pain' (b280). Furthermore, we found high frequencies of categories in chapter b7 'Neuromusculoskeletal and movement-related functions', namely 'Functions of joint mobility' (b710), 'Muscle power and tone' (b730 and b735), 'Gait pattern' (b770), and 'Voluntary movement' (b760). Pain, limited joint mobility, decreased muscle power, and increased muscle tone are regularly observed in clinical practice. According to the ICF model, these (impairments in) 'Body functions' may affect the level of relevant activities and participation in major life areas, such as walking and self-care, and consequently employment and social and domestic life. The high frequency of concepts addressing 'Activities and participation' emphasize their importance. Regarding 'Contextual factors', 'Products and technology for mobility or for use in daily living' (e1) were frequently reported, which can both facilitate or hinder the aforementioned 'Body functions' and 'Activities and participation'.

Table 5.5. Relative frequency of second-level categories identified in studies using common measures (n=189).

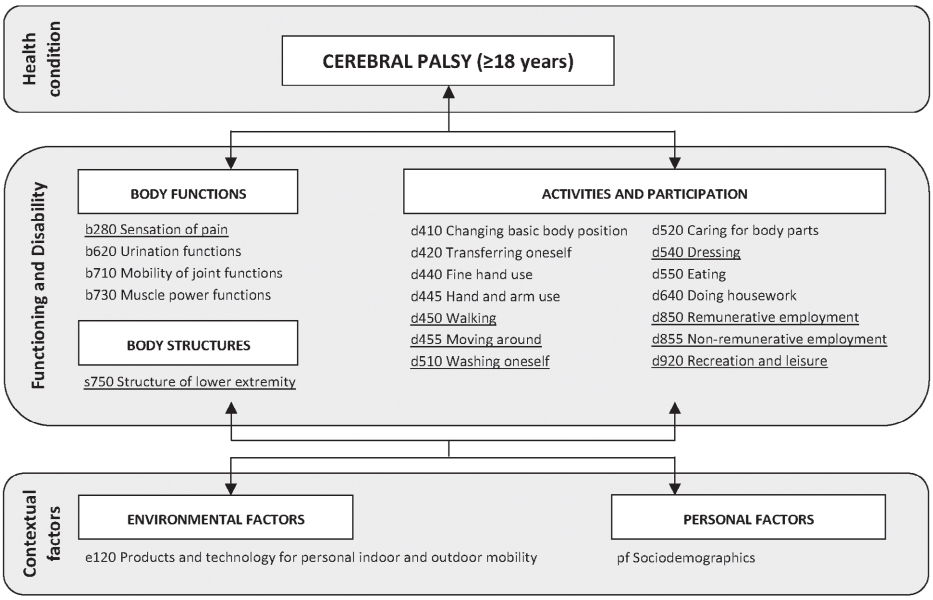
ICF code	Chapter	Used in number of studies, *n* (%)
b	***Body functions***	
b280	Sensation of pain	71 (37.6)
b710	Mobility of joint functions	36 (19.0)
b620	Urination functions	30 (15.9)
b730	Muscle power functions	30 (15.9)
b735	Muscle tone functions	27 (14.3)
b152	Emotional functions	26 (13.8)
b455	Exercise tolerance functions	23 (12.2)
b525	Defecation functions	23 (12.2)
b770	Gait pattern functions	22 (11.6)
b760	Control of voluntary movement functions	21 (11.1)
b130	Energy and drive functions	20 (10.6)
b134	Sleep functions	20 (10.6)
b144	Memory functions	20 (10.6)
b126	Temperament and personality functions	19 (10.1)
b140	Attention functions	14 (7.4)
b164	Higher-level cognitive functions	13 (6.9)
b114	Orientation functions	12 (6.3)
b320	Articulation functions	12 (6.3)
b235	Vestibular functions	11 (5.8)
b210	Seeing functions	10 (5.3)
s	***Body structures***	
s750	Structure of lower extremity	41 (21.7)
s760	Structure of trunk	27 (14.3)
s730	Structure of upper extremity	13 (6.9)
s770	Additional musculoskeletal structures related to movement	10 (5.3)
d	***Activities and participation***	
d450	Walking	63 (33.3)
d850	Remunerative employment	52 (27.5)
d855	Non-remunerative employment	47 (24.9)
d510	Washing oneself	42 (22.2)
d540	Dressing	42 (22.2)
d455	Moving around	40 (21.2)
d920	Recreation and leisure	38 (20.1)
d410	Changing basic body position	35 (18.5)
d440	Fine hand use	35 (18.5)
d520	Caring for body parts	34 (18.0)
d640	Doing housework	32 (16.9)
d445	Hand and arm use	31 (16.4)
d550	Eating	31 (16.4)
d420	Transferring oneself	29 (15.3)
d415	Maintaining a body position	28 (14.8)
d460	Moving around in different locations	28 (14.8)
d760	Family relationships	28 (14.8)
d465	Moving around using equipment	27 (14.3)
d530	Toileting	26 (13.8)

Table 5.5. Continued

ICF code	Chapter	Used in number of studies, *n* (%)
d430	Lifting and carrying objects	24 (12.7)
d750	Informal social relationships	24 (12.7)
d630	Preparing meals	19 (10.1)
d330	Speaking	17 (9.0)
d570	Looking after one's health	17 (9.0)
d650	Caring for household objects	17 (9.0)
d770	Intimate relationships	15 (7.9)
d240	Handling stress and other psychological demands	14 (7.4)
d166	Reading	13 (6.9)
d210	Undertaking a single task	13 (6.9)
d350	Conversation	13 (6.9)
d360	Using communication devices and techniques	13 (6.9)
d560	Drinking	13 (6.9)
d870	Economic self-sufficiency	13 (6.9)
d910	Community life	13 (6.9)
d175	Solving problems	12 (6.3)
d345	Writing messages	12 (6.3)
d470	Using transportation	12 (6.3)
d177	Making decisions	11 (5.8)
d310	Communicating with - receiving - spoken messages	11 (5.8)
d335	Producing nonverbal messages	11 (5.8)
d475	Driving	11 (5.8)
d620	Acquisition of goods and services	11 (5.8)
d930	Religion and spirituality	10 (5.3)
e	***Environmental factors***	
e120	Products and technology for personal indoor and outdoor mobility	32 (16.9)
e110	Products or substances for personal consumption	23 (12.2)
e115	Products and technology for personal use in daily living	21 (11.1)
e580	Health services, systems and policies	19 (10.1)
e399	Support and relationships, unspecified	13 (6.9)
pf	***Personal factors***	
pf-sd	Personal factors, sociodemographics	30 (15.9)
pf	Personal factors, unspecified	25 (13.2)
nc	***Not covered***	
nc-bc	Not covered, body composition	19 (10.1)
nc	Not covered, unspecified	18 (9.5)
nc-hc	Not covered, health condition	16 (8.5)
nd	***Not defined***	
nd-gh	Not defined, general health	18 (9.5)
nd	Not defined, unspecified	14 (7.4)
nd-pb	Not defined, physical behavior	14 (7.4)
nd-ph	Not defined, physical health	11 (5.8)
nd-funct	Not defined, functioning	11 (5.8)

Note. Only ICF categories measured in ³5% of all studies applying common measures are presented. Categories are ordered according to their relative frequency within each component.

Figure 5.2. International Classification of Functioning, Disability and Health (ICF) framework,[9] including the most frequent categories studied in adults with cerebral palsy.



Note. Only second-level ICF categories present in ≥15% of the studies are depicted here; those present in ≥20% of the studies are underlined.

The patient-oriented measures and clinical assessments found in the literature presumably reflect the instruments and assessments that are used in clinical practice. The Short Form Health Survey, Barthel Index, and Functional Independence Measure are the most widely used outcome measures in adults with CP, and have a common focus on 'Mobility' (d4) and 'Self-care' (d5). These instruments are also widely used in other populations with physical and mental disabilities such as stroke and traumatic brain injury.[30,31] Recently, the ICF Research Branch developed a generic set of categories that can be applied for documenting functioning in clinical (rehabilitation) settings.[32] Comparable to the present results, 21 of the 30 categories in the ICF Generic-30 Set (often also called ICF Rehabilitation Set) are from the component 'Activities and participation', whereby 13 are 'Mobility' (d4) and 'Self-care' (d5) categories.

Furthermore, 89% of the body function categories included in the ICF Generic-30 Set corresponds to the 'Body functions' frequently reported in the studies included in this review. This match of categories and consistency with clinically relevant instruments supports the notion that the ICF provides a universal language that can be used to describe outcomes of adults with CP. Nevertheless, since the population of adults with CP is very heterogeneous and presents itself with very specific and often increasing health-related

issues that go beyond the aspects of functioning addressed by the ICF Generic-30 Set,[20] a CP-specific ICF Core Set would have added value in clinical practice. For example, this review identified certain sensory functions and functions related to fatigue, or activities such as fine hand use, that are not included in the ICF Generic-30 Set.

We identified only few 'Body structures' in the literature on adults with CP. In this component, only structures related to 'Movement' (s7), most frequently the trunk and lower extremities, were regularly measured, usually by clinical assessments with specialized equipment (i.e. radiography). These body structures were mainly measured in adults with CP with lower-functioning GMFCS levels; this is no surprise given the more severely affected deformities that are common in people whose gross motor function is more impaired.[33] Likewise, few concepts were linked to 'Personal factors', which suggests a lack of representation of important interactions between personal characteristics and functional status in published studies on adults with CP, or may reflect the type of studies included in this review. Most of these were conducted in rehabilitation settings and included outcome measures that describe functioning or determine treatment efficacy, potentially explaining the focus on body functions and activities and participation outcomes. Another concern may be that personal factors are still not classified in the ICF. Finally, some concepts were unable to link to the ICF. For example, 6% of the concepts were not covered by the ICF or were insufficiently defined to allow linking to an ICF category. Notably, concepts such as physical behaviour – often measured by accelerometry – or those related to body composition (e.g. waist circumference) were often measured but could not be linked to the ICF.

A population-specific ICF Core Set facilitates the development of standards. This review presents a state-of-the-art of research in adults with CP. The total of 332 different outcome measures identified reflects the large variation in outcomes that are considered relevant to study in adults with CP, but at the same time it indicates a lack of standardization for frequent outcomes. Among the large quantity of outcome measures, we found several that were CP-specific, such as the GMFCS and Manual Ability Classification System. The GMFCS and the Manual Ability Classification System are, however, intended to classify the level of an individual's gross motor function and manual performance respectively.[24,34] Some of the included studies used the GMFCS as an outcome measure though. Consequently, this may have affected the present overview, since the GMFCS represents ICF categories in chapter d4 'Mobility'. Including them as outcome measures may therefore have slightly overestimated the frequency in this chapter. However, in almost half of the studies, the GMFCS was applied as a participant characteristic and thus was not included in our frequency analysis.

Systematic reviews with ICF linking of outcome measures have been previously conducted for other conditions addressing physical and cognitive disabilities.[30,31,35] While some of these used random samples of the literature or included only clinical trials,[30] others linked a selection of the identified measures on the basis of a relatively high occurrence rate or type of measure.[31,35] In the current systematic review, all eligible literature from a comprehensive sample was selected and a variety of study designs were included. For the linkage of outcome measures, a bottom-line occurrence rate (i.e. used in two or more studies) was considered, regardless of its type. We were able to demonstrate by which type of measure the relevant areas of functioning and disability were most commonly addressed. Clinical assessments were often applied to study cognitive functions, neuromusculoskeletal and movement-related functions, and structures related to movement, whereas patient-oriented and non-tool measures were used to study activities and participation, mainly chapters d4 to d9.

The present methodology was in line with the systematic review conducted for the ICF Core Sets for children and young people with CP.[14] Minor differences were, however, present. For example, our literature search was more comprehensive (5472 vs 698 screened). On the other hand, Schiariti et al.[14] linked every outcome measure, although in some cases only the domains or purposes of measures were linked. Despite only linking the common outcome measures, we linked all items included in these measures. Finally, Schiariti et al.[14] used the ICF for Children and Youth, whereas we linked the extracted concepts to the 2001 reference version of the ICF. Apart from these differences in methodology, the distinction between the children/young people and adult populations with CP was mainly demonstrated by the results of both reviews. For example, control of voluntary movement was by far the most studied body function in children and young people, whereas for adults sensation of pain was most common. In 'Activities and participation', walking was the most frequent category in both populations. However, for children and young people, other 'Mobility' categories (d4), such as 'Moving around' or 'Changing and maintaining body positions', continued to be most frequent, whereas for adults we identified 'Employment' (d8), 'Self-care activities' (d5), and 'Recreation' (d9) as the most frequent categories after that of 'Walking'. With regard to the differing ICF frameworks, the ICF Core Sets for children and young people with CP contain eight categories that only exist in the ICF for Children and Youth. However, we did not expect to find these categories (e.g. 'Acquiring language') in research on the adult population. In the end, the shared focus on movement-related functions, mobility, and self-care strengthens the idea that these domains are relevant for individuals with CP throughout the lifespan. Nevertheless, each stage of life has its own areas of attention. Our findings highlight that when young people with CP transition into adulthood, there is a shift of attention on specific aspects of functioning, namely towards participation in major life areas. A recent follow-up study of individuals with CP aged

between 16 and 34 years demonstrated that, in young adulthood, housework, employment, and intimate relationships became much more relevant, while education and selected recreational activities became less relevant.[19] At the same time, difficulty in participation increased during the transition into the mid- and late-twenties.[19] Comparing the results of the literature reviews on children/young people and adults with CP emphasizes the shifting of relevant outcomes for individuals with CP when entering adult life.

This systematic literature review shows that functioning of adults with CP is an emerging field of research, as evident by the increasing number of articles published on this topic during the 16-year timeframe of this review. A small part of this research seems to be experimental: only 5% involved randomized controlled trials. Considering individuals with CP receive most of their treatment during childhood, it is not surprising that research examining the effects of interventions, such as randomized controlled trials, is not frequently found in the literature on adults with CP. On the other hand, from a clinical perspective, it is surprising to find that the rehabilitation-oriented studies included relatively young participants (median 31y), as young adults with CP generally do not receive rehabilitation care.[36] Nevertheless, it can be concluded that there is a paucity of intervention studies targeting the long-term consequences of living with CP.

Some limitations should be considered when interpreting the results of this review. First, our selection was limited to studies and outcome measures in English, and to studies published between 2000 and 2017. Also, qualitative studies were not included, since this is considered a separate preparatory study in the ICF Core Set development process. These criteria were in line with the ICF methodology,[11] but some important concepts were potentially missed since qualitative research captures direct experiences of persons in their natural setting, often referring to environmental and personal factors. Similarly, certain concepts that only recently received attention in the scientific literature might have been missed. Second, most studies were conducted in Europe, North America, and the Western Pacific. Any concepts that might be specifically relevant in low- and middle-income countries were therefore missed. Finally, initial agreement on ICF categories between the reviewers was modest. However, a strength of this review was that each step was conducted independently by two reviewers, and discussions with a third reviewer always led to consensus. As this is the first study in the development of an ICF Core Set for adults with CP, these limitations will presumably be levelled out in the other preparatory studies. For example, in the expert survey all six WHO regions will be represented, so aspects of functioning in both low- and high-income countries will be captured.

CONCLUSION

This systematic review identified the most frequent outcomes used in studies of adults with CP, of which pain, mobility, self-care, employment, and recreation were most frequent. The broad range of ICF categories identified in this study emphasizes the heterogeneity of functioning and disability in adults with CP, but there is limited focus on environmental and personal factors in research, supporting the need to explore other perspectives as well. The present results will be combined with the results of the other preparatory studies. Together, all four preparatory studies capture the complementary perspectives of researchers, patients, and clinicians, and will serve as the scientific basis for the development of an ICF Core Set for adults with CP for use in both research and clinical practice.

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6

Multimorbidity risk assessment in adolescents and adults with cerebral palsy: a protocol for establishing a core outcome set for clinical research and practice

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ABSTRACT

Background: Estimates of multimorbidity, defined as the presence of at least two chronic conditions, some of which attributable to modifiable behaviours, are high in adults with cerebral palsy (CP). An assessment protocol evaluating multimorbidity risk is needed in order to develop and evaluate effective interventions to optimize lifelong health in individuals with CP. The aim of this protocol paper is to describe the development of a core outcome set (COS) for assessing multimorbidity risk in adolescents and adults with CP, to be used in clinic and research.

Methods: The expert consortium will first define the target population and outcomes to be measured. Through a process of literature review and an international Delphi survey with expert clinicians and researchers, we will then determine which outcome measurement instruments (OMIs) can best measure those outcomes. The resulting OMIs will be used in a feasibility study with adolescents and adults with CP from an international clinical research network. Finally, a face-to-face stakeholder meeting with adolescents and adults with CP, their families/caregivers and researchers and clinicians who are experts in CP, will be organized to reach final agreement on the COS.

Discussion: This COS will guide clinicians and researchers in assessing multimorbidity risk in adolescents and adults with CP. The inclusion of experts and individuals with CP from international locations for establishing the COS lends strong support to its generalizability. Evidence of its feasibility and approval from all stakeholders will enable implementation in clinical practice, and guide future research using the COS in individuals with CP.

BACKGROUND

Cerebral palsy (CP) is a well-recognized neurodevelopmental disability commencing in early childhood and continuing throughout life, and is the most common motor disability in childhood.[1] The disability itself results from non-progressive disturbances to the developing fetal or infant brain, and the resultant motor disorders are often accompanied by disturbances of cognition, behaviour and communication, to name only a few.[2] Population-based studies report prevalence estimates of CP ranging from 1.5 to greater than 3 per 1000 live births.[3-7] As CP presents itself early in life, much research has focused on children with CP; however, given the longer lifespan apparent in most persons with CP,[8] clinicians and researchers have started to focus on the impact of CP and associated health issues with a lifespan approach. Indeed, adults with CP are a growing community who are now recognized as outnumbering children 3:1 in some countries.[9]

A prominent concern for individuals with CP is their physical behaviour and reduced cardiorespiratory endurance.[10-12] Physical behaviour is defined as the behaviour of a person in terms of body postures (e.g. sitting and standing), movements (e.g. walking and cycling) and/or daily activities (e.g. sports and gardening) in his/her own environment, and therefore consists of both physical activity and sedentary behaviour.[13] Cardiorespiratory endurance is the capacity of the body to perform physical activity, which is dependent mainly on the aerobic or oxygen-requiring energy systems.[10] Adolescents and adults with CP have reduced cardiorespiratory endurance,[14] which is a risk for cardiovascular disease and cardiovascular-related mortality.[11] Also, children, adolescents and adults with CP engage in significantly less physical activity and increased sedentary behaviour compared to typically developing peers.[15-19] Low levels of physical activity and increased sedentary behaviour can partly be explained by reduced mobility following from the condition itself, as well as accompanying physical pain and fatigue that progressively worsen with aging.[20] Among individuals with CP, differences exist in physical activity levels[21] and obesity prevalence[22], which are contingent upon the functional status of individuals, as determined by the Gross Motor Function Classification System (GMFCS).[23] Reduced cardiorespiratory endurance and physical activity, and increased sedentary behaviour, are associated with risk for cardiovascular (i.e. coronary heart disease, cerebrovascular disease, peripheral arterial disease) and cardiometabolic (i.e. diabetes and obesity) disease in persons with CP,[17,24,25] which may become higher later in life.[26,27] Recent research in middle-aged adults with CP revealed high-estimates of multimorbidity, which were significantly more prevalent among obese versus non-obese persons with CP.[12]

Multimorbidity has been defined as the presence of at least two chronic conditions.[12] Among individuals with CP, chronic conditions apart from CP itself, such as hypertension,

dyslipidemia, hyperglycemia, insulin resistance, and obesity are emerging in the literature.[17,24,26] Results from a population-representative sample of adults with CP showed that this population had significantly greater age-adjusted prevalence of hypertension (30.0% vs 22.1%) and obesity (41.4% vs 29.7%) compared to adults without CP.[28] Despite the significant progression of disability that is known to occur during the aging process in CP,[20] there has been a lack of attention devoted to understand the pathophysiology to develop multimorbid conditions in adolescents and adults with CP, beyond those stemming from the primary brain injury in infancy. Multimorbidity risk could be attributed to a shared number of modifiable behaviours such as physical inactivity and/or sedentary lifestyles, poor diet, and inadequate sleep.[29] This highlights the importance of screening for, and understanding of risk exposures for multimorbidity in individuals with CP.

Over the last decade, a number of generic and CP specific instruments and protocols assessing multimorbidity risk factors have been developed. As a result, studies evaluating these risk factors in adolescents and adults with CP are using a variety of outcome measurement instruments (OMIs) (e.g., self-report questionnaires, accelerometry-based activity monitors, biomarkers and performance-based tests), which might possibly be measuring the same outcome, and thus causing difficulty synthesizing knowledge from the published literature and when generalizing findings.[30] Moreover, the psychometric quality (i.e. reliability, validity, sensitivity) of OMIs tends to vary and/or published evidence is lacking. Altogether making it inconvenient for clinicians and researchers to select the most appropriate OMIs for the outcome of interest. In order for clinicians and researchers to work with individuals with CP on plans for effective interventions – including advice pertaining to physical behaviour, nutrition and sleep – to reduce multimorbidity risk, it is vital to reach consensus on the outcomes to assess, the ways to assess them, and ultimately leading to routine clinical practice.

Lately, there is an increasing recognition for identifying core sets of outcomes that enable comparison of clinical trials for a particular condition. Moreover, establishing a core outcome set (COS) may be useful for routine health screening. Currently, there is no established COS for adolescents and adults with CP for the purpose of evaluating multimorbidity risk factors. A search of "cerebral palsy" through the Core Outcome Measures in Effectiveness Trials (COMET) database resulted in six matches, all of which focus on children with CP.[31] Common Data Elements (CDEs) exist for CP through a joint effort between the CP CDE Working Groups and the National Institute of Neurological Disorders and Stroke.[32] Within the CDEs is a summary of core and supplemental recommendations that is highly recommended as a start-up resource for clinical research in this population. Although this set of CDEs was recently developed (2016), it only applies to children and adolescents

aged 0 to 18 years and does not specify instruments specific to adults with CP or measures that assess multimorbidity risk.[33]

The aim of this protocol paper is to describe the process of developing a COS of OMIs for multimorbidity risk in adolescents and adults with CP to be used in clinic and research. This work includes (1) identifying what outcomes should be measured; (2) determining how to best measure those outcomes; and (3) measuring these outcomes in an international cohort of individuals with CP. The final COS will be made in consultation with individuals with CP and their families and caregivers and with representatives of the clinical and research community who are working with people with CP. The inclusion of adolescents and adults with CP and their families and caregivers is critical to ensure that OMIs are meaningful, appropriate, and acceptable to inform decisions about assessment of multimorbidity risk in this population. We will include adolescents with CP in the assessments of multimorbidity risk, as this will capture a pivotal transition period, and may highlight the importance of engaging in positive behaviours early on to attenuate multimorbidity risk later in life. This study is part of a program of research aiming to ultimately understand, treat and prevent multimorbidity in adolescents and adults with CP through modifiable behaviours (e.g. physical behaviour, sleep and nutrition) and to develop an international database that will allow for harmonization of data and the ability to document changes over time in this population.

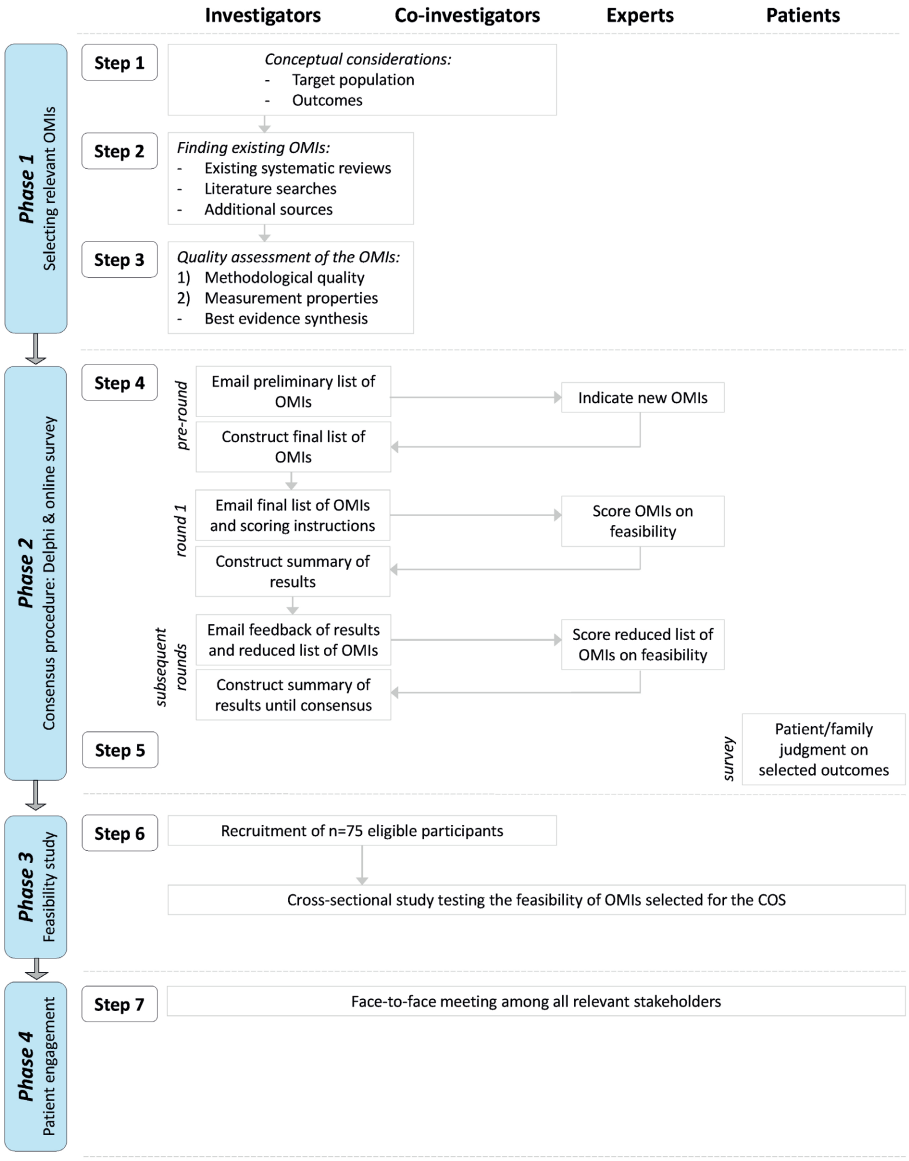
METHODS

This study protocol is registered with the COMET Initiative (http://www.comet-initiative.org/studies/details/1130) and follows recently published guidelines from a collaboration between the COMET Initiative and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN).[30] Slight adjustments were made to the original flowchart,[30] as we chose to include a pilot testing phase (Figure 6.1). Phase 1 has begun, and the target population and outcomes to be measured have already been defined.

Investigators and co-investigators

Four authors (PM, JB, MR, JWG) will have an investigating role in the COS development. After deciding on the conceptual considerations in consultation with co-investigators (MP, EH, WS, AB, OV, RB), they will first perform a review of the literature and extract relevant OMIs. Secondly, they will carry out a consensus procedure with experts to obtain agreement on selected OMIs to be included in the COS. Third, they will coordinate a cross-sectional feasibility study in which the COS will be tested in an international cohort of adolescents and adults with CP at four sites. Finally, they will organize a stakeholder meeting to review and finalize the COS of OMIs for multimorbidity risk.

Figure 6.1. Main steps in the COS development including roles of all involved at each step.



Schematic outline of the different phases and steps included in the development of a COS for multimorbidity risk assessment in adolescents and adults with cerebral palsy. Roles of all involved at each step are indicated. COS, core outcome set; OMI, outcome measurement instrument; CP, cerebral palsy.

Phase 1: Selecting relevant OMIs

Step 1: conceptual considerations

We defined a target population and outcomes to be measured, in line with the COSMIN-COMET guideline.[30] This was done via an in-person meeting with the co-investigators from four research centres (Hamilton, Canada; Ann Arbor, USA; Rotterdam and Utrecht, The Netherlands), at the 29th European Academy for Childhood Disability conference (2017). During this meeting, the target population was defined as adolescents (14-18 years) and/or adults (>18 years) with CP. Furthermore, the following outcomes were decided to be important for assessing multimorbidity risk in the target population: physical behaviour, nutrition, sleep, cardiorespiratory endurance, body composition, blood pressure, and lipids/glucose. Including risk behaviours (i.e. physical behaviour, nutrition, and sleep) is important to identify which patients require intervention. Measuring cardiorespiratory endurance, body composition, blood pressure and lipids/glucose will allow clinicians and researchers to observe the benefits of improved risk behaviours.

Step 2: Finding existing OMIs

In order to find all existing OMIs addressing the defined outcomes, we will use three sources of information, including (1) existing systematic reviews, (2) literature searches, and (3) additional sources (e.g. conference proceedings).[30] Additional sources are considered optional since it is unlikely that one will find OMIs of good quality that were not already identified from a systematic search of the literature.[30]

The COSMIN database of systematic reviews of OMIs will be consulted to see if systematic reviews, describing our target population and any of the seven outcomes, exist. Candidate OMIs for each outcome will further be identified by electronic searches of the following databases: EMBASE and Medline (Ovid), PsycINFO, and PubMed. The electronic searches will be carried out by two researchers with experience in conducting systematic reviews (PM, JB). We will develop a search strategy which will include the following major themes: "cerebral palsy", "adolescent OR adult", and each outcome on their own. Key terms within the search strategy will be aligned to medical subject headings and expanded to include more descriptive terms. Searches consistent with "measurement properties" will not be included in the search strategy, since evidence on measurement properties of relevant OMIs is expected to be limited in our target population, exposing a risk of missing relevant studies (see Appendix 6.1). Eligible publications will be randomized controlled trials, longitudinal (including experimental and cohort studies) and observational (including cross-sectional, cohort, and case-control studies) studies, written in English. Studies will be grouped by outcome and repeated where appropriate (i.e. if there is >1 outcome within a single study).

The two researchers will screen titles and abstracts independently and select references using a predetermined set of inclusion/exclusion criteria. If there are any discrepancies, these will be resolved by consulting other investigators (JWG, MR). Upon agreement on the final selection of studies, the two researchers will record each OMI for each outcome used in an eligible study. We will also extract characteristics of the study sample (i.e. sample size, mean age, sex, type of CP, and GMFCS level(s)). Data extracted will be crosschecked for accuracy between the two researchers.

A group of experts that will be consulted during the second phase of the COS development process will serve as additional sources for finding OMIs. The group will be requested to provide any additional OMIs that are considered relevant to an outcome but were not identified in existing systematic reviews or in the literature searches.

Step 3: Quality assessment of the OMIs

The quality of the OMIs that result from step 2 will be assessed in accordance with the COSMIN-COMET guideline.[30] The quality assessment will include two parts: (1) evaluating the methodological quality of the studies included from the literature searches, and (2) evaluating the quality of the OMIs (i.e. their measurement properties). Since the literature search will not be limited to studies on measurement properties of OMIs, we will use a combination of the COSMIN checklist and the McMaster critical review form.[34,35] The COSMIN checklist will be applied for evaluating the methodological quality of studies on measurement properties of OMIs,[34] while the McMaster critical review form will be applied to assess the methodological quality of the other study types (e.g. clinical trials and observational studies).[35] The quality of the OMIs will be evaluated by applying criteria for good measurement properties.[36] We will first evaluate the content validity of the included OMIs and where applicable the remaining measurement properties.[30] Both researchers (PM, JB) will perform the OMI evaluation, and will crosscheck each other's quality assessments to ensure accuracy and completeness. Evaluations of the methodological quality of the studies and the quality of the OMIs will be combined into a best evidence synthesis, grading the body of evidence for each OMI.[30] Feasibility aspects of the OMIs including applicability (for the target population), patient feasibility, assessor/clinician feasibility, and practical feasibility will be considered in the next phase of the study.

Phase 2: Consensus procedures: Delphi & online survey

Step 4: Select an OMI for each outcome included in the COS

We will use the Delphi survey method[37] as a consensus procedure to obtain agreement on the selected OMIs included in developing a COS using experts in the area of multimorbidity

risk in adolescents and adults with CP. In a Delphi procedure, interactions between experts occur via a series of individual surveys, preserving both anonymity and balance in participation from the experts.[38] In contrast to an in-person consensus method, a Delphi procedure can be conducted via email survey and is therefore accessible to participants regardless of location and involves no cost.[39]

Experts

To remain consistent with the international aspect of the protocol, we will include a group of eight experts that consist of clinical and research experts in this field. The experts will be from Canada (n=2), USA (n=2), and The Netherlands (two locations, n=4). The investigators (PM, JB, MR, JWG) discussed and confirmed a priori that each international location must consist of at least one clinical and one research expert. To be considered a clinical expert, the individual must have worked with adolescents and/or adults with CP for at least 5 years. To be considered a research expert, the individual must have published one or more articles related to an identified outcome of multimorbidity risk in this population (adolescents and/or adults with CP).

Delphi survey

The initial stage of the Delphi survey will be a pre-round to obtain a list of OMIs that is as complete as possible. Based on the results from the literature searches performed by the two researchers, a list of studies with OMIs will be identified and divided into the seven defined outcomes: (1) physical behaviour, (2) nutrition, (3) sleep, (4) cardiorespiratory endurance, (5) body composition, (6) blood pressure and (7) lipids. Experts will be provided the results from the literature searches via e-mail, and requested to provide any additional OMIs that are relevant to an outcome but are not identified in the literature searches. These could include OMIs that are being used in clinical practice, ones used by a colleague, and/or ones that were read in an abstract or article or in a student's thesis. Any proposed OMIs will be required to have a reference or abstract attached, to allow the two researchers to evaluate the quality of both the study and the OMI as per Step 3.[30]

In round 1 of the Delphi survey, experts will receive an updated list of OMIs pertaining to each of the seven outcomes, which will be delivered by e-mail. The investigators will provide the experts with a spreadsheet consisting of seven tabs, one for each outcome. Every tab will include all associated OMIs that were obtained during step 2 and the Delphi pre-round, accompanied by a brief note of the methods/equipment used, a short description of the samples in which the OMI was used and graded evidence of the OMI resulting from step 3. A detailed description of the characteristics of each included study will be provided separately to assist experts in reviewing the OMIs. Study characteristics will include author and year

of publication, the outcome(s) studied, the sample characteristics extracted in step 2, and the methodological quality of the study evaluated in step 3. Experts will be given detailed instructions and an instructional video outlining how to score each OMI on a 1–10 scale (1=lowest, 10=highest) for five different aspects of feasibility: applicability, patient feasibility, clinician feasibility, practical feasibility and overall rating. A comment box will be provided to allow experts the option to provide additional information to the researchers (i.e. explain responses or raise concerns), or to indicate that they are ignorant or uncertain. Experts will have 2 weeks to score the OMIs for feasibility. Reminder e-mails will be sent after 1 week and at 1 day before the end of the 2-week period. Mean scores will be calculated after receiving and aggregating the expert scores. OMIs with a mean overall score ≥7 will be retained, those with scores <6 will be omitted and those with scores of 6–7 will be discussed among the investigators using the expert comments and quality scores. Moreover, we will examine differences between clinician and researcher scores and describe these results.

In subsequent rounds of the Delphi survey, experts will be presented the results from the previous round. All experts will see aggregated scores for each OMI, and a synopsis of the comments made by each expert (if applicable). Experts will be asked to consider the feedback (i.e. aggregated scores and comment synopsis) and again score the feasibility aspects for the remaining OMIs with an option to provide their rationale in a comment box. In these rounds, experts also will be asked to identify their preferred OMI for each outcome and to explain why. Similar to round 1, experts will have 2 weeks to score the OMIs for feasibility with reminder e-mails provided at the same time points. The expert scores will be processed in a similar fashion and extended with preferred OMI scores. This process will continue until a single OMI per outcome is selected, based on ≥70% agreement among experts. The investigators will attempt to identify a provisional COS pertaining to the seven outcomes from the scores after two rounds. This will be based on aggregated scores (mean and median), expert opinion (i.e. rationales and additional information from the comments), and the quality of the studies and OMIs. The provisional COS will be presented to all experts, who will be asked whether they agree or disagree with the OMI for each outcome in the COS. If an expert disagrees with the suggested COS, they will be asked to provide their comments and reasons for disagreement.[40] From the decisions and comments made by the experts, a provisional COS will be presented and evaluated for final agreement. The COS will only become final after feasibility testing (phase 3) and stakeholder engagement (phase 4) (see below).

Step 5: patient/family judgement on relevance and completeness of selected outcomes

We will conduct a short online survey with patients with CP or families/ caregivers of people with CP, to rate the importance of each outcome as something they would like their family doctor to measure and discuss with them.

Phase 3: feasibility study

Step 6: feasibility test of the COS in the target population

After developing a COS for multimorbidity risk assessment for use in clinical research and practice, the next stage will be to test the feasibility of the COS in a cohort of adolescents and adults with CP. Aspects of feasibility to be assessed from the perspectives of the clinicians and researchers will include ease of assessment, time required for completion and their confidence in the COS to assess multimorbidity risk. Time requirement and interpretation of results will be assessed (see below) to determine feasibility from the patient perspective.

Participants

The feasibility study will focus on adolescents and adults aged 14 years and over, with a diagnosis of CP. We will include individuals with CP across all GMFCS levels (levels I–V), from three different international locations: Hamilton, ON, Canada; Ann Arbor, MI, USA and Rotterdam and Utrecht (combined), The Netherlands. The knowledge to be gained from this multinational study will be far superior to the minimal information that would be gained if we were to conduct the study at a single site, which has constrained the generalizability of research in this area.[41]

Recruitment strategy

Individuals with CP will be recruited during clinical visits to an adult rehabilitation centre or a child and youth clinic in Hamilton, ON, Canada; Ann Arbor, MI, USA and Rotterdam and Utrecht, The Netherlands. During clinical visits, a physician (JWG, EH or WS) or a study coordinator (PM or JB) from our research team will introduce the study to the patient, at which point the patient will have an opportunity to consent to participate in the study. Members of our team have used a similar recruitment strategy successfully in the past,[26] and we are confident in achieving a total sample size of 75 (25 per geographical region) for testing the feasibility of the COS. As feasibility testing of the COS will be cross-sectional in nature, we will not include a control group at this time. We plan for a future grant application to fund an intervention study using the findings of our feasibility study, which will incorporate a control group.

Sample size

An a priori criterion for success of this feasibility study is that a subsequent intervention trial would be feasible if the outcome variables were collected for ≥70% of participants. Using a 95% confidence interval (CI) for the proportion of eligible participants who complete the assessment, a margin of error of 0.05, a lower bound CI of 0.70 and an expected completion

rate of 75%, the required sample for the feasibility study will be at least 75 participants. We aim to recruit five participants per GMFCS level per location (i.e. 5 participants * 5 GMFCS levels * 3 locations), for a total of 75 participants. As this is a cross-sectional study (i.e. single time commitment), we will not factor in the attrition rate.

Assessments

Eligible participants who have provided written consent to participate in the feasibility study will be assessed. Participants will be invited to visit the relevant setting, in which we will execute the OMIs selected for the COS. Assessments will be conducted by the clinicians and researchers involved, where applicable with support from research/laboratory assistants. Based on the outcomes that have been identified in step 1, we estimate that it will take 3–4h to conduct the total set of OMIs. Naturally, the collected data will provide insight into the risk profile of the individual participant. We hope that the measures will be integrated into clinical care as much as possible. It is conceivable that the total data collection time may be spread over a single assessment or multiple assessments (e.g. body composition and blood pressure measurements in clinic, but an additional session for measurement of cardiorespiratory endurance). The total time required will be explored in our feasibility study. The COS will be qualitatively evaluated to examine its acceptability as a whole, by both the participants and clinicians/researchers. After the measurements the participants will be asked about their experience of the COS, including time required to complete the assessments, via a short survey. Upon completion of all measurements, we will question the clinicians and researchers who conducted the assessments about the ease of assessment, completion time and their confidence in the COS, also via a short survey. Together with the collected data, the feedback from the participants, clinicians and researchers will provide a clear indication of the feasibility of the COS for future use in clinical research and practice.

Phase 4: patient and family/caregiver engagement

Step 7: final agreement on the COS among stakeholders

As a final step and after taking into consideration the qualitative evaluations from study participants, clinicians and researchers, we will organize a face-to-face stake- holder meeting to reach final agreement on the COS. Adolescents and adults with CP and their families and/ or caregivers, as stakeholders in this project, will be recruited with support from the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) family/participant education forum. The AACPDM education forum is held annually at the AACPDM conference. Prior to the meeting, we will work with the AACPDM administrative leaders to have an advertisement positioned on their website asking for adolescents and

adults with CP (and their families/caregivers) to participate in a meeting to help review and finalize a COS for multimorbidity risk. We will invite four adolescents and four adults with CP of varying GMFCS levels, who did not participate in the feasibility study, and their families and/or caregivers (if applicable), to take part in the meeting, which will occur during the AACPDM 2018 conference (9–13 October 2018).

Dissemination

Details of the finalized COS will be disseminated through publication in a scientific journal, presentation(s) at international scientific conferences and research rounds at clinics and academic institutions at each international location.

DISCUSSION

The aim of this project is to develop and test the feasibility of a COS to assess multimorbidity risk in adolescents and adults with CP. Ultimately, the COS will be used to understand, treat and prevent multimorbidity in this population, while being utilized in a clinical and/or research setting. The development of this COS is expected to have the potential to be generalized to other types of child-onset neurodevelopmental disabilities.

A strength of the proposed work is the inclusion of clinical and research experts in this field (COS development) and individuals with CP (feasibility study), from international locations. The knowledge to be gained from an international study will be significant and meets a major limitation in multimorbidity risk research in this population (i.e. studies of small sample sizes that are geographically isolated). If we are able to conduct the feasibility study successfully and receive positive feedback from individuals with CP, their families/caregivers and clinicians and researchers, our next step will be to apply for funding to conduct an intervention study in this population aiming to prevent multimorbidity risk, including other geographic locations worldwide. In the meantime, the development and feasibility testing of a COS for adolescents and adults with CP will improve the consistency of CP research moving forward. Ultimately, we aim to utilize the COS in clinic to work towards developing a database that will allow for harmonization of data and the ability to document changes over time, which will enhance and accelerate our understanding of multimorbidity risk and presentation in this population, and will help to overcome the issues of current small-scale studies. As well, performing the COS assessment in clinic will allow us to obtain a risk profile for the patient, which can help inform an individualized treatment plan.

A challenge we faced with this protocol was selecting when to engage individuals with CP and their families/ caregivers as key stakeholders in COS development. Ideally, we would have included these stakeholders throughout the study from the very beginning to the end. Despite not including individuals with CP in phase 1 of the project, we believe that the outcomes we selected align with the top research priorities identified in part by individuals with CP and their families: understanding how to prevent secondary impairments related to aging with CP and identifying effective long-term exercise strategies to improve activity and health across their lifespan.[42] Moreover, in addition to the Delphi survey among professionals, we will also conduct an online patient/family survey to inform us whether the target population agrees that the outcomes to measure are relevant. Due to the focus on knowledge synthesis in the Delphi survey with research rigor and the terminology involved in quality assessments of studies and OMIs, we decided it would be more pragmatic to develop a provisional COS amongst clinicians and researchers, and then bifurcate to feasibility testing and a stakeholder meeting, to incorporate perspectives from individuals with CP and their families/caregivers and come to a final agreement on the COS. A former study that attempted to develop a COS with patient perspectives from the onset of the idea was reported as challenging.[43]

Despite an effort to include expert clinicians and researchers working with adolescents and adults with CP who are knowledgeable of multimorbidity, none of these individuals considered themselves as experts in the outcomes of nutrition and sleep in CP. This identifies an important gap in clinical research in this population; if nutrition and sleep are to be considered important components of multimorbidity risk prevention in people with CP,[44] clinicians and researchers need to be trained in these outcomes in order to assess and manage these components of health.

Trial status

At the time of submission, we have included experts for the Delphi survey. Recruitment for the feasibility study will start in June 2018 subject to the ethics approval from all institutions involved.

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Appendix 6.1. Complete search strategy for Embase.

Population of interest: adolescents and adults with cerebral palsy

('cerebral palsy'/exp/mj OR (((cerebral* OR brain OR spastic) NEXT/2 (pals* OR paralys* OR hemipleg* OR diplegi* OR paresis)) OR 'encephalopathia infantilis'):ab,ti) AND (('adolescence'/exp OR 'adolescent'/de OR (teenage* OR puberty):ab,ti) OR ('adult'/exp OR (adult* OR elderly OR older OR aging OR pensioner OR retiree OR (grow* NEXT/1 up*)):ab,ti))

AND

Construct of interest (2,3): body size and body composition

('anthropometric parameters'/exp OR 'body composition'/exp OR obesity/exp OR 'BMI (body mass index)' OR 'body mass index' OR 'Quetelet index' OR adiposit* OR obesit* OR overweight OR ((body) NEAR/1 (height OR mass OR size OR composition OR fat OR lipid)) OR ((fat OR adipose) NEAR/2 (distribution OR mass OR tissue)) OR ((waist OR hip OR waist-hip) NEAR/1 (circumference OR ratio)):ab,ti)

OR

Construct of interest (4): physical behavior

('physical activity'/exp OR 'physical inactivity'/exp OR 'sedentary lifestyle'/exp OR sitting/exp OR 'energy expenditure'/exp OR 'motor activity'/de OR accelerometer/de OR accelerometry/de OR actimetry/de OR ((sedentary OR physical OR motor) NEAR/1 (lifestyle OR activit* OR inactivity)) OR ((caloric OR energy) NEAR/1 (expenditure)) OR sitting OR acceleromet* OR actimetry OR actigraph* OR ((activity) NEAR/1 (monitor OR tracker)):ab,ti)

OR

Construct of interest (5): sleep

(sleep/exp OR 'sleep disorder'/exp OR sleep* OR dream* OR dyssomnia* OR hyposomnia* OR hypersomnia* OR insomnia* OR parasomnia* OR sleeplessness OR sleepiness OR somnolence OR tiredness OR tired OR ((sleep) NEAR/2 (disorder* OR disturbance OR paralysis)):ab,ti)

OR

Construct of interest (6): nutrition

(nutrition/exp OR 'feeding behavior'/exp OR 'dietary intake'/exp OR feeding OR nutrition OR diet OR dieting OR ((diet* OR nutrition*) NEAR/1 (survey* OR assessment OR state OR status)) OR ((food OR feed OR energy OR calor* OR dietary OR nutrient) NEAR/1 (uptake OR intake OR consumption)) OR ((feeding OR eating OR drinking OR alimentary OR nutrition*) NEAR/1 (behavior* OR habit* OR pattern*)):ab,ti)

OR

Construct of interest (7): blood pressure

('blood pressure'/exp OR 'blood pressure monitoring'/exp OR 'abnormal blood pressure'/exp OR 'blood pressure measurement'/de OR 'hypertension encephalopathy'/de OR 'blood pressure monitor'/exp OR (((blood OR vessel* OR vascul* OR intravascul* OR venous OR arter*) NEAR/3 (pressure OR tension*)) OR hypotens* OR hypertens* OR prehypertens* OR normotens*):ab,ti)

OR

Construct of interest (8): blood lipids

(dyslipidemia/exp OR hyperlipidemia/exp OR hypolipemia/exp OR cholesterol/exp OR triacylglycerol/de OR dyslipid* OR hyperlipid* OR hypolip* OR cholester* OR triacylglycerol OR triglyceride* OR 'lipid profile':ab,ti)

NOT

Limitations

([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Note. Construct of interest (1) cardiorespiratory endurance was not included in the search strategy, since an existing, up-to-date systematic review was already identified. The search strategy was translated for MEDLINE/Ovid, MEDLINE/Pubmed, and PsychINFO.

7

Focus on risk factors for cardiometabolic disease in cerebral palsy: Toward a core set of outcome measurement instruments

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ABSTRACT

Objective: To identify existing outcome measurement instruments (OMIs) assessing risk factors for cardiometabolic disease in adolescents and adults with cerebral palsy (CP) reported on in the literature or used in the field.

Data Sources: The COnsensus-based Standards for the selection of health Measurement INstruments database of systematic reviews and 4 electronic databases (Embase, MEDLINE/Ovid, MEDLINE/Pubmed, PsychINFO) were searched up to June 19, 2017, that yielded 2594 articles. Experts in the field were consulted to identify any additional OMIs.

Study Selection: Two reviewers independently applied inclusion criteria to select eligible studies using or evaluating measurement properties of OMIs assessing 1 of 8 outcomes: cardiorespiratory endurance, body size, body composition, physical behavior, sleep, nutrition, blood pressure, and blood lipids and glucose. Studies with an experimental or observational design including ³10 adolescents or adults with CP were included.

Data Extraction: One reviewer extracted data that were summarized for study and sample characteristics, outcomes, OMIs used, and if applicable data on measurement properties. Two reviewers rated the methodological quality and the quality of the OMIs. Feasibility for clinical practice and research was rated by experts in the field.

Data Synthesis: Ninety OMIs were identified from 56 included articles and by the experts. Seventy OMIs pertained to cardiorespiratory endurance, body size, body composition, and physical behavior, whereas only 5 were identified for sleep and nutrition. Overall synthesis revealed that there is moderate to poor evidence for good quality of OMIs in this population. Based on feasibility for clinical practice, experts agreed on a single OMI per outcome (and 2 for cardiorespiratory endurance) to be included in a core set.

INTRODUCTION

Emerging literature is demonstrating that individuals with cerebral palsy (CP) have a higher prevalence of chronic conditions and multimorbidity compared to the general population, including cardiometabolic diseases.[1-3] Traditional risk factors like high blood pressure are common among adults with CP,[3] but other factors like health-related fitness and lifestyle behaviors are also known to contribute to the risk for cardiometabolic disease.[4-6] For some individuals with CP this may be the inevitable consequence of their mobility impairments,[7] but it may also relate to secondary conditions resulting from their primary condition,[8] such as musculoskeletal problems or fatigue. Age further increases the risk of cardiometabolic disease in adults with CP.[9] Since individuals with CP are living longer lives,[10] it becomes important to develop specialized assessment and prevention strategies focusing on multimorbidity risk, and in particular, cardiometabolic health of people with CP

Cardiovascular diseases and metabolic conditions share a number of modifiable risk factors.[11] According to the World Health Organization, lifestyle behavior changes are important ways to minimize the risk of cardiometabolic disease. In people with CP, promotion of health-related fitness and physical activity has gained much focus recently.[12-17] More recently, sleep and nutrition have been suggested as additional factors to optimize the overall health status of individuals with CP.[18] Recommendations for exercise and daily physical behavior (physical activity and sedentary behavior[19]) specific to persons with CP were recently described,[20] but recommendations pertaining to sleep and nutrition still require further research.[18] In addition, multi-factorial lifestyle intervention programs focusing on health-promoting behaviors (exercise, physical behavior, sleep, and nutrition), taking into account the different primary and secondary consequences of CP, have not yet been developed.

The management of cardiometabolic health is focused on reduction of risk factors through primary prevention, or by screening persons on risk factors for cardiometabolic disease followed by lifestyle intervention programs.[21] Given the high prevalence of cardiometabolic disease in adults with CP, screening them from an early age onwards is a critical strategy in their health management.[2,22,23] However, screening programs for individuals with CP focusing on risk for cardiometabolic disease are lacking. Furthermore, there are no clear recommendations regarding the outcome measurement instruments (OMIs) to assess risk factors for cardiometabolic disease for use in this particular, heterogeneous population. Such recommendations are essential because healthcare providers need OMIs that are closely related to their (lifestyle) intervention programs. Developing a core set of evidence-based and feasible OMIs will facilitate the standardization of assessment (i.e., screening

and monitoring) in people with CP. It will also minimize inconsistencies in reporting and facilitate comparison across clinical sites or studies.[24,25] Broader uptake of such a core set will allow for the development of larger databases of longitudinal information,[26] which can be aggregated for statistical purposes to improve our understanding of risk for chronic conditions in this population.

The multisite CP – Multimorbidity risk Assessment and Prevention consortium intends to develop a core set of OMIs assessing risk factors multimorbidity (i.e., the presence of multiple chronic diseases) in CP, including cardiometabolic disease, in which perspectives of all stakeholders (clinicians, researchers, and individuals with CP and/or their caregivers) are captured.[27] In order to do so, an overview of existing OMIs and their quality first needs to be provided. The present study aimed to (1) identify all existing OMIs assessing outcomes related to cardiometabolic health in adolescents and adults with CP; (2) select 1 OMI for each outcome based on quality and feasibility for clinical practice and research.

METHODS

This study was performed as part of a larger project on the development of a core set of OMIs for multimorbidity risk in adolescents and adults with CP, of which details can be found in the study design.[27] We followed recently published guidelines from a collaboration between the Core Outcome Measures in Effectiveness Trials (COMET) Initiative and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)[28] and report according to the Core Outcome Set–STAndards for Reporting (COS-STAR) Statement.[29]

Conceptual considerations

The target population and outcomes were determined by the CP – Multimorbidity risk Assessment and Prevention consortium during an in-person meeting among clinicians and researchers with leading expertise in this field in May 2017 in Amsterdam, the Netherlands. The target population was defined as post pubertal adolescents (14-18 years) and adults (>18 years) with CP. The following 8 outcomes were selected, representing health-related fitness, lifestyle behaviors, and traditional (bio)markers of cardiometabolic health: (1) cardiorespiratory endurance; (2) body size; (3) body composition; (4) physical behavior; (5) sleep; (6) nutrition; (7) blood pressure; (8) blood lipids and glucose.[27]

Systematic literature review

As our first source, we consulted the COSMIN database of systematic reviews to identify existing, up-to-date systematic reviews of OMIs measuring any of the determined outcomes in the CP population.

As our second source, 4 electronic databases (Embase, MEDLINE/Ovid, MEDLINE/Pubmed, PsychINFO) were searched from January 1, 2000, until June 19, 2017, by combining search terms for the CP population with terms for the determined outcomes. Two reviewers (JB, PM) independently screened titles and abstracts of the resultant references, followed by full-text reviews of eligible articles, and finally, manual checking of reference lists of included studies. Inclusion criteria: studies using, or evaluating measurement properties of, an OMI measuring at least 1 of the outcomes; including ≥10 adolescents (14-18 years) or ≥10 adults (>18 years) with CP; experimental or observational study design; and English peer-reviewed publications. Studies were excluded if the participants' mean age was <14 years, when no relevant OMIs were used or accurately defined, or when none of the outcomes were reported as an endpoint. Therefore, studies that reported an outcome solely as sample characteristic (e.g., body height and weight) but did not define how the outcome was measured were excluded. Reference lists of included studies were checked to find other candidate OMIs.

As our third source, prior to the consensus rounds of the Delphi procedure, experts were invited to propose additional OMIs that were not obtained from existing systematic reviews or in the literature search after they were informed on the results. These additional OMIs could have been ones that were being used in clinical practice, ones used by colleagues, ones used in a different population but deemed appropriate, or from a conference abstract or student's thesis. Proposals had to be accompanied by a reference, abstract, or student's thesis, in order for the reviewers to determine the quality.

Quality assessment

The first reviewer (JB) extracted relevant data from included studies, which was checked by the second reviewer (PM). To avoid duplication, multiple articles on the same study sample were combined. Study and participant characteristics (including CP type and severity), reported outcomes, and each OMI were recorded. Type of CP was defined as spastic unilateral, spastic bilateral, ataxic, dyskinetic, or mixed.[30] The severity of motor impairment was determined by the Gross Motor Function Classification System (GMFCS)[31,32].

The 2 reviewers conducted a 2-part quality assessment to assess (1) methodological quality, and (2) quality of the OMIs. Overall quality of each OMI was determined by combining the results of the 2 parts into a best-evidence synthesis.[28]

Methodological quality of studies on measurement properties was assessed using the COSMIN checklist.[33] For each box corresponding to a measurement property that was reported on, items were rated as excellent, good, fair or poor.[34] In line with recent adaptations to the checklist,[35] the item concerning sample size (requiring n≥30 for a fair rating) was

ignored. Instead, we reported this as an additional comment to the methodological quality score. Methodological quality of randomized controlled trials (RCTs) or observational studies was assessed using 13 or 10 items of the McMaster critical review form, respectively.[36] Three items were only applicable to RCTs, 2 other items concerning measurement properties were ignored because we used more comprehensive criteria (part 2, quality of the OMIs). Items were rated as yes (meets criterion), no (does not meet criterion), or na (not applicable).[36] For RCTs, sum scores of 13, 11-12, 9-10, and 8 or lower were considered excellent, good, fair, and poor; in observational studies this was 10, 9, 7-8, and 6 or lower.

Quality of the OMIs was assessed by rating results on measurement properties as positive, negative, or unknown (Table 7.1, upper panel).[37] Content validity was rated first, because it should be clear that all content of the OMI was relevant, comprehensive, and comprehensible with respect to the outcome of interest and target population.[28] If content validity was rated negative or unknown, the OMI was excluded from further consideration. Other measurement properties were also assessed if data were available from the included studies.

The overall quality of each OMI was constructed by a best-evidence synthesis, taking into account the number of studies using the OMI, the methodological quality of these studies, and the consistency of the results on measurement properties of the OMI.[37] This information, along with a summary table of included studies, was presented to the experts in our Delphi surveys (Appendix 7.1).

Delphi procedure

A purposeful sample of experts from 4 clinical sites in Canada, the United States, and the Netherlands was invited to participate based on their clinical and research experience in the field of cardiometabolic health in adolescents and adults with CP, including pediatric and adult physiatrists and physical therapists, and those with expertise in the field of exercise physiology and physical behavior. Their role was to review and evaluate all OMIs on quality and feasibility, and eventually anonymously agree on the most suitable OMI per outcome for use in clinical practice and research.

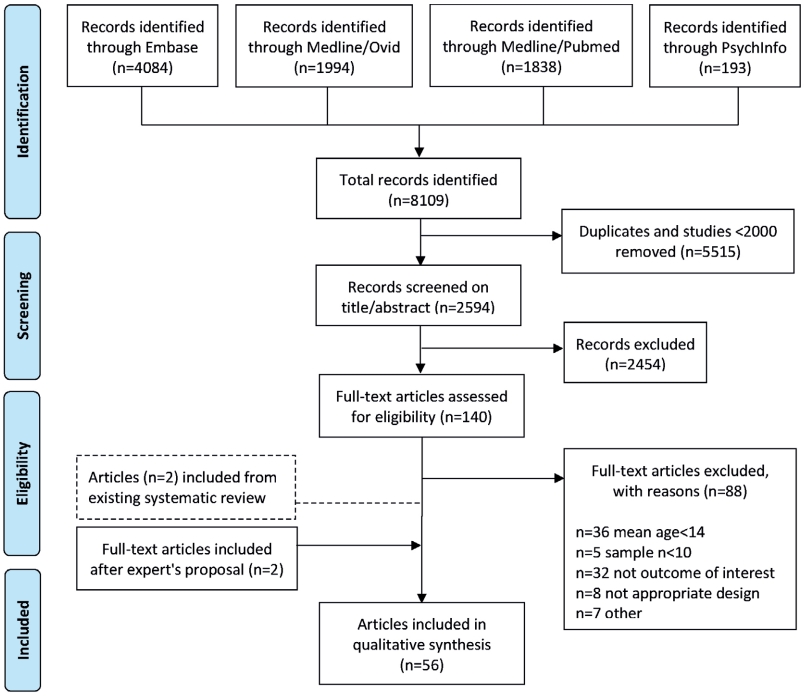
In round 1, each expert was sent the complete list of OMIs, a summary table of included studies, and scoring instructions. The OMIs, sorted per outcome, were clarified by a short description, characteristics of study population in which they were applied, and the overall quality score. Experts were instructed to critically consider the quality and study population, and subsequently rate each OMI on a 10-point numeric rating scale (1=lowest, 10=highest) for 4 aspects of feasibility and 1 overall rating (Table 7.1, lower panel). A comment box allowed experts to explain responses or raise concerns, or to indicate they were not familiar with or uncertain about a given OMI or outcome.

Table 7.1. Measurement properties and feasibility aspects for each outcome measurement instrument

	Measurement property	Definition	Quality
Quality assessment by the investigators	*Content validity*	The degree to which an OMI is an adequate reflection of the construct to be measured	+ All items refer to relevant aspects of the construct to be measured AND are relevant for the target population AND are relevant for the purpose of the OMI AND together comprehensively reflect the construct to be measured ? Not all information for '+' reported – Criteria for '+' not met
	Criterion validity	The degree to which scores of an OMI are an adequate reflection of a 'gold standard'	+ Convincing arguments that gold standard is 'gold' AND correlation with gold standard ^{3}0.70 ? Not all information for '+' reported – Criteria for '+' not met
	Construct validity	The degree to which the scores of an OMI are consistent with hypotheses based on the assumption that the OMI validly measures the construct to be measured	+ At least 75% of the results are in accordance with the hypotheses ? No correlations with OMI(s) measuring related construct(s) AND no differences between relevant groups reported – Criteria for '+' not met
	Reliability	The proportion of the total variance in the measurements which is due to 'true' differences between patients	+ ICC or weighted Kappa ^{3}0.70 ? ICC or weighted Kappa not reported – Criteria for '+' not met
	Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured	+ SDC or LoA < MIC ? MIC not defined – Criteria for '+' not met
	Feasibility aspect	**Associated question(s)**	
Feasibility assessment and selection of OMIs by the experts	*Applicability*	How *applicable* is the OMI for the target population, with regard to age and severity?	
	Patient feasibility	Is the OMI *understandable* and/or *executable* by the patient? Is the *time to complete* this OMI feasible for the patient? Is the *burden* of this OMI not too excessive for the patient?	
	Assessor feasibility	Is the OMI *executable* by the assessor (or clinician)? Is the *time to administer* this OMI feasible for the assessor (or clinician)? Are outcomes *easy to analyze* and *interpretable* for the assessor (or clinician)?	
	Practical feasibility	Are the *necessary materials* and/or *locations* for this OMI available or obtainable to you? Are the *possible costs* of this OMI feasible for you? Is the OMI available in your *language*?	
	Overall feasibility	Considering all the aspects and associated questions above, how would you score the overall feasibility of this OMI?	

Investigators assessed the quality of each OMI on content validity and other measurement properties, if possible.[34] Subsequently, experts in the Delphi procedure rated each OMI on the feasibility aspects and provided an overall feasibility score (10-point numeric rating scale). OMI, outcome measurement instrument; ICC, intraclass correlation coefficient; SDC, smallest detectable change; LoA, limits of agreement; MIC, minimal important change.

Figure 7.1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of article selection process.



After receiving the experts' scores, mean ratings were calculated and a synopsis of the experts' comments was composed for each OMI. OMIs with mean overall feasibility scores ≥7 were classified appropriate, those with scores below 6 were classified inappropriate, and those with scores 6–7 were regarded uncertain. The investigators (JB, PM, JWG, MR) discussed the uncertain OMIs and determined whether or not they were appropriate, taking into account the experts' comments, overall quality, and applicability across subgroups based on CP type and GMFCS level. OMIs classified as inappropriate, based on experts' ratings and after discussion among investigators, were omitted. In the subsequent rounds, a modified list and feedback from the previous round was sent to the experts, who then, using the same approach, rated the remaining OMIs. In these rounds, experts were also instructed to consider the feedback and asked to identify their preferred OMI for each outcome and to explain why.

Achievement of final consensus was indicated by ≥70% agreement among experts on a single OMI for each outcome. This cutoff value was determined by the investigators a priori, based on varying cutoffs of 50% to 80% reported in the literature,[38] and in consideration of the panel size. Accounting for possible lack of familiarity or uncertainty among 1 of the experts, agreement among 6 of 8 (75%), or 5 of 7 (71%) experts, would indicate consensus.

Statistical analysis

Results for each round were collated and descriptive statistics (i.e., mean and standard deviation) were performed on the feasibility scores using Microsoft Excel 2010.

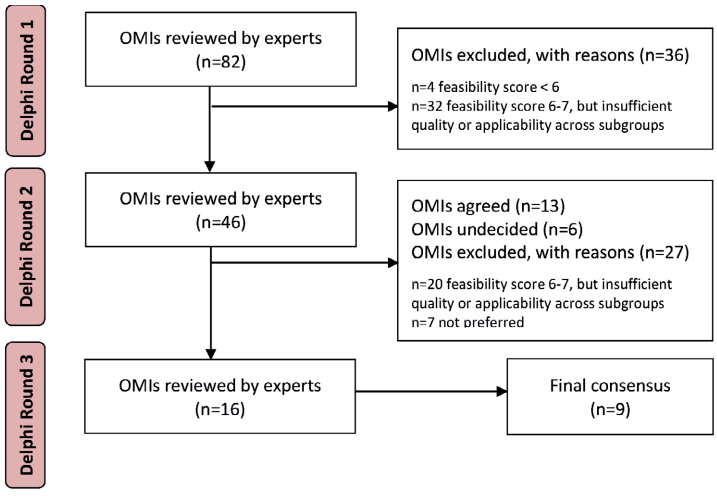
RESULTS

Existing OMIs

Two systematic reviews were found.[39,40] The first included only studies of adolescents (10-18 years) with CP.[39] The second included studies of adolescents (14-18 years) and adults (≥18 years) with CP.[40] Only the latter was selected for inclusion due to age eligibility, from which 5 eligible articles were derived.[40] A total of 2594 records were screened after the database search, before selecting another 49 eligible articles (Figure 7.1). Two other articles were included after experts' additional OMI proposals.[41,42] Finally, 56 articles were included: 32 were single articles of individual studies, and 24 represented multiple articles of 6 studies. Therefore, a total of 38 unique studies including 3699 individuals with CP were represented by the included articles (characteristics presented in Appendix 7.1).

The 8 selected outcomes were reported 78 times; a total of 90 OMIs were obtained (Table 7.2). Body size, body composition, and physical behavior were the most frequently measured outcomes, while sleep and nutrition were least frequently measured. Eight OMIs were excluded based on poor content validity. Overall quality syntheses were constructed for the remaining 82 OMIs.

Figure 7.2. Flow diagram of outcome measurement instrument selection process.



OMI, outcome measurement instrument.

Table 7.2. Outcomes and outcome measurement instruments obtained from literature and through experts

Outcome	Frequency of reports, n (%)	OMIs obtained, n
Physical behavior	16 (43%)	17*
Objective system		8*
Self-report		9
Nutrition	2 (5%)	3
Sleep	2 (5%)	3*
Cardiorespiratory endurance	9 (24%)	11*
Laboratory		8
Field		2*
Body size	20 (54%)	20*
Body composition	16 (43%)	22
Circumferences		5
Density measures		17
Blood pressure	7 (19%)	8
Manual		1
Automated		5
Novel measures		2
Blood lipids and glucose	6 (16%)	6
Fasting		4
Non-fasting		2
Sum	78	90

Note. Relative frequency of reports (%) is relative to the number of included study samples (i.e. the denominator is 38). The number of reports and the number of OMIs obtained from literature do not always correspond, since (1) some studies reported multiple OMIs for the same outcome, and (2) the same OMI was sometimes reported in multiple studies. *OMIs were proposed by experts for this outcome. OMI, outcome measurement instrument.

Delphi rounds

All experts completed a total of 3 surveys between December 2017 and April 2018, with successive rounds resulting in truncated surveys. Figure 7.2 presents the number of OMIs that remained after each round for each outcome. After round 1, 40 OMIs were classified as appropriate, 4 as inappropriate, and 38 as uncertain. After consideration by the investigators a total of 46 OMIs remained. After round 2, 22 OMIs were appropriate and 24 were uncertain, of which 4 were considered appropriate, hence 26 remained. Of these, 13 were preferred and agreed-on by the experts, 6 were undecided and 7 were not preferred thus also excluded. Consensus was reached for sleep (n=1, 100%), nutrition (n=1, 86%), and blood lipids and glucose (n=1, 71%). Consensus was also reached for body size (n=3, 88%), body composition (n=5, 88%), and blood pressure (n=2, 100%), where multiple methods were acceptable for a similar OMI. For example, systolic and diastolic blood pressure should be measured with an automated sphygmomanometer (i.e., 1 OMI), regardless of the actual device (i.e., multiple methods). Hence, 10 agreed-on

methods reflected 3 agreed-on OMIs. Consensus was not yet reached for cardiorespiratory endurance (n=3; 50%, 33% and 17%, respectively), nor for physical behavior (n=3; 63%, 25% and 12%, respectively). After reviewing the experts' comments and considering the subgroups in which these 6 remaining OMIs were applied, the investigators selected 3 (cardiorespiratory endurance, n=2; physical behavior, n=1), which were then proposed together with the other 6 agreed-on OMIs (including 10 methods for 3 OMIs) in round 3. Again, no consensus was reached for cardiorespiratory endurance (n=2; 57% and 43%, respectively). For the other 7 outcomes, all experts agreed on the proposed OMIs without opposing arguments. Table 7.3 presents the final selection; the obtained OMIs and selection process are described in more detail below.

Health-related fitness

1. Cardiorespiratory endurance: 11 OMIs were obtained, but 1 was excluded over poor content validity. Despite certain advantages of a field test, a laboratory test on a bicycle or arm-crank ergometer was preferred. Similarly, a maximal exercise test was preferred over a submaximal test, mainly because of reported negative criterion validity of the latter.[43] Two OMIs were selected with the caveat that local, practical feasibility would be a deciding factor: (1) the continuous incremental protocol[14,44,45] with 12-second workload increments requires automated control of the ergometer, while (2) the McMaster all-out protocol[5,46,47] with 2-minute workload increments can be conducted by manual control of the ergometer.

2. Body size: dependent on sample characteristics, different methods for the same outcome parameters were identified from the literature (20 OMIs). Height and weight were selected: for persons with GMFCS level I-II, they should be measured in a standing position (stadiometer, digital standing scale), and for persons with GMFCS level III-V in supine lying or seated positions (digital [wheel] chair scale). In case of contractures, height should be measured segmentally. Body mass index can be calculated, but the experts emphasized not to use it as a surrogate of body composition because of its underestimation of body fat particularly in this population.[48]

3. Body composition: similar to body size, different methods for the same parameters were identified from the literature (22 OMIs). These parameters included body density measures, such as skinfold thickness measurements, bioelectrical impedance analysis or dual-energy x-ray absorptiometry body scans. Body circumference measures were, however, rated more feasible. Waist circumference was selected: it should be measured in supine lying position, after expiration, at the narrowest part of the torso.

Table 7.3. Final selection of outcome measurement instruments.

Outcome	Selected OMIs	Consensus achieved		Quality*	Mean overall feasibility†
		Round 2	Round 3		
Physical behavior	Activ8 system		x	Excellent methodological quality, content validity ++, criterion validity ++	7,5
Nutrition	Food Frequency Questionnaire	x		No reported use in target population, content validity +	7,2
Sleep	Pittsburgh Sleep Quality Index	x		No reported use in target population, content validity ++	8,2
Cardiorespiratory endurance	(1) Continuous incremental protocol		x	Fair-Excellent methodological quality, content validity +, reliability +	6,8
	(2) McMaster all-out protocol			Fair-Good methodological quality, content validity +	7,1
Body size	Height and weight, multiple methods accepted	x		Good-High methodological quality, content validity +	[6,9 – 8,0]
Body composition	Waist circumference, multiple methods accepted	x		Fair-Excellent methodological quality, content validity ++	[7,0 – 7,8]
Blood pressure	Automated sphygmomanometer, multiple devices accepted	x		Fair-Excellent methodological quality, content validity ++	[8,8 – 8,8]
Blood lipids and glucose	Non-fasting venous blood test	x		Fair-Good methodological quality, content validity ++	6,9

Note. A full list of all the OMIs (n=90) including quality ratings are provided online. *Rating of evidence for the quality of the measurement property according to Terwee et al.[34] †Mean overall feasibility score from Delphi Round 2.

Lifestyle behaviors

4. Physical behavior: 17 OMIs were obtained, but 5 had poor content validity. Self-report questionnaires were considered practically feasible, but their overall quality was limited. Two self-report questionnaires were still included in round 2 (the Physical Activity Scale for Individuals with Physical Disabilities[49] and the Physical Activity Recall Assessment for people with Spinal Cord Injury[50]); however, objective activity monitoring systems were rated higher. Following experts' comments, the Activ8[41] was selected because of low cost, wearability during bathing and swimming, and its ability to measure types of physical behavior on top of volume and intensity.[41]

5. Sleep: 2 OMIs were obtained from the literature, and the Pittsburgh Sleep Quality Index (PSQI)[51-54] was proposed by experts. Despite a lack of publications using it in our target population, the PSQI was rated highest and preferred by all experts.

6. Nutrition: 3 OMIs were obtained, but 1 was excluded over poor content validity. A Food Frequency Questionnaire (FFQ)[55] was rated more feasible than a 3-day Food Diet History[56].

Traditional (bio)markers

7. Blood pressure: 8 OMIs were obtained from the literature. Automated sphygmomanometers were preferred over a manual apparatus since the former do not require trained personnel. The actual device does not need to be uniform across sites, as long as it is regularly calibrated and a proper cuff size is used on the patient. Measurements should be performed in a seated position, after 10 minutes of rest, on the least affected side.

8. Blood lipids and glucose: 6 OMIs were obtained, but 1 was excluded over poor content validity. Venous blood measurements in a fasting state scored slightly higher on applicability than in a non-fasting state, however, the latter was selected to prioritize overall feasibility. Experts indicated to standardize the measurement with respect to timing (>1h after last meal) and diet (avoid high fat content meals). Preferred markers to obtain from the non-fasting venous blood measurement are total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, TC/HDL-C ratio, triglycerides, and glucose.

DISCUSSION

This study aimed to identify all existing OMIs measuring risk factors of cardiometabolic disease in adolescents and adults with CP, and to select 1 OMI for each outcome based

on quality and feasibility, before establishing a preliminary core set of OMIs for risk factors of cardiometabolic disease in this population. A systematic literature review identified 90 OMIs with generally poor evidence on their quality in adolescents and adults with CP. Clinical and research experts gave informed comment on the feasibility of each OMI and came to an anonymous consensus on 9 OMIs pertaining to 8 outcomes related to cardiometabolic health for use in clinical practice and research.

In regard to measuring cardiorespiratory endurance, lab-based maximal exercise tests were more frequently reported in the literature compared to field-based tests, and these were also selected by the experts. In line with the systematic review of Lennon et al.[40] and the Delphi study of Verschuren et al.[57], this type of testing was preferred over an easier, minimal expertise requiring field-based test. Expressing preference between an extensive lab-based test, or a basic field-based test, reflects balancing between best-evidence measures and clinical utility. The current study had a strong emphasis on clinical utility, but in the end, the evidence we found on clinimetric properties of cardiorespiratory endurance test protocols was decisive in the selection of this OMI. Despite the agreement with the literature, however, lab-based tests might already be regularly applied in the clinical work setting of our experts, which could also explain their preference. This was not the case for body composition, where measurements such as dual energy X-ray absorptiometry or bioelectrical impedance analysis were not preferred, but this possibly also reflected experts' inaccessibility or unfamiliarity with these instruments. Despite providing a more objective assessment, evidence for the quality of these OMIs was more limited than evidence for waist circumference. This quick and easy to use OMI has already been adopted in the general population, and according to Ryan et al.[48], among other measures waist circumference is the best predictor of cardiometabolic risk in adults with CP regardless of age and GMFCS level.

Feasibility seemed to have less effect on selecting an OMI for the assessment of physical behavior, where an objective activity monitoring system was selected. Regarding the practical and assessor feasibility (i.e., costs, analyses and interpretation), one might expect a self-report questionnaire to score higher than an activity monitoring system. However, we found limited positive evidence for criterion validity of self-report questionnaires, which largely explained the choice of the experts. The modest set of OMIs we identified for measuring physical behavior and cardiorespiratory endurance in persons who rely on a wheelchair for daily mobility (GMFCS levels IV-V) was a concern. Fortunately, positive evidence for the Activ8 system to identify wheelchair propulsion was recently reported,[58] but further validation of this OMI in the non-ambulatory CP population is still needed. With regard to cardiorespiratory endurance, some experts suggested to translate the protocols for a bicycle ergometer to arm- or wheelchair ergometers. In the next phase of

our core set development,[27] we will aim to determine whether the selected protocols can be performed on different ergometers by non-ambulatory persons with CP. Similarly, for physical behavior, we will aim to determine whether the Activ8 is feasible and provides valid results in the non-ambulatory population.

Results of our literature review confirmed that there has been an increasing interest in health-related fitness and physical activity promotion in people with CP, while sleep management and nutritional studies have received little attention to date.[18] Comments from the experts confirmed that OMIs for the latter 2 outcomes were relatively unknown, despite our encouragements to request information directly from colleagues who might have more expertise in these areas. A recent systematic review in children with CP revealed that there are no psychometric data on currently used sleep measures in these youth.[59] We concluded that this also holds true for adolescents and adults with CP. Nevertheless, the currently selected questionnaire (PSQI) has positive construct validity in the general population and in other populations with a physical disability.[53,54] Regarding nutrition, various assessment methods are available for the general population, with accompanying risk of misreporting.[60] No validated tool to measure nutrition in adolescents and adults with CP was found in the literature. Because of this lack of evidence, the selection was thus mainly based on feasibility aspects. To our knowledge, the next phase of our core set development (i.e., feasibility study) will presumably be the first to apply an FFQ in a sample of adolescents and adults with CP.

As hypertension, hyperlipidemia, and hyperglycemia are among the key metabolic changes that increase the risk of cardiovascular disease,[11] assessment of blood pressure and blood lipids and glucose had to be part of the core set. With the current selection of an automated sphygmomanometer, standard measurement of blood pressure in clinical practice and research is considered to be very feasible. Measuring levels of blood lipids and glucose requires more expertise and specialized analysis, and, particularly for younger individuals, blood draws may not always be feasible for the patient.

Towards a core set of OMIs for risk factors of multimorbidity

A core set generally recommends *what* should be measured and reported in all clinical trials of a specific population.[61] Comprehensive core sets based on the International Classification of Functioning, Disability and Health have been developed for children and youth with CP of different age ranges, and recommendations for OMIs have also been published.[62] These sets can be used on a population-wide basis, but only in age ranges 0 to 18 years. Similarly, the recently developed set of Common Data Elements (CDEs) for CP does not consider specific CDEs for adults.[63] For those individuals with CP at transition or adult ages, Core Outcome

Sets are not yet available. Moreover, both the International Classification of Functioning, Disability and Health Core Sets for children and youth with CP and the CP CDEs are broad-ranging. Trial developers thus still need to select their primary outcomes and OMIs of interest. In contrast, the current core set of OMIs with a focus on cardiometabolic disease is being developed as part of a larger project to assess multimorbidity risk in adolescents and adults with CP.[27] In clinical practice, however, it might not be feasible to apply the total set that was currently selected. Moreover, as existing OMIs may be further validated and new OMIs may be developed, the ones selected for the current, preliminary core set might need to be reconsidered and replaced when new evidence becomes available.[28]

Perhaps even more important than a recommendation for research, our ultimate aim is to establish a core set that is feasible for clinical practice that can be used to screen, monitor, and intervene on risk factors for multimorbidity in CP. Follow-up programs for children with CP have already demonstrated their value in preventing and reducing the number of specific health issues.[64-66] Such effects might also be achievable for multimorbidity risk in the next decades, but this requires further investigation of prevention strategies and multi-factorial (lifestyle) interventions. Although some of the selected OMIs still require further validation in the CP population –particularly body composition, sleep and nutrition– this initial selection already provides an evidence- and consensus-based starting point for further discussion and refinement. In a next publication we will report on a survey among adolescents and adults with CP addressing the importance of the outcomes, as well as an empirical multisite study to evaluate the feasibility of the selected OMIs in a clinical setting.[27] These steps are expected to result in a final core set that, in future, enables screening for risk factors in clinical practice, as well as merging (prospectively) collected data into larger databases and performing meta-analyses.[26] Taken together, this harmonization of measured outcomes will improve our understanding of multimorbidity, specifically cardiometabolic disease, in this population.

Study limitations

Certain limitations must be mentioned. Because we only selected studies published since 2000 and in English, it is possible that studies were missed. Our aim was to find all OMIs that were being used in current clinical practice and research, hence the publication year cutoff. Moreover, additional OMIs were proposed by experts themselves. Clinimetric and psychometric data were limited. As such, we had to rely on experts' individual views on feasibility and clinical utility of each OMI, which was in line with our aim of developing a feasible COS. Although the guideline provided a systematic approach, clear directions for consensus procedures were not defined.[28] In addition, standardized methods for conducting and scoring a Delphi procedure are generally lacking. Finally, our sample of only 8 experts may not reflect a broad international perspective. Their fields of practice and research

directly relate to cardiometabolic health in the CP population, but for example including internists or dieticians may have strengthened our results. Views of patient stakeholders were not yet represented. We purposefully invited clinicians and researchers to participate in this preliminary work, as we assumed that quality ratings of OMIs would be hard to understand for patients. Therefore, the preliminary set will now be tested in a clinical setting and validated by patients and their families or caregivers.

CONCLUSIONS

Literature suggests that there are many different OMIs available to measure risk factors for cardiometabolic disease in adolescents and adults with CP. However, evidence of good quality is often lacking and feasibility for daily practice varies greatly. Moreover, OMIs to measure sleep and nutrition in this population are very limited. Nonetheless, clinicians and researchers with an expertise in this field have anonymously agreed on a preliminary core set of OMIs measuring risk factors for cardiometabolic disease: (1) a continuous incremental maximal exercise test on a bicycle-, arm-, or wheelchair ergometer (12-second or 2-minute intervals) to measure cardiorespiratory endurance; (2) standing or supine/seated height and weight to measure body size; (3) supine waist circumference to measure body composition; (4) the Activ8 system to measure physical behavior; (5) the PSQI to measure sleep; (6) an FFQ to measure nutrition; (7) an automated sphygmomanometer to measure blood pressure; (8) a non-fasting venous blood measurement to measure blood lipids and glucose. This preliminary core set will now be evaluated by the target population and tested in clinic, before any final recommendations can be made.

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Appendix 7.1. Summary table of the included studies.

Study		Study characteristics			Sample characteristics													Outcomes	Methodological quality			
						Age		Gender (%)		CP type (%)				GMFCS level (%)						COSMIN		McMaster	
	First author	Year	Country	Design	n	Mean	Range	M	F	SU	SB	ADM	U	I	II	III	IV	V			notes	RCT	Obs.
1	Bania[66]	2014	Australia	Measurement properties	24	18,7	14-22	46	54		100				63	38			PB	R=Good, V=Excellent	Poor size, long time interval (12 weeks)		
	Bania[67]	2014	Australia	Cross-sectional	45	18,5	16-22	51	49		100				60	40			PB				Good (9)
	Bania[68]	2016	Australia	RCT	48	18,4	14-22	54	46		100				60	40			PB			Good (11)	
2	de Groot*[69]	2012	Netherlands	Measurement properties	20	28,8	18-49	80	20	50	50			75	25				CE	V=Excellent	Poor size		
	de Groot*[70]	2012	Netherlands	Measurement properties	20	28,8	18-49	80	20	50	50			75	25				CE	R=Good	Poor size		
3	Claridge[50]	2014	Canada	Cross-sectional	42	33,5	18-75	50	50	74 (spastic)		19	7	12	21	24	26	17	PB				Fair (8)
	McPhee[71]	2015	Canada	Cross-sectional	42	33,5	18-75	50	50	74 (spastic)		19	7	12	21	24	26	17	PB, BS, BC, BP, LG				Good (9)
	McPhee[72]	2015	Canada	Cross-sectional	42	33,5	18-75	50	50	74 (spastic)		19	7	12	21	24	26	17	BS, BC, BP, LG				n.a.
	McPhee[73]	2017	Canada	Cross-sectional	41	33,7	18-75	49	51	73 (spastic)		20	7	12	22	24	24	17	PB, BS, BC,				Excellent (10)
4	Ryan[48]	2014	Ireland	Cross-sectional	55	37,5	18-65	56	44	27	62		11	24	33	18	15	11	BS, BC, BP, LG				Good (9)
	Ryan[6]	2014	Ireland	Cross-sectional	41	36,5	18-62	46	54	37	54		10	32	44	24			PB, BS, BC, BP, LG				Good (9)
	Ryan[74]	2014	Ireland	Measurement properties	18	31,9	≥18	56	44	44	56			50	39	11			PB, BS	V=Excellent	Poor size		
5	Slaman*[43]	2013	Netherlands	Measurement properties	41	20,2	16-24	56	44	59	41			59	41				CE, BS, BE	V=Excellent	Fair size		
	Slaman[14]	2014	Netherlands	RCT	57	20	16-24	47	53	51	47		2	58	32	9	2		PB			Excellent (13)	
	Slaman[15]	2014	Netherlands	RCT	57	20	16-24	47	53	51	47			58	32	9	2		PB, CE, BS, BC, LG			Good (12)	
	Slaman[75]	2015	Netherlands	RCT	57	20	16-24	47	53	51	47		2	58	32	9	2		PB			Good (12)	
	Russchen[44]	2014	Netherlands	Cross-sectional	56	20	16-24	48	52	52	46		2	55	38	7			PB, CE, BS				Fair (8)
	Nooijen[45]	2014	Netherlands	Cross-sectional	50	20	16-24	50	50	56	42		2	60	40				CE, BS, BC, LG				Fair (7)
	Nooijen[76]	2014	Netherlands	Cross-sectional	48	20	16-24	48	52	56	44			60	31	8			PB				Fair (7)
6	Nieuwenhuijsen[77]	2009	Netherlands	Cross-sectional	56	36,4	25-45	63	38		100			23	50	20	7		PB				Good (9)
	van den Berg-Emons[49]	2011	Netherlands	Measurement properties	56	36,3	25-45	63	38		100			23	50	20	7		PB	V=Good	Good size, unclear whether missing data		
	Nieuwenhuijsen[46]	2011	Netherlands	Cross-sectional	42	36,4	25-45	69	31		100			26	55	19			PB, CE				Good (9)
	van der Slot[5]	2013	Netherlands	Cross-sectional	43	36,6	25-45	63	49		100			26	51	19	5		PB, CE, BS, BC, BP, LG				Good (9)
	Slaman[47]	2013	Netherlands	Cross-sectional	36	36	25-45	64	36		100			25	58	17			PB, CE				Fair (8)
7	Bartlett[78]	2010	Canada	Cohort	135	14,6	11-18	56	44	73 (spastic)		22	5			38	35	27	PB, BS, BC				Fair (7)
8	Benigni[79]	2011	France	Cross-sectional	365	35,8	17-63	54	46	NR				NR					N, BS				Fair (8)
9	Bhambhani*[80]	1993	Canada	Measurement properties	11	NR	19-33	100	0	NR				All wheelchair users					CE	R=Fair	Poor size, inadequate statistics		

Study			Study characteristics		Sample characteristics														Outcomes	Methodological quality			
						Age		Gender (%)		CP type (%)				GMFCS level (%)						COSMIN		McMaster	
	First author	Year	Country	Design	n	Mean	Range	M	F	SU	SB	ADM	U	I	II	III	IV	V			notes	RCT	Obs.
10	Brunton[81]	2010	Canada	Cohort	230	14,7	11-18	55	45	NR				27	17	14	23	18	PB				Fair (7)
11	Claridge†[41]	2017	Netherlands	Measurement properties	14	35,4	21-58	64	36	50	50			43	36	21			PB	V=Excellent	Poor size		
12	De Macedo[82]	2008	Brazil	Cross-sectional	20	24,6	16-38	NR	NR	100				NR					BS, BC				Fair (8)
13	Dickerson[83]	2002	USA	Cross-sectional	15	29,3	NR	73	27	NR				All non-ambulant					BS, BC				Fair (8)
14	Gaskin[84]	2008	Australia	Cross-sectional	51	38,2	19-66	63	37	51		49		6	24	16	25	29	PB				Fair (7)
15	Haapala†[42]	2015	USA	Measurement properties	137	11,3	2-25	58	42	NR				30	10	16	17	27	BS, BC	V=Good, R=Good	Adequate size		
16	Hamrah Nedjad[85]	2013	Sweden	Cross-sectional	159	37	17-74	55	45	13	70	17		Ambulant 27, non-ambulant 73					PB				Fair (7)
17	Hartman[56]	2004	Israel	Cross-sectional	69	NR	1-29	NR	NR		100			Mainly non-ambulant					N, BS, BC				Low (6)
18	Hildreth[86]	1998	USA	Measurement properties	20	NR	20-55	65	35	15	60	25		Ambulant 55, non-ambulant 45					BS, BC	V=Good	Poor size, unclear whether missing data		
19	Iiyama[87]	2008	Japan	Cross-sectional	16	41	19-53	88	13	NR				6	13	38	6	38	BP				Fair (7)
20	Jahnsen[88]	2003	Norway	Cross-sectional	406	34	18-72	51	49	38	44	17	1	43	13	22	19	3	PB				Fair (8)
21	Kloyiam[89]	2011	Ireland	Cross-sectional	14	24,9	18-40	100		NR				All ambulant					CE				Low (6)
22	McCormick[90]	2016	USA	Cross-sectional	10	NR	NR	NR	NR	NR				NR					S				Fair (8)
23	Noble[91]	2014	UK	Cross-sectional	10	22,5	18-27	70	30		100			20	50	30			BC				Fair (8)
24	Peterson[4]	2012	USA	Cross-sectional	43	37,3	18-66	53	47	NR				67 (I-III)			33 (IV-V)		BS, BC, LG				Excellent (10)
25	Peterson[92]	2013	USA	Cross-sectional	11	36	NR	73	27	NR						64	36		CE, BS, BC, BP				Fair (8)
26	Peterson[93]	2014	USA	Cross-sectional	112	34	NR	46	54	NR				8	18	26	26	22	BS, BC, LG				Good (9)
27	Peterson[94]	2015	USA	Cross-sectional	41	38,8	18-65	NR	NR	NR				10	12	22	29	27	BC				Excellent (10)
28	Rabani[95]	2014	Israel, Jordan, Palestine	Cross-sectional	222	16,7	13-22	59	41		100				62	27	11		PB, BS				Good (9)
29	Rimmer[96]	2011	USA	Cross-sectional	117	NR	12-18	NR	NR	NR				Ambulant and non-ambulant					BS				Low (5)
30	Saebu[97]	2011	Norway	Cross-sectional	139	NR	18-30	NR	NR	NR				Ambulant and non-ambulant					PB				Fair (8)
31	Satonaka*[98]	2012	Japan	Measurement properties	16	43,7	NR	63	38			100		Ambulant 56, wheelchair users 44					CE, BS, BP	V=Good	Tests performed on same day	Poor size	
32	Satonaka[99]	2014	Japan	Cross-sectional	19	47,6	NR	42	58	NR				NR					CE, BS, BP				Fair (8)
33	Trinh[100]	2016	Australia	Cross-sectional	45	28,3	25-46	51	49	NR				27 (I-III)			15	58	BS, BC				Fair (7)
34	Usuba[101]	2015	Canada	Cross-sectional	54	29,5	23-42	54	46	NR				22	13	13	22	30	PB				Excellent (10)
35	van der Slot[102]	2007	Netherlands	Cross-sectional	16	28	25-35	44	56	100				All ambulant					PB, BS, BC				Fair (8)
36	van Eck[103]	2008	Netherlands	Cross-sectional	72	14,4	12-16	64	36	50			50	69	8	14	8		PB, BS				Fair (8)
37	Vogtle[104]	2014	USA	Before-after	26	42,3	23-63	38	62	NR				Ambulant 46, non-ambulant 54					S			Fair (8)	
38	You[105]	2015	Japan	Cross-sectional	47	36,4	NR	66	34	NR				All ambulant					CE				Low (6)

*Derived from Lennon et al.[40] † Obtained during preliminary Delphi round. CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; M, male; F, female; SU, spastic unilateral; SB, spastic bilateral; ADM, ataxic dyskinetic or mixed type; U, unknown type; PB, physical behavior; N, nutrition; S, sleep; CE, cardiorespiratory endurance; BS, body size; BC, body composition; BP, blood pressure; LG, blood lipids and glucose levels; R, reliability (including reliability and measurement error); V, validity (including construct and criterion validity); NR, not reported.

8

General Discussion

Advances in healthcare have contributed to almost normal life expectancies for individuals with cerebral palsy (CP), with the majority living into later adulthood. Recently, lifespan issues and longitudinal research in adults with CP have received increased interest from researchers, healthcare professionals, and patients. Accordingly, this thesis focused on the level and long-term course of functioning, disability, and health in adults with CP, and on standardization of outcome measurement in this population. First, we aimed to improve our knowledge on the *consequences of CP at (increasing) adult age*. Second, we identified the *most studied outcomes for adults with CP*, using the International Classification of Functioning, Disability and Health (ICF)[1] framework. Finally, we developed a preliminary *core outcome measurement set* specifically for risk factors of chronic disease, specifically cardiometabolic disease, in individuals with CP. The current chapter discusses the main findings in the context of existing literature and describes methodological considerations. Furthermore, some guidance on how to adopt these findings into practice is provided, and directions for future research are described.

MAIN FINDINGS

The main findings of this thesis are summarized in Figure 8.1. We found that pain is a highly prevalent health issue in adults with CP, which increases from people's thirties to their forties. Besides age, prevalence and characteristics of pain were associated with sex and the level of physical disability classified by the Gross Motor Functioning Classification System (GMFCS)[2]; females and those with GMFCS level II and IV had pain more frequently. Fatigue was the second most common health issue, which often co-occurred with pain. Other health issues remained stable over time, as did their perceived general health. Nevertheless, adults with CP had increasing concerns about their health and perceived an increasing impact of their CP on daily functioning activities. This was reflected in a decrease in independency in self-care and mobility on the long-term. We also found a decline in walking performance. In their forties, the majority of ambulant adults with CP no longer covered short distances by foot but opted for a wheelchair. Furthermore, we found that employment status remained stable over time, but weekly work hours decreased and employment was much lower compared to the general population. Females, adults with GMFCS level IV-V, and those with intellectual disability experienced (a) poorer (course of) employment outcomes. The most studied outcomes for adults with CP, according to literature published in the past decades, were: pain (body functions), walking, moving around, washing, dressing (activities), employment, and recreation/leisure (participation). Since adults with CP are known to have increased risk for developing cardiometabolic disease, we developed a core outcome measurement set for risk factors of cardiometabolic disease. We found that evidence for quality of measurement instruments is often lacking and that feasibility for clinical practice varies greatly. Clinicians and researchers with

expertise in this area, however, anonymously agreed on a core set that will be evaluated in 2019 in clinical sites in different countries.

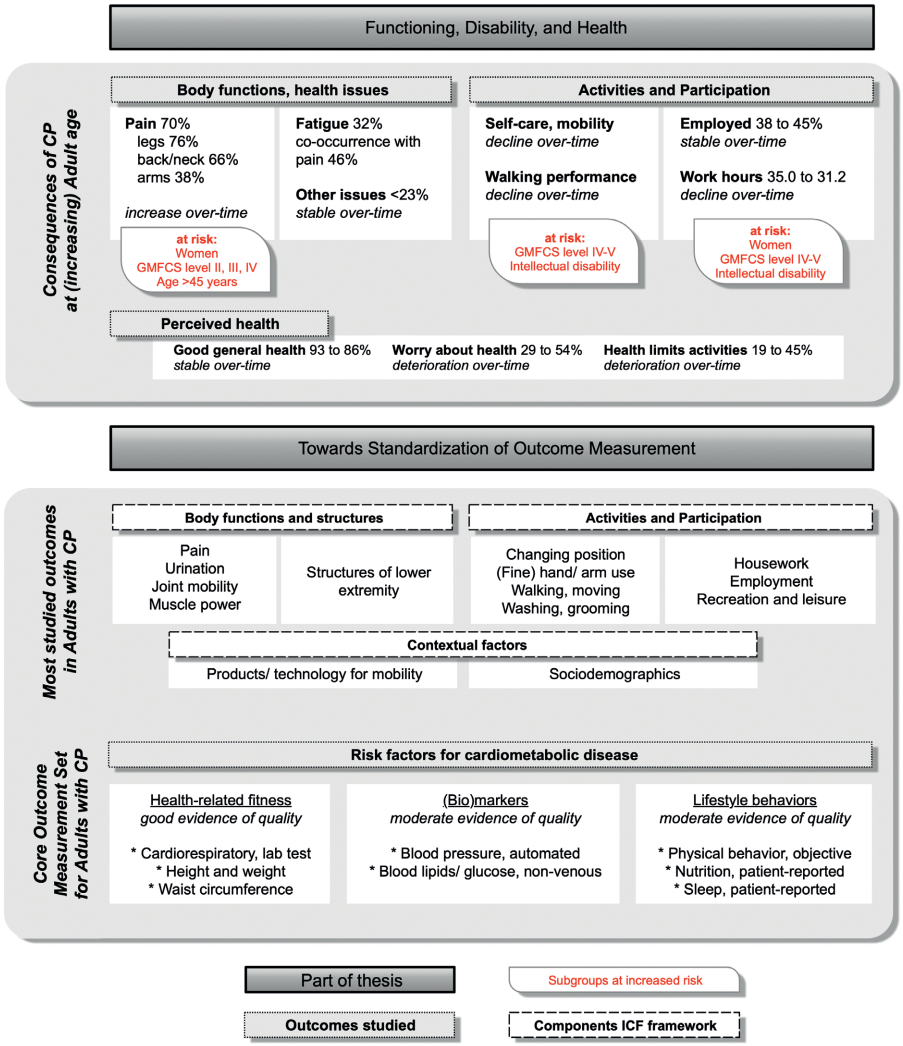
In line with the content of this thesis (Figure 8.1), this general discussion contains two sections. The first section is entitled *"Functioning, disability, and health of aging adults with CP"* and discusses the main findings of ***Chapters 2-4***. In these chapters, we studied the long-term consequences of CP at adult age and for individuals of different sex, GMFCS level, or intellectual disability, focusing on common health issues, self-care, mobility, and employment. The second section is entitled *"Towards standardization of outcome measurement in adults with CP"* and discusses the core outcomes for adults with CP we identified in ***Chapter 5***, as well as the development of the core outcome measurement set for monitoring risk factors of chronic disease in CP (***Chapter 6-7***).

FUNCTIONING, DISABILITY, AND HEALTH OF AGING ADULTS WITH CP

Health issues

Pain is one of the most common secondary health issues in individuals with CP,[3-6] but a reliable prevalence estimate was lacking nor was it clear whether pain changed with increasing age. In ***Chapters 2-3***, we found that pain was highly prevalent in adults with CP and increased with age. Our meta-analysis (***Chapter 2***) demonstrated that pain is prevalent in 70% of adults with CP. This reliable estimate, determined in a large international sample of 1,243 adults with CP, is much higher compared to the general population, in which pain is prevalent in around 20%.[7] Women were more likely to report pain than men, and a higher risk of pain was demonstrated for adults with GMFCS level II and IV. Age or the presence of intellectual disability did not affect the overall mean pain prevalence. Adults with CP reported pain predominantly in the legs, while in the general population, pain is most commonly located in the back.[7] Clinically, this may be explained by walking limitations with increased biomechanical strain causing an overload to the musculoskeletal functions of the legs.[4, 8] This assumption is supported by the increased risk of pain in the legs in adults with GMFCS level III, a subgroup of individuals with CP with abnormal biomechanics and joint loading in walking. Pain was slightly less prevalent in the back/neck, and even less in the arms in adults with CP. Prevalence of pain in the arms increased with age, which could be explained by increased use of walking aids or wheelchairs as a consequence of the walking decline that is observed with aging in CP.[9] Direct causes of pain were not studied in this meta-analysis and are still considered to be versatile in the CP population.[10]

Figure 8.1. Schematic overview of the main findings of this thesis.



Although we did not find an association between overall pain prevalence and age in our meta-analysis, we demonstrated that pain increased after a 10-year follow-up period in our prospective cohort study (***Chapter 3***), from 58% in people's thirties to 71% in their forties. Unfortunately, reliable longitudinal subgroup analyses were impossible due to the small sample size. Whether the above-mentioned associations between pain and sex and GMFCS level also are also longitudinal thus remains unknown. To date only one other longitudinal study reporting on pain in adults with CP also observed an increase in pain after a 7-year follow-up period.[4] Population based research showed that pain is already prevalent in one-third of children and

adolescents with CP and increases with age.[11] So even before entering adulthood, pain seems to be a highly prevalent health issue for individuals with CP. Health professionals should therefore aim to monitor and treat pain from an early age onwards, and researchers should attempt to identify the primary causes and update treatment and therapies for pain in individuals with CP. This research idea is supported by researchers, health professionals, and adults with CP, who ranked it as the number one idea on a recent patient-centered research agenda.[12]

Chapter 3 also investigated the long-term course of other health issues that are common in CP. No changes were observed over time for presence of epilepsy, respiratory problems, constipation, or bowel and bladder incontinence, but gastrointestinal problems were reported more frequently at follow-up. Severe fatigue, only measured at follow-up, was present in 32% of adults with CP and co-occurred with pain in 46% of those reporting pain. Co-occurrence of pain and fatigue has previously been reported for adults with CP,[6] and also for the general population.[13] Possible explanations for this co-occurrence of fatigue next to pain include having a chronic condition such as arthritis, side effects of pain medication, or the association with anxiety or depression.[13] In both the general population and for adults with CP, depression is more common in persons who report both pain and fatigue.[6, 13] Although we did not study any psychological symptoms, we found that both pain and fatigue were explanatory for a poorer perceived health. Adults with CP became increasingly more worried about their health and perceived greater impact of their health problems on activities of daily living, despite that the majority continued to report good general health. This ambiguous finding confirms the existence of a "disability paradox" that can be explained by response shift phenomena, referring to a change in the meaning of one's perception of the measured construct general health.[14, 15] Individuals with CP seem to deal with their health issues and functional limitations as part of their lifelong disability, and thus rate their general health as any other.

Self-care and mobility

Earlier studies of adults with CP have demonstrated that limitations are present in activities of daily living such as self-care and mobility,[9, 16, 17] but longitudinal reports were scarce. In ***Chapter 3***, we objectively studied the long-term course of self-reported self-care and mobility, and found that the independency to perform these activities deteriorated in adults with CP. Although most of our study participants reported similar levels of self-care and mobility performance around their forties compared to their thirties, almost 30% reported they became less independent in performing these activities as they aged. Possibly, the (increasing) presence of secondary health issues may have played a role here. Previous research has shown that pain and fatigue contribute to decreasing mobility in adults with CP,[4] and that epilepsy, urinary incontinence, and gastrointestinal problems are also associated with lower functional status.[18]

Focusing on the walking performance of adults with CP over time, we observed that walking short distances at home decreased with age, and that walking longer distances outdoors was already limited at a young adult age. This walking decline is frequently reported in people with CP, and indeed initiates early in adulthood.[9] Besides an older age, walking decline has been associated with a person's initial walking ability, distribution of motor impairment (i.e. unilateral or bilateral), and presence of pain or fatigue.[9] Environmental factors that typically change in early adulthood, such as a person's social environment or vocational pursuits, may result in additional stress and demands on walking. Walking decline is thus a multidimensional construct that includes changes in body functions, secondary health issues, participation, and contextual factors. Moreover, it is difficult to interpret due to the diversity of outcome measures used to capture walking. We investigated what adults with CP actually did in their daily environment (performance), not their capacity to walk, although these are known to be related.[19] Performance change is potentially more sensitive to alterations in contextual factors, whereas capacity change may be more sensitive to alterations in body functions. The degree to which impaired body functions, secondary health issues (pain, fatigue), participation, and contextual factors are explanatory for the walking decline over the lifespan in adults with CP has to be further investigated. Nonetheless, our findings provide evidence for functional deterioration in aging with CP.

Employment

Employment is an important life area in which adults with CP experience restrictions in participation.[20-23] ***Chapter 4*** described the long-term course of employment in adults with CP and identified subgroups at risk for unemployment. Adults with CP showed a stable employment rate over a 14-year period of around 40% from their late twenties to their forties. Employment rate was consistently lower compared to the general population (around 80%), and particularly low among adults with GMFCS levels IV-V and among those with intellectual disability. Somewhat unexpected, we did not find any associations between employment and educational level. Others have reported that a high educational level was predictive of achieving competitive employment in adults with CP.[21, 24] Implications for a link between a higher education level and having competitive work, as opposed to sheltered work, could be made from our study, but more detailed subgroup analyses were impossible due to the sample size.

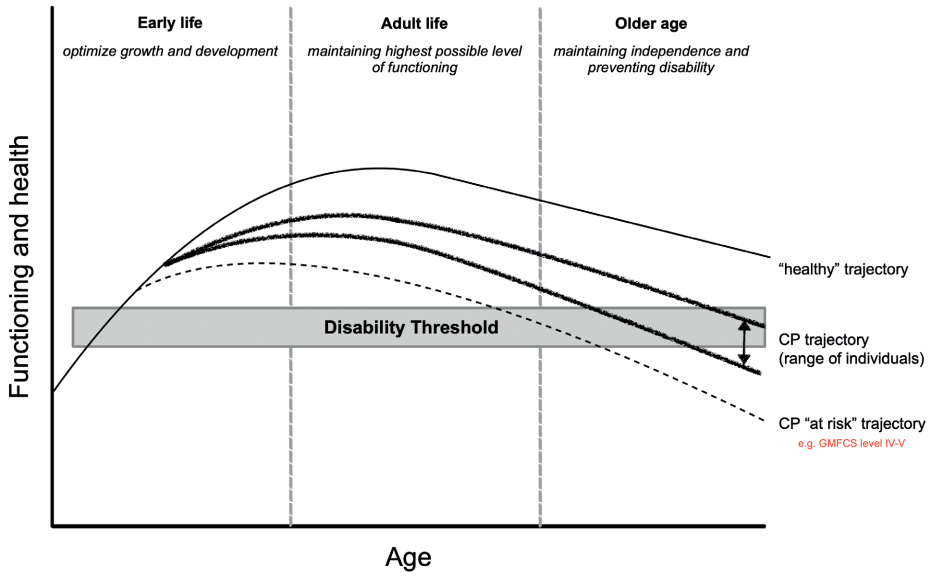
Despite a long follow-up period, we studied employment until only halfway the expected working life. Literature suggests that employment decreases in adults with physical disabilities (including CP) from their forties onwards.[23, 25] We found some reason to confirm this scenario, since weekly work hours decreased with increasing age. This, in turn, is complementary to literature describing that individuals with disability are more engaged in part-time work than their non-disabled peers.[26] Subgroup analyses in our study

demonstrated that this particularly holds for women, whereas men remained stable full-time work hours. This phenomenon of growing part-time employment among women is also observed in the general population, likely explained by a cultural feature of women in a dual role of employee and primary caregiver.[27]

Lifespan perspective

The findings of ***Chapters 2-4*** discussed above, and shown in Figure 8.1, clearly fits with the structure of the ICF framework. Despite its potentiality to describe functioning, disability, and health in a broad biopsychosocial context, the ICF does not allow us to describe any longitudinal consequences of a specific health condition. To better understand the consequences of CP at (increasing) adult age, it is important to also apply a temporal perspective on important outcomes for this population. The 'lifespan approach to health'[28, 29] may provide this perspective and is consistent with the ICF. In this conceptual model, outcomes of functioning and health can be depicted as a trajectory that can be influenced by contextual factors. Figure 8.2 presents proposed trajectories for people with CP and subgroups at risk that were studied in ***Chapters 2-4*** of this thesis, supported by complementary literature. Although full trajectories are hard to create, this figure offers an initial attempt to approach the consequences of CP at adult age from a lifespan perspective.

Figure 8.2. Proposed lifespan perspective on important outcomes of functioning, disability, and health for adults with CP.



The bandwidth of the CP trajectory indicates that functioning and health may vary across a range, dependent on certain personal characteristics. For example, employment is influenced by sex (i.e. women represent the lower limit of the bandwidth). Furthermore, adults with GMFCS levels IV-V and those with intellectual disability were at risk for unemployment, depicted by an "at risk" trajectory. Figure 8.2 also includes a horizontal bar representing the disability threshold. This bar indicates that, at a certain point in life, functional decline may reach a disabling level. The health issues and activity limitations we observed in our studies – whether or not interrelated – may cause an accelerated decline in functioning and health. Some adults with CP though state that their participation in life does not depend on maintaining independency, but on being able to manage and control their environment.[30]

One of the key aspects of the lifespan approach to health is the influence from the environment.[28] In early adulthood, changes will occur in a person's social environment or vocational, which may affect their functioning in a positive or negative sense. Positive influence from the environment can also be exerted by healthcare providers who may assist, through treatment and therapy, to counter a functional decline in individuals with CP. With that in mind, it is worrying that funding for studies of clinical interventions comprised only 19%, and CP in adulthood only 4%, between 2001 and 2013.[31] Our own extensive literature review of publications on adults with CP (2000-2017, ***Chapter 5***) demonstrated that only 11% of studies concerned intervention research. This means that the vast majority of research on adults with CP has been observational to date; this thesis is no exception. Recently, an American community of people living with CP and those providing healthcare to people with CP established a research agenda for CP.[12] Similar actions are currently being undertaken by the Dutch CP-Net. The number one priority on the American research agenda was "investigate the issues around aging with CP, to understand not only how to treat adults now, but also to update our treatments and therapies (for children with CP) to prevent secondary healthy issues and functional loss". This confirms the importance of a lifespan perspective and the demand for new evidence of effective interventions. Another highly prioritized research topic concerned "which outcomes are important to monitor/ treat early on in life to prevent development of health problems later on in life?". In the next section, this question will be addressed.

TOWARDS STANDARDIZATION OF OUTCOME MEASUREMENT IN ADULTS WITH CP

Core outcomes

The results of ***Chapter 5*** showed that, based on the existing literature, the most studied outcomes for adults with CP address pain, neuromusculoskeletal functions, mobility, self-

care, employment and recreation/leisure. As such, the prevalence and long-term course of pain, mobility, self-care, and employment that were studied in the first part of this thesis provide important knowledge on functioning of adults with CP. This comprehensive systematic review also demonstrated that to date, mostly young adults with CP are studied; the mean age of all included study samples was only 31 years.

For children and youth with CP, movement-related body functions, mobility, and self-care were also highly relevant outcomes in the ICF.[32] However, pain and employment, as the most studied body impairment and participation outcome in adults with CP, were not often studied in children and youth with CP. Furthermore, outcomes addressing the ICF component activities and participation were more prevalent in the adult population compared to children and youth. These findings can be understood from the physiological and emotional differences that exist between children and adults. Children require attention to growth and experience developmental issues that are not typically present in adults; hence the difference in focus of (clinical) research. Each phase of the lifespan has its specific developmental challenges and therefore demands priority to specific outcomes, which is evident from the multiple ICF core sets for children and youth with CP (<6 years, 6-13 years, and 14-18 years[32, 33]). The increasing attention for transition to adulthood is an important contribution to our knowledge and treatment approach. In the Netherlands, supported transition to adult roles is emerging, with modular interventions focused on participation outcomes showing promising effects.[34-37]

Our finding of a strong focus on the ICF component activities and participation is in line with the advances in rehabilitation medicine in the last decades.[38, 39] Where the approach was initially mainly biomedical, nowadays a client-centered approach is often used and treatment goals are aimed at participation in major life areas.[39] Adults with CP may, however, not benefit from these advances, indicated by the large decline in use of rehabilitation services after pediatric care.[40, 41] The findings of the first part of this thesis indicate motives to visit an adult rehabilitation specialist. Adequate access to adult care is thus important[18] but requires better recognition and knowledge of the consequences of CP with advancing age, as well as appropriate follow-up and treatment to optimize functional status of people with CP. In addition to rehabilitation medicine, adults with CP eventually also visit other care providers. The ability to use a core set of outcomes in a universal language such as the ICF is then very valuable, both for interdisciplinary communication and to indicate the core areas.

It must be emphasized that the most studied outcomes identified in ***Chapter 5*** only represent the perspective of researchers. To develop an ICF core set, perspectives of health professionals and of adults with CP should also be reflected.[42] After all, there must

be agreement on what adults with CP want from their healthcare, what clinicians are aiming to achieve, and what researchers are focusing on. In addition to the present systematic review, qualitative and empirical studies are currently being conducted in order to develop an ICF core set for adults with CP.[43] A previous qualitative study reported on experienced problems of young adults with CP to determine relevant topics for healthcare providers to target. The most frequent experienced problems included functional mobility, self-care activities, active recreation, and employment.[37] So far, these are in line with the researchers' perspective described in ***Chapter 5***. From the lifespan perspective to health, it can be expected that healthcare needs of adults with CP change over time, necessitating routine follow-up.[44] Ongoing and future research can help to identify the core outcomes for adults with CP from all perspectives, before determining how these outcomes can best be measured.

Outcome measurement instruments

The total amount of 332 different outcome measurement instruments used in research on adults with CP (***Chapter 5***) not only reflects the large variation in outcomes that are considered relevant, but also indicates the lack of standardization in outcome measurement. This lack of standardization was already apparent in ***Chapter 2***. Although we only studied one outcome (i.e. pain), we had to include a variety of measurement procedures in our meta-analysis. A similar variety in pain assessment tools for children with CP was recently found.[45] We were able to dichotomize presence of pain and to convert scales of pain interference and pain intensity to common ones. Other outcomes of functioning and health, however, are more difficult to quantify and there are various measurement instruments to reflect them. This causes inconsistencies in reporting and induces difficulties in comparing and/or combining findings.[46] Moreover, quality of the instruments varies and the feasibility for clinical practice also differs considerably.[47] Standardizing outcome measurement, in other words developing core outcome measurement sets, can be a solution to this problem.[48] An example of this approach is the development of a core outcome measurement set for cardiometabolic disease risk.

Core outcome measurement set for cardiometabolic disease risk

Emerging evidence demonstrates that individuals with CP have a high prevalence of chronic diseases, including cardiometabolic conditions, compared to the general population.[49-51] Management of cardiometabolic health encompasses reduction of risk factors through prevention or by screening on risk factors potentially followed by (lifestyle) intervention programs.[52] Therefore, in ***Chapter 7***, we established a preliminary core outcome measurement set for risk factors of multimorbidity, focusing on cardiometabolic disease. Prior to identifying and selecting outcome measurement instruments, we selected the outcomes by a minimal approach (i.e. only researchers and clinicians were involved) since there is consensus on

risk factors of cardiovascular disease and metabolic conditions that are similar across populations.[53] The selected outcomes and outcome measurement instruments, selected by means of a Delphi survey with international clinical and research experts, were (1) a continuous incremental maximal exercise test on a bicycle-, arm-, or wheelchair ergometer (12-second or 2-minute intervals) to measure cardiorespiratory endurance; (2) standing or supine/ seated height and weight to measure body size; (3) supine waist circumference to measure body composition; (4) the Activ8 system to measure physical behavior; (5) the Pittsburgh Sleep Quality Index to measure sleep; (6) a Food Frequency Questionnaire to measure nutrition; (7) an automated sphygmomanometer to measure blood pressure; (8) a non-fasting venous blood measurement to measure blood lipids and glucose.

In the development of the core outcome measurement set, we emphasized on the quality of the outcome measurement instruments as well as their feasibility for clinical practice (***Chapter 6***). As in ***Chapters 2*** and ***5***, we identified many different outcome measurement instruments for the same outcomes. Evidence of good quality of these instruments was often lacking. For some outcomes, results of the Delphi survey with clinical and research experts reflected a combination of evidence of quality and feasibility for clinical practice. For other outcomes, one or the other was more decisive. For example, the results of the Delphi survey showed that cardiorespiratory endurance should be measured by the gold-standard maximal exercise test adjusted to persons with CP (i.e. evidence of quality, but low feasibility), while sleep can be measured by a generic patient-reported questionnaire (i.e. no evidence of quality, but high feasibility). All selected outcome measurement instruments are generic with slight modifications for adults with CP. This is an advantage, since use of generic measures facilitates comparison between patient populations. Furthermore, many of the measurements can be performed outside the rehabilitation clinic.

METHODOLOGICAL CONSIDERATIONS

Study designs

The first aim of this thesis was addressed by a meta-analysis and a prospective cohort study; two study designs that are considered high in level of evidence.[54] A major strength of our meta-analysis is that we included individual participant data, which allowed us to study subgroup effects on a large scale, resulting in reliable prevalence and risk estimates. On the other hand, all data came from cross-sectional measurements which prevented cause-effect relationships from being studied. Our prospective cohort study was unique for its considerable follow-up length after baseline. A drawback was that certain outcome measurement instruments or classification systems were not yet available at baseline, hence, outcomes and clinical characteristics were not consistently measured at all time points.

The second aim was addressed by a systematic literature review and included specific methods of analysis: the ICF linking rules.[55] Strength of this review was the use of a comprehensive search strategy and inclusive selection criteria, thereby providing a complete overview of the literature on adults with CP in the preceding 16 years. Furthermore, despite moderate initial agreement in the ICF linking, each step was conducted independently by two reviewers. Limitations were that no methodological quality assessment on the included studies was performed, and that only the commonly used identified outcome measurement instruments were linked to the ICF.

For the third aim, another systematic literature review was conducted, followed by a Delphi survey. Comparable strengths can be acknowledged; a comprehensive search strategy was used and all steps (study selection, methodological quality, quality of measurement properties) were performed by two reviewers. A limitation was that the search strategy did not include terms consistent with "measurement properties", and that it was designed to identify studies on adolescents and adults with CP. We therefore may have missed outcome measurement instruments that have been assessed for their measurement properties in other populations but are applicable to individuals with CP. However, measurement properties should preferably be tested in individuals with CP, and it is uncertain whether findings on measurement properties can be translated between patient populations. The Delphi survey allowed us to capture the views of clinicians and researchers internationally and anonymously, but the inclusion of only eight experts may have led to a selection bias. Finally, a limitation in the development of the core outcome measurement set was that views of patient stakeholders were not yet represented. But as indicated in our protocol paper as a next step the preliminary core set will be evaluated by the target population and tested in clinic.

Generalizability

The chapters in the first part of this thesis (***Chapters 2-4***) described two study samples. The first included a large sample (n=1,243), which is outstanding for studies on adults with CP. Distribution of the demographic and clinical characteristics were representative,[56] and individual participant data were collected from multiple studies carried out in multiple countries, resulting in high generalizability of the results. However, the varying contexts in which these individual studies were done might have influenced the results of our meta-analysis. The second cohort sample was a smaller, regional sample but presented only minor loss to follow-up, limiting a potential selection bias. Loss to follow-up was not selective regarding age, sex, CP type, GMFCS level, or intellectual disability, and the distributions of these characteristics were similar to those reported in large population-based studies.[56] Due to the size of the sample, however, results should be interpreted carefully, specifically those from subgroup analyses.

CLINICAL IMPLICATIONS

The research described in this thesis provides important leads to awareness of the consequences of CP at adult age, and of early detection of secondary health issues and cardiometabolic disease risk. The prevalence of health issues is increased in adults with CP compared to the general population and some of these are associated with poorer perceived health and functional loss. Many of the health issues and comorbidities experienced by adults with CP are also commonly seen in the general population with advancing age. To timely prevent these, clinicians should routinely screen and treat adults with CP – not just for issues associated with the disability, but also for risk factors of conditions that are common to aging in general. Three specific implications for clinical practice are elaborated below. Our findings suggest that for individuals with CP, the threshold for disability may be reached at an earlier age (Figure 8.2) as a consequence of increasing health issues and decline of functional status. The rate and gradient of decline in functioning and health is partly determined by non-modifiable personal factors, but also by some behavioral factors that are modifiable through prevention and intervention programs, such as a healthy lifestyle intervention.[35, 36] Therefore, a first implication is to make such programs available to (young) adults with CP, evaluate them regularly, and adjust when necessary or when new evidence becomes available. The outpatient clinic of Rijndam Rehabilitation offers specific programs for adults like 'Dealing with long-term consequences of CP' and 'Healthy lifestyle for brain injury' (including CP).[57, 58] Furthermore, our young adult team, as a transitional service for individuals aged 16 to 25 years, aims to (1) continue rehabilitation care, (2) monitor and treat the condition, (3) optimize autonomy, and (4) educate on long-term consequences.[59] These initiatives and best practices are shared between centers in The Netherlands to accelerate the availability of transition care throughout the country.

Second, as discussed above, outcome measurement and treatment to optimize functional status is a core component of healthcare shared across multiple disciplines and specialties. So besides ensuring adequate access to rehabilitation care for adults with CP, if possible access to primary care should be supported when adequate. Providers of primary care must be educated on specific consequences of CP, treatment options in primary care, and on providers and treatment options in specialized rehabilitation care. This can be done by sharing information on the national CP-Net website,[60] or by organizing regional information meetings. For example, results of this thesis were used in the recent symposium 'Impact of CP in adulthood' where we also received considerable interest from primary care providers.

Third, routine outcome monitoring in adulthood should be facilitated. A combined follow-up and treatment register for CP is currently being implemented in the Netherlands.[61]

Many positive experiences have been gained for the follow-up of people with CP in other countries. For example, Scandinavians have been able to prevent major hip surgery later in life by continuing to follow children with hip problems.[44] We recommend that the Dutch CP register will expand with registrations of outcomes that are important at adult age. The expected ICF core set for adults with CP, of which initial results are described in this thesis, can serve as a scientific basis for outcome selection. The core outcome measurement set for risk factors of chronic disease could be implemented immediately. In fact, the feasibility of this core set is currently being evaluated in Rijndam Rehabilitation. This core set, however, focuses on cardiometabolic disease risk and other comorbid health conditions may still be overlooked. Evidence is also pointing towards increased risk of musculoskeletal issues and mental issues compared to the general population.[62-64] Developing core outcome measurement sets for the latter conditions is recommended, so clinicians can possibly apply a core set of a specific cluster of health issues rather than a continuum of outcomes, which might offer opportunities in terms of feasibility. To further minimize cost and burden for both patient and clinician/therapist, outcomes may be measured from a distance. For example, patient-reported outcome measures can be collected through web-based applications.

DIRECTIONS FOR FUTURE RESEARCH

The previous sections already introduced some directions for future research. Briefly, further studies are required to preserve insight into the level and long-term course of functioning and health of adults with CP. Standardized monitoring of personal characteristics and outcome measurement of individuals with CP will serve as a basis for future research. Moreover, multicenter research and international collaborations are important ways to synthesize knowledge of effectiveness of prevention and intervention strategies. Finally, collaboration with patient stakeholders is essential to meet the needs of adults with CP across the lifespan. Some specific recommendations for future research are discussed below.

There is a shortage of experimental studies in this population, including those showing how pain can best be treated in the adult with CP. Different treatment methods to improve outcomes related to pain, fatigue, and early functional loss should be explored. These will not only help us to understand how to treat adults now, but also to update our treatment and therapies for children with CP to early prevent some of the secondary health issues at adult age.

This thesis further uncovered the lack of research in adults with CP above middle age, despite the fact that adults with CP are known to have near-normal life expectancies. More insight is needed into the needs and levels of functioning of adults with CP above the age

of 45. Longitudinal studies with lengthy follow-up are needed to explore determinants of healthy aging with CP.

We have demonstrated that merging data leads to better study results of outcomes and potential determinants. Standardization of outcome measurement will make this much easier, but the success of outcome standardization lies in its implementation. The Dutch CP register aims to develop web-based monitoring applications using GemsTracker (GEneric Medical Survey Tracker), enabling multi-center distribution of forms and questionnaires in clinical practice and research. These actions will improve the feasibility of conducting core outcome measurement instruments. Ongoing research will in the near future result in an ICF core set for adults with CP. This core set should complement the ICF core sets for children and youth with CP to facilitate age-specific monitoring across the lifespan. This may provide a base for the development of a series of core outcome measurement sets, of which the one for cardiometabolic disease risk is an example. Systematic development and selection of core outcome measurement sets is key to effectively monitor adults with CP, and their implementation needs to be evaluated.

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Summary

SUMMARY

This thesis focuses on the consequences of aging with cerebral palsy (CP) and on outcome measurement of functioning and health in this population. The first part (***Chapters 2-5***) aimed to describe the level and long-term course of functioning and health in adults with CP, for which the International Classification of Functioning, Disability, and Health (ICF) was used. This framework was also used to describe the most studied outcomes in adults with CP since 2000, in order to identify core outcomes for this population from the researchers' perspective. The last part (***Chapters 6-7***) focused on outcome measurement for a specific set of outcomes, namely risk factors for cardiometabolic disease; comorbid conditions for which people with CP have increased risk. Results of this thesis may contribute to the development of systematic follow-up of adults with CP, in which core outcomes are monitored and treated, ultimately allowing us to design appropriate interventions and prevention strategies for people aging with CP.

Chapter 1 contains a general introduction on the topics that are addressed in this thesis, including a description of the population, an introduction on the ICF framework to describe functioning and health, and some background on outcome measurement and core set development. This chapter concludes with the aims and outline of this thesis.

Chapter 2 describes a systematic literature review and meta-analysis of individual participant data addressing pain in adults with CP. Seventeen eligible studies were included from a comprehensive literature search. We obtained the individual participant data from 15 studies, including a total of 1,243 adults with CP from Europe, West Asia, Australia, and North America. In this large pooled database, we determined a pain prevalence estimate of 70% in adults with CP. Women were more likely to report pain than men and adults with Gross Motor Function Classification System (GMFCS) levels II and IV had a higher pain prevalence compared to adults with GMFCS level I. Pain was mostly located in the legs, but also common in the neck/back and arms. Adults with GMFCS level III had increased risk of pain in the legs, while adults of 45 years and older had increased risk of pain in the arms. Pain intensity and pain interreference with daily activities and employment were mild on average and did not differ between subgroups. The prevalence estimate found in this meta-analysis is the most reliable to date and underscores the need for routine pain screening in adults with CP.

In ***Chapter 3***, we studied long-term changes in perceived health, health issues, self-care and mobility in a representative Dutch cohort of adults with CP. Outcomes were measured at baseline (21-31 years), 4-year follow-up (25-35 years), and 14-year follow-up (35-45

years) using self-report questionnaires. Most participants continued to report good general health, but at a later age more adults became worried about their health and more adults perceived higher impact of health issues on activities of daily living. The proportion of adults with CP reporting pain increased from 55% to 71% in 10 years' time. Gastrointestinal problems increased, while the presence of epilepsy, respiratory problems, constipation, and bowel and bladder incontinence did not change. Severe fatigue was present in 32% of the participants and often co-occurred with pain. Regarding self-care and mobility, the Barthel Index showed a small but significant decrease over time, and the percentage of adults with CP walking short distances decreased (83% to 71% inside the house). For walking long distances this percentage was already limited in young adulthood.

The course of employment over 14 years was studied for this cohort in ***Chapter 4***. Overall, the employment rate remained stable over time (38-45%) but significantly lower compared to the general population (69-83%). Adults with an intellectual disability, adults with bilateral CP, and adults with GMFCS levels IV and V had the lowest employment rates. The employment rate, however, increased over time for adults with intellectual disability (sheltered work) and for adults with bilateral CP. Among those employed the weekly work hours decreased by an average of 4 hours/week as they aged, which was comparable to the general population. Work hours specifically decreased for women (9 hours/week).

Chapter 5 describes a systematic literature review that identified the most studied outcomes of functioning reported in studies on adults with CP published since 2000. Using a comprehensive literature search we included 199 studies, which describe a large variety of outcomes in a total of 32,933 adults with CP (18-84 years). The overall distribution of the type of CP and GMFCS was representative of the population, but the majority of studies included small samples of adults around the age of 30. The results further highlight a lack of experimental research, a limited focus of research on older adults with CP, and a wide variety in outcome measurement instruments used in clinical practice and research. The most commonly used outcome measurement instruments were linked to the ICF in order to determine the most studied – or core – outcomes in adult CP research so far. Pain, joint mobility (body functions), mobility, self-care, employment, and recreation (activities and participation) were the most studied outcomes.

The study protocol in ***Chapter 6*** describes the rationale and design for the development of a core set of outcome measurement instruments for multimorbidity risk in adolescents and adults with CP to be used in clinical and research. First, the target population and the outcomes to be measured are defined. By means of a literature review and a Delphi survey with international clinical and research experts, the outcome measurement instruments

that can best measure these outcomes are determined. These instruments are tested in a feasibility study with adolescents and adults with CP from an international clinical research network. Chapters 7 describes the initial results of this project, that aims to standardize outcome measurement between centers, and ultimately to guide clinical practice and research (understanding, treating and preventing) on multimorbidity risk, focusing on cardiometabolic disease, in this population.

Chapter 7 describes the results of the first steps of the core set development. We defined the target population as adolescents (14-18 years) and adults (>18 years) with CP, and selected the following outcomes addressing eight risk factors of cardiometabolic disease: cardiorespiratory endurance, body composition, physical behavior, sleep, nutrition, blood pressure, and blood lipids/glucose. A total of 90 existing outcome measurement instruments for these outcomes were identified in the literature. We assessed their quality according to the Consensus-based standards for the selection of health measurement instruments (COSMIN). Results were then presented to a panel of experts who scored each instrument on aspects of feasibility in three iterative rounds. We found that many of the identified outcome measurement instruments lacked evidence of good quality in the defined target population of adolescents and adults with CP. Furthermore, only some instruments were available to measure sleep and nutrition. Feasibility scores provided clear indications of the application of each instrument in clinical practice. The experts anonymously agreed on a preliminary core set of 9 outcome measurement instruments to measure the eight risk factors for cardiometabolic disease.

Chapter 8 of this thesis contains the general discussion. The main findings are interpreted and discussed in the context of published literature on adults with CP. The importance of a lifecourse perspective in research and treatment of people with CP is emphasized. In addition, standardization of outcomes and measurement instruments, and systematic follow-up of people with CP is elaborated. Finally, methodological considerations and clinical implications are discussed, as well as directions for future research in this field.

Samenvatting

SAMENVATTING

Dit proefschrift richt zich op de gevolgen van ouder worden met cerebrale parese (CP) en op het meten van uitkomsten op het gebied van functioneren en gezondheid in deze populatie. In het eerste deel (***Hoofdstukken 2-5***) wordt het niveau en het langetermijn beloop van functioneren en gezondheid bij volwassenen met CP beschreven, waarvoor de Internationale classificatie van het menselijk functioneren (ICF) werd gebruikt. Ditzelfde raamwerk werd gebruikt om de uitkomsten te beschrijven die sinds 2000 het meest zijn onderzocht bij volwassenen met CP. Hiermee konden de belangrijkste uitkomsten voor deze populatie worden bepaald vanuit het perspectief van onderzoekers. Het laatste deel (***Hoofdstukken 6-7***) focust zich op meetinstrumenten voor een specifieke set van uitkomsten, namelijk risicofactoren voor cardiometabole aandoeningen; secundaire aandoeningen waarvoor mensen met CP een verhoogd risico hebben. De resultaten van dit proefschrift kunnen bijdragen aan de ontwikkeling van systematische follow-up van volwassenen met CP, waarbij de belangrijkste uitkomsten op het gebied van functioneren en gezondheid worden gemonitord en behandeld. Dit kan ons uiteindelijk in staat stellen om passende interventies en preventiestrategieën te ontwerpen voor mensen die ouder worden met CP.

Hoofdstuk 1 bevat een algemene introductie op de onderwerpen die in dit proefschrift worden behandeld, waaronder een beschrijving van de populatie, een inleiding over het ICF-raamwerk om het functioneren en de gezondheid te beschrijven en achtergrondinformatie over het meten van uitkomsten en het ontwikkelen van zogenaamde core sets. Het hoofdstuk besluit met de doelstellingen en de opzet van dit proefschrift.

Hoofdstuk 2 beschrijft een systematische literatuurstudie en meta-analyse van data van individuele deelnemers gericht op pijn bij volwassenen met CP. Zeventien studies kwamen in aanmerking na een uitgebreid literatuuronderzoek. We verkregen de data van individuele deelnemers uit 15 studies, waardoor in totaal 1.243 volwassenen met CP uit Europa, West-Azië, Australië en Noord-Amerika werden geïncludeerd. In deze grote samengevoegde database vonden we een nauwkeurige schatting van de prevalentie van pijn van 70%. Vrouwen rapporteerden vaker pijn dan mannen en volwassenen met Grof Motorisch Functionering Classificatie Systeem (GMFCS) niveaus II en IV hadden een hogere prevalentie van pijn in vergelijking met volwassenen met GMFCS niveau I. Pijn was voornamelijk aanwezig in de benen, maar ook vaak in de nek/rug en armen. Volwassenen met GMFCS niveau III hadden een verhoogd risico op pijn in de benen, terwijl volwassenen van 45 jaar en ouder een verhoogd risico hadden op pijn in de armen. De intensiteit van pijn en impact van pijn op dagelijkse activiteiten en werk waren gemiddeld mild en verschilden

niet tussen subgroepen van verschillend geslacht, leeftijd of GMFCS niveau. De in deze meta-analyse gevonden pijn prevalentie is tot op heden de meest betrouwbare schatting, en benadrukt dat pijn periodiek dient te worden gemonitord bij volwassenen met CP.

In ***Hoofdstuk 3*** bestudeerden we langetermijn veranderingen in ervaren gezondheid, gezondheidsproblemen, zelfverzorging en mobiliteit in een representatief Nederlands cohort van volwassenen met CP. Uitkomsten werden gemeten op baseline (21-31 jaar), 4-jaar follow-up (25-35 jaar), en 14-jaar follow-up (35-45 jaar) met behulp van zelf gerapporteerde vragenlijsten. De meeste deelnemers bleven op de langetermijn een goede algemene gezondheid rapporteren, maar op latere leeftijd maakten meer deelnemers zich zorgen over hun gezondheid en ervoeren meer deelnemers een hogere impact van gezondheidsproblemen op activiteiten in het dagelijks leven. Het aantal volwassenen met CP met pijn steeg van 55% naar 71% over 10 jaar tijd. Gastro-intestinale problemen namen toe, terwijl de aanwezigheid van epilepsie, ademhalingsproblemen, constipatie en incontinentie van de darmen en de blaas niet veranderde met de leeftijd. Ernstige vermoeidheid was aanwezig bij 32% van de deelnemers, vaak samen met pijn. Zelfverzorging en mobiliteit, gemeten met de Barthel Index, lieten een kleine maar significante achteruitgang zien en het percentage volwassenen met CP dat korte afstanden lopend aflegt nam af (83% naar 71% in huis). Lange afstanden lopen was voor de meerderheid al beperkt vanaf een jongvolwassen leeftijd.

Ook het beloop van betaalde arbeidsparticipatie over een periode van 14 jaar werd bestudeerd voor dit cohort (***Hoofdstuk 4***). Het percentage volwassenen met CP met betaald werk bleef stabiel over de tijd (38-45%), maar was wel lager dan in de algemene bevolking (69-83%). Volwassenen met bilaterale CP, volwassenen met GMFCS niveau IV en V en volwassenen met een verstandelijke beperking, hadden minder vaak betaald werk. De kans op het hebben van betaald werk nam echter toe met de leeftijd voor volwassenen met bilaterale CP en voor volwassenen met een verstandelijke beperking (op een sociale werkplaats). De volwassenen die werkten gingen gemiddeld 4 uur/week minder werken naarmate zij ouder werden, maar dit was vergelijkbaar met de algemene bevolking. De arbeidsuren daalden vooral onder vrouwen met CP (9 uur/week).

Hoofdstuk 5 beschrijft een systematische literatuurstudie waarin de meest onderzochte uitkomsten van functioneren in volwassenen met CP zijn beschreven in studies die sinds 2000 zijn gepubliceerd. Op basis van een uitgebreide zoekactie hebben we 199 studies geïncludeerd die diverse uitkomsten beschrijven van in totaal 32.933 volwassenen met CP (18-84 jaar). De verdelingen van het type CP en GMFCS niveau waren representatief voor de populatie, maar de meeste studies werden uitgevoerd bij kleine aantallen van vooral jongvolwassenen van rond de 30 jaar. De resultaten benadrukken verder een gebrek aan

experimenteel onderzoek, een beperkte focus van onderzoek bij oudere volwassenen met CP, en een grote verscheidenheid in meetinstrumenten die worden gebruikt in de klinische praktijk en onderzoek. De meest gebruikte meetinstrumenten werden gelinkt aan de ICF om de tot nu toe meest onderzochte ('core') uitkomsten in het onderzoek naar volwassen met CP in kaart te brengen. Pijn, gewrichtsmobiliteit (lichaamsfuncties), mobiliteit, zelfverzorging, werk en recreatie (activiteiten en participatie) waren de meest bestudeerde uitkomsten.

Het onderzoeksprotocol in ***Hoofdstuk 6*** beschrijft de aanleiding en opzet voor de ontwikkeling van een core set van meetinstrumenten om het risico op multimorbiditeit bij adolescenten en volwassenen met CP te meten in de praktijk en onderzoek. De eerste stap betreft het definiëren van de doelpopulatie en de te meten uitkomsten. Aan de hand van een literatuurstudie en een Delphi studie met internationale en deskundige clinici en onderzoekers wordt bepaald welke meetinstrumenten deze uitkomsten het beste kunnen meten bij deze doelpopulatie. Deze meetinstrumenten worden vervolgens toegepast in een haalbaarheidsstudie met adolescenten en volwassenen met CP in een internationaal klinisch onderzoeksnetwerk. Hoofdstuk 7 beschrijft de voorlopige resultaten van dit project, dat uiteindelijk gericht is op het verbeteren van de klinische praktijk en onderzoek om het risico op multimorbiditeit, met de nadruk op cardiometabole aandoeningen, systematisch te monitoren in deze populatie.

Hoofdstuk 7 presenteert de eerste stappen om te komen tot deze core set. Het consortium definieerde de doelpopulatie als adolescenten (14-18 jaar) en volwassenen (> 18 jaar) met CP, en selecteerde de volgende acht uitkomsten die het risico op cardiometabole aandoeningen in kaart brengen: cardiorespiratoir uithoudingsvermogen, lichaamssamenstelling, beweeggedrag, slaap, voeding, bloeddruk en bloed lipiden- en glucosewaarden. In de literatuur vonden we in totaal 90 bestaande meetinstrumenten voor deze uitkomsten. De kwaliteit van deze meetinstrumenten werd beoordeeld volgens bestaande normen. De resultaten werden vervolgens voorgelegd aan een panel van deskundigen die werden gevraagd om ieder instrument te scoren op aspecten van de haalbaarheid in drie iteratieve rondes. We constateerden dat veel van de gevonden meetinstrumenten een gebrek aan bewijs van goede kwaliteit in onze doelpopulatie hadden. Verder bleken er weinig instrumenten beschikbaar om slaap en voeding te meten. De haalbaarheidsscores gaven duidelijke indicaties voor de (fictieve) toepassing van ieder instrument in de klinische praktijk. De deskundigen zijn anoniem tot consensus gekomen over een voorlopige core set van 9 meetinstrumenten om de risicofactoren voor cardiometabole aandoeningen te meten.

Hoofdstuk 8 van dit proefschrift bevat de algemene discussie. Hier worden de belangrijkste bevindingen geïnterpreteerd en bediscussieerd binnen de context van huidige literatuur over volwassenen met CP. Het belang van een levensloop perspectief in het onderzoek en de behandeling van mensen met CP wordt benadrukt. Daarnaast krijgen het standaardiseren van uitkomsten en meetinstrumenten, en het systematisch opvolgen van mensen met CP die ouder worden voldoende aandacht. Tot slot worden de toegepaste methodologieën en de klinische implicaties van de resultaten besproken, alsook onze aanbevelingen voor toekomstig onderzoek op dit gebied.

Dankwoord

DANKWOORD

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van dit proefschrift. Ook dank ik graag alle leden van de grote commissie voor hun tijd om tijdens de verdediging met mij in gesprek te gaan over de resultaten.

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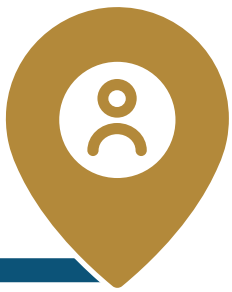
About the author



CURRICULUM VITAE

Joyce Lisanne Benner was born on the 21st of September, 1988 in Alphen aan den Rijn, The Netherlands. She received her athenaeum degree at Jac P Thijsse College in Castricum in 2006 and then proceeded to study Human Movement Sciences at the VU University in Amsterdam. After the first year she switched to the Amsterdam University of Applied Sciences to study Physiotherapy. She obtained her Bachelor degree in 2011 before returning to the VU University. From 2011 to 2014 she studied the Master of Human Movement Sciences, from which she graduated cum laude. Her thesis involved a research project on physical fitness in children with spina bifida who use a manual wheelchair at the HU University of Applied Sciences, Utrecht, where she continued to work as a research assistant after her graduation. Parallel to her studies at the VU University, she worked as a physical therapist in a private practice in Amsterdam. To gain additional experience in the field of rehabilitation medicine, she also worked part-time at the Center for Adapted Sports Amsterdam of Reade Rehabilitation in Amsterdam.

In 2015, she started as a PhD student at the department of Rehabilitation Medicine of Erasmus University Medical Center, on the 'CP impact' study. From 2016 to 2019 she worked on this and several other research projects on adults with cerebral palsy, including the international 'Pain pooling', 'Multimorbidity risk assessment and prevention', and the 'Development of an ICF core set for adults with CP'. All these studies focused on the aging adult with cerebral palsy and the results were synthesized in this thesis.

Currently, she is working as a researcher at the Centre for Orthopaedic Research Alkmaar (CORAL) of the Northwest Clinics in Alkmaar. Joyce likes to do sports (field hockey, cycling, running) and lives together with her husband Tjerk in Amsterdam, The Netherlands.

LIST OF PUBLICATIONS

Van Gorp M, Hilberink SR, Noten S, **Benner J**, Stam HJ, van der Slot WMA, Roebroeck ME. The epidemiology of cerebral palsy in adulthood: A systematic review and meta-analysis of the most frequently studied outcomes. *Submitted*

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*Shared first authorships.

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: Joyce Benner
Erasmus MC Department: Rehabilitation Medicine
Research School: NIHES

PhD period: 2015-2019
Promotor: Prof. dr. H.J. Stam
Supervisors: Dr. M.E. Roebroeck & Dr. S.R. Hilberink

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- Grant Application, BCF Career, Amsterdam	2019	0.9
- Research Integrity, Erasmus MC, Rotterdam	2018	0.3
Research skills		
- Regression analysis, NIHES Erasmus MC, Rotterdam	2015	1.9
- Longitudinal data-analysis, EpidM VUMC, Amsterdam	2015	3.0
In-depth courses		
- Systematic literature search, Medical library Erasmus MC, Rotterdam	2016	0.6
- EndNote, Medical library Erasmus MC, Rotterdam	2016	0.2
Presentations		
- Poster presentation: Outcomes measured in adults with cerebral palsy: a systematic review using the International Classification of Functioning, Disability and Health (ICF). EACD 31st annual conference, Paris	2019	0.3
- Oral presentation: Understanding and preventing multimorbidity in adolescents and adults with cerebral palsy: an emphasis on health-promoting behaviors. Regional meeting for rehabilitation physicians, Rotterdam	2018	0.5
- Oral presentation: Developing an ICF Core Set for adults with cerebral palsy: results of a systematic literature review. PhD-day VvBN, Amsterdam	2018	0.5
- Seminar: Understanding and preventing multi-morbidity in adolescents and adults with cerebral palsy: an emphasis on health-promoting behaviours. AACPDM 72nd annual meeting, Cincinnati	2018	0.5
- Poster presentation: Multi-morbidity risk assessment and prevention in clinical practice: establishing and testing a core outcome set for adolescents and adults with cerebral palsy. AACPDM 72nd annual meeting, Cincinnati	2018	0.3
- Oral presentation: Aging with cerebral palsy comes with deterioration of health and functioning. ISPRM 12th world congress, Paris	2018	0.5
- Oral presentation: Multimorbidity risk assessment in adolescents and adults with cerebral palsy: establishing a core outcome set for clinical research and practice. Research meeting department of Rehabilitation Medicine	2018	0.5
- Oral presentation: Cerebrale parese in de maatschappij: maatschappelijk functioneren. Symposium 'Impact van CP op volwassen leeftijd', Rotterdam	2018	0.5
- Oral presentation: Course of employment in adults with cerebral palsy over a 14-year period. AACPDM 71st annual meeting, Montréal	2017	0.5
- Oral presentation: Long-term deterioration of perceived health and functioning in adults with cerebral palsy. EACD 29th annual conference, Amsterdam	2017	0.5
- Poster presentation: Course of employment in adults with cerebral palsy over a 14-year period. EACD 29th annual conference, Amsterdam	2017	0.3
- Oral presentation: Impact van langdurige beperkingen op het dagelijks leven van volwassenen met cerebrale parese. Research meeting department of Rehabilitation Medicine	2016	0.5

1. PhD training

	Year	Workload (ECTS)
Presentations		
- Oral presentation: Long-term deterioration of perceived health and functioning in adults with cerebral palsy. DCRM 2016, Maastricht	2016	0.5
- Oral presentation: Stability of employment in adults with cerebral palsy in the long-term. DCRM 2016, Maastricht	2016	0.5
- Oral presentation: Ontwikkeling van gezondheidsklachten, zelfverzorging, mobiliteit en arbeidsparticipatie van volwassenen met cerebrale parese: studie protocol. Research meeting department of Rehabilitation Medicine	2015	0.5
International conferences and symposia		
- EACD 31st annual conference, Paris	2019	0.9
- COMET 7th meeting, Amsterdam	2018	0.3
- AACPDM 72nd annual meeting, Cincinnati	2018	1.2
- ISPRM 12th world congress, Paris	2018	0.6
- AACPDM 71st annual meeting, Montréal	2017	1.2
- EACD 29th annual conference, Amsterdam	2017	0.9
- DCRM 2016, Maastricht	2016	0.6
Seminars and workshops		
- PhD-day VvBN, Amsterdam	2018	0.3
- Workshop 'Ik hoor het aan je stem', Vena, Rotterdam	2018	0.1
- Upper Limb Stroke Rehabilitation Summer School, University of Leuven, Leuven	2018	0.6
- Symposium 'Impact van CP op volwassen leeftijd', Rotterdam	2018	0.3
- PhD-day VvBN, Rotterdam	2017	0.3
- PhD-day Erasmus MC, Rotterdam	2017	0.2
- Masterclass 'Patiëntmetingen voor kwaliteitsevaluatie, gebruik in de spreekkamer en onderzoek', DICA, Utrecht	2016	0.3
- Symposium 'Ouder worden met een lichamelijke beperking', BOSK, Utrecht	2016	0.2
Didactic skills		
- Training 'HBO-docent medisch-biologische vakken'; Vrije Universiteit, Amsterdam	2017-2018	22.5
Other		
- Participating in research meetings, department of Rehabilitation Medicine	2015-2019	6.0
- Project member 'Implementatie behandelmodule Gezonde Leefstijl bij hersenletsel', Rijndam Revalidatie, Rotterdam	2017-2018	2.0
- Organizing member symposium 'Impact van CP op volwassen leeftijd', Rotterdam	2016-2018	2.0
- Work visit CanChild McMaster University, Hamilton	2017	4.0
- Organizing member PhD-day VvBN, Rotterdam	2017	0.5
- Interview 'Het is niet mijn lichaam, maar mijn hoofd dat de grenzen bepaalt', BOSK Magazine	2017	0.2
- Organizing research meetings, department of Rehabilitation Medicine	2016-2017	2.0
- Contribution to 'Zorgen om de revalidatiezorg aan volwassenen met cerebrale parese', BOSK & Rijndam Revalidatie	2016	1.0

2. Teaching activities

	Year	Workload (ECTS)
Lecturing		
- Courses of Bachelor program Physical Therapy, AUAS, Amsterdam	2017-2018	6.0
Supervision of students		
- Co-supervising scientific internship student Movement Technology	2019	0.5
- Supervising review assignment of medical students	2019	0.4
- Supervising bachelor theses of students Physical Therapy	2018	2.5
- Supervising review assignment of medical students	2017	0.4
Other		
- Contribution to scientific course Clinical Technology	2017	0.2
Total		**72**

AACPDM, American Academy for Cerebral Palsy and Developmental Medicine; AUAS, Amsterdam University of Applied Sciences; BCF, Business Career in Life Sciences; BOSK, Dutch association of physically disabled person and their parents; COMET, Core Outcome Measures in Effectiveness Trials; DCRM, Dutch Congress of Rehabilitation Medicine; DICA, Dutch Institute for Clinical Auditing; EACD, European Academy of Childhood Disability; ISPRM, International Society of Physical and Rehabilitation Medicine; VvBN, Vereniging voor Bewegingswetenschappen Nederland.

Awards:
Erasmus Trustfonds Travel Grant, ISPRM 2018
AACPDM Student Travel Scholarship, AACPDM 2017