Ageing with Cerebral Palsy after being treated with Orthopaedic Interval Surgery Approach during childhood

BY

JACQUES DU TOIT

DIVISION OF ORTHOPAEDIC SURGERY
DEPARTMENT OF SURGICAL SCIENCES
FACULTY OF MEDICINE AND HEALTH SCIENCES
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SUPERVISORS

Prof Robert P Lamberts MSc (Pedagogy, Hum Mov Sc.), PhD (Exercise Sc.), FECSS

Dr Nelleke G Langerak MSc (Biomed Health Sc., Hum Mov Sc.), PhD (Biomed. Eng.)

UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY 100 1918·2018

SUPERVISORS

Prof Dr Robert Patrick Lamberts

Division of Orthopaedic Surgery & Institute of Sport and Exercise Medicine, Department of Surgical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg. Cape Town, South Africa

Division of Exercise Science and Sports Medicine, Department Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa

Dr Nelleke Gertrude Langerak

Neuroscience Institute, Division of Neurosurgery, Department of Surgery, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, South Africa

CO-INVESTIGATOR

Dr Maaike Maria Eken

Division of Orthopaedic Surgery, Department of Surgical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg. Cape Town, South Africa

DECLARATION

I, Jacques du Toit, hereby declare that the work contained in this PhD thesis is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

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LIST OF ABBREVIATIONS

1DSPM	1 Dimensional Spatial Parametric Mapping
3DGA	3 Dimensional Gait Analysis
BMI	Body Mass Index
CFCS	Communication Function Classification System
CP	Cerebral Palsy
CTSIB	Clinical Test of Sensory Interaction on Balance
EDACS	Eating and Drinking Ability Classification System
FMS	Functional Mobility Scale
GDI	Gait Deviation Index
GGI	Gillette Gait Index
GMFCS	Gross Motor Function Classification System
GMFCS-ER	GMFCS-Expanded and Revised
GMFM	Gross Motor Function Measure
HHD	Handheld Dynamometer
HREC	Human Research Ethics Committee
HRQoL	Health-related Quality of Life
Hz	Hertz
IC	Initial Contact
ICC	Intraclass Correlation Coefficient
ICF	International Classification of Function, Disability and Health
ISA	Interval Surgery Approach
IQR	Interquartile Ranges
LIFE-H	Life Habits Questionnaire
MACS	Manual Ability Classification System

MCID	Minimal Clinically Important Difference
ND	Non-Dimensional
ODI	Oswestry Disability Index
PROM	Passive Range of Motion
RCT	Randomised Controlled Trial
ROM	Range of Motion
SD	Standard Deviation
SDR	Selective Dorsal Rhizotomy
SES	Social Economical Status
SUN	Stellenbosch University
TFO	Time to Foot Off
TORCHES	Toxoplasmosis, Rubella, Cytomegalovirus, Herpes & Syphilis
TUG	Timed Up and Go
TD	Typically Developed
UCT	University of Cape Town
UMN	Upper Motor Neuron syndrome
WHO	World Health Organisation

INTRODUCTION AND LITERATURE REVIEW

HISTORY OF CEREBRAL PALSY

Cerebral Palsy (CP), a varied group of permanent neuromuscular disorders, has been studied and described since ancient times by the Greeks, Romans and, especially, the Egyptians. The mummy of Pharaoh Siptah is probably the oldest example of an individual with CP. The diagnosis was based on his shortened leg, equino-cavovarus foot deformity, the arms positioned on the abdomen as well as his clenched hand. It is, however, acknowledged that these deformities could also be ascribed to other congenital deformities or, perhaps, post mortem modifications as a result of grave robberies.[1]

William John Little, a British surgeon, was one of the first to describe children with CP which subsequently became known as Little's Disease.[2] Interestingly, although widely acknowledged as a pioneer in the field of CP, Little never used the actual term *CP*. His vast experience in assessing and treating children with CP resulted in numerous papers and lectures describing and classifying the disease, its unique clinical presentation, aetiology, changes during individual's development and the non-surgical, as well as surgical treatment of CP. Surgical treatment consisted mainly of tenotomies. With his increased experience in this field he cautioned as to the limitations of surgery, for example, a tenotomy performed for incorrect indications.[2] Examples of Little's work include his landmark article *On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities*[3] and the lecture course on *The deformities of the human frame*.[4] Based on his research he also tried to define CP for the first time as "a birth injury as a result of difficulties during labour in which the child has partially suffocated".[3]

A Canadian professor of clinical medicine, William Osler, continued Dr Little's work and popularised the term *CP* based on the Latin word for *brain* and the Greek word for *paralysis.* His book, *Cerebral Palsies of Children*, published in 1889, set the tone for further research and work on CP.[5] Through the years, research and work on CP has fluctuated due to contrasting findings and relatively poor surgical outcomes. Prominent figures in the history of medicine, however, realised the importance of this disease entity and have widely studied and contributed to the field. Examples of these eminent researchers include: Hippocrates, the father of medicine, and Sigmund Freud, an Austrian neurologist and psychiatrist. Both of them

made significant contributions to the field of CP[1,6] and their observations and recommendations still apply today.

DEFINITION

Since 1861 when William John Little defined CP as "a birth injury as a result of difficulties during labour in which the child has partially suffocated"[3] we still, as yet, have no universally accepted definition of CP. Concerted efforts have been made by numerous individuals and consensus groups, but due to the complexity of the condition, the diversity in aetiology and clinical presentation as well as the ever changing clinical profile when attempting to define a condition within a rapidly growing child, it is no wonder that no single definition can adequately withstand close scrutiny.

In 1956, American neurologist Myer Perlstein, emphasised the importance of the secondary sequela of CP defining the condition as "any symptom complex arising from non-progressive brain lesions".[7,8]

In 1957 MacKeith and Polani convened a CP interest group and named it the *Little Club.* They defined CP as "a permanent but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development".[8,9]

Some of the original *Little Club* members adjusted their original definition to emphasise that non-progressive brain disorders and disorders of short duration should not be included in the definition of CP. Their definition, "a disorder of posture and movement due to a defect or lesion of the immature brain" and "for practical purposes disorders of short duration, due to progressive disease or due solely to mental deficiency were excluded"[8,10] did add value as it tried to encapsulate CP within this confusing myriad of congenital abnormalities in children.

Between 1987 and 1990 several consensus meetings, held in Europa and America, were published by Mutch et al. These research works underlined the heterogeneity of the condition: "an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development".[8,11]

In 2000, the *Surveillance of CP in Europe* group published their revised definition which concluded that CP is "an umbrella term; is permanent but not unchanging; involves a disorder of movement and/or posture and of motor function; is due to a non-progressive interference, lesion, or abnormality; and the interference, lesion, or abnormality is in the immature brain".[12]

Since then great inroads have been made in trying to define CP in a manner that would be internationally acceptable, but also practically applicable in daily practice and research. During an international multidisciplinary workshop, held from 11 – 13 July 2004 in Bethesda MD (USA), it was recognised that motor deficits are often accompanied by other neurodevelopmental impairments. The workshop group generated a report on the Definition and Classification of CP on April 2006. The current near universally accepted definition, as derived from this report, states:

Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non- progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.[13]

The importance of this definition lies in its emphasis on numerous disturbances, or comorbidities, additional to the motor disorders which affect people with CP. These comorbidities include: eating and swallowing disorders, urinary disorders, gastrointestinal disorders, anxiety, depression, intellectual disability, visual impairment, language and speech disorders, dysarthria, auditory limitations and cardiovascular problems.

EPIDEMIOLOGY AND AETIOLOGY

It is exceedingly difficult to accurately report on the epidemiological aspects of CP due to: the difficulty in defining and classifying CP, the wide range of potential causes, the myriad of childhood conditions which can erroneously be described as CP, cultural resistance to acknowledge childhood disabilities and, frequently, the reluctance of governments to acknowledge the extent of the problem. These challenges are multiplied by the indiscriminate use of terminology which include, for example, incidence and prevalence and the non-rigid

allocation of children to their geographic, topographic or functional groups. These challenges are even more prevalent in developing countries.

Prevalence

The global prevalence of CP is reported to be 2 - 3 per 1 000 live births[14,15] with a recent meta-analysis by Oskoui et al., between 1985 and 2011, reporting a global prevalence of 2.11 per 1 000 live births.[16] From 1960 to the early 1990s trends showed a steady increase in prevalence from 1.5 to 2.5 per 1 000 live births but since then the prevalence has remained relatively stable at ± 2.5 per 1 000 live births.[15]

Highly developed industrialised countries, like the United States of America, have a slightly lower prevalence ranging from 1.8 to 1.9[17] and in Europe 1.77 to 1.9 per 1 000 live births.[18] In spite of initial concerns about the rising prevalence of CP in developed countries due to improved neonatal care and neonatal survival, a meta-analysis has reported an overall stability in CP prevalence.[16]

Lesser developed or developing countries are expected to have a higher prevalence of CP when considering that 80% of children with disabilities live in these geographical areas.[19] The paucity of available literature and the multiple confounding factors within these environments make accurate estimations as to the prevalence of CP extremely challenging. In addition, it is debatable how accurate these findings are.[19] Prevalence ranges from 2 - 10 per thousand live births with China and India reporting 1.5 - 2.5/1 000 live births,[20] Uganda 1.8 - 2.3/1 000[21] and South Africa 10/1 000.[14]

Survival rate

Death in children with CP has become a rare occurrence and most children assigned this diagnosis survive into adulthood. This, together with the fact that CP is the most common major motor disorder of childhood, contributes to the fact that a significant ratio of people with CP are adults.[22]

Although scarce, mortality in children with CP is centred on infancy with a linear relationship between the number of major disabilities (for example manual dexterity, intellect, vision and ambulation) which an infant with CP has and his/her eventual life expectancy or progression into adulthood.[23] Hutton concluded that in the United Kingdom children with CP and no major disability have a 99% probability to survive to age 30. In children who have 4 associated disabilities, however, only 33% survived to adulthood.[22,23] Between 1983 and 2002, Strauss et al. evaluated the survival of 47 259 children receiving CP services in the state of California over a 20 year period. They found that the life expectancy indicated in earlier studies had increased by approximately 5 years and that mortality in children with severe disabilities had decreased by 3.4% per year.[24]

A recent study investigating survival and mortality in persons born with CP in Western Australia from 1956 - 2011, concluded that the mortality of children with severe CP had shifted from childhood to early adulthood and that, once again, the mortality rate increased along with the increasing severity of disabilities. Twenty-two percent of individuals with minimal impairment survived to age 58 years.[25]

Very few studies have investigated survival and mortality in CP as well as progression into adulthood in developing countries.[26] Children with severe disabilities are more likely to die young due to poor medical care, malnutrition and infection.[27]

Aetiology

The aetiology of CP is multifactorial and much more complex than the perseverative preoccupation of the literature with birth asphyxia. Aetiological factors may present as isolated entities, or in combination with numerous risk factors, and this may have an influence on the CP subtypes. Advanced diagnostic modalities, especially neuroimaging and evidence-based population studies, have significantly improved our analytical and diagnostic capabilities, but in spite of this a large group of children with CP still present with an unsure aetiology.

However, it is accepted that in the developed, or so called industrialised world, the main risk factors for CP are low birth weight and gestational age[16,17] whereas in resource poor settings aetiology seems to be closer related to the perinatal and postnatal periods.[20,28]

Causes of CP can be attributed to the prenatal, perinatal and postnatal periods. Risk factors include prenatal chorioamnionitis and maternal infections of which toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis (TORCHES) are the most well-known. However, malaria and HIV are important causes in certain geographic and endemic areas. Low birth weight, prematurity, atypical intrauterine growth, multiple gestations and birth asphyxia are common risk factors as well. Just as important, but less frequently recognised as possible causative factors are: placental pathology, thyroid disease, perinatal ischaemic stroke and coagulation disorders, maternal fever during labour and inflammation.[15] Exposure to alcohol and drug abuse can result in central nervous system damage in the developing foetus. Congenital malformations of the central nervous system cause severe CP and frequently this is erroneously attributed to birth asphyxia rather than the malformation. Kernicterus due to rhesus blood group incompatibility has declined as a causative factor for CP but is still prevalent in developing countries. Genetic factors can influence CP risk at numerous points along the aetiological pathway. This highlights an alternative hypothesis that CP, just like autism and epilepsy, can be considered a brain developmental disorder. Although one single devastating risk factor can cause CP, more frequently multiple risk factors combine to cause motor impairment along with numerous non motoric abnormalities.[29]

CLASSIFICATION

Currently CP classifications exist for impairment levels and activity limitation, but not for restriction of participation.[30] The major classifications of impairments are subdivided in: Movement Disorders (Physiologic) and Topography (Limb Distribution/Geographic). Activity Limitation, or functional classifications, include: Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Communication Function Classification System (CFCS) and Eating and Drinking Ability Classification System (EDACS).

The aim of any good classification is to render insight into the underlying condition thus affording guidance regarding treatment, the natural progression of the disease and, to a certain extent, a prognosticative dimension. Although no singular classification currently used in CP can achieve all of these very ambitious endpoints, the more recent incorporation of activity limitation classifications has made great inroads in achieving this goal. When combining movement disorder with topographical classification in addition to one, or more,

activity limitation classification/s, the researcher or clinician is able to accurately and consistently reproduce his/her findings and thus consistently subcategorise children with CP.

Movement Disorders (Physiologic)

The variety of movement disorders can be broadly divided into spastic (Pyramidal) and non-spastic (Extrapyramidal) types (**Figure 1.1**).

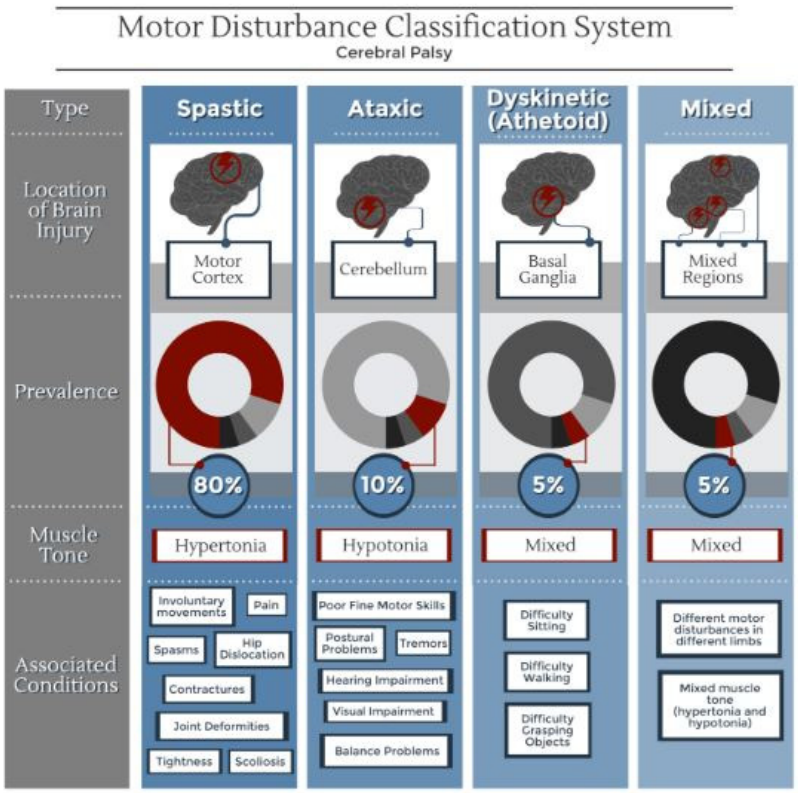

Figure 1.1. Physiological classification of CP: Movement disorders and location of brain damage (adapted from Reiter & Walsh, PC - www.abclawcenters.com).

Extrapyramidal CP can be further subdivided based on abnormal/involuntary tone and movements. The terms *extrapyramidal* and *pyramidal CP* are, in fact, strictly incorrect and in most individuals with CP both pathways are involved. It is therefore useful to refer to the predominant as well as the secondary movement disorder when employing the physiological classification. Advantages of the physiological classification is that it can suggest possible causative factors as well as the area of brain damage. It cannot, however, aid in management strategies on its own merits.[31] The motor disturbances consist of the spastic, ataxic, dyskinetic

and mixed type of which the most common type is spasticity. **Figure 1.1** renders useful information regarding the prevalence, location of the brain injury, the predominant muscle tone abnormality as well as expected associated conditions for the different types of motor disturbances.

Topography (Limb Distribution/Geographic)

The topographic classification describes which part of the body, or limb, is affected by the motor impairment. It subdivides spastic CP in unilateral (monoplegia, hemiplegia) and bilateral (diplegia, triplegia, quadriplegia and total body involvement) as per Figure 1.2.

- Monoplegia: A rare form of spastic cerebral palsy affecting only one limb.
- Hemiplegia: One side of the body is affected with the upper limb usually more involved than the lower limb.
- Diplegia: Both sides of the body are involved with the lower limbs being more affected. There is always some degree of upper limb involvement but to a much lesser degree than the lower limbs.
- Triplegia: Both lower limbs and one upper limb involvement.
- Quadriplegia: All four limbs are involved with the addition of poor trunk control.
- Total Body Involvement: All four limbs are involved with the addition of poor trunk and neck control.

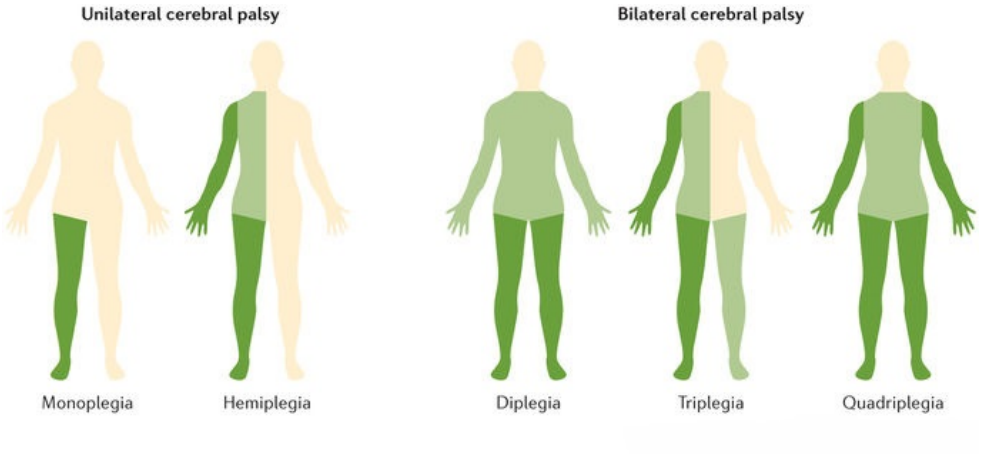

Figure 1.2. Topographical classification of CP (from www.nature.com)

The topographical classification can provide insight into some aetiological factors. A diplegic CP, for example, may suggest periventricular leukomalacia due to prematurity as a possible cause. The classic topographic subdivisions usually present with typical abnormalities which

render a degree of guidance as regards treatment, for example miserable malalignment with spastic diplegic CP. However, when used in isolation, a major drawback of the topographical classification is that it renders limited information regarding functional abilities or disabilities.

Gross Motor Function Classification System (GMFCS)

In 1997 Palisano et al. introduced the GMFCS which assesses the severity of gross motor function, or more specifically, ambulatory function (sitting and standing including the use of mobility aids).[32] The original classification was however limited to an upper age of 12 years and the fact that individuals were rated according to their best capabilities. The GMFCS has since been expanded to the GMFCS-Expanded and Revised (GMFCS-ER) version (Figure 1.3). This version divides the classification into 5 age groups, up to the age of 18 years, and assesses the child's typical performance rather than his/her utmost capabilities.[33]

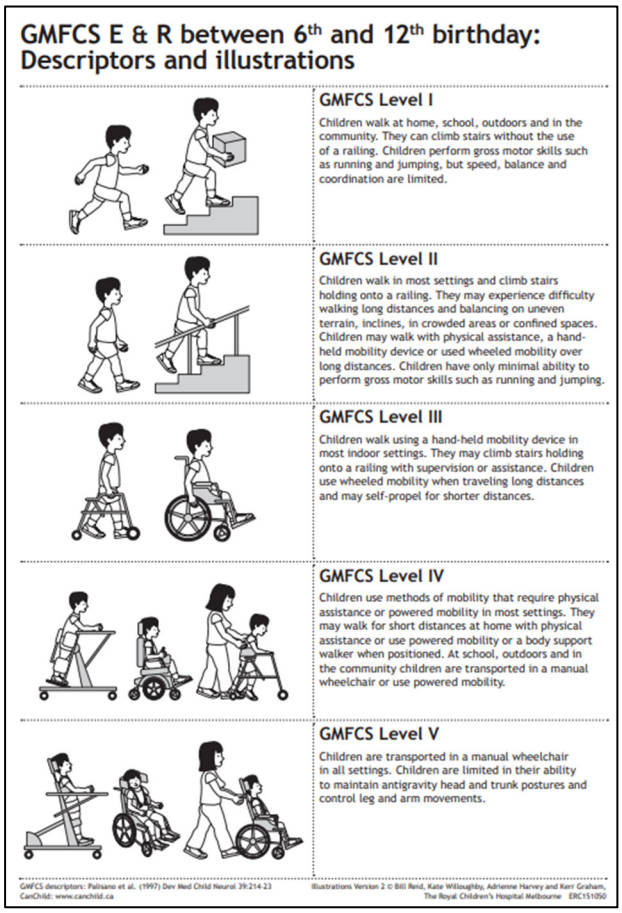

Figure 1.3. GMFCS E&R for age: Example 6th to 12th birthday
(GMFCS descriptors: Palisano et al. (1997) Dev Med Child Neurol 39:214–23 CanChild: www.canchild.ca, Illustrations Version 2 © Bill Reid, Kate Willoughby, Adrienne Harvey and Kerr Graham, The Royal Children's Hospital Melbourne ERC151050)

The GMFCS has been extensively validated and moderated with excellent inter- and intra-reliability having been shown for all ages. A linear improvement of reliability, however, is noticed as the assessment age increases.[34,35] The GMFCS has also been assessed for stability in the adult population and it has been found to successfully incorporate the concepts of the World Health Organisation's International Classification of Functioning, Disability and Health model (ICF).[36–38]

Manual Ability Classification System (MACS) and mini-MACS

In 2006 the MACS, as per Figure 1.4, was developed as a classification system similar to the GMFCS, but specifically for the upper limbs.[39] The MACS showed excellent reliability for children 4 to 18 years, but was subsequently adjusted in 2016 to the mini-MACS (Figure 1.5) by Eliasson et al. after relatively poor inter-rater reliability was shown for the MACS for ages 1 to 4.[40]

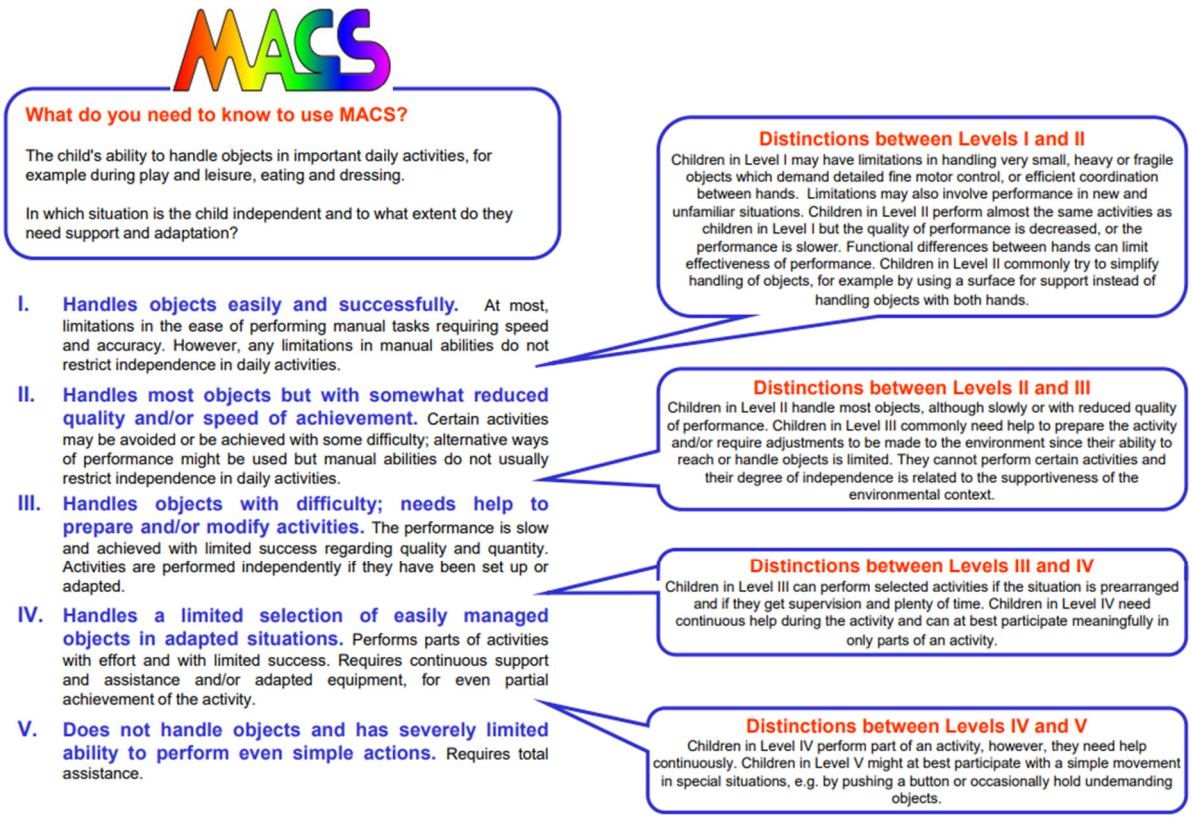

Figure 1.4. Manual Ability Classification System (MACS)
(http://www.macs.nu/download-content.php)

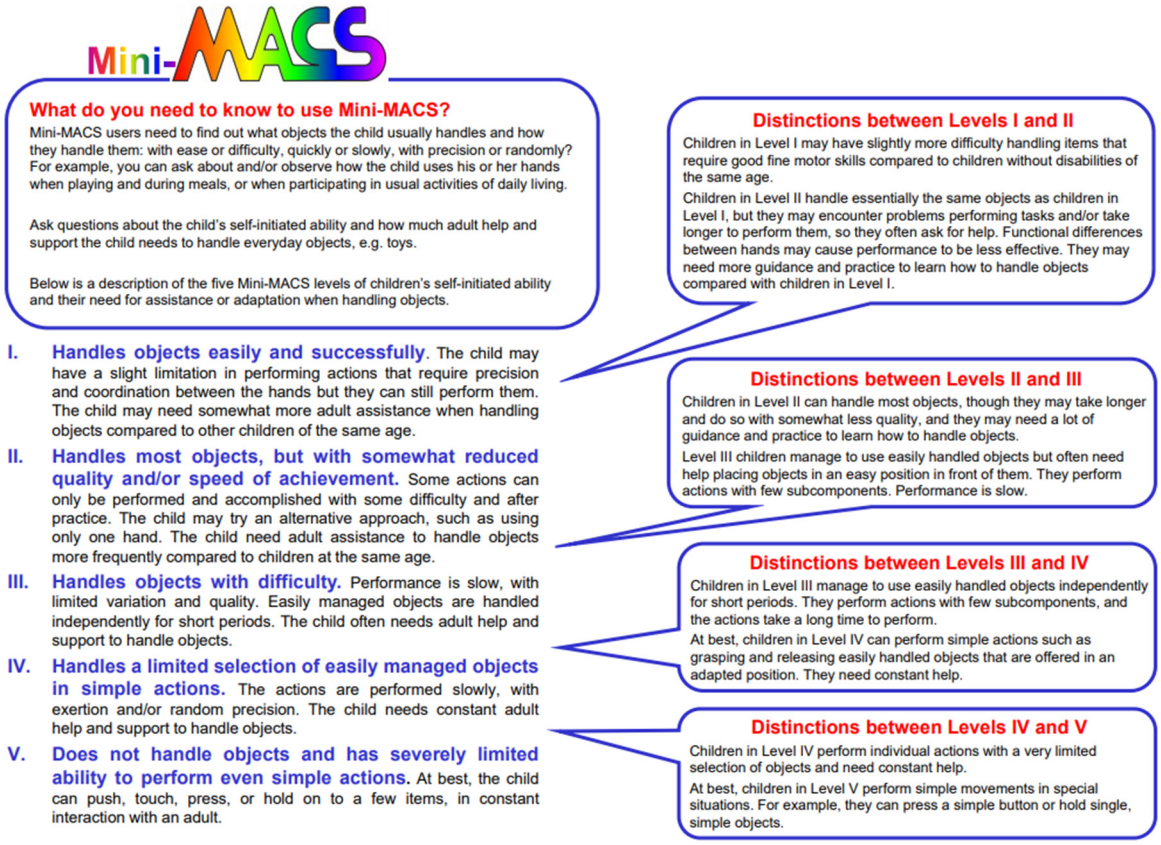

Figure 1.5. Mini Manual Ability Classification System (MACS)
(http://www.macs.nu/ download-content.php)

The MACS is a simple 5 level scale which is used when looking at hand and arm function in children with CP aged 1 - 4 and 4 - 18 years. It assesses upper limb performance in general conditions in activities of daily living. The MACS aids the treating physician in assessing the child's upper limb functional needs and further aids informed decision making with regards to upper limb surgical and non-surgical interventions.[39,40]

Communication Function Classification System (CFCS)

Hidecker et. al designed and subsequently validated the CFCS in 2011 (Figure 1.6). This functional classification adds value in that it assesses everyday communication in all settings and with familiar partners.[31,41]

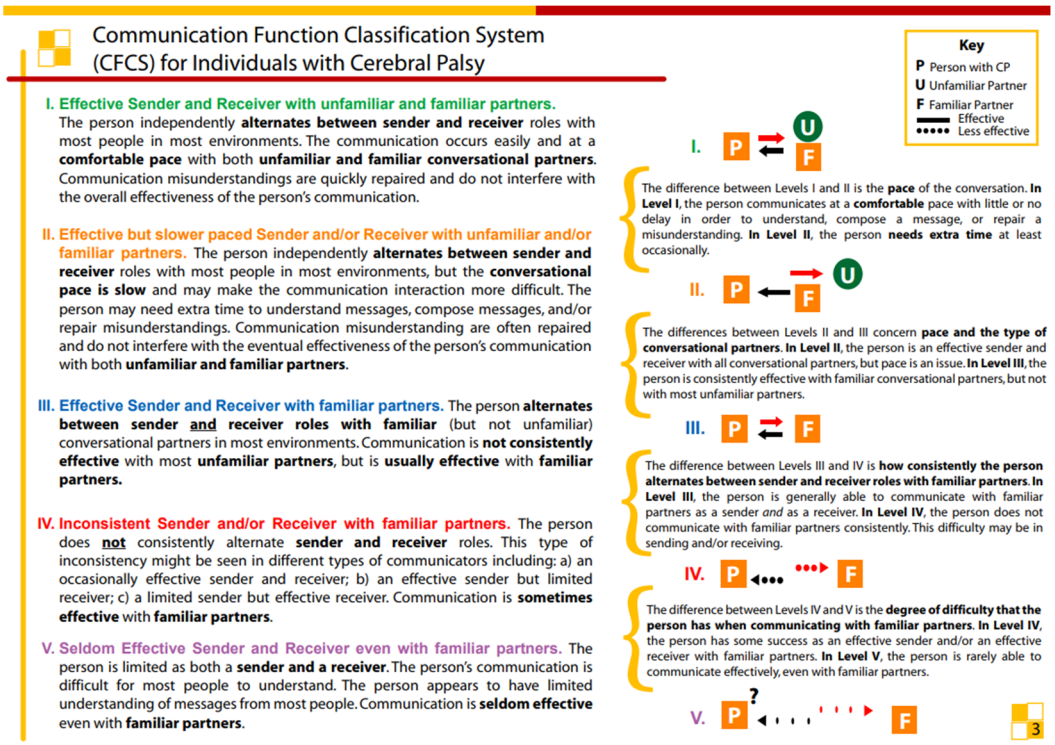

Figure 1.6. Communication Function Classification System (CFCS) for Individuals with CP *(http://cfcs.us/wp-content/uploads/2018/11/CFCS_English_CP.pdf)*

Eating and Drinking Ability Classification System (EDACS)

Seller et al. developed and validated the EDACS, as per Figure 1.7, in 2014.[42] The EDACS assesses eating and drinking abilities in children with CP from age 3 onwards. The 5 level scale assesses efficiency and safety of eating and drinking and the three tier scale gauges the level of assistance required in bringing sustenance to the mouth.[31]

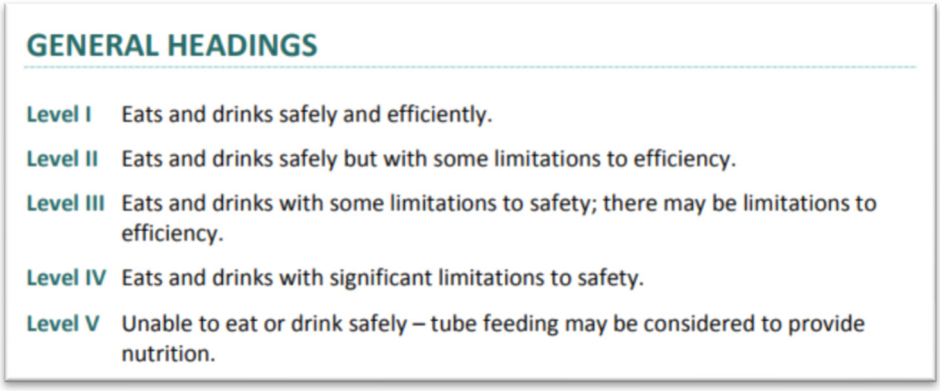

Figure 1.7: Eating and Drinking Ability Classification System *(https://www.sussexcommunity.nhs.uk/downloads/get-involved/research/chailey-research/edacs/edacs-classificationsystem-english.pdf)*

INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH (ICF-MODEL)

To establish a general understanding as to the outcomes of different treatment options, outcome assessments should be identified and quantified across a broad spectrum. In 1980 the World Health Organisation (WHO) published the International Classification of Impairments, Disabilities and Handicaps (ICIDH). This classification, based on the *consequences of disease*, was developed to code a wide range of information regarding various aspects of health.[43] In the early 1990s an international effort to revise and reshape this classification system was initiated. After 9 years of study and input, the WHO published a new classification system, the International Classification of Functioning, Disability and Health, or ICF.[43] The ICF focuses on the *components of health*, rather than on the consequences of disease.

This ICF-model (Figure 1.8) provides a broad perspective within which to appreciate the spectrum of functioning and disability across an individual's lifespan. It seeks to identify and classify abnormalities across two components: (i) *Body Function* and *Structure*; and (ii) *Activities* and *Participation.* These components are defined as follows:

Body functions: physiological functions of body systems (including psychological functions).

Body structures: anatomical parts of the body such as organs, limbs and their components.

Activities: execution of a task or action by an individual.

Participation: involvement in a life situation.

The ICF also recognised the importance of certain *contextual factors,* including environmental and personal factors, which may act as either obstacles or facilitators in shaping the level of functioning and disability. Environmental factors refer to the physical, social and attitudinal environments in which people live and conduct their lives, whilst personal factors are related to the person and, as such, they impact on his/her functioning (*e.g.* lifestyle, social background, education, life events, race/ethnicity).

Taking these two components and contextual factors into account, the ICF-model provides a biopsychosocial framework used to identify and quantify clinical recommendations/ assessments and it has proven to be useful in the field of CP.[44–46]

Figure 1.8. International Classification of Functioning, Disability and Health (ICF)
(policyoptions.irpp.org-Source World Health Organisation 2001)

MANAGEMENT

Upper motor neuron features

Currently no cure is available for the non-progressive lesion in the immature brain which causes CP. A large part of the treatment approach is there for directed towards the progressive musculoskeletal manifestations and its sequela. We attempt to prevent, modify or cure the positive and negative features of the upper motor neuron syndrome (UMN) in CP which causes a pathological neural and mechanical pathway eventually leading to irreversible musculoskeletal pathology as per Figure 1.9.[47]

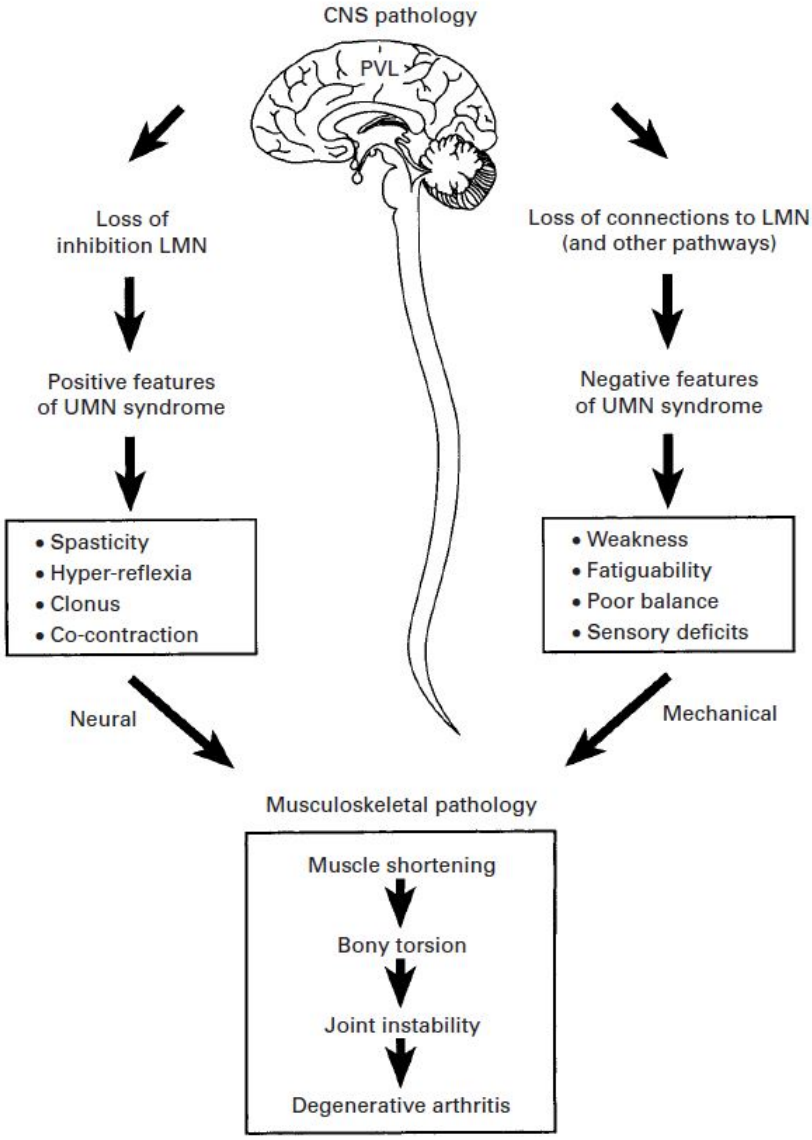

Figure 1.9. Overview of the neuro-musculoskeletal pathology in CP[47]

Evolution of Management

In the past, movement normalisation and orthopaedic interventions have been regarded as the most important interventional aspects when treating a child with CP. With time, localised anti spasticity medications and motor learning interventions have become an important part of CP management principles.

In addition to this, over the past 10 years, those involved in cerebral palsy care and treatment have adopted the principles of the ICF. This treatment mode entailed a more balanced and *life orientated* approach which addressed the person's body structure, function, activities and participation which, in turn, could cause disabilities.[48]

A myriad of treatment modalities are postulated and applied in the treatment of children with cerebral palsy. Currently, however, a high level of evidence exists to guide and recommend appropriate interventions and management principles in the treatment of these individuals. In spite of this *Evidence Based Medicine* treatment principles are yet to be universally applied.[48]

Treatment Principles

In an ideal world, a child with CP should be treated from an early age by a multidisciplinary team. The child would be assessed and discussed multiple times to accurately define the type of CP (topographic, geographic and functional) and to institute a standardised but also individualised treatment approach.[49] Repeated assessments may entail group discussions with the child and/or parents, clinical examination, gait and or visual/laboratory evaluation in the ambulatory child as well as psychosocial assessment/s.

Modern treatment principles for individuals with CP adopt the so-called *stratified approach*. Complementary strategies are used, either in combination or sequentially, and may include physical therapy, orthotics and serial casting. These strategies are accompanied by measures to reduce spasticity by either pharmacological, orthopaedic or neurosurgical treatment interventions. Lever arm disease and contractures are best addressed with orthopaedic surgery.[50]

The following section presents an example of a stratified approach per age category:[49]

Age 1 to ± 6 years:

1. Conservative treatment by physiotherapy, stretching and orthotics.
    - Optimising and maintaining joint range of motion and prevention of joint contractures
    - Increase muscle strength, prevent or control muscle fatigue and poor selective muscle control
    - Improve balance
    - Address or modulate sensory deficits
    - Assess tone and consider non-surgical tone reduction:
        - ✓ Tone reduction unnecessary?
        - ✓ Should oral tone reduction medication be tried or adjusted?
        - ✓ Is focal tone reduction by botox indicated?
        - ✓ Is the person a good candidate for an intrathecal baclofen pump?
        - ✓ Is the person a good candidate for an SDR procedure?
2. Initiate Hip Surveillance and treat the hip abnormalities via a structured approach.
3. Initiate Spine Surveillance and treat the spinal abnormalities via a structured approach.

Age 5 to 10 years:

1. Assess tone and consider if surgical tone reduction is warranted.
2. When issues relating to abnormal muscle tone have been addressed and the child's mobility has matured and is stable, one would consider correction of the remaining deformities:
    - Contractures
    - Lever arm dysfunction e.g. increased femoral anteversion, abnormal tibial torsion
    - Foot and ankle abnormalities e.g. equino-planovalgus foot
3. Continue hip and spine surveillance and treat accordingly.

The philosophy of this treatment regime is to optimise joint moment generating capacity via spasticity management and correction of bone malalignments and contractures.

Treatment options

An excellent systematic review of interventions by Novak et al. graded evidence of different management options into *favourable* and *unfavourable*. Thereafter these interventions were recommended (or not) on the following basis: Do it, Probably do it, Unknown in CP, Probably do not do it and Do not do it.[48] These were further subdivided in accordance with a clinically applicable traffic light approach: Green light *go* interventions, Yellow light *measure* interventions and Red light *stop* interventions, as per **Figure 1.10**.

As described by Novak et al, a wide variety of treatment options exist. These can focus on spasticity treatment, contracture management, orthopaedic surgery, improvement of strength, motor activities and function as well as self-care, to name but a few. Unfortunately, the lack of evidence based practice still regularly occurs within the cerebral palsy field[51] despite numerous good quality systematic and/or evidence based reviews which afford guidance as to what treatment modalities are proven to be effective.[48,50] The problem of poor evidence based cerebral palsy care has become even more prevalent after the much needed adaption and incorporation of the ICF perspective which emphasises treatment via a holistic approach.

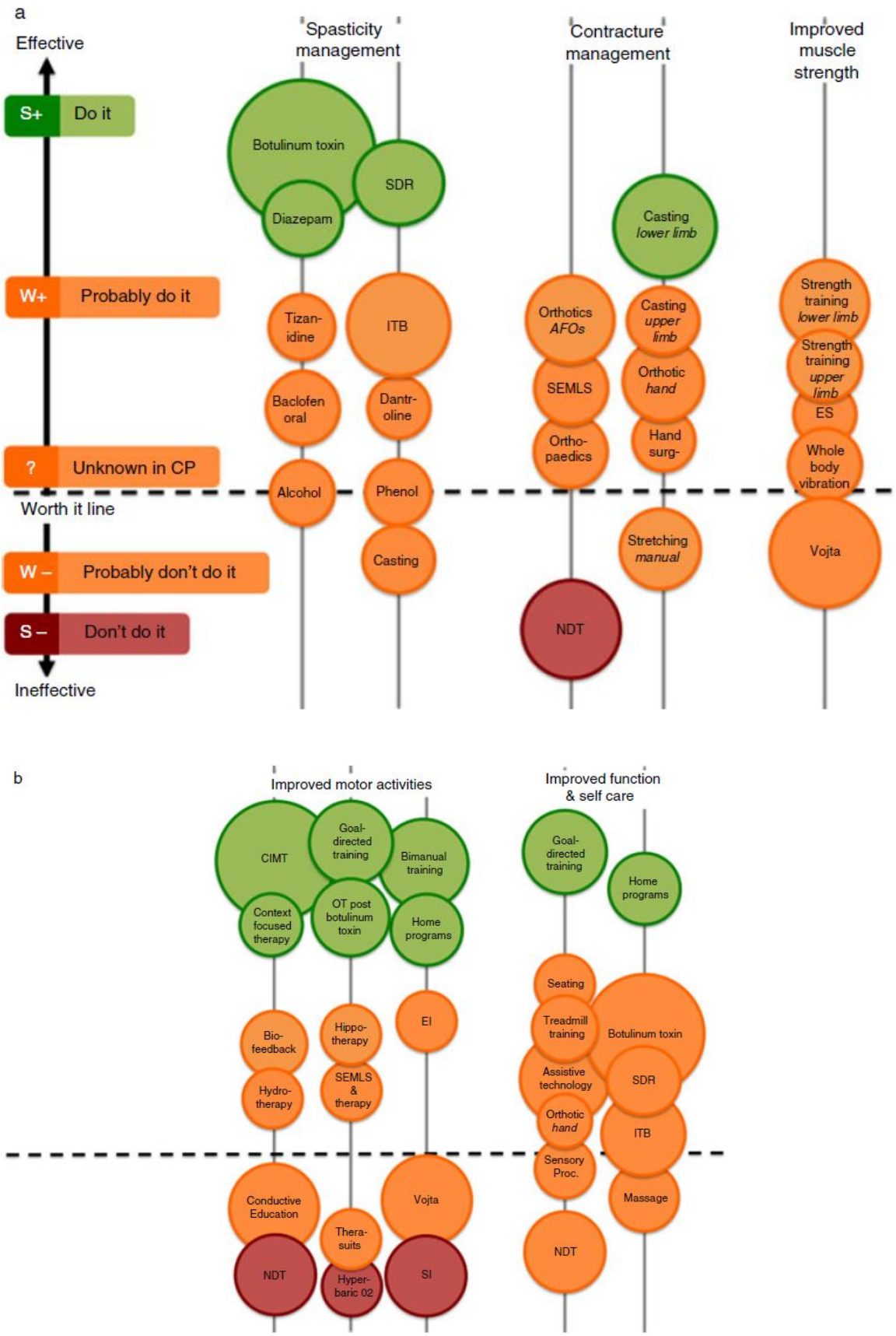

Figure 1.10. Evidence for CP interventions by outcomes (Copied from Novak et al.).[48]

Allied Health Therapy

Stretching has been shown to reduce spasticity in the short term. Bower et al. showed that various kinds of intensive therapy regimes do not yield superior outcomes when compared to standard low intensity regimes which can be combined with strength training.[52] The importance of stretching and strengthening in realising the positive effects of other spasticity treatment modalities cannot be overemphasised.

Orthoses are commonly prescribed for the treatment of spasticity but their effect on the neurophysiology of spasticity remains unclear.[53] Orthoses are used to prevent, or correct, deformities and to overcome activity limitations. The most common orthosis is the ankle foot orthosis. Its primary role is preventing contractures, secondary to prolonged spasticity and muscle strength imbalance around the ankle, rather than decreasing spasticity. This is achieved by limiting unwanted ankle movements, specifically ankle plantar flexion. In children with spastic diplegic CP, preventing plantar flexion through the use of Ankle Foot Orthosis has been found to improve walking efficiency.[54]

Serial casting is based on the concept of the distraction histogenesis of shortened muscles, thus enabling the treatment of joint contractures and improving the range of movement of a contracted joint.[54] There is good quality evidence for serial casting of lower limb contractures, especially the ankle joint.[48]

Spasmolitica

In general, the sedative and cognitive side effects of oral medications for the treatment of spasticity, often overshadow the perceived improvement in spasticity and leave the person with a minimal improvement in global function.[52] Oral medication should be individualised to suite the specific needs and problems of a specific person.

Diazepam offers a reversible option for systemic or generalised spasticity. The postsynaptic action of GABA is enhanced by diazepam.[52] In a randomised control trail of 180 children, Mathew et al. showed that diazepam significantly reduces muscle over activity when compared to placebo and that using diazepam in conjunction with dantrolene is more effective than using either alone.[55] The side effect profile of diazepam, especially sedation, is an area of concern and has to be carefully titrated per treatment aim and the individual.[52]

On the other hand, dantrolene sodium has a more peripheral action as it prevents calcium release from the sarcoplasmic retinaculum in the muscles, thus effectively weakening said muscle.[52] Dantrolene sodium has been shown to effectively reduce spasticity in children with CP,[56] but individuals are at risk of generalised weakness, sedation and hepatotoxicity.

Another oral treatment is tizanidine which reduces tonic stretch reflexes. It acts as an alpha-2 noradrenergic agonist. Very few clinical trials are available in the English literature on tizanidine.[52] From Russia, Brin et al. reported improved motor abilities clinically and on electroneuromyography.[57] Sedation is once again an area of concern.

Oral baclofen is a g-aminobutyric acid B agonist and its mechanism of action reduces the release of substance P and excitatory neurotransmitters.[58] Baclofen is one of the most commonly prescribed oral treatment modalities for individuals with CP. However, in spite of it being commonly prescribed, a recent systematic review concluded that there is insufficient data to support, or refute, the use of oral baclofen for the treatment of spasticity.[58] This should be carefully considered when prescribing oral baclofen as there are several potential side effects when using this off-label drug for children with CP. These include: poor blood brain barrier penetration, a short half-life, large inter-individual variability in absorption and elimination, systemic side effects e.g. confusion and polyuria as well as potentially severe adverse effect e.g. seizures and severe withdrawal syndrome.[58]

Chemodenervation

Chemodenervation entails injectable treatment modalities to prevent nerve and/or muscle transmission and function. Examples of perineural injections are phenol or ethyl alcohol and botulinum toxin for intramuscular injections.[52]

Botulinum toxin types A and B impair the release of acetylcholine at the neuromuscular junction thus producing reversible and focal weakness of skeletal muscles.[54] Several studies have indicated a reduction in focal spasticity with especially lower limb function improving significantly. Only modest improvement in function could be shown in randomised trails, but this can be largely ascribed to the limits of the study design rather than the limitations of botulinum toxin therapy.[59–61] Significant benefits have been shown especially with regards to the gastrocnemius-soleus complex. Botulinum toxin A is superior to placebo injections to

reduce spasticity in the gastrocnemius-soleus muscle complex in the short term, but only equal to serial casting. The evidence is mixed when combining the two treatment modalities.[50] Long term benefits and/or adverse effects of focal botulinum toxin injections are currently unsure.[62] Botulinum toxin A should thus be used for very specific indications within a multidisciplinary setting where long term monitoring and follow-up is readily available. However, botulinum toxin continues to fulfil a valuable role in the management of CP and there is undoubtedly an important place for its use in the in the treatment of spastic equines in younger children. This allows individuals to adapt to the use of orthotics and thus make functional gains before they reach the age where orthopaedic surgical intervention is indicated.[63]

Another option is phenol and alcohol. Both agents are injected in the perineural area causing reversible axonal denervation. Functional reinnervation occurs over a period of up to 2 years. The technical challenge posed by the alcohol and phenol injection is to correctly target the nerve. Individuals frequently require electrical stimulation and sedation or anaesthesia and this, combined with the side effects of pain and/or paraesthesia, has been the main reason for botulinum toxins being the treatment modality of choice for focal spasticity.[52] The outcomes of studies investigating the use of phenol and alcohol for the treatment of spasticity in CP have been favourable.[64,65]

In a recent non-controlled randomised study comparing the effectiveness of phenol versus botulinum toxin A, botox injections showed better treatment outcomes in spasticity reduction, functional outcome measures and range of movement of joints. The botox injections also had less clinical side effects than phenol.[66]

Neurosurgery

The intrathecal baclofen pump uses baclofen, a γ-aminobutyric acid (GABA) B agonist which depresses the release of excitatory neurotransmitters at the spinal level. Baclofen is the most commonly used muscle relaxant. Muscle relaxants work at the level of the muscle and spine to reduce muscle activation by the spinal reflex arc and spasticity which occurs due to a lack of descending inhibition. Due to its lipophilic properties, baclofen does not cross the blood–brain barrier easily. To thus achieve adequate central nervous system concentrations on oral

baclofen, individual's risk dose dependent side-effects which include sedation, increased frequency of seizures and hypoventilation.[26] Baclofen administration via the intrathecal route with an implantable pump is thus the treatment method of choice. Moderate evidence as to the benefit of intrathecal baclofen exists.[48] The use of intrathecal baclofen is especially indicated in more severely disabled individuals (gross motor function classification system Levels IV and V).[67]

Another neurosurgical procedure which reduces lower extremity spasticity is *Selective Dorsal Rhizotomy (SDR).* Muscle tone is reduced as a result of transecting a percentage of lumbar rootlets and disrupting the reflex arc at the spinal cord level. This procedure has particular appeal as it interrupts the abnormal reflex circuit that maintains spasticity. An expanding body of research suggests that SDR is highly effective in improving the neurological factor of spasticity, which may lead to gait and function improvements.[68] SDR has important South African roots as it was substantially refined and reintroduced by Professor Warwick Peacock at Red Cross Children's Hospital in the 1980s.[69] Langerak et al. conducted the first long-term follow-up studies of individuals with CP who had undergone SDR during childhood.[70–73] The findings of this SDR research project indicated that more than 15 years after surgery, this neurosurgical procedure had been effective in improving function (neuromuscular function, spinal function and functioning in daily activities). However, SDR is not the most effective treatment option for all children with CP and is thus reserved for children who meet the strict selection criteria. Many of the individuals receiving SDR will also require subsequent orthopaedic procedures. A systematic review by Grunt et al. concluded that there is very little conformity with regards to the selection criteria for SDR and that future research and consensus meetings are needed to better define the inclusion and exclusion criteria for SDR.[74] The *ideal* child who fulfils all the SDR criteria is indeed few and far between and this highlights the need for children with CP to be individualised.[68]

Orthopaedic surgery

The aim of orthopaedic surgical interventions in ambulatory people with CP is to optimise joint moment thus generating capacity via spasticity management and correction of bone malalignments and contractures.[49]

Musculotendinous surgery for reduction of joint contractures and spasticity and improved function of muscles of the lower extremities can include:

- Iliopsoas lengthening at insertion or *over the brim* for hip flexion contractures
- Adductor longus and/or brevis and/or gracilis lengthening or tenotomies for hip adduction contractures
- Medial hamstring lengthening (semitendinosis, semimembranosus, gracilis) and/or lateral hamstring lengthening (biceps femoris) for knee flexion contractures
- Rectus femoris tendon transfer for extension knee gait in swing
- Gastrocnemius-soleus lengthening or recession for ankle equines
- Tibialis anterior and/or posterior tendon transfer or split for mobile subtalar varus or foot supination, adduction deformities

Another orthopaedic surgery option is osteotomies for the correction of bony malalignments, thus aiding in the correction of lever arm dysfunction:

- Proximal femoral varus and/or derotation osteotomies and/or acetabuloplasties for hip subluxation or dislocation
- Derotation osteotomies for increased femoral anteversion and/or abnormal tibial torsion
- Distal femoral osteotomies for malrotation, varus or valgus malalignment
- Distal femoral extension osteotomies combined with distilisation of the patella tendon for knee flexion contractures

In addition, correction of foot deformities should not be underestimated in people with CP. These can include:

- Calcaneal osteotomies (lateral column lengthening, valgus or varus osteotomies, lateral slide osteotomies)
- Medial and/or lateral wedge osteotomies for mid-foot abnormalities
- Open or closing osteotomies of the first ray for pronation or supination deformities
- Tibialis anterior and/or posterior tendon transfer or split for subtalar varus or foot supination, adduction deformities

- Fractional lengthening of peroneus longus for cavovarus foot deformities
- Triple arthrodesis for severe and immobile foot deformities

The general approach to orthopaedic interventions has experienced some fascinating changes over time. The perspective shifted from *single event surgery*, where abnormalities were treated during isolated time periods for isolated abnormalities, to *interval surgery approach (ISA)*, where one broad problematic anatomical area was addressed per surgical event. Currently we aim to utilise *Single Event Multi Level Surgery (SEMLS)* where all, or most, of the abnormalities are addressed at the same time.

A systematic review by McGinley et al. in 2012 on the findings of SEMLS emphasised the lack of good quality studies to properly assess the outcomes of SEMLS.[75]

ORTHOPAEDIC TREATMENT APPROACHES IN DEVELOPED VS DEVELOPING COUNTRIES

As previously discussed, we would expect developing countries to have a higher prevalence of CP than developed countries. Prevalence ranges from 2 - 10 per thousand live births in developing countries with China and India reporting 1.5 - 2.5/1 000 live births,[20] Uganda 1.8 - 2.3/1 000[21] and South Africa 10/1 000.[14]

There is general agreement that a multi-disciplinary approach and SEMLS followed by intense rehabilitation is currently the accepted gold standard for the treatment of children with CP.[50] SEMLS can be defined as two or more soft tissue or bony procedures at two or more anatomical levels during one surgical setting.[76] However, it is postulated that less than 30% of children with CP in South Africa and other developing countries receive appropriate orthopaedic interventions at the appropriate times and have access to rehabilitative services.[77] Due to the high prevalence of CP, scarcity of appropriate multidisciplinary CP care centres, lack of highly skilled rehabilitative services and severe financial constraints, it is intuitive that a large percentage of children with CP within developing countries will not have access to SEMLS. A few tertiary centres offer this treatment approach but most children will receive: no treatment at all *or* single-level surgery *or* a selective combination of procedures.

However, to date, very little conclusive evidence exists as to the tested superiority of SEMLS over the more traditional *single-level* or *interval surgery* approaches.[50] Several good quality

retrospective studies have shown an improvement in gait and/or functional ability following SEMLS, but there have been very few available prospective studies, studies with controls and only one pilot randomised clinical trial.[75,76] Thomason et al. supplied therapeutic Level II evidence in a single centre randomised control trial that SEMLS combined with intensive postoperative physical therapy, when compared to physical therapy alone, improved the gait of children with spastic diplegic CP. Only minor improvements in other domains were shown until 24 months after surgery.[76] Obvious and important advantages of SEMLS are that the child with CP requires only *one* hospital admission, *one* major theatre session and *one* intensive rehabilitation session.

Outcomes: Body function and structure

Physical status

Orthopaedic interventions do not have a direct effect on the cause of spasticity. However, numerous studies have reported a reduction in muscle tone in children with CP in the short and intermediate term.[78–83] This is especially pertinent with regards to soft tissue procedures of the lower limbs, specifically the gastrocnemius-achilles and hamstrings tendon complex.[84] Passive range of movement (PROM) does improve with orthopaedic interventions, specifically ankle dorsiflexion and knee extension.[85] Muscle strength seems to be reduced 6 - 12 months after multi-level orthopaedic surgery, but Seniourou et al.[86] found that this can be regained with strength training. Pooled analysis of the meta-analysis and systematic review by Amirmudin et al. revealed no evidence of any change in muscle strength post SEMLS orthopaedic interventions in the intermediate or long term.[85]

Gait

Improved gait patterns, based on 3D gait analysis, have been reported after combined hamstring releases and rectus femoris transfers,[87] but also with additional triceps surae lengthening.[88] This positive outcome was also noted after hip flexor releases and achilles tendon lengthening in a 4 year follow-up study.[89] Once again, the pooled analysis by Amirmudin et al. reported an improvement in gait one year after SEML which extended into the intermediate term.[85]

Spinal deformities and back pain

A strong link exists between the development of spinal deformities and CP, most notably scoliosis[90,91] with an estimated prevalence of between 15 and 80%.[92] The challenge with spinal deformities and CP is to define the risk factors which indicate progression in children, as well as the adult CP individual. Saito et al. concluded that the risk factors for progression of scoliosis in spastic CP is a curve of 40 degrees before the age of 15 years, total body CP, bedridden individuals and individuals with a predominant thoracolumbar curve. Unfortunately, this article shows selection bias as to the CP spectrum as all individuals included in the study were non-ambulatory with severe spastic CP and severe disabilities. The study was published before the introduction of the GMFCS, but most of these individuals would resort to the GMFCS V group.[90]

More recently, Yoshida et al. published their findings regarding the natural history of scoliosis progression in a more heterogeneous group of individuals classified as GMFCS I-V, although 90% of these individuals were still categorised as belonging to the GMFCS IV-V group. The risk factors for progression were hip displacement, a Cobb angle of at least 30 degrees before the age of 10 years, the onset of scoliosis before the age of 6 years and possibly the subtypes of CP.[91]

Persson-Burke et al. highlighted the association between the GMFCS level and the development of scoliosis.[92] Supporting this investigation is the finding that an inverse relationship exists between the development of scoliosis and ambulatory abilities with the individual presenting poor ambulatory abilities being at risk.[93,94]

Research has shown that the curve tends to progress, even after skeletal maturity has been reached, in adults with CP.[95,96] Curve progression in non-ambulatory individuals varies between 3 and 4.4 degrees per year.[96]

Evidence of progression of degenerative spinal changes in the ambulatory adult with CP is scarce. Lee et al. indicated that thoracic kyphosis and lumbar lordosis, as well as the Cobb angle in scoliosis, do progress in adults with CP classified in GMFCS Level IV-V but are considered stable in adults with CP classified in GMFCS Level I-III.[97]

Adults with CP experience a 15% higher frequency of significant pain when compared to the normal population[98] and 38 - 83% of adults with CP report experiencing pain at regular intervals.[98–102] The pain was most frequently reported as originating from the back, hip and

general lower extremities.[98,102–104] It is uncertain whether progressive changes in spinal curvature are related to the increase in back pain in adults with CP.

Outcomes: Activity and participation

Balance

Adults with CP subjectively experience a decline in balance and ambulatory ability. This is especially true before the age of 35 years, where most ambulatory individuals experience a drastic decline in both parameters[24,105,106] and a devastating loss of independence could be the ultimate secondary outcome.[105,107,108] There is, however, a paucity of literature which objectively quantifies functional mobility, balance and physical status in adults with CP, with sources frequently only referring to a decline in PROM[38,109] and muscle weakness.[110] It is however important to note that none of these studies classify subtypes of CP. No distinction is thus made between the different levels of the Gross Motor Function Classification System (GMFCS)[111] and no specific details are supplied as to the interventions which individuals received that may have influenced their physical status. In addition, most studies were conducted in a developed country context.

Functional Mobility

Walking ability after having received single event multi-level surgeries (SEMLS) in childhood, as defined by the Gillette Gait Index (GGI), did not alter with long-term follow-up. This implies that orthopaedic surgery is a useful modality in prolonging mobility or delaying deterioration in children with bilateral spastic CP.[112] This is in contrast with changes noted in the stability of GMFCS levels where individuals, as a group, have exhibited significant fluctuations to a lower GMFCS classification up to 5 years post SEMLS.[113]

Recent evidence suggests large improvements in gait with more equivocal evidence for changes in gross motor function. In a randomised controlled trial (RCT) conducted at the Royal Children's Hospital in Melbourne, the SEML surgery group was compared to a control group that received only progressive resistance strength training. A 57% improvement in gait, according to the Gillette Gait Index (GGI), and a 4.9% improvement in gross motor function, according to the GMFM-66, was noted.[76]

Life habits

In addition, a one year follow-up study showed that functional status and quality of life were better in a group of children with CP who had received single or multi-level orthopaedic surgery than in a non-surgical group.[112] However, it was also noted that improved functional well-being did not automatically entail improved psychosocial well-being.[114]

A review of the current available literature emphasises the importance for comparative studies between SEMLS and ISA as well as long term follow-up studies on both of these cohorts.

AGEING WITH CEREBRAL PALSY

Past research on individuals with CP more frequently focused on body structure and function. In the last decade, however, there has been a paradigm shift towards a broader biopsychosocial view.[22] Limited attention has been afforded to the challenges which affect the adolescent, young adult, middle aged and geriatric individual diagnosed with CP, especially if assessed on a more global scale. In the last decade numerous studies have been done within the ICF framework investigating body structure and function, activity limitation and participation.[115–119] Assessing the adult with CP within this framework has yielded a much better understanding as to the issues and challenges experienced by the adult with CP.

For the adult with CP, as well as the individual transitioning into the phase of adulthood, less than positive outcomes have been the norm in most areas within the ICF framework.[26] When compared to the general population, an individual adult with CP can expect an increase in: cardio-metabolic and pulmonary morbidity, premature symptoms of ageing, osteoporosis and arthritis, spinal deformities and back pain, sarcopenia, general pain, nutritional challenges such as dysphagia, general malnutrition and global functional limitations.[115] Up to 70% of young adults with CP experience challenges related to the activities of daily living[116] and exhibit a progressive decline in functional reserve and overall strength.[117] Symptoms of depression and other psychological issues are also more commonly noted in the adult with CP.[118] Within the ICF, *participation* is defined as involvement in life situations, and this is consistently curtailed in children and adults with CP.[26] To conclude, it is abundantly clear that the health related quality of life in the individual with CP is consistently lower when compared to the general population.[119]

An area of CP that has not received much attention within the ICF framework is the adult in a developing world setting who frequently received either adjusted or very limited treatment or care as a child. For instance, the outcomes of adult with CP who received orthopaedic management via the ISA approach within the developing world setting, is unclear.

THESIS OUTLINE

Overarching research aim and chapter layout

The overarching research aim of this PhD thesis is to determine, the physical status and changes in gait, spinal curvatures and the level of activity and participation (in line with the domains of the ICF framework) during ageing in ambulant adults with cerebral palsy and spastic diplegia, who have been treated with an orthopaedic interval surgery approach (ISA) in childhood.

This PhD dissertation focusses on adults who were born, grew-up and are still living in a developing country (South Africa) where, up to today, most children with CP are still treated with an ISA (as SEMLS is not always available). It needs to be highlighted that the aim of this thesis was NOT to study the relationship between the orthopaedic ISA and the status and/or changes over time with ageing.

In addition, the thesis is specifically concerned with ambulant adults with CP and spastic diplegia who, in most cases, were classified as GMFCS Levels I and II and a limited section as GMFCS Level III. In other words, adults with relatively mild to moderate levels of CP were included in this study. The findings of this thesis are therefore not transferable to adults with more severe implications of CP and classified as GMFCS Levels IV and V.

This thesis consists of six chapters. Following the literature review (**Chapter 1**), the next four chapters are based on research studies (**Chapters 2 - 5**) with the summary and conclusion being presented in the last chapter (**Chapter 6**). The research studies contain a cross-sectional study focussing on the physical status, functional mobility and balance of ambulant adults with CP and spastic diplegia (**Chapter 1**), while the remaining three Chapters are based on a six-year follow-up study design focussing on changes in spinal curvatures (**Chapter 3**), gait (**Chapter 4**) and the level of accomplishment and satisfaction of activities and participation in daily life (**Chapter 5**). **Chapter 6** aims to summarise the main results of the four research

chapters (**Chapters 2 - 5**) through discussing and linking the findings that would elucidate a discussion of the clinical implications. In addition, study limitations and ideas for potential future research are described. The chapter concludes with take home messages, which can be used in daily clinical practice.

Study population

The thesis specifically focuses on adults with CP and spastic diplegia, living in South Africa, who received their first orthopaedic interventions, based on an ISA, in childhood more than 25 years ago. Baseline data for this research project was collected in 2011, while a six-year follow-up was conducted in 2017. Thirty adults with CP participated in the initial study and their characteristics are presented in **Table 1.1**.

Table 1.1. Overview of participants' characteristics at baseline study (2011) (n=30)

Variable	Median (IQR)/n (%)
Gender, male: female	12 (40) : 18 (60)
Age (years)	32.8 (28.1-39.3)
Age at first ISA (years)	4.6 (3.6-7.3)
BMI	23.8 (20.6-29.9)
SES (housing index) *	
low	10 (33)
middle	11 (37)
high	9 (30)

*Abbreviations: BMI, body mass index; SES, socio-economic-status. *housing index: number of people divided by the number of rooms in the house, excluding bathroom and kitchen.*

The pre-operative (before first orthopaedic intervention) GMFCS levels were retrospectively classified based on detailed clinical reports, while the gross motor functional status was also determined during the 2011 and 2017 assessments (see Figure **1.13**).

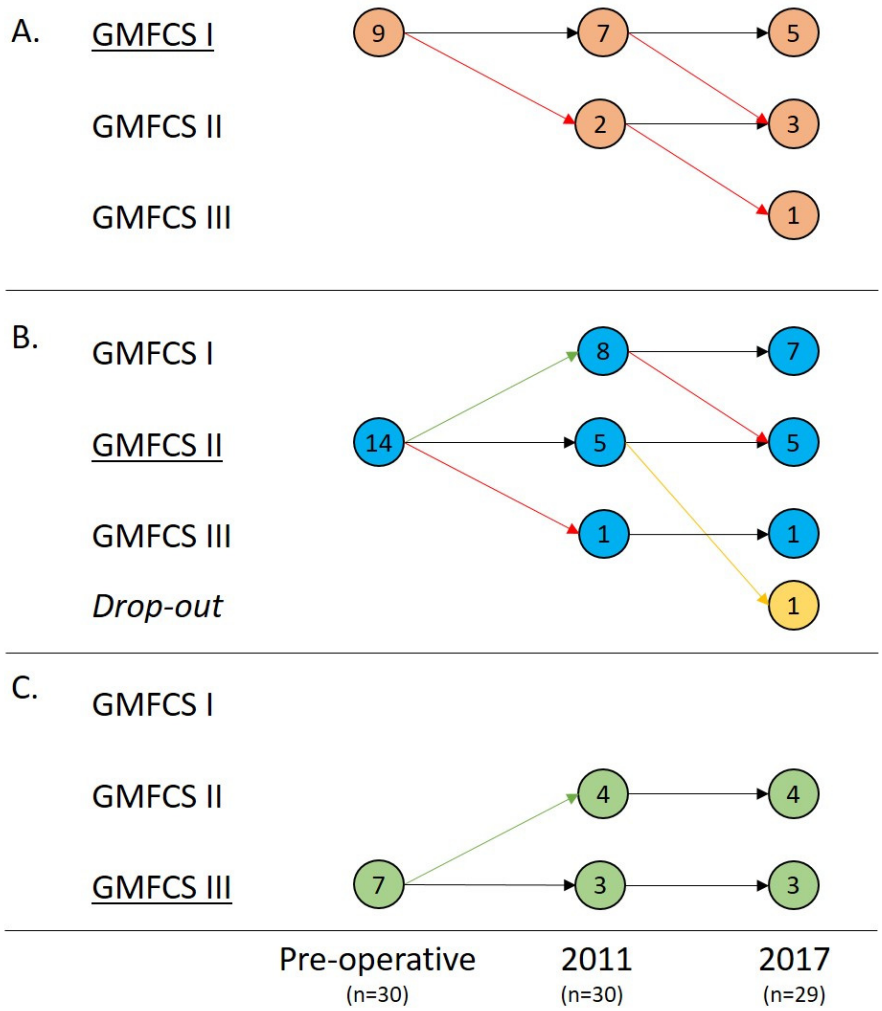

Figure 1.13. Overview of the changes in GMFCS level from pre-operative to 2011 and 2017

Pre-operative, 9 participants were classified as GMFCS Level I, 14 as Level II and 7 as Level III. This later changed to 12 as GMFCS Level I, 12 in GMFCS Level II and 5 in GMFCS Level III. The change in distribution over time is illustrated in **Figure 1.13** with section A showing the change in adults who were pre-operatively classified as GMFCS Level I, section B showing the change in adults who were pre-operatively classified as GMFCS Level II and section C showing the change in adults who were pre-operatively were classified as GMFCS Level III.

It is important to state that the aim of this thesis is not to relate the outcomes of the studies to the type and number of ISA the participants received during their childhood. However, this research work wishes to provide the reader thereof with insight into which surgical procedures were performed as per the overview presented in **Table 1.2**.

Table 1.2. Overview of the number of participants who received soft-tissue and/or bony surgery at lower extremities, with a specification of repetitions performed (baseline: n=30)

Orthopaedic intervention	One intervention	One repetition	Two or more repetitions	Total received the intervention
	n	n	n	n (%)
Soft-tissue surgery				
Achilles tendon	18	8	2*	28 (93)
Gastrocnemius (Vulpius)	6	1		7 (23)
Rectus Femoris	8	1		9 (30)
Hamstrings	13	3	1**	17 (57)
Adductors	10	1		11 (37)
Psoas	6			6 (20)
Abductor Hallucis Longus	3			3 (10)
Tibialis Posterior	2	1		3 (10)
Peroneus	2	1		3 (10)
Bony Surgery				
Femoral derotation	5			5 (17)
Tibial derotation	3	1		4 (13)
Ankle/foot corrections	9	1	1*	11 (37)
Toe corrections	0	1		1(3)

** 3 repetitions per orthopaedic intervention, ** 4 repetitions per orthopaedic intervention*

RESEARCH AIMS AND STUDY POPULATION PER CHAPTER

Chapter 2 is a cross-sectional study which aims to quantify the physical status of adults with CP and spastic diplegia living in a developing country and who had received their first orthopaedic intervention with ISA more than 25 years ago. The three aims investigating this study cohort are to determine: I) the physical status, functional mobility and balance of ambulant adults with CP and spastic diplegia; II) differences within these parameters between adults with CP classified in GMFCS Levels I, II and III compared to matched TD adults, and III) whether associations exist with these parameters and individual characteristics.

Twenty-eight of the original 30 adults with CP were included in this research study. One adult had relocated and was unable to participate and another adult declined due to health reasons (not CP related).

Chapter 3 presents a six-year follow-up study which focuses on gait changes in adults with CP and spastic diplegia who are living in a developing country and who received their first

orthopaedic intervention based on ISA more than 25 years ago. The three research aims with this study cohort are to determine: I) whether their gait pattern had changed during a six-year adult ageing period; II) to what degree the gait of adults with CP differs to matched TD adults; and III) whether there are associations between the established gait deviation index (GDI) and individual characteristics. Twenty-nine of the original 30 adults with CP were included in this research study, while one adult was not able to participate in the study due to health reasons (not CP related).

Chapter 4 presents a six-year follow-up study that focuses on changes in spinal curvature in adults with CP and spastic diplegia in individuals who are living in a developing country and who received their first orthopaedic surgical intervention based on ISA more than 25 years ago. The three research aims with this study cohort are to determine: I) changes in spinal curvatures and the level of disability due to pain during a six-year adult ageing period; II) whether changes differ between adults with CP classified in different GMFCS levels; and III) whether spinal curvatures can be associated with individual characteristics and the level of disability due to pain.

In the 2011 study 29 adults with CP were included in this study as one participant was pregnant at the time and therefore X-rays could not be taken. At the six-year follow-up study two participants were not able to participate (due to relocation and non-CP related health reasons), which means that 27 adults with CP participated in this study.

Chapter 5 presents a six-year follow-up study focusing on changes in levels of accomplishment and satisfaction in activities and participation in daily life of adults with CP and spastic diplegia who are living in a developing country and who received their first orthopaedic intervention based on ISA more than 25 years ago. The three research aims with this study cohort are to determine: I) the change in level of accomplishment and satisfaction in daily activities and participation (based on the Life-Habits questionnaire), functional mobility and pain frequency over a six-year adult ageing period; II) comparative levels of accomplishment and satisfaction with matched TD adults; and III) whether associations were observed between outcomes of the Life-Habits questionnaire and individual characteristics,

functional mobility and pain frequency experienced. As in the gait, study 28 adults with CP participated in this study, since two of the original 30 did not participate due to relocation and health reasons (not CP related).

Chapter 6 aims to summarise the main results of the four research chapters (Chapters 2 - 5) through discussing and linking the findings that would elucidate a discussion of the clinical implications. In addition, study limitations and ideas for potential future research will be described. The chapter will be concluded with *take home messages* that can be used in daily clinical practice.

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PHYSICAL STATUS, FUNCTIONAL MOBILITY AND BALANCE OF AMBULANT ADULTS WITH CEREBRAL PALSY AND SPASTIC DIPLEGIA

INTRODUCTION

Cerebral palsy (CP) is known as one of the most common causes of physical disability in childhood, with an incidence of 2-3 per 1000 live births.[1] Prevalence in developing countries, such as South Africa, was estimated to be similar or even higher, ranging from 2-10 per 1000 live births.[2] CP is caused by a permanent lesion of the cerebral motor cortex of the immature brain that occurs pre-, peri- or post-natal up to 2 years of age,[3] and is commonly characterized by primary motor impairments, such as abnormal muscle tone, loss of selective motor control, dependence on reflex patterns for ambulation, muscle paresis and muscle co-activation.[3,4] As a consequence of these primary motor impairments, children with CP often develop contractures, bony deformities, reduced muscle mass and a decrease in passive range of motion (PROM).[3]

Due to improved health care and medical advances, the life expectancy of individuals with CP has improved over the last decades.[5] As a result, the largest cohort with CP today are adults.[5] A recent shift took place towards more research studies focusing on adults with CP. Several studies showed that adults with CP subjectively reported a decline in ambulatory ability and balance during adulthood, with a majority of ambulant individuals reporting a drastic decline before the age of 35.[6–9] This decline could ultimately result in a loss of independence.[6–8,10] Limited studies are however available that objectively quantified physical status, functional mobility and balance in adults with CP, only showing a limited PROM[11,12] and muscle weakness.[13] These studies do however not classify subtypes of CP, distinguish between different levels of the Gross Motor Function Classification System (GMFCS)[14] or specify interventions that individuals received, which may influence physical status. In addition, most studies were conducted in developed countries, whereas almost no studies were conducted in developing countries.

Previous research has shown that most individuals with CP are diagnosed with spastic diplegia,[15] of which the majority is ambulant.[16] To improve and/or maintain functional mobility, individuals with CP and spastic diplegia often undergo orthopaedic interventions during childhood. While the preferred and golden standard treatment regime in developed countries nowadays is a single-event multilevel surgery (SEMLS),[17] individuals with CP in developing countries are still frequently treated with orthopaedic interval surgery approach (ISA) during childhood, which entails multiple interventions at different time points.[18] It is

however unknown how the physical status is of adults with CP and spastic diplegia, who are living in a developing country.

Therefore, in the current study we aimed 1) to examine physical status, functional mobility and balance of ambulant adults with CP and spastic diplegia living in a developing country and have been treated with orthopaedic interventions follow ISA, 2) to investigated differences in physical status, functional mobility and balance of these adults with CP classified in different GMFCS levels and matched TD adults, and 3) to determine whether associations exist between physical status, functional mobility, balance and individual characteristics. This information will add to the existing literature regarding body function and structure of adults with CP within the International Classification of Function, Health and Disability (ICF) model.

METHODS

Study cohort

Adults with CP were recruited from a former research study,[19] originally recruited from the database of a school for children with special needs (Cape Town, South Africa). Inclusion criteria for the former study were a diagnosis of CP and spastic diplegia, with or without mild upper extremity involvement, able to walk with or without assistive devices, i.e. GMFCS level I, II or III and having received orthopaedic interventions following an interval surgery approach (ISA). Individuals with other neuromuscular disorders or another type of CP (e.g. athetoid, ataxic or mixed type) were excluded. In addition, individuals were excluded if they underwent a neurosurgical intervention such as a Selective Dorsal Rhizotomy (SDR). For logistical reasons, participants had to live within a 100km radius from the testing facilities in Cape Town. TD adults were matched for age, gender, BMI and socio-economic status (SES). The study was approved by the by the local institution (UCT: 013.2017; SUN: N17/04/035) and conducted in line with the principles set out in the Declaration of Helsinki (2013).[20] Informed consent was obtained from each participant.

Procedure

Based on a structured interview, participants' characteristics were obtained including age, gender, socio-economic status (SES) and current health status. SES was estimated based on housing density,[21] by dividing the number of people living in the house by the number of rooms within the house (excluding kitchen and bathroom). Height and weight were taken. From adults with CP, Gross Motor Function Classification System (GMFCS) level, the number and type of orthopaedic interventions participants received during childhood were obtained.

Physical exam

The physical assessment of the lower extremities was performed according to the guidelines of Novacheck and Gage (2007),[22] including passive range of motion (PROM), muscle strength, selective motor control, contractures and muscle tone, which were all assessed bilaterally. For all outcome measures, the average of both legs was calculated. All assessments were performed in adults with CP and TD adults and conducted by the same paediatric orthopaedic surgeon.

Passive Range of Motion

Passive range of motion (PROM) of the hip (flexion, extension, abduction, adduction, external, rotation, internal rotation), knee (flexion, extension, unilateral popliteal angle, bilateral popliteal angle, thigh foot angle, bimalleolar axis) and ankle (dorsiflexion with knee flexed, dorsiflexion with extended knee, plantar flexion) were assessed using a goniometer.

Strength

Maximal isometric force was measured using handheld dynamometry (HHD; microFET2, Procare B.V., Groningen, NL) from hip flexors, extensors, abductors and adductors, knee flexors and extensors and ankle dorsiflexors and plantar flexors. Measurements were conducted in standardized positions (**Table 2.1**), according to manufacturer's recommendations. A 'make' test was used, where participants were instructed to increase

muscle force gradually by pushing maximally for five seconds against the resistance given by the investigator.[23] Per leg, peak isometric forces of three trials were recorded. In case the last value was the highest value, additional trials were performed until the last trial was not the highest. Torque was calculated by multiplying the force with the lever arm, defined as the distance between the position of the HHD and the estimated joint center of rotation. Torque values were normalized for bodyweight. The average of the three trials per leg (six trials in total) was calculated and taken into account as maximum isometric torque per muscle group.

The HHD has a force measurement range of 3.6 to 660N, with a sensitivity of 0.4N. Inter-assessor reliability of this instrument in individuals has been shown to be high in individuals with CP (intraclass correlation coefficient (ICC) > 0.90).[24]

Table 2.1. Standardized position for each muscle group conducted with HHD

Muscle group	Position participant	Placement HHD
Hip flexors	Sitting	Anterior thigh, 3cm proximal to patella
Hip extensors	Prone	Posterior thigh, 5cm proximal to knee joint
Hip abductors	Side	Lateral thigh, 5cm proximal to knee joint
Hip adductors	Supine	Medial thigh, 5cm proximal to knee joint
Knee flexors	Sitting	Anterior tibia, 5cm proximal to malleoli
Knee extensors	Sitting	Posterior calf, 5cm proximal to malleoli
Ankle dorsiflexors	Supine	Dorsal surface of metatarsal heads
Ankle plantar flexors	Supine	Plantar surface of metatarsal heads

Selectivity

Selectivity was determined for hip flexors, extensors, abductors and adductors, knee flexors and extensors and ankle dorsiflexors and plantar flexors and classified into 0: only patterned movement, 1: partially isolated movement or 2: completely isolated movement.[22]

Muscle tone

Muscle tone of hip flexors, hip adductors, knee flexors, knee extensors and ankle plantar flexors were determined, bilaterally, using the Ashworth scale,[25] classified into 0: no increase in tone, 1: slight increase in tone, 2: more marked increase in tone, 3: considerable increase in tone or 4: rigid limb. Tests were performed at moderate speed (180°/s) using standardized procedures. Moderate reliability of the Ashworth Scale was shown in individuals with CP.[26]

Functional mobility and balance

Standing balance

All participants performed the Clinical Test of Sensory Interaction on Balance (CTSIB) test to assess balance.[27] Participants were asked to stand as long as they could 1; on a firm surface with eyes open, 2: on a firm surface with eyes closed, 3: on foam with eyes open and 4: on foam with eyes closed with a maximum of 30sec. Performance was scored unable (score 0), less than 30sec (score 1), 30sec unstable (score 2) or 30sec stable (score 3). Moderate interrater reliability was shown for the CTSIB for individuals with CP.[28]

Functional mobility and dynamic balance

Functional mobility and dynamic balance was assessed using the 'timed up and go' test (TUG).[29] Participants were asked to stand up from a standard chair, walk a distance of 3m (marked on the floor) as fast as they could, turn, walk back and sit down again. Participants used their routine assistive devices. The time to complete the task was measured using a stopwatch. The test was performed three times per participant and the average was taken into account.

Statistical analysis

Normality of outcome measures was tested using the Shapiro-Wilk test. PROM, strength and TUG were not normally distributed and therefore these outcomes were presented in median and interquartile ranges (IQR) (non-parametric variables). Frequency analyses were used to present results of motor control, muscle tone and the CTISB test. Differences in outcome measures between TD adults and adults with CP classified in GMFCS I, II and III were

investigated using a Kruskal-Wallis test. In case of a significant group effect, post hoc testing was performed using Mann-Whitney U test (Bonferroni correction: $p=0.05/4$; $p<0.0125$). Associations between muscle strength, TUG and participant's characteristics, including GMFCS, BMI and SES, were examined using Spearman's rank correlation. A Bonferroni correction was applied to compensate for multiple testing ($p=0.05/4$; $p<0.0125$). Statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Graphs were constructed using PRISM version 6 (GraphPad Software, San Diego, CA, USA).

RESULTS

Participants' characteristics

From the cohort of thirty participants, twenty-eight adults with CP participated in this study and were matched (age, gender, BMI and SES) with twenty-eight TD adults. Participants' characteristics are presented in **Table 2.2**. Eleven adults with CP classified in GMFCS level I (39%), twelve as level II (43%) and five as level III (18%). Participants received different orthopaedic interventions, such as Achilles tendon (n=28; 100%) and hamstring lengthening (n=16; 57%). Other soft tissue procedures were performed on adductors (n=10; 36%), rectus femoris (n=8; 29%), psoas (n=6; 21%) and tibialis posterior (n=3; 11%). Bony surgeries included ankle/foot corrections (n=11; 39%), femoral derotation (n=4; 14%) and tibial derotation (n=4; 14%). None of the adults with CP received spinal surgery.

The majority of adults with CP had no other diagnosis influencing their medical status. Health issues that were reported were hypertension (n=5, 18%), asthma (n=3, 11%), diabetes (n=3, 11%), incontinence (n=3, 11%) and/or mental health condition (e.g. depression, anxiety) (n=5, 18%).

Table 2.2. Participant's characteristics of adults with CP classified as GMFCS level I, II and III and TD adults. Data expressed as median [IQR] or n (%).

	CP			TD
Parameter	**GMFCS I** (n=11)	**GMFCS II** (n=12)	**GMFCS III** (n=5)	(n=28)
Age (y:mo)	37:10 [28:10 – 42:6]	43:2 [37:7 – 46:3]	35:0 [28:5 – 51:8]	38:0 [32:4 – 46:0]
BMI (kg/m^2)	23.6 [19.9 – 29.7]	28.3 [23.9 – 30.8]	32.6 [29.4 – 41.5]	26.9 [23.5 – 29.4]
SES	1 [0.8 – 2.0]	1.3 [0.6 – 2.0]	1.3 [0.8 – 1.5]	0.8 [0.7 – 1.1]
Gender (m/f)	7 (64) / 4 (36)	4 (33) / 8 (67)	1 (20) / 4 (80)	12 (43) / 16 (57)
Number of interventions	1 [1 – 6]	5 [4 – 8]	5 [3 – 7]	n.a.
Number of surgical events	1 [1 – 4]	3 [2 – 5]	3 [3 –5]	n.a.

Abbreviations: SES, socio-economic status is based on housing density (number of people divided by the number of rooms in the house, excluding bathroom and kitchen);[21] IQR, interquartile range.

Physical exam

Passive Range of Motion

Adults with CP classified in GMFCS level I, II and III showed significantly reduced PROM in hip flexion, hip abduction, and ankle dorsiflexion with knee extended (**Table 2.3**). PROM in hip flexion was also larger in adults with CP classified in GMFCS level I than III. In addition, PROM of knee popliteal angles (unilateral and bilateral) and ankle dorsiflexion with knee flexed were significantly reduced in adults with CP classified in GMFCS level I and II compared to TD adults. Knee flexion PROM was significantly reduced in adults with CP classified in GMFCS level II and III compared to TD adults. Finally, knee extension was significantly reduced in adults with CP classified in GMFCS level II compared to TD adults.

Table 2.3. Physical exam: PROM in degrees (°) in median and IQR.

Parameter	**GMFCS I** (n=11)	**GMFCS II** (n=12)	**GMFCS III** (n=5)	**TD** (n=28)
Hip				
Flexion	125 [120 – 130]) [a,b]	113 [104 – 117] [c]	108 [99 – 116] [a,d]	135 [125 – 142] [b,c,d]
Extension	18 [13 – 20]	19 [16 – 23]	18 [9 – 20]	20 [15 – 23]
Abduction	43 [41 – 48] [e]	45 [38 – 48] [f]	38 [35 – 49] [g]	55 [51 – 68] [e,f,g]
Adduction	25 [25 – 28]	28 [23 – 29]	25 [23 – 34]	25 [21 – 30]
External rotation	43 [35 – 50]	44 [35 – 48]	40 [36 – 45]	48 [43 – 53]
Internal rotation	55 [50 – 58]	59 [53 – 64]	53 [41 – 60]	53 [48 – 60]
Knee				
Flexion	138 [128 – 143]	133 [120 – 138] [h]	128 [100 – 135] [i]	145 [140 – 148] [h,i]
Extension	5 [0 – 10]	1 [0 – 7] [j]	3 [-5 – 19]	7 [5 – 10] [j]
Popliteal angle (uni)	43 [30 – 43] [k]	38 [31 – 45] [l]	30 [19 – 40]	15 [8 – 20] [k,l]
Popliteal angle (bi)	29 [13 – 33] [m]	21 [20 – 29] [n]	18 [0 – 23]	4 [0 – 9] [m,n]
Thigh – foot angle	12 [9 – 14]	11 [5 – 18]	10 [6 – 13]	10 [7 – 12]
Bimalleolar axis	18 [13 – 23]	16 [8 – 29]	19 [14 – 23]	16 [8 – 23]
Ankle				
Dorsiflex. (knee flex.)	18 [10 – 20] [o]	13 [8 – 18] [p]	13 [10 – 21]	23 [18 – 25] [o,p]
Dorsiflex (knee ext.)	5 [3 – 10] [q]	0 [-3 – 3] [r]	0 [-1 – 3] [s]	14 [10 – 18] [q,r,s]
Plantar flexion	40 [33 – 45]	39 [35 – 44]	38 [28 – 50]	45 [40 – 53]

Abbreviations: PROM, passive range of motion; TD, typically developed adults; CP, adults with cerebral palsy; GMFCS, gross motor function classification system; IQR, interquartile ranges. Significance was set at: $p < 0.0167$. [a] $p = 0.015$; [b] $p = 0.014$; [c] $p < 0.001$; [d] $p = 0.001$; [e] $p < 0.001$; [f] $p < 0.001$; [g] $p = 0.002$; [h] $p = 0.001$; [i] $p = 0.005$; [j] $p = 0.009$; [k] $p < 0.001$; [l] $p < 0.001$; [m] $p < 0.001$; [n] $p < 0.001$; [o] $p = 0.003$; [p] $p < 0.001$; [q] $p = 0.001$; [r] $p < 0.001$; [s] $p = 0.001$.

Strength

Maximal isometric torque was reduced in adults with CP classified in GMFCS I, II and III compared to TD adults for hip abductors, knee extensors, ankle dorsiflexors and ankle plantar flexors (**Figure 2.1**). In addition, adults with CP classified in GMFCS III compared to GMFCS I showed significantly reduced torque levels for hip flexors, abductors, knee extensors and ankle dorsiflexors.

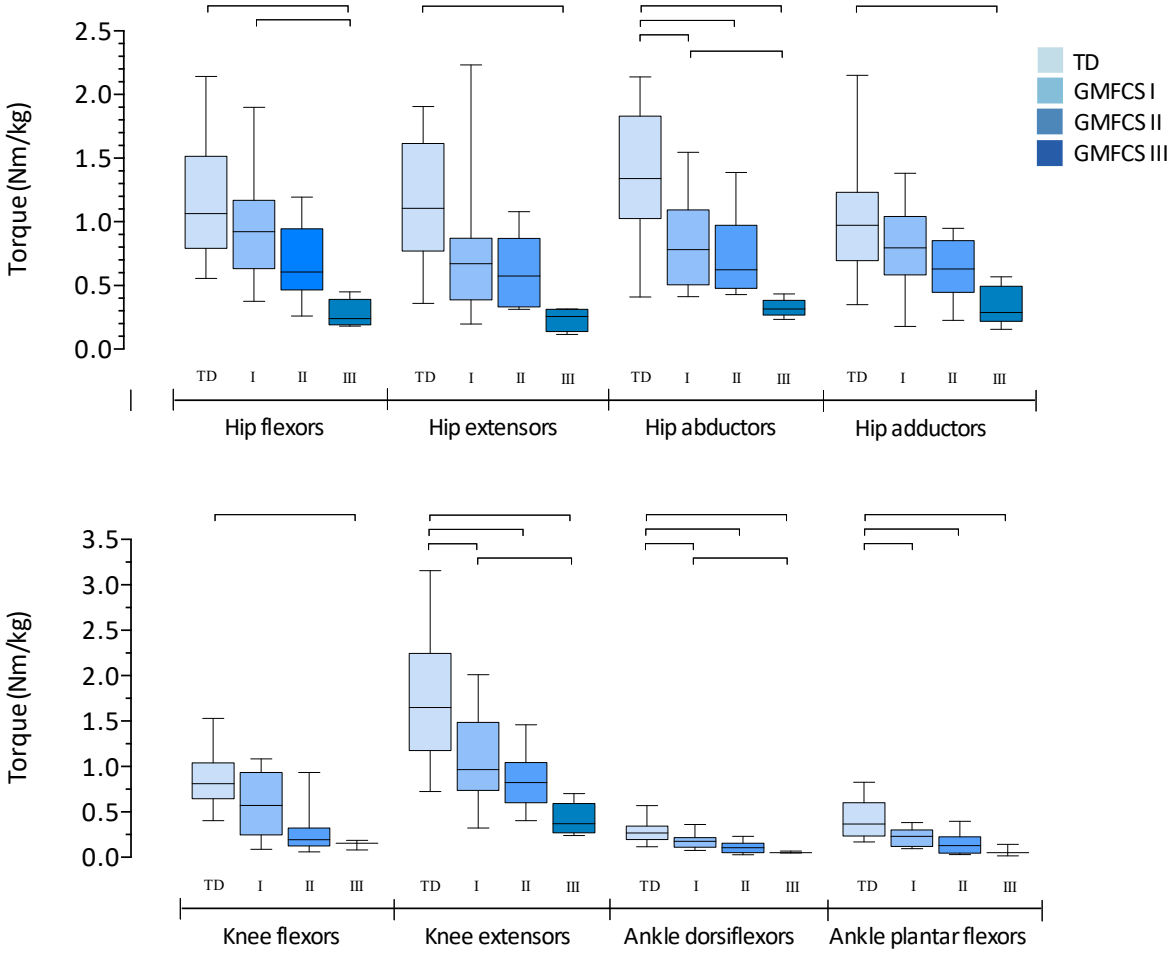

Figure 2.1. Boxplots, representing medians and whiskers (min-max), of maximal isometric torque (in Nm/kg) of TD adults and adults with CP classified in GMFCS I, II and III. Significance was set at: $p < 0.0167$.

Selectivity

Significant group effects were found for all movement directions (hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexion, ankle plantar flexion: $p<0.001$; hip abduction: $p=0.002$; hip adduction: $p=0.001$). Posthoc testing showed that there were also differences in motor control between adults with CP classified in GMFCS I, II and III and TD peers as shown in (**Figure 2.2**).

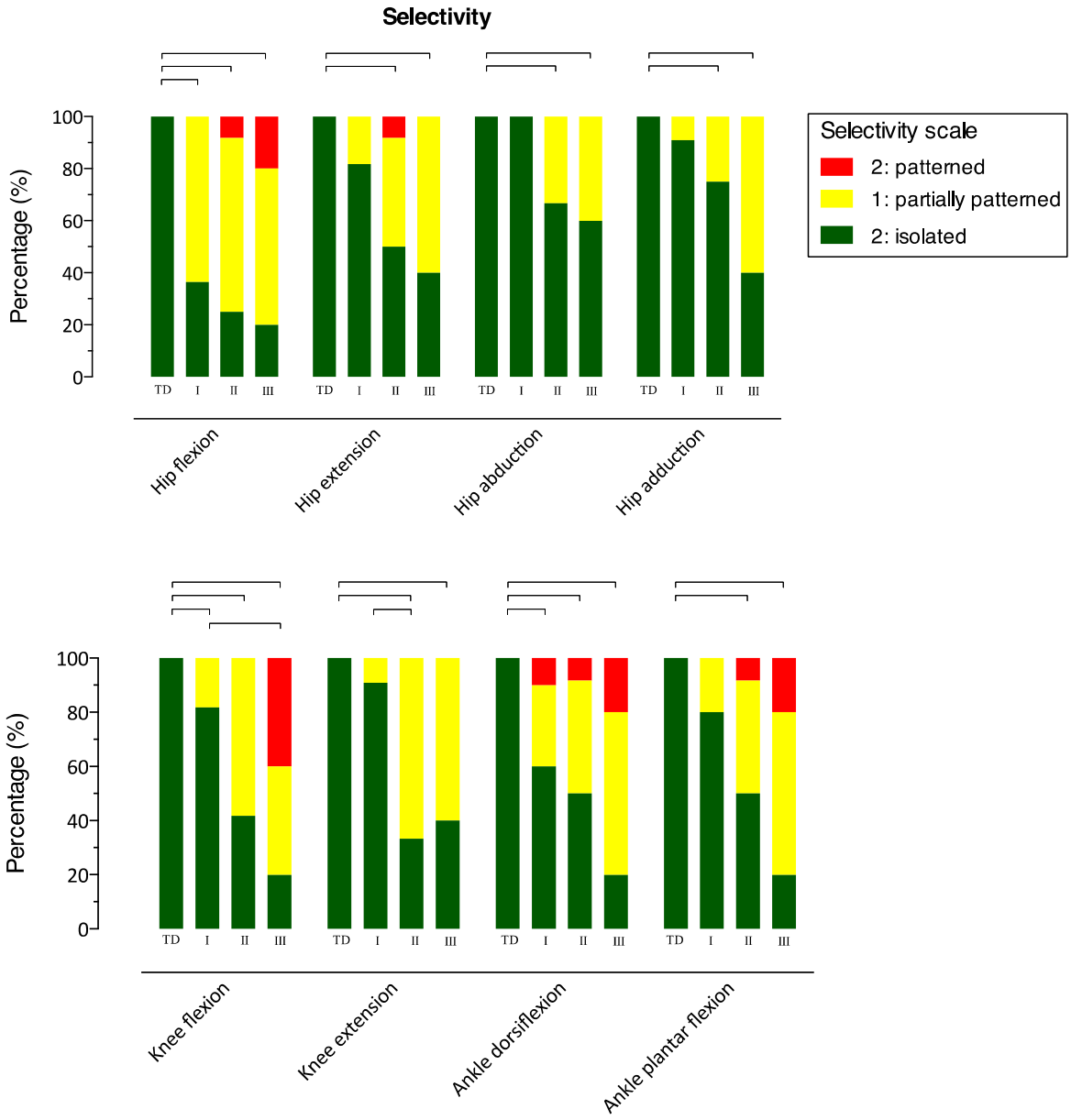

Figure 2.2. Stacked bar graphs of motor control for TD and adults with CP classified in GMFCS I, II and III.

Muscle tone

Significant group effects were observed for all muscle groups (hip adductors, knee flexors, knee extensors, ankle plantar flexors: $p<0.001$), except for hip flexors ($p=0.016$). Posthoc tests showed that muscle tone was significantly more present in all adults with CP compared to TD adults in all the movement directions except for the hip flexors of adults with CP classified in GMFCS I. In addition, no significant differences in muscle tone were observed between GMFCS levels (**Figure 2.3**).

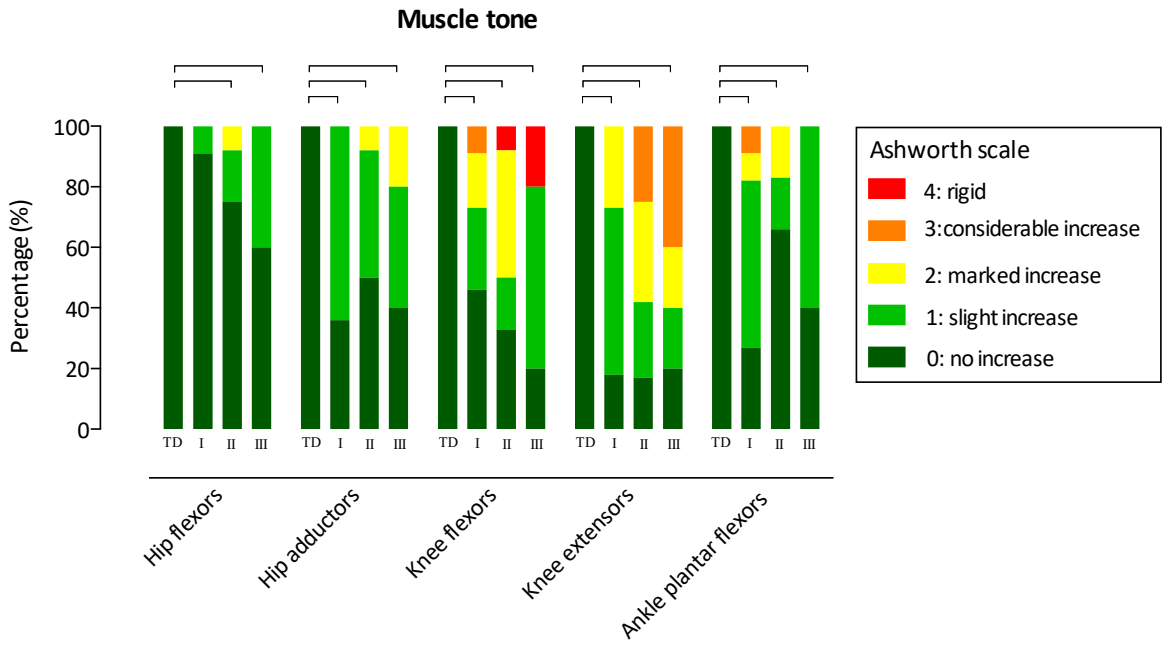

Figure 2.3. Stacked bar graphs of muscle tone for TD and adults with CP classified in GMFCS I, II and III.

Functional mobility and balance

Standing balance

Significant group effects were observed in both conditions of the CTSIB on the foam surface with eyes open ($p=0.006$) and eyes closed ($p<0.001$), but not for the conditions on the firm surface (eyes open: $p=0.066$; eyes closed: $p=0.020$). Posthoc tests showed that adults with CP classified in GMFCS II had a lower score than TD adults on the foam surface with eyes open, and adults with CP classified in all GMFCS levels had lower scores than TD adults on the foam surface with eyes closed (**Figure 2.4**).

All adults with CP classified in GMFCS I had a maximal score on the firm surface with both eyes open and closed, and the majority (82%) had a maximal score on the foam surface with eyes open, while more than half (54%) had difficulties in maintaining their balance on the foam surface with their eyes closed (score 1: 18%; score 2: 36%).

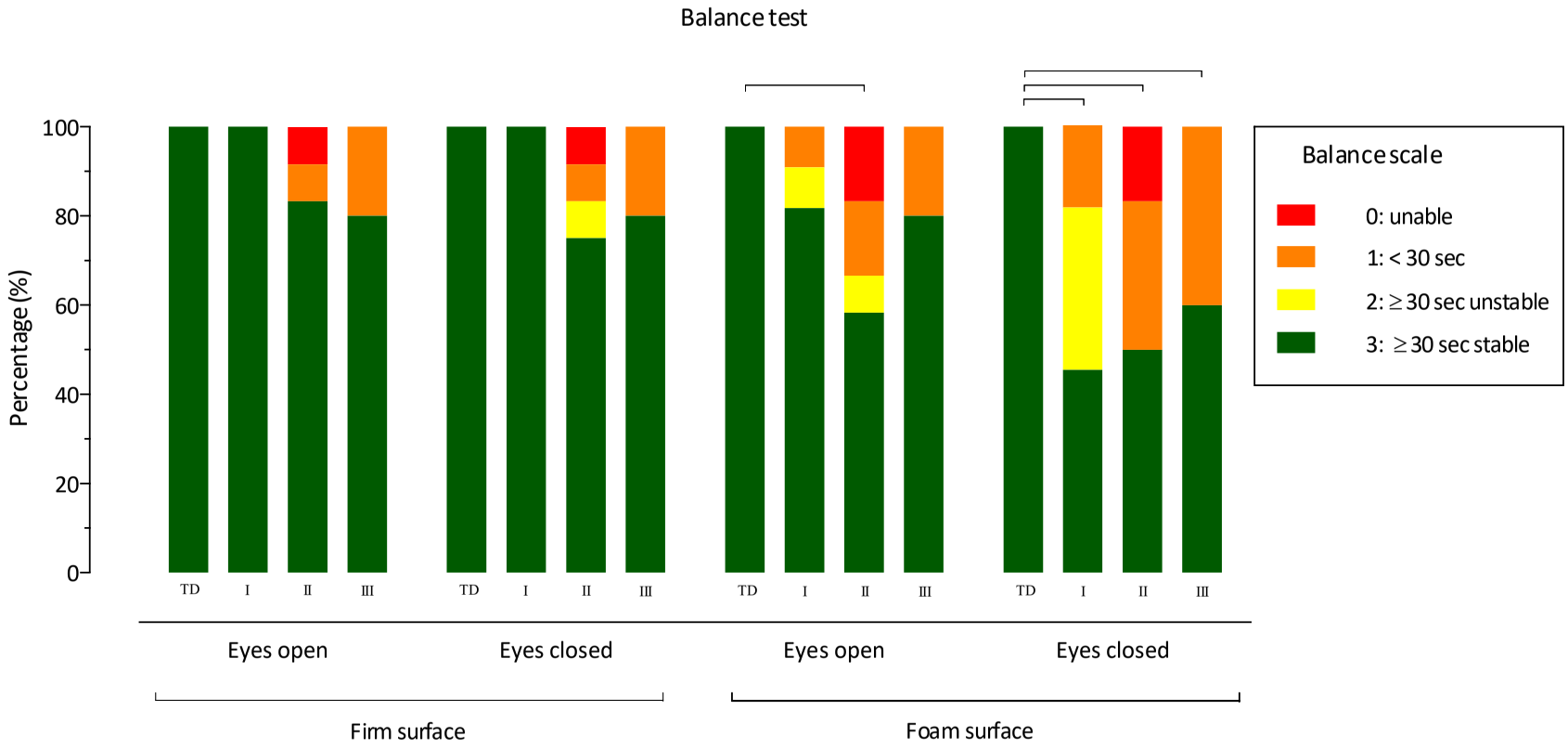

Figure 2.4. Stacked bar graphs of balance test for TD and adults with CP classified in GMFCS I, II and III.

The majority of adults with CP classified in GMFCS II had a maximal score on the firm surface with eyes open (82%) and eyed closed (75%), and more than half had a maximal score on the foam surface with eyes open (58%) and eyes closed (50%), while two adults with CP classified in GMFCS II (17%) were not able to stand on the foam surface with either eyes open or closed. The majority of adults with CP classified in GMFCS III had a maximal score on the firm surface with both eyes open (80%) and closed (80%) and on the foam surface with eyes open (n=4; 80%) and eyes closed (60%), while few participants stood unstable for 30s on either firm or foam surfaces (score 1). All TD adults had a maximal score on all conditions of the CTSIB, i.e. were able to stand for 30 seconds stable on both firm and foam surfaces with eyes open and closed.

Functional mobility and dynamic balance

Two adults with CP classified in GMFCS level III (40%) were not able to perform the TUG test (not able to stand up from chair independently). TD adults performed the TUG test significantly faster (median [IQR] = 3.8 [3.5 – 4.1] sec) than adults with CP classified in GMFCS level I (median [IQR] = 5.8 [4.7 – 6.7] sec, $p<0.001$), level II (median [IQR] = 9.1 [7.9 – 10.0] sec, $p<0.001$) and level III (mean (SD) = 19.3 [11.6 – 23.0] sec, $p=0.005$). In addition, adults with CP classified in GMFCS level I were significantly faster than adults with CP classified in GMFCS level II ($p<0.001$) and level III ($p=0.010$). Finally, adults with CP classified in GMFCS level II were significantly faster than level III ($p=0.009$).

Associations

Associations between torque, TUG and participants' characteristics are presented in **Table 2.4**. Negative associations were observed between torque and the TUG test, GMFCS and BMI. In addition, a negative association was observed between TUG test and GMFCS. No associations were observed between TUG test and BMI and SES.

Table 2.4. Spearman rho correlations between torque, TUG and participants' characteristics.

	TUG		GMFCS		BMI		SES	
Torque	r	p	r	p	r	p	r	p
Hip								
Flexion	-0.51	0.008*	-0.62	<0.001*	-0.55	0.003*	0.10	0.598
Extension	-0.24	0.264	-0.40	0.047	-0.61	0.001*	-0.03	0.891
Abduction	-0.50	0.009*	-0.56	0.002*	-0.57	0.002*	0.02	0.934
Adduction	-0.55	0.003*	-0.51	0.006*	-0.65	<0.001*	0.10	0.631
Knee								
Flexion	-0.61	0.002*	-0.58	0.002*	-0.47	0.017	-0.08	0.700
Extension	-0.55	0.004*	-0.53	0.005*	-0.54	0.004*	-0.08	0.710
Ankle								
Dorsiflexion	-0.57	0.007*	-0.62	0.002*	-0.81	<0.001*	-0.01	0.982
Plantar flexion	-0.49	0.018	-0. 50	0.013*	-0.67	<0.001*	-0.20	0.356
TUG			0.87	<0.001*	0.37	0.062	0.05	0.801

*Abbreviations: TUG, Timed Up and Go; GMFCS, Gross Motor Function Classification System; BMI, body mass index; SES, socio-economic status. * Significance was set at: p < 0.0167.*

DISCUSSION

The main findings of this study are that these adults with CP show severe impairments in different components of their physical status compared to TD peers across their lower extremities. Clinically, these impairments are considered detrimental for functional capacity in individuals with CP, and may cause a decrease in independence when ageing with CP.

Adults with CP showed restricted PROM compared to TD adults in hip flexion and abduction, knee flexion, knee popliteal angle, and ankle dorsiflexion. In addition, there is a noticeable trend towards more restrictions in PROM with increasing GMFCS levels, which is in agreement with previous research among children and adolescents with CP.[30] PROM of hip abduction, hip external rotation, knee extension and popliteal angle found in the current study were consistent with results shown by Nordmark et al. (2009) in adolescents with CP classified in GMFCS level I-III.[30] Ankle dorsiflexion seemed to be slightly reduced in adults with CP in the current study, compared to the adolescents with CP reported in the study by Nordmark et al. (2009). Hence, although PROM of adults with CP in the current study was restricted in some of the movement directions when comparing outcomes with TD adults, PROM may not

deteriorate to a large extent in ambulant adults with CP and spastic diplegia. However, a long-term follow-up study is needed to confirm this hypothesis. Previous research by You & Yamasaki (2014) showed even more severe restrictions in PROM of lower extremities in adults with CP.[12] No information was however provided in the latter study about the GMFCS level of the participants, which could explain different outcomes compared to the current study in the observed PROM.

Adults with CP showed to be limited in their muscle strength, in this study presented as torque, compared to TD adults, especially in hip flexors, hip abductors, knee extensors, ankle dorsiflexors and ankle plantar flexors. Torque levels were also associated with GMFCS level, indicating that lower torque levels were observed with increasing GMFCS levels. Torque levels ranged from 40-65% across lower limb muscle groups in adults with CP classified in GMFCS level I relative to torque levels of TD adults, whereas torque levels of adults with CP classified in GMFCS level II and III reached 25-60% and 15-30%, respectively. These muscle strength profiles are consistent with the literature describing muscle weakness in individuals with CP compared to their TD peers.[31–34] A loss of muscle volume,[35] altered muscle quality,[36] and changes in activation properties[37] may explain the relative muscle weakness compared to TD peers. Torque levels presented in the current study of knee extension were however lower compared to levels presented by previous research of de Groot et al. (2012),[38] which could be explained by different set ups for testing, i.e. computer-controlled dynamometer vs. HHD.

Adults with CP showed to have more impairments in selectivity compared to TD adults. More than half of adults with CP classified in GMFCS II and III showed partially isolated movements or only patterned movements in hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexion and ankle plantar flexion. Selectivity was least limited in hip abduction and adduction. During ageing with CP, limited motor control may cause limitations in walking ability.[39]

In this study, it was shown that increased muscle tone was most prominent in knee flexors, knee extensors and ankle plantar flexors, whereas muscle tone was least prominent in hip flexors. Muscle tone seemed to be independent of GMFCS level, which was consistent with previous research.[40] The presence of muscle tone across GMFCS levels can be explained by

the fact that none of the adults with CP in this study received interventions that reduced muscle tone.

Functional mobility and balance showed to be considerably reduced in adults with CP compared to TD adults. More specifically, adults with CP showed more difficulties in standing balance than TD adults when standing on a foam surface (based on CTSIB test), especially with closed eyes, while standing balance was similar in adults with CP and TD adults when standing on a firm surface. No differences were observed between the adults with CP classified in different GMFCS levels in standing balance. Functional mobility and dynamic balance, based on the TUG test, varied however largely between GMFCS levels, indicating that adults with CP classified in higher levels of GMFCS showed more limitations in functional mobility and dynamic balance. This is in consistent with previous research of Morgan et al. (2013).[41] Previous research by Opheim et al. (2009) showed that adults with CP most frequently reported problems with balance as one of the factors that contribute to a deterioration in walking ability.[9] The outcomes of previous and current research highlight the importance of maintaining balance during ageing with CP.

Reduced levels of muscle strength were associated with a slower performance on the TUG test, higher GMFCS level and higher BMI. In addition, functional mobility and dynamic balance were associated with GMFCS level. Although this is not surprising, these associations highlight that adults with CP are prone to develop a vicious cycle, in which impairments at the level of body function and structure of the ICF model such as reduced muscle strength may lead to more limitations in functional mobility and dynamic balance, which then again may lead to more sedentary behaviour, an increase in BMI, and potentially restrictions in activity and participation. Appropriately designed interventions may prevent further deterioration of functional mobility in adults with CP. Strength or balance training can potentially be beneficial for rehabilitation programs in ambulant adults with CP. In a recent study, Gillett et al. (2018) indicated that deterioration in particularly muscle strength is associated with functional decline with ageing in adults with CP.[42] In the latter study, however, muscle strength of only plantar and dorsi flexor muscle groups was taken into account, while from current results it can be suggested that muscle weakness of large lower limb muscle group, especially around hip and knee, can also contribute to impaired functional mobility and dynamic balance.

Hence, future research is necessary to investigate whether strength training of particularly these muscle groups may contribute to functional skills, such as standing and walking.

An important limitation that should be taken into account while interpreting results of the current study is that only a small number of adults with CP classified in GMFCS level III was included. From these results based on the small number (n = 5), no firm conclusions can be drawn. Future research is recommended to include larger samples of individuals with CP classified in GMFCS level III.

Conclusion

In the current study, we found that ambulant adults with CP and spastic diplegia, who were living in a developing country and received orthopaedic ISA treatment in childhood, showed limitations in physical status, functional mobility and balance, relative to TD adults. These outcomes may serve as reference for clinical practice as well as future intervention studies. Negative associations that were found between muscle strength and functional mobility and dynamic balance, GMFCS level and BMI highlight the importance of the implementation of muscle strength training in rehabilitation programs during ageing in adults with CP. This information can be used in future studies to appropriately design interventions to prevent deterioration in functional capacity and promote healthy ageing in adults with CP.

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BIOMECHANICAL ANALYSIS OF GAIT AND WAVEFORM DATA IN AMBULANT ADULTS WITH CERBRAL PALSY

A SIX-YEAR FOLLOW-UP STUDY AFTER INTERVAL SURGERY APPROACH

INSIGHTS FROM A DEVELOPING COUNTRY

INTRODUCTION

Traditionally cerebral palsy (CP) was more often described as a paediatric disorder.[1] However, with improved medical care, life expectancy for individuals with CP have increased significantly, with the majority of children surviving into adulthood.[1–4] Hence, ageing with CP has become an important and relevant topic. Despite the fact that CP is a non-progressive disorder,[5] the clinical manifestation might change throughout life.[6] Motor abnormalities, like increased muscle tone and impaired selective motor control with its sequelae, can have a great impact on the ageing process in individuals with CP.

Overall about 80% of the individuals with CP are diagnosed with the spastic subtype.[7] The increased muscle tone can be addressed with non-surgical (e.g. medication) or surgical approaches (orthopaedic or neurosurgical), aiming to prevent contractures, bony deformities and other secondary abnormalities in the long-term.[8]

In the ideal world, children with CP should be followed up from a young age and receive an individualised treatment plan designed by a multidisciplinary team.[9] However, unfortunately, this is not always possible, especially in developing countries. As for example in Africa, there are often problems with access to health care facilities (due to financial, transport or stigma issues) as well as health care specialists and medical services.[10]

Therefore, the treatment regime for an ambulant child with spastic diplegia growing up in a developed country can differ significantly from a child living in a developing country. For example a child living in a developed country can be exposed to conservative treatment, botuline toxine injections followed by 'Single Event Multi Level Surgery' (SEMLS) at the appropriate time (e.g. between 5 – 10 years), while the child in a developing country might only have access to conservative treatment and orthopaedic interventions based on an 'Interval Surgery Approach' (ISA). The main difference between SEMLS and ISA is that with SEMLS a number of abnormalities is addressed at the same time, while with ISA the children receive pockets of surgical interventions at multiple times.[11]

There are a number of publications on the outcomes of orthopaedic surgery based on SEMLS and this procedure seems to have positive results (especially regarding improved gait pattern).[12] However, there is limited literature about long-term outcomes after SEMLS and

especially ISA. Research on long- term outcomes may have important clinical implications for the adult with CP.

There is an increased number of research studies completed on adults with CP, showing self-reported deterioration in functional mobility with ageing, though the literature doesn't specify whether the participants received interventions in childhood and no follow-up data during adulthood was included.[13]As also concluded by the systematic review on 'Paediatric Cerebral Palsy in Africa', there is a need for longitudinal studies that objectively investigate clinical outcomes over time.[10]

Therefore, the aim of this study was to determine whether the gait pattern of adults with CP and spastic diplegia, who underwent orthopaedic interventions based on ISA at least 25 years ago, was: i) changed during adulthood (six-year follow-up period); ii) differs to the gait pattern of typical developed (TD) peers; and iii) was related to functional level (Gross Motor Function Classification System (GMFCS)[14] and contextual factors.

METHODS

Participants

This is a six-year follow-up study (2011 vs 2017) of thirty adults with CP. For the baseline study, they were initially recruited from a database of a school for learners with special needs in Cape Town, South Africa.[11] Inclusion criteria for the study were a diagnosis of CP and spastic diplegia (with mild unilateral upper extremity involvement allowed), able to walk with or without assistive devices (GMFCS level I, II or III)[14] and received their first orthopaedic interventions for soft-tissue or bony deformities of the lower extremities based on an ISA more than 25 years ago. Exclusion criteria were listed as a diagnosis of dyskinetic, ataxic or mixed type of CP, and living further than a 100km radius from the testing facilities in Cape Town, South Africa. For the follow-up, the same 30 participants were contacted and asked for their participation in current study. Reference data were based on 41 typical developed (TD) adults with no history of orthopaedic or neurological pathology.

After agreement, all participants signed a written informed consent, which was approved by the local Human Research Ethics Committees (HREC 013/2017 and N17/04/035) and conducted in line with the principles set out in the Declaration of Helsinki (2013).[15]

Participants' personal characteristics were reviewed at the intake of the current study. This included age, gender, Body Mass Index (BMI), type of orthopaedic interventions received in childhood and level of GMFCS[14] at baseline and the current study. In addition, socio-economic-status (SES) was estimated by housing density, which was calculated by dividing the number of people living at home, by the number of rooms in the house (excluding kitchen and bathroom). Herewith SES categories were defined as followed: Low SES: index >1.5; normal SES: 1.0 – 1.5; high SES: <1.0.[16]

3D gait analysis

The gait assessments of baseline and follow-up study were performed at the gait laboratory of the Neuromechanics Unit, Central Analytical Facilities (CAF), Tygerberg, of Stellenbosch University. Participants were asked to walk at a self-selected, comfortable speed on a 20-m walkway of which eight meter was used for data capturing. Participants were allowed to use their assistive device(s) if that was what they normally used in the community. Reflective markers were attached to bony landmarks of the lower extremities, according to a modified Helen-Hayes marker set used for the lower body Plug-in Gait model (now known as the Conventional Gait Model). Gait kinematics were established through the collection of 3D marker trajectories recorded with a ten-camera motion capture system (Vicon, Oxford Metrics, UK), including eight MXT20 and two Bonita cameras, sampling at 200 Hz. At least five trials per participant were captured, from which three trials with best quality and consistent data were selected for further analysis. Per trial one gait cycle (left and right strides) was used for further analysis, resulting in six gait cycles per participant.

Data processing

The gait data of the baseline and current study were processed using a similar procedure in Vicon Nexus. This included marker trajectory reconstruction, marker labelling, gap filling of

labelled trajectories where necessary, running of the Plug-in Gait model and filtering of model outputs with standard fourth-order zero lag low-pass Butterworth filter with a cut-off frequency of 6 Hz. Gait cycle events were detected, and the trial kinematics were checked for validity and feasibility using the reference videos (sagittal and frontal plane). Thereafter, custom code scripts in MATLAB (MATLAB R2017a, The MathWorks, Inc., Natick, Massachusetts, United States) were used to extract discrete points of the gait cycle. MATLAB coding was also used to normalize the entire gait cycle to 100% (based on 101 data points). This resulted in continuous kinematic gait data, which was entered into PRISM (GraphPad Prism version 7.02, GraphPad Software, San Diego, CA, USA)) to plot gait wave forms in three planes for the pelvis, hip, knee and ankle.

The following discrete kinematic gait parameters were analysed: Pelvis: mean tilt, range of motion (ROM) in sagittal and transverse planes; Hip: maximal extension and adduction, mean rotation, ROM in sagittal and frontal planes; Knee: initial contact (IC) flexion, ROM in sagittal plane, maximal extension and flexion; Ankle: IC and mean dorsi/plantar flexion, maximal plantar flexion and dorsiflexion, and mean foot progression. Based on nine of these parameters, the Gait Deviation Index (GDI) was calculated according to Schwartz and Rozumalski,[17] which is a validated outcome measure to quantify participants' gait pattern. In addition, spatiotemporal parameters were also reported including dimensional and non-dimensional (ND)[18] walking speed, cadence and time to foot off (TFO).

Statistical analysis

The homogeneity of the data was tested with a Shapiro-Wilk normality test, and participants' characteristics were analysed as parametric or non-parametric data accordingly. As most gait parameters were normally distributed, parametric statistical analyses was applied for the gait data analyses. Paired t-tests were used to compare gait parameters at baseline (CP 2011) with results of the six-year follow-up (CP 2017) study. In addition, the Cohen's d effect size was calculated to describe the magnitude of change in the GDI over this period, classified into: 0.0-0.2: trivial effect; 0.2-0.5: small effect; 0.5-0.8: moderate effect; and >0.8: large effect. Independent t-tests were completed to determine differences between the follow-up study of adults with CP and TD adults (CP 2017 versus Reference values). In addition, to improve

visualisation of the gait patterns, the data was also shown in graphs of the three planes (x-y-z). To detect differences in the waveforms of gait of adults with CP between baseline and the follow-up study, a one-way analysis of variance (ANOVA) by one-dimensional spatial parametric mapping (1DSPM) was used.[19] All 1DSPM analyses were implemented using the open-source 1DSPM code (vM0.1, www.spm1d.org) in MATLAB. Significance was set at $p < 0.05$. Lastly, Spearman rho correlations were determined between current GDI and GMFCS, BMI and SES. To compensate for multiple comparisons a Bonferroni corrected alpha-level of $p < 0.01$ ($p < 0.05 / 5$) was applied for comparisons of the (pelvis, hip, knee and ankle) kinematic data and spatiotemporal parameters, and $p < 0.016$ ($p < 0.05 / 3$) for the associations (GDI vs GMFCS, BMI and SES). The statistical analyses were completed with SPSS (v25, Dell Inc, Austin, Texas, USA).

RESULTS

Participants

Of the thirty adults with CP and spastic diplegia who participated in the baseline study (2011), one person was not able to take part in the six-year follow-up, due to health reasons (not CP related). Therefore, 29 people were included of which their characteristics are shown in **Table 3.1**.

Table 3.1. Participant's characteristics of adults with CP (n=29) at baseline (2011) and six-year follow-up (2017). Data expressed as mean (SD), median [IQR] or n (%).

Characteristics	CP baseline	CP 6-year follow-up
Gender (m/f)	12 (41) / 17 (59)	12 (44) / 17 (59)
Age, y:mo	32:9 (7:8)	39:1 (7:9)
GMFCS, level I/II/III	15/10/4	12/12/5
SES, housing index	1.3 [0.8 - 2.0]	1.0 [0.8 - 2.0]
BMI, kg/m^2	23.7 [21.1 - 29.5]	27.8 [22.5 - 31.4]

Abbreviations: y:mo, year:month; GMFCS, Gross Motor Function Classification Scale; SES, Social-economic Status; BMI, Body Mass Index; SD, Standard Deviation; IQR, interquartile range.

The gait data was compared to reference values, based on a cohort of 41 TD adults (19 male, 22 female), mean (SD) age 36:5 (6:1) (y:mo) and BMI median [Interquartile ranges (IQR)] of 24.1 [22.4 - 26.6]. All 29 adults with CP were still ambulant at the six-year follow-up study, though there were some changes in GMFCS level distribution, including a deterioration from level I to II (20%) and level II to III (10%) (**Figure 3.1**).

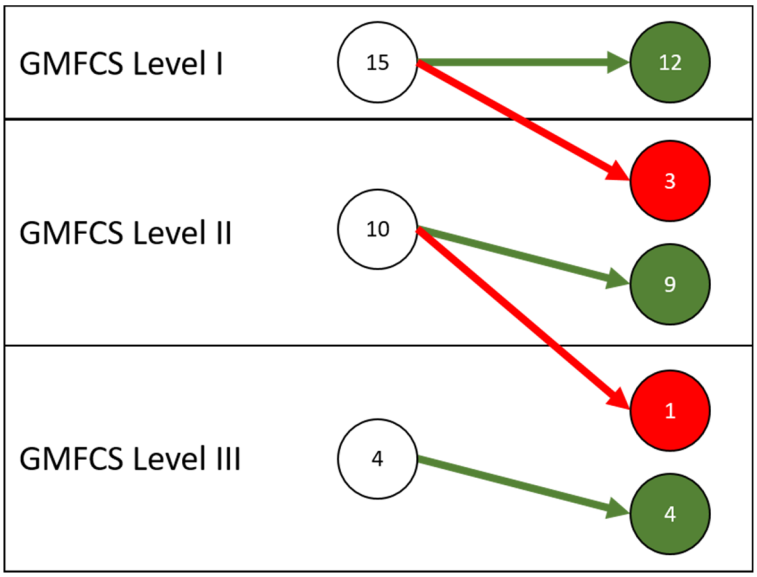

Figure 3.1. Change in GMFCS levels of CP cohort (n=29) between baseline and six-year follow-up study.

Gait parameters

The GDI of the baseline study (mean (SD): 68.5 (9.8)) did not change during the six-year follow-up period (71.0 (11.7)). This was confirmed by the Cohen's d effect size, showing a small effect of d [95%CI] = 0.25 [0.01 – 0.48]. ND spatiotemporal parameters significantly deteriorated, showing a reduction in walking speed and cadence and an increase in TFO. In addition, several changes in gait kinematics were observed, including an overall increased pelvic tilt and decreased knee flexion during swing phase, while maximum knee extension and ankle dorsi- and plantarflexion improve (**Table 3.2**). These changes were confirmed by the waveforms of kinematic gait parameters, presented in **Figure 3.2** (significant changes highlighted in yellow), showing primarily changes in the sagittal plane of the pelvis, knee and ankle.

The GDI of adults with CP (mean (SD): 99.2 (8.5)) was significantly lower compared to TD adults. In addition, significant differences in other spatio-temporal parameters and gait kinematics were observed between adults with CP and TD adults, except for maximal hip adduction and mean foot progression (**Table 3.2**).

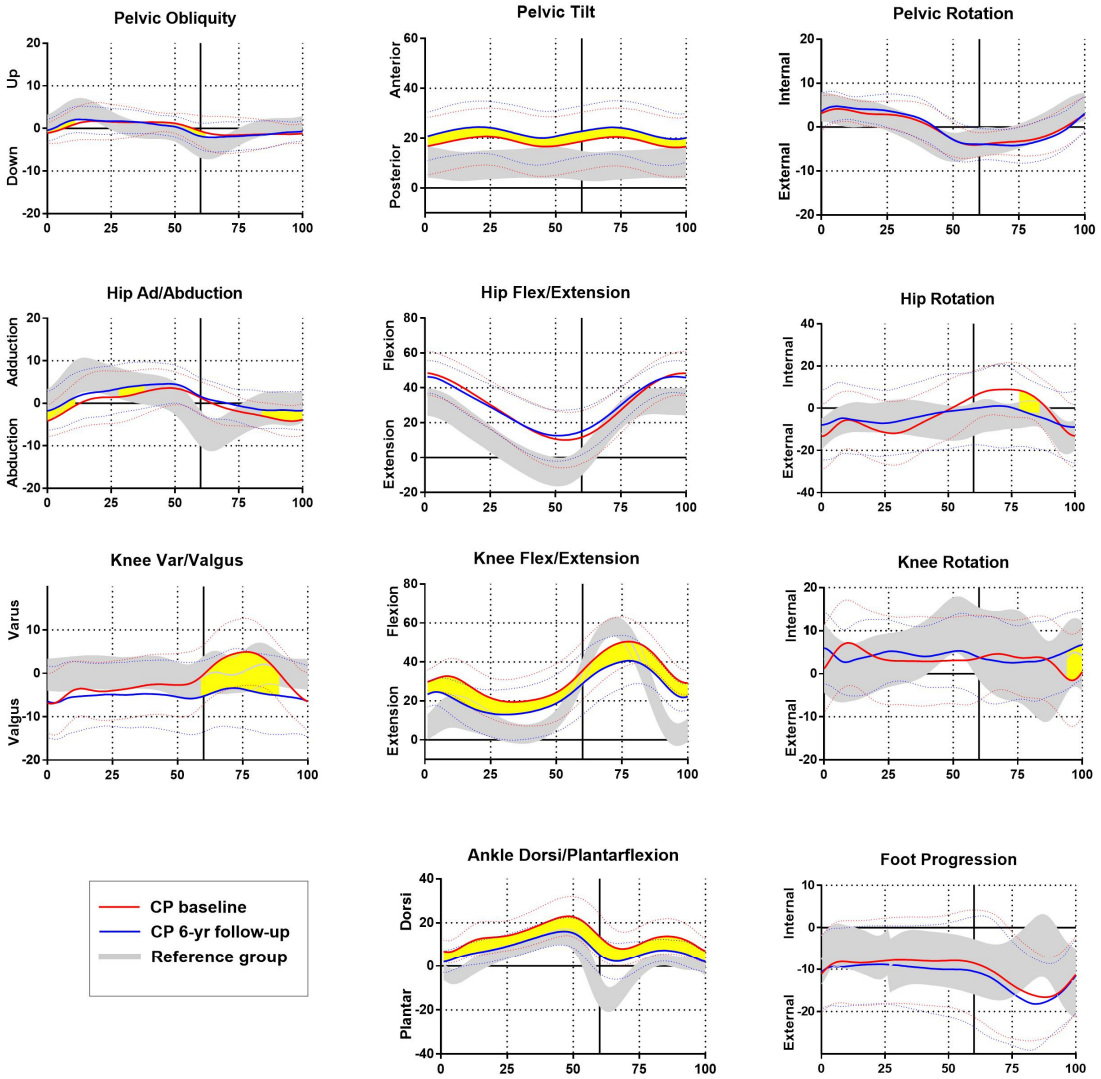

Figure 3.2. Kinematic data (mean +/- 1 standard deviation) for adults with CP assessed at baseline (2011) and six-year follow-up (2017) study in relation to the Reference data.

Table 3.2. Overview of gait parameters for the adults with CP and Reference group.

Parameters	CP 2011		CP 2017		Reference		2011 vs 2017 CP	2017 CP vs Reference
	Mean	SD	Mean	SD	Mean	SD		
Pelvis								
Mean tilt	18.6	11.6	22.4	10.4	9.5	5.8	3.8*	-12.8#
ROM tilt	9.4	4.1	10.2	4.5	3.5	1.3	0.8	-6.7#
ROM rotation	14.9	5.3	16.7	6.7	10.9	4.1	1.7	-5.8#
Hip								
Maximum extension	9.2	16.0	11.4	14.4	-8.6	8.0	2.2	-20.0#
ROM flexion/extension	41.0	10.9	37.3	10.8	42.5	5.0	-3.6*	5.1#
Maximum adduction	6.5	4.5	7.2	6.0	7.1	3.9	0.7	-0.1
ROM abduction/adduction	13.8	4.4	12.2	4.2	14.9	3.7	-1.6*	2.7#
Mean rotation	-2.7	14.1	-3.8	16.8	-5.7	6.2	-1.1	-1.9
Knee								
IC flexion	29.5	9.1	22.6	8.9	5.1	5.8	-6.9*	-17.5#
Maximum extension	16.6	13.9	9.4	14.2	0.5	5.3	-7.2*	-9.0#
Maximum flexion	53.7	13.7	45.2	11.9	58.8	4.7	-8.6*	13.7#
ROM flexion/extension	37.1	12.4	35.7	11.8	58.4	5.0	-1.4	22.6#
Ankle/Foot								
Mean dorsi/plantarflexion	13.8	7.6	7.8	5.9	1.8	2.5	-6.0*	-6.0#
Maximum plantarflexion	2.3	7.6	-2.6	7.3	-16.5	5.5	-5.0*	-13.9#
Maximum dorsiflexion	26.4	10.5	18.3	6.5	14.2	3.4	-8.2*	-4.1#
IC dorsi/plantarflexion	7.7	6.7	2.1	6.1	-1.2	3.3	-5.6*	-3.3#
Mean foot progression	-10.4	12.1	-11.7	12.3	-9.6	6.4	-1.4	2.1
Spatiotemporal distance parameters								
ND Speed	0.30	0.10	0.26	0.10	0.42	0.06	-0.05*	0.16#
ND Cadence	0.52	0.10	0.47	0.13	0.57	0.04	-0.05*	0.10#
TFO	62.0	5.0	66.2	7.4	62.0	1.8	4.2*	-4.3#

Abbreviations: ROM: range of motion; IC: initial contact; ND: non-dimensional; TFO: Time to foot off; SD: standard deviation. Significant differences with Bonferroni corrected alpha-level of $p < 0.008$ between *2011 and 2017 CP studies and #2017 CP studies and Reference values.

Associations

Participants' current gait pattern, based on the GDI (2017), was related to their GMFCS levels ($r = -0.83$; $p<0.001$). There was also a negative association with BMI, meaning that, people with a lower BMI had a better gait pattern ($r= -0.46$; $p=0.011$).

DISCUSSION

This is the first follow-up study describing the gait pattern of adults with CP and spastic diplegia, who grew up and living in a developing country (South Africa). This means that these adults did not receive orthopaedic interventions based on SEMLS in childhood, but multiple interventions on an interval bases, called ISA.[11] The data provides insight in gait pattern changes during six-years of ageing with CP in reference to a cohort of TD peers.

Six-years after the baseline study (median age (y:mo) of 32:9 versus 39:1), all participants were still ambulant. Though, 30% of the cohort deteriorated by one GMFCS level (from GMFCS Level I to II or Level II to III). There were also changes determined in spatio-temporal and kinematic gait parameters and waveforms of gait kinematics. Especially changes in the sagittal plane were observed, though the direction of change varied, either moving away or becoming closer to the reference values (TD group). More specifically, as the SPM results indicate, adults with CP showed continuous increased anterior pelvic tilt and reduced knee flexion during swing, while the knee extension improved in stance and the ankle waveforms showed better dorsi- and plantarflexion throughout the gait cycle in relation to a typical gait pattern.

Overall, the gait pattern, based on GDI, did not change (mean (SD): 68.5 (9.8) vs 71.0 (11.7)), which was confirmed by the small Cohen's effect size. This index was also comparable to the mean (SD) GDI of 68.9 (12.1) of a cohort of adults with CP and spastic diplegia (age range: 22 – 44 years), who underwent Selective Dorsal Rhizotomy (SDR), with additional ISA in childhood.[20] However, the waveforms differed between the cohort of the current study and the SDR cohort. This can be explained by the emphasis of the SDR to release the spasticity from the lower extremities, resulting in no 'spasticity signs' in their kinematic data.[21] This explains the main differences between the two studies, with the double bump pattern and

slowed (decreased slope in the graph) and decreased knee flexion at early swing in the cohort who did not undergo SDR.

Compared to the TD cohort, the adults with CP and spastic diplegia who underwent only orthopaedic interventions based on ISA walked with a flexed gait (increased anterior pelvic tilt, hip and knee flexion, and dorsiflexion). In addition, the gait was characterised by a stiff knee gait pattern often caused by increased spasticity (as described above). These gait abnormalities are common in ageing CP population, with 68% reported excessive hip flexion and 94% with stiff knee gait.[22]

As described in a systematic review on gait function and decline, adults with CP are at risk of gait deterioration based on their physical status as a child, diagnoses of bilateral CP, age and increased levels of pain and fatigue.[13] Although these observations were not highlighted in the current study, associations between GDI and GMFCS level, BMI and SES were investigated. As expected, GDI was strongly associated with level of GMFCS and BMI. Future research is recommended to investigate whether improvements in GDI may occur when BMI reduces in adults with CP. Interestingly, no relationships was found with SES, meaning that the gait is not affected by possible worse housing situation, access to transport and health care, and possibly suboptimal nutrition.

This study has a variety of limiting factors, which were related to the study design of the baseline study (2011). First, a relatively small sample was included, which did not allow to distinguish between GMFCS levels. Since GMFCS level was associated with the gait pattern (GDI), future research is recommended to recruit a larger sample in order to investigate changes in gait per GMFCS level. Second, no childhood or pre-operative data was available for the participants. Lastly, it was not clear whether changes in gait kinematics were clinically relevant, which is a common issue in clinical research. A change during the six-year ageing period can be calculated to be significant for a certain parameter, but this does not automatically mean that it has an impact in clinical practice and was maybe (partly) caused by a measurement error.

Conclusion

In conclusion, adults with CP and spastic diplegia walked with a flexed and stiff knee gait pattern, though they were still ambulant and showed no change in their GDI during the six-year ageing period, while there were some changes observed in spatiotemporal and kinematic gait parameters In addition, it is important to note that GDI associated strongly with GMFCS level and BMI. It is helpful to provide this information to young individuals with CP and to motivate them about the benefits of becoming / staying functionally mobile, physically active and have optimal body composition. The outcomes of this study have important implications for clinicians and parents living in a developing country like South Africa, where access to optimal health care is not guaranteed and children often receive only conservative treatment and orthopaedic interventions based on ISA.

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SPINAL CURVATURES AND LEVEL OF DISABILITY DUE TO PAIN IN AMBULANT ADULTS WITH CERBRAL PALSY

A SIX-YEAR FOLLOW-UP STUDY AFTER INTERVAL SURGERY APPROACH

INSIGHTS FROM A DEVELOPING COUNTRY

INTRODUCTION

Cerebral palsy (CP) is defined as a permanent, non-progressive lesion of the developing brain that results in an abnormal development of movement and posture.[1] The incidence of CP is estimated at 2 to 3 per 1000 live births.[2] The term encompasses a heterogeneous group of conditions characterized by abnormal muscle tone, muscle paresis, impaired selective motor control and co-activation.[3] Due to the combination of these primary motor impairments, individuals with CP often develop a spinal deformity.[4]

Previous research has shown that there is a strong link between CP and the development of scoliosis, with estimated prevalence rates between 15 and 80%.[5,6] The wide range in prevalence is due to variations in the populations being studied, such as differences in age, severity of neurological dysfunction, and the extent of impairment of physical function.[7] The highest rates of scoliosis were found in cohorts with spastic CP (69%)[6] and rates increased with Gross Motor Function Classification System (GMFCS) level.[5]

Early research has shown that curves tend to progress after skeletal maturity during ageing in adults with CP.[8] Progression of spinal deformities in adults with CP may negatively impact individual's mobility and function, and/or may lead to an increase in pain. Most studies that investigated progression of spinal deformities in CP focused on individuals who underwent procedures that are known to influence curves, such as selective dorsal rhizotomy (SDR)[9,10] or intrathecal baclofen,[11] and on individuals who were institutionalized residents.[6] Evidence about the degenerative changes that might occur during ageing in an ambulant population with CP is however limited. In a retrospective study, Lee et al. (2015) showed that scoliosis Cobb, thoracic kyphosis and lumbar lordosis angles deteriorated in adults with CP classified in GMFCS level IV and V, while these angles seemed to remain stable in GMFCS level I-III.[12] However, changes in curves of ambulant adults with CP were not presented per GMFCS level.

Potential changes in spinal curves may be related to increasing pain in adults with CP. Previous research showed that 38 - 83 % of adults with CP reported to suffer from pain,[13–20] compared to 15% in the general population.[17] Pain was most frequently reported in the back, hip and lower extremities.[13,17,21,22] This pain can negatively affect their daily functioning and reduce their quality of life.[14–16] In addition, pain has been shown to increase with age in adults with CP,[13,14] which could be caused by spinal deformities. Eventually, these changes in impairments

at the level of body function and structure may lead to restrictions on the level of activity and participation of the International Classification of Function, Disability and Health (ICF) model.

Therefore, the aims of the study were to investigate changes in spinal curvatures and the level of disability due to pain during ageing in ambulant adults with CP and spastic diplegia, to investigate whether changes differ between adults with CP classified in different levels of GMFCS, and to investigate whether spinal curvatures associate with individual characteristics and the level of disability due to pain.

METHODS

Participants

At baseline in 2011, a group of thirty adults with CP was recruited from a database of a special needs school for disabled children in Cape Town, South Africa. Inclusion criteria for the baseline study were a diagnosis of CP and spastic diplegia, with or without mild unilateral upper extremity involvement, who were able to walk with or without assistive devices (Gross Motor Function Classification System (GMFCS) Expanded and Revised level I, II or III [23]) and received orthopaedic surgery during childhood following an interval surgery approach.[24] Those who received SDR were excluded, as well as participants who had a diagnosis of other neuromuscular disorders and/or another type of CP, i.e. dystonia, athetosis, ataxia or hypotonia. For logistical reasons participants had to live within a 100km radius from the testing facilities in Cape Town.

In 2017, the same cohort of adults with CP was recruited for the six-year follow-up study. Before taking part in the study, all participants signed a written informed consent. The study was approved by the by the local institution (UCT: 133.2016; SUN: 013.2017) and conducted in line with the principles set out in the Declaration of Helsinki (2013).

Procedure

Individual's characteristics were obtained including age, gender, socio-economic status (SES). SES was estimated based on housing density,[21] by dividing the number of people living in the house by the number of rooms within the house (excluding kitchen and bathroom). BMI was

calculated from height and weight that were taken. Furthermore, Gross Motor Function Classification System (GMFCS) level, the number and type of orthopaedic interventions participants received during childhood were obtained.

X-rays

At baseline and in the six-year follow-up study, X-rays were taken in standing position with frontal and lateral views. Scoliosis was determined from frontal views using Cobb's angle measurements. Cobb's angles of 10-29°, 30-39° and >40° were considered as mild, moderate and severe scoliosis respectively.[7,25] Thoracic kyphosis and lumbar lordosis curves were determined from lateral views. Kyphosis describes the sagittal convexity of the thoracic spine, measured from superior endplate of T3 to inferior endplate of T12. Lordosis describes the sagittal concavity of the lumbar spine, measured from the superior endplate of L1 to the inferior endplate of L5. Ranges of 20-50° for thoracic kyphosis and of 20-60° for lumbar lordosis were considered normal.[26] A change of 10° or more in scoliosis Cobb, thoracic kyphosis or lumber lordosis angles was considered a minimal clinically important difference (MCID).[27] In the six-year follow-up study, the prevalence of spondylolysis and spondylolisthesis was evaluated from lateral and oblique radiographic views. Spondylolysis has previously been defined as a defect in pars articularis of the vertebral arch.[28] Spondylolisthesis was measured as a percentage of the displacement of the vertebra body and was graded according to the Meyerding system (Grade I for 25%, II for 50%, III for 75% or IV for 100%).[29]

Disability due to pain

Participants completed the Oswestry Disability Index (ODI) 2.0 questionnaire, which assesses self-reported level of disability due to pain in daily life. Participants were asked to rate to what extent back and/or lower limb pain affected the performance of ten activities, i.e. personal care, lifting, sitting, standing, walking, sleeping, sex life, social life and travelling. The scale ranged from no problems (score 0) to severe problems (score 5). The ODI has previously been shown to be valid and reliable to measure self-reported disability.[30,31] A change of 5 points or more in ODI total score was considered a MCID.[32] Based on the number of applicable

questions a Total ODI score was calculated, which was categorized as: 0 – 20%: minimal disability, 21 – 40%: moderate disability, 41 – 60%: severe disability, 61 – 80%: house bound and 81 – 100%: bed bound.

Statistical analysis

Based on power calculation, a minimum sample size of n=25 was calculated ($\alpha = 0.05$; $\beta = 0.20$; effect size = 0.50).[33] Normal distribution of data was assessed by the Shapiro-Wilk test. Normally distributed data were presented as mean and standard deviation (SD) and non-normally distributed data was presented as median and interquartile ranges (IQR). Differences in curvature (in degrees) and ODI scores between baseline and six-years follow-up were analysed using a Wilcoxon rank test, for the total cohort and separately for GMFCS levels. In addition, Cohen's d effect sizes were calculated to describe the magnitude of change, classified into: 0.0-0.2: trivial effect; 0.2-0.5: small effect; 0.5-0.8: moderate effect; and >0.8: large effect. Spearman's rho was calculated to identify associations between curvatures of scoliosis Cobb angle, thoracic kyphosis and lumbar lordosis and participant's characteristics (current age, gender, GMFCS, BMI, SES) and Total ODI score. SPSS version 25 (Dell Inc, Austin, Texas, USA) was used to analyse the data. The level of significance adapted to correct for multiple testing.

RESULTS

Participant's characteristics

At baseline, X-rays were taken from 29, out of the original cohort of 30, adults with CP, since one participant was pregnant. Twenty-seven adults with CP, out of the 29 (93%), participated in the six-year follow-up study. Reasons for exclusion were that one adult suffered from severe illness and one adult moved out of the 100km radius of Cape Town. Participant's characteristics are presented in **Table 4.1**. Participants received different orthopaedic interventions, such as Achilles tendon (n=27; 100%) and hamstring lengthening (n=15; 56%). Other soft tissue procedures were performed on adductors (n=9; 33%), rectus femoris (n=7; 26%), psoas (n=6; 22%) and tibialis posterior (n=3; 11%). Bony surgeries included ankle/foot

corrections (n=11; 37%), femoral derotation (n=4; 15%) and tibial derotation (n=4; 15%). None of the adults with CP received spinal surgery. For the whole cohort, mean follow-up time after first orthopaedic intervention was 34:2 (7:3) years:months. No differences were observed in the number of interventions or surgical events between participants of GMFCS levels I, II and III.

Table 4.1. Descriptive statistics of adults with CP classified as GMFCS level I, II and III. Data expressed as mean (SD) or median [IQR] or n (%).

Parameter	All participants (n=27)	GMFCS I (n=11)	GMFCS II (n=12)	GMFCS III (n=4)
Age (y:mo)	39:7 [35:0 – 45:9]	37:10 [28:10 – 42:6]	43:2 [37:7 – 46:3]	42:8 [28:8 – 52:4]
Height (m)	1.61 [1.52 – 1.71]	1.67 [1.61 – 1.73]	1.54 [1.48 – 1.63]	1.55 [1.41 – 1.68]
BMI (kg/m^2)	27.8 [22.6 – 31.6]	23.6 [20.1 – 29.7]	28.3 [23.9 – 30.8]	36.0 [29.0 – 42.4]
Gender (m/f)	12 (44) / 15 (56)	7 (64) / 4 (36)	4 (33) / 8 (67)	1 (25) / 3 (75)
SES	1.0 [0.8 – 2.0]	1.0 [0.8 – 2.0]	1.3 [0.6 – 2.0]	1.1 [0.8 – 1.3]
Number of interventions	4 [2 – 6]	1 [1 – 6]	4.5 [4 – 7.5]	4.5 [2.5 – 6.5]
Number of surgical events	3 [2 – 4]	1 [1 – 4]	3 [2 – 4.8]	3.5 [2.3 – 4.75]

Abbreviations: SD, standard deviation; IQR, interquartile ranges; BMI, body mass index; SES, socio-economic status; GMFCS, Gross Motor Function Classification System.

Curvature

At baseline (2011), 11 of the participants (41%) showed mild scoliosis, and no moderate to severe scoliosis was observed, while at six-years follow-up (2017), eight of them (29%) showed mild scoliosis and one (4%) showed moderate scoliosis. At baseline, two participants (7%) showed thoracic hyperkyphosis and 9 participants (33%) showed hypokyphosis, while none showed hyperkyphosis and 2 (7%) showed hypokyphosis at six-years follow-up. At baseline, five participants (19%) showed lumbar hyperlordosis, while four participants (15%)

showed hyperlordosis at six-years follow-up. At both baseline and six-year follow-up, one participant (4%) showed hypolordosis.

Baseline and follow-up data of scoliosis Cobb, thoracic kyphosis and lumbar lordosis angles are presented in **Table 4.2** and **Figure 4.1**. No changes in scoliosis Cobb and lumbar lordosis angles were observed (**Table 4.2**), while thoracic kyphosis angle increased significantly across the total cohort ((median [IQR] = 7.0° [0.0 – 14.0°]; p<0.001).

Table 4.2 Scoliosis Cobb, thoracic kyphosis and lumbar lordosis angles in degrees (°) at baseline and six-year follow-up (median [IQR]).

	Scoliosis Cobb	Thoracic kyphosis	Lumbar lordosis
Total cohort (n = 27)			
baseline	8.0 [6.0-12.0]	22.0* [18.0-36.0]	48.0 [36.0-60.0]
6-yr follow-up	5.0 [2.0-12.0]	32.0* [28.0-41.0]	49.0 [39.0-56.0]
GMFCS I			
baseline	8.0 [6.0-10.0]	22.0 [18.0-50.0]	50.0 [40.0-56.0]
6-yr follow-up	2.0 [1.0-6.0]	35.0 [28.0-45.0]	47.0 [39.0-57.0]
GMFCS II			
baseline	9.0 [6.0-12.0]	20.0 [13.5-34.5]	45.0 [30.0-66.0]
6-yr follow-up	8.0 [3.3-16.5]	31.0 [28.0-38.5]	51.0 [39.0-61.8]
GMFCS III			
baseline	7.0 [6.0-14.0]	28.0 [6.5-30.0]	44.0 [32.5-58.5]
6-yr follow-up	12.0 [3.0-21.0]	29.5 [19.5-38.0]	46.0 [40.3-51.3]

** p < 0.0125*

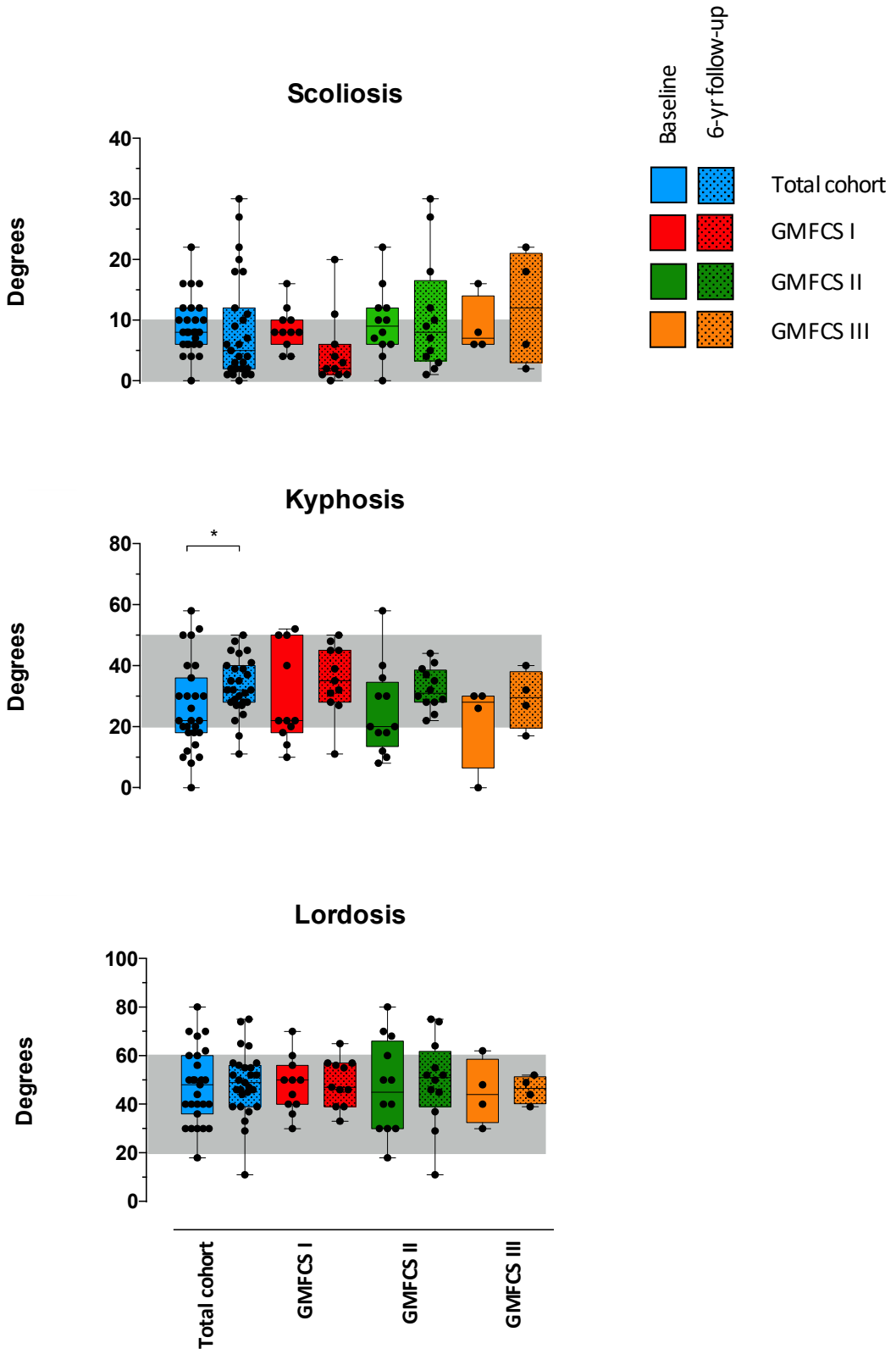

Figure 4.1. Boxplots presenting scoliosis Cobb, thoracic kyphosis and lumbar lordosis angles in degrees (°) at baseline (2011; solid boxes) and six-year follow-up (2017; dotted boxes), for the total cohort and for GMFCS level I, II and III separately. $^{*}p < 0.0125$.

Figure 4.2 presents the effect sizes for the changes in curves separately for the total cohort, and for adults with CP classified in GMFCS level I, II and III separately. The changes in curves varied, especially within adults with CP classified in GMFCS III. A large effect in adults with CP classified in GMFCS level I was observed showing a decrease in scoliosis Cobb angle. In addition, moderate effects were observed for the total cohort and adults with CP classified in GMFCS level II showing an increase in thoracic kyphosis angle.

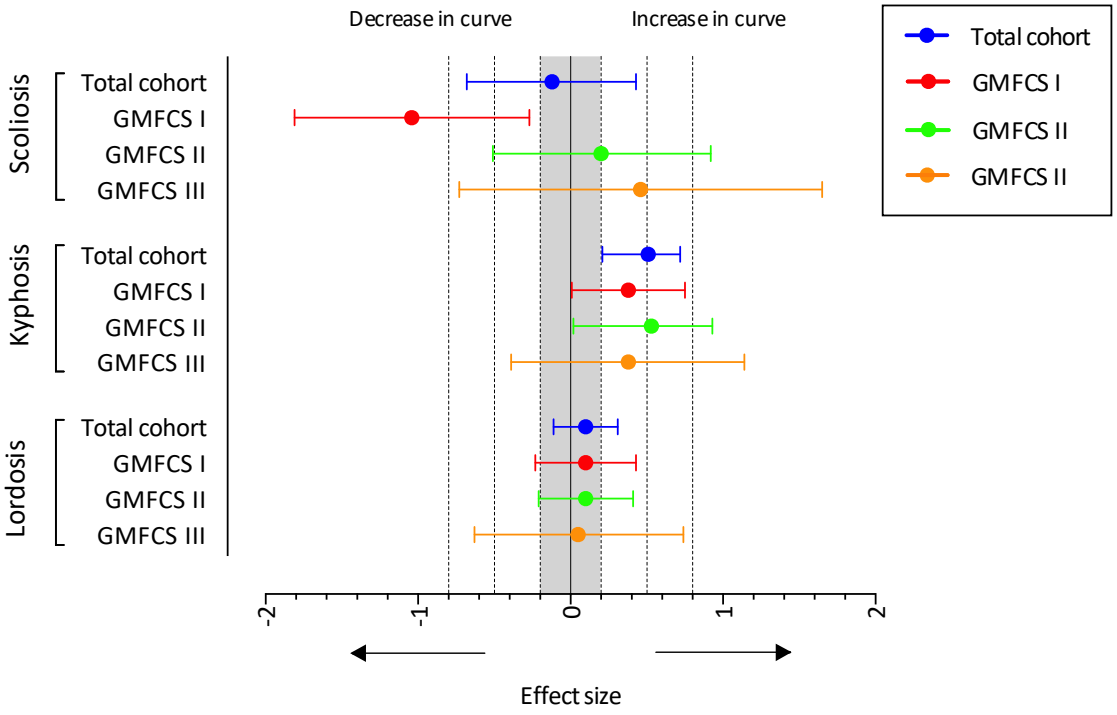

Figure 4.2. Overview of the effect sizes of changes in scoliosis Cobb, thoracic kyphosis and lumbar lordosis, for the total cohort and for GMFCS level I, II and III separately. Dots indicate the mean change and whiskers indicate the 95% CI. (Cohen effect sizes [95%CI]: 0.0-0.2: trivial effect; 0.2-0.5: small effect; 0.5-0.8: moderate effect; >0.8: large effect).

Adults with CP classified in GMFCS I, II and III did not show spondylolysis or spondylolisthesis at the six-year follow-up study.

Disability due to pain

All participants (n=27) completed the ODI questionnaire at baseline and six-years follow-up. No significant differences were observed in Total ODI scores for all participants and separately per GMFCS level (**Figure 4.3**). The vast majority of the participants reported minimal disability due to pain at baseline (74%) and at six-years follow-up (63%), while moderate disability was reported by six participants at baseline (22%) and seven participants six-years follow-up (26%), and severe disability by one participant at baseline (4%) and three participants six-years follow-up (11%).

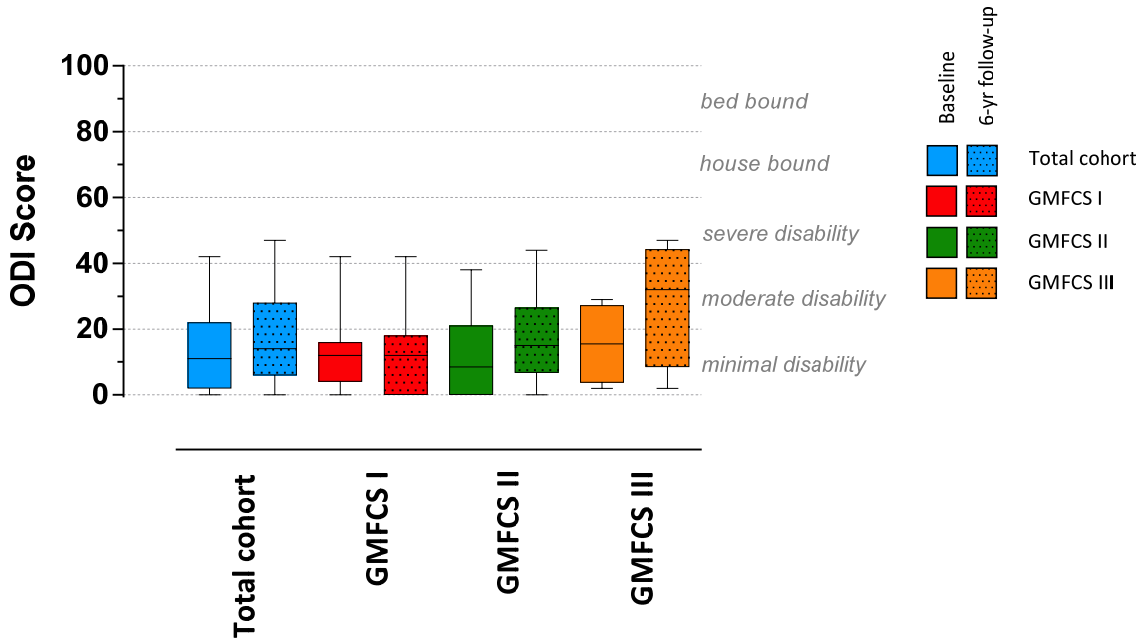

Figure 4.3. Boxplots of Total ODI scores at baseline and six-years follow-up of the total cohort and for GMFCS level I, II and III separately. Score: 0 – 20%, minimal disability; 21 – 40%, moderate disability; 41 – 60%, severe disability; 61 – 80% house bound; 81 – 100%, bed bound.

Associations

Results regarding associations of spine curvature with participants' characteristics and Total ODI score are presented in **Table 4.4**. Negative associations were observed for lumbar lordosis angles with age.

Table 4.4. Associations between curvatures, participants' characteristics and disability due to pain.

	Cobb scoliosis		Thoracic kyphosis		Lumbar lordosis	
Characteristics	r	p	r	p	r	p
Age	0.06	0.745	-0.42	0.023	-0.44	0.016*
Gender	0.27	0.169	0.21	0.295	0.38	0.045
GMFCS	0.43	0.022	-0.26	0.184	-0.11	0.570
BMI	0.26	0.191	-0.17	0.379	-0.06	0.756
SES	0.03	0.861	0.42	0.020	0.19	0.333
Disability due to pain						
Total ODI score	0.40	0.028	0.11	0.565	0.17	0.383

** p < 0.0167*

DISCUSSION

This study provides evidence that spinal curves are relatively stable in ambulant adults with CP and spastic diplegia classified in GMFCS I, II and III over a period of six years. Although results indicated that an increase in thoracic kyphosis angle occurred in the total cohort, no differences were observed for the GMFCS levels separately, and median changes showed that curvatures remained within the normal ranges. These findings are consistent with observations of a retrospective study,[12] indicating that ambulant adults with CP (GMFCS level I-III) do not seem to develop severe spinal deformities during ageing.

The general trend in the data showed a stable scoliosis curve. However, changes in scoliosis curve could occur at individual level. Two participants (GMFCS II and III) showed considerable increases (16° and 17°, respectively), and one participant changed of being categorised as mild to now moderate scoliosis (from 22 to 30°). In addition, the incidence of scoliosis found in current study showed to be considerably higher than in the typical developed (TD) population (curve ≥10°: 33% vs. 8-9%).[34,35] Despite the overall stability in scoliosis Cobb angles, these results warn physicians to monitor individual progression of spinal deformities closely in adults with CP.

Results showed that thoracic kyphosis angles increased for the total cohort, although, the magnitude of the change was moderate, while within the GMFCS level groups no change was observed and small to moderate Cohen effect sizes were reported. In addition, none of the adults with CP showed hyperkyphosis at the six-year follow-up study, indicating that the

changes in thoracic kyphosis angles remained within normal ranges. Furthermore, the percentage of adults with CP who showed hypokyphosis decreased (baseline: 33%; six-year follow-up: 7%). These results suggest that thoracic kyphosis angles changed towards normal ranges, which is also commonly observed with ageing in the TD population.[36,37]

No changes were observed in lumbar lordosis curves in adults with CP. There was even a decrease in incidence of hyper lordosis observed, changing from 19% at baseline to 15% six-year follow-up. The lordosis curves were however considerably larger in our cohort (median: baseline=48.0°; six-years follow-up=49.0°) than observed in a TD cohort previously published (median=39.0°).[39]

No changes in the level of disability due to pain were observed in ambulant adults with CP, which is in line with the results of the spinal curvature. Previous research by Opheim et al. however did show that the impact of pain on work and activities of daily life increased in adults with CP (SF-36; bodily pain subscale) over a period of six years.[15] The differences in findings could be caused by different study populations that were included. Where current study focused on adults with CP and spastic diplegia classified in GMFCS I-III, Opheim et al. included adults with different subtypes of CP (GMFCS I-V; unilateral and bilateral CP), in which adults who were classified in higher GMFCS levels could have reported more severe changes in the impact of pain on daily life.

Although non-significant, we found a modest trend towards larger scoliosis Cobb angles with higher GMFCS level, which has been commonly presented in previous research that focused on individuals after SDR, intrathecal baclofen, or adults with CP living in an institution.[6,9–11] Results of current study also showed that lumbar lordosis angles were negatively associated with age, which is in consistence with a previously observed trend for the TD population.[39] Future research is recommended to monitor whole body posture, including lower extremity, as consequences of ageing with CP may extend beyond the spinal column. Important to note is that no associations were observed between the spine curvatures of adults with CP and their SES.

An important limitation that should be taken into account while interpreting results of the current study is that only a small number of participants classified as GMFCS III was included. Another limitation of this study is that no follow-up data for spondylolisthesis and

spondylolysis were available, and therefore these results could not be reported as part of the six-year follow-up study.

CONCLUSION

The results showed that scoliosis Cobb and lumbar lordosis angles were stable in ambulant adults with CP over a six-year period. Thoracic kyphosis angles showed to increase (with a moderate effect size) for all adults with CP, though not when investigated separately for GMFCS level I, II and III, and curvatures remained within normal ranges. No changes in the level of disability due to pain were observed. Hence, although adults with CP and spastic diplegia are at risk to develop spinal deformities during ageing, progression of spinal curves does not seem to occur in all ambulant adults with CP. However, severe individual changes could occur, highlighting the importance to individually monitor progression of spinal curvature in adults with CP.

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AGEING WITH CEREBRAL PALSY AND SPASTIC DIPLEGIA; LONG-TERM FOLLOW-UP OF THE LEVEL OF ACCOMPLISHMENT AND SATISFACTION IN ACTIVITY AND PARTICIPATION IN DAILY LIFE

A SIX-YEAR FOLLOW-UP STUDY AFTER INTERVAL SURGERY APPROACH

INSIGHTS FROM A DEVELOPING COUNTRY

INTRODUCTION

One of the most common causes of lifelong physical disability acquired during childhood is cerebral palsy (CP),[1] with an international prevalence of 2 to 3 per 1000 life births.[2,3] This prevalence is estimated to be higher in African countries with a range between 2 to 10 per 1000 live births.[4] This wide range of estimated prevalence could be explained by methodological differences, though it is likely that the prevalence of CP is indeed higher in Africa because of the level of perinatal complications, such as birth asphyxia and neonatal infections.[5]

According to these numbers, CP is considered as one of world's largest diagnostic groups in adults with a physical impairment.[6] Furthermore, based on a stable incidence rate[7] and longevity of individuals with CP, currently most persons with CP are adults.[8] Although awareness to focus on rehabilitation for adults with CP raised recently, health care providers nowadays still often lack knowledge to offer appropriate care to support adults with CP in their physical disability during daily life. Especially research on adults with CP who live in developing countries, such as South Africa, is limited.

While CP is the result of a non-progressive brain insult, secondary impairments may alter as the person matures. Previous research has shown that adults with CP report fatigue[9,10] and pain[9,11] to be major issues in daily life. In addition, previous research has shown that adults with CP complain earlier in life about age-related physiological changes, such as deterioration of balance and mobility, compared to age-matched controls.[12,13] These factors could severely affect participation, as well as how satisfied individuals are with their participation in daily life.

Recognition that the level of activity and participation in adulthood may be limited highlights the need for long-term follow-up studies that take into account the course through ageing in CP. Although activity and participation restrictions have been widely reported in adults with CP, limited follow-up studies on how the limitations change when adults with CP age are available, especially in those who live in developing countries. Previous research showed that the level of accomplishment and satisfaction in activity and participation was relatively high in adults with CP who were living in South Africa.[14,15] However, no long-term follow-up information is available yet. Knowledge about the long-term outcomes may support practitioners in optimizing interventions at an early age. In addition, long-term outcome

studies are essential to guide future decisions in healthcare, education and social services, which is highly important for developing areas.[16]

Therefore, the primary aim of this study was to investigate the change in level of accomplishment and satisfaction in daily activities and participation (based on the Life-Habits questionnaire), functional mobility and pain frequency of adults with CP and spastic diplegia, living in a developing country, over a six-year period. The secondary aim was to compare levels of accomplishment and satisfaction with typically developed (TD) adults. And the third aim was to explore potential associations between outcomes of the Life-Habits questionnaire and personal factors, functional mobility and pain frequency in adults with CP.

METHODS

Study design

For this study, we recruited adults with CP from a database of a school for children with special needs (Cape Town, South Africa) at baseline (2011). The inclusion criteria were the following: A diagnosis of spastic diplegia, with or without mild unilateral upper extremity involvement, the ability to walk with or without assistive devices (Gross Motor Function Classification System (GMFCS) Expanded and Revised level I, II or III [17]), and underwent orthopaedic interventions during childhood following an interval surgery approach (ISA).[18] Exclusion criteria were: A diagnosis of dystonia, athetosis, ataxia or hypotonia, a neurological intervention such as a Selective Dorsal Rhizotomy (SDR) and living outside of a 100km radius from the testing facilities in Cape Town. For the baseline study, thirty adults with CP were recruited,[15] who were contacted again to participate in the six-years follow-up study in 2017. In addition, TD adults from similar backgrounds, matched to the CP cohort in 2017 for gender, body mass index (BMI) and socio-economic status (SES), were recruited. TD adults were excluded in case of any neuromuscular disorders and/or other physical impairments. Prior to enrolment, all participants signed a written informed consent. The study was approved by the by the local institution (UCT: 013.2017; SUN: N17/04/035) and conducted in line with the principles set out in the Declaration of Helsinki (2013).[19]

Participants' characteristics

Characteristics, as gender, age, weight, height and body mass index (BMI), were obtained from all participants. In addition, GMFCS level were noted for the participants with CP. SES was estimated by their housing density, calculated by dividing the number of people living in the house by the number of rooms in the house (excluding kitchen and bathroom), which was divided into low SES (>1.5), normal SES (≥1.0 and 1.5≤) or high SES (<1.0).[20] Based on individual interviews, contextual factors were obtained such as children, marital status, living situation, highest educational degree, employment and their main income.

Life Habits questionnaire

Levels of accomplishment and satisfaction in activity and participation was assessed by using the Life-Habits 3.1 questionnaire (Life-H), consisting of 77 life habits divided into different domains: 'nutrition', 'fitness', 'personal care', 'communication', 'housing', 'mobility', 'responsibilities', 'interpersonal relationships', 'community life', 'education', 'employment' and 'recreation'.[21] Every domain contained 4 to 8 life habits. For each life habit, levels of accomplishment and satisfaction were obtained. The level of accomplishment was scored on 1) the level of difficulty, categorized into: 'no difficulty', 'with difficulty', 'accomplished by a proxy', 'not accomplished', or 'not applicable', and 2) the type of assistance, categorized into: 'no assistance', 'assistive device', 'adaption', 'human assistance' required to accomplish it. In addition, participants were asked to indicate how satisfied they were with the level of accomplishment for each life habit on a 5-point scale, ranging from 'very dissatisfied' to 'very satisfied'.[22] A score was calculated (taking into account when questions were 'not applicable' for the participant) for each domain, ranging from 0 to 10 for accomplishment and from -10 to 10 for satisfaction. Accomplishment scores were categorized into three levels based on weighted domain scores: (I) score ≥ 8.0: independent without difficulties (with or without assistance); (II) score 5-8: independent with difficulties (with or without assistance); (III) score ≤ 5: dependent, i.e. carried out with human assistance. Satisfaction scores were divided into two categories: (I) score < 0.0: dissatisfied; (II) score ≥ 0.0: satisfied.

The Life-Habits 3.1 questionnaire has been shown to be a valid[23] and reliable[21,23] measure to assess the level of accomplishment and satisfaction in daily activity and participation and it has been used in different study cohorts of children [23–25] and (young) adults [26,27] with CP.

Functional Mobility Scale

The Functional Mobility Scale (FMS) was used to classify participants' level of mobility for three different distances, 5m, 50m, and 500m, in their daily environment (performance level), taking into account the use of an assistive device. The scale is based on a 6-level ordinal grading system, i.e. level 1: use of a wheelchair, level 2: use of walker or frame, level 3: use of crutch(es), level 4: use of stick(s), level 5: independent on level surfaces and level 6: independent on all surfaces.[28] The FMS has been shown to be a valid and reliable measure to assess functional mobility in individuals with CP.[28,29]

Frequency of pain

All participants were asked how often they experienced pain in their back (head/neck, upper back, lower back), upper limbs (shoulder, arm) and lower limbs (leg, hip, knee). The frequency of pain was divided into 'never', 'occasionally', 'weekly' and 'daily'.

Statistical analysis

Participants' characteristics were summarized using descriptive statistics. Since outcomes of the Life-H were not normally distributed, median values and interquartile ranges (IQR) of the accomplishment and satisfaction scores were calculated for all the domains. In addition, total scores were calculated by averaging over eleven domains (excluding Education; see results). Differences in accomplishment and satisfaction scores, FMS and frequency of pain between baseline and six-years follow-up within participants with CP were tested using a Wilcoxon rank test. In addition, the Cohen's d effect size was calculated to describe the magnitude of change in the total accomplishment and satisfaction scores over this period, classified into: 0.0-0.2: trivial effect; 0.2-0.5: small effect; 0.5-0.8: moderate effect; and >0.8: large effect.

Differences in outcomes of Life-H and pain frequency between the six-year follow-up of participants with CP and TD participants were tested using a Mann-Whitney U test.

Spearman's rank correlation was calculated to establish associations between Life-H total accomplishment and satisfaction scores and 1) participant's characteristics, such as age, SES, and BMI, 2) FMS and 3) frequency of pain. To correct for multiple testing, a Bonferroni alpha-level of was applied per outcome.

RESULTS

Participants' characteristics

In the baseline study, 30 adults with CP were included. Twenty-eight (93%) of the original cohort participated in the six-year follow-up study. One adult with CP suffered from severe illness and one adult moved. Participants' characteristics of 28 adults with CP at baseline and six-year follow-up and 28 TD adults are presented in **Table 5.1**.

In the six-year follow-up study, eleven adults with CP were classified in GMFCS level I (39%), 12 in GMFCS level II (43%) and 5 in GMFCS level III (18%). No difference in SES was observed between TD adults and adults with CP, with 11% of TD adults and 36% of adults with CP having a 'low' SES, 43% of TD adults and 32% of adults with CP having a 'normal' SES and 46% of TD adults and 32% of adults with CP having a 'high' SES.

Table 5.1. Participants' characteristics and contextual factors

	CP Baseline	CP 6-year follow-up	TD
Participants' characteristics	n=28	n=28	n=28
Gender, male/female	12 / 16	12 / 16	12 / 16
Age (y:mo), mean (SD)	32:11 (7:8)	39:3 (7:11)	38:8 (7:8)
BMI, kg/m^2, mean (SD)	26.1 (6.2)	27.8 (6.3)	27.8 (6.5)
SES, median (IQR)	1.3 [0.8 – 2.0]	1.2 [0.8 – 2.0]	0.8 [0.7 – 1.1]
Contextual factors			
Children, n (%)			
No children	18 (64)	14 (50)	9 (32)
1 child	4 (14)	7 (25)	4 (14)
2 children	3 (11)	4 (14)	10 (36)
3 children	2 (7)	0 (0)	5 (18)
>3 children	1 (4)	3 (11)	0 (0)
Marital status, n (%)			
Single	13 (46)	12 (43)	8 (29)
Single, divorced	2 (7)	2 (7)	1 (4)

Relationship	8 (29)	2 (7)	14 (50)
Married	5 (18)	12 (43)	16 (57)
Living Situation, n (%)			
Living on own	0 (0)	0 (0)	8 (29)
With (grand) parents	15 (54)	11 (39)	1 (4)
With partners	12 (43)	13 (46)	14 (50)
With others (family, friends)	1 (4)	4 (15)	5 (18)
Highest obtained degree in education, n (%)			
Primary	10 (36)	2 (28)	0 (0)
Secondary	5 (18)	3 (11)	8 (29)
Higher education	13 (46)	17 (61)	20 (71)
Employment, n (%)			
Paid employed	9 (54)	14 (54)	22 (78)
Self employed	4 (11)	3 (11)	1 (4)
House carer	0 (0)	0 (0)	1 (4)
Sheltered work	2 (4)	1 (4)	0 (0)
Voluntary work	2 (4)	1 (4)	0 (0)
Unemployment (health reason)	2 (7)	0 (0)	0 (0)
Unemployment (other reason)	6 (21)	8 (29)	4 (14)
Student	3 (11)	0 (0)	0 (0)
Main income, n (%)			
Paid job	11 (39)	17 (61)	23 (82)
Disability grant	11 (39)	11 (39)	n/a
Family income	6 (21)	0 (0)	5 (18)

Abbreviations: TD, adults who typically developed; CP, adults with cerebral palsy and spastic diplegia; IQR, interquartile range; BMI, body mass index; and SES, socio-economic status.

Life-Habit questionnaire

Domain scores of the Life-H are shown in **Table 5.2**. No differences were observed in accomplishment and satisfaction scores in adults with CP between baseline and six-years follow-up. This was confirmed by Cohen's effect sizes found for the total accomplishment score (0.25; 95%CI = 0.00 – 0.50) and for the total satisfaction score (-0.13; 95%CI = -0.59 – 0.33), indicating a small effect for the total accomplishment score and trivial effect for the total satisfaction score between the baseline and six-years follow-up study. Accomplishment scores of adults with CP were significantly lower than TD adults for the following domains: 'nutrition', 'personal care', 'housing', 'mobility', 'community life', 'recreation' and the total score. Adults with CP were less satisfied with 'personal care', 'housing', 'mobility', 'responsibilities', 'community life' and the total score than TD adults (**Table 5.2**).

Figure 5.1 provides an overview of the Life-H data categorized for level of dependency and difficulties with accomplishing activities and participation in daily life, as well as being dissatisfied or satisfied with these accomplishment levels. At the six-years follow-up study,

79% of the adults with CP were independent in accomplishing life habits overall (total score), and 21% were independent, but experienced difficulties. The highest rates of difficulties in the level of accomplishments were observed in the domains 'housing', 'mobility', and 'recreation', showing that 43%, 64%, and 39% (respectively) of adults with CP experienced difficulties or was dependent in accomplishing the life habits. At the follow-up study, adults with CP reported to be overall satisfied with their level of accomplishing daily activities and participation (total score). Only some dissatisfaction was observed for domains 'personal care', 'mobility', 'employment' and 'recreation' (4% for all these domains).

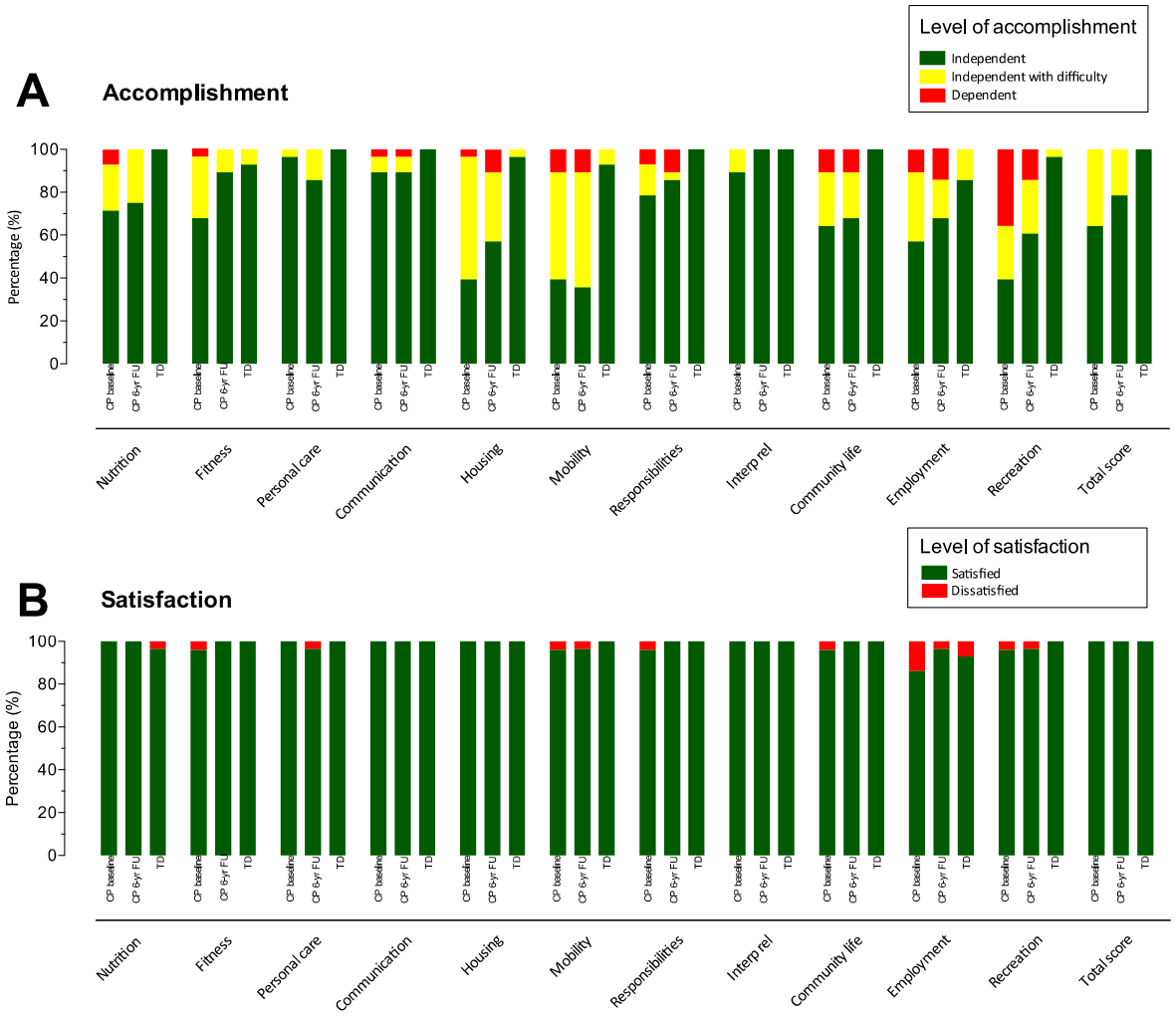

Figure 5.1. Bar graphs indicating percentages of Accomplishment (top graph) and Satisfaction (bottom graph) scores of the Life-H for TD adults, adults with CP at baseline and six-years follow-up.

Table 5.2 Life-Habits accomplishment and satisfaction scores for TD adults and adults with CP at baseline and six-years follow-up.

	Accomplishment *Range [0 to 10]*				
	CP Baseline	CP six-years follow-up	TD		
	Median [IQR]	Median [IQR]	Median [IQR]	U	p
Nutrition	10.0 [7.8 – 10.0]	10.0 [7.9 – 10.0]*	10.0 [10.0 – 10.0]*	238.0	<0.001
Fitness	9.6 [7.5 – 10.0]	9.4 [8.8 – 10.0]	10.0 [9.6 – 10.0]	254.5	0.012
Personal care	9.8 [8.9 – 10.0]	9.7 [8.9 – 10.0]*	10.0 [10.0 – 10.0]*	182.0	<0.001
Communication	10.0 [8.8 – 10.0]	10.0 [9.9 – 10.0]	10.0 [9.9 – 10.0]	375.0	0.726
Housing	7.4 [6.2 – 8.9]	8.3 [7.1 – 8.9]*	10.0 [9.0 – 10.0]*	165.5	<0.001
Mobility	7.3 [6.4 – 9.4]	7.4 [6.2 – 8.5]*	10.0 [10.0 – 10.0]*	105.5	<0.001
Responsibilities	10.0 [8.3 – 10.0]	10.0 [10.0 – 10.0]	10.0 [10.0 – 10.0]	333.0	0.112
Interpersonal rel.	10.0 [8.9 – 10.0]	10.0 [10.0 – 10.0]	10.0 [10.0 – 10.0]	377.0	0.529
Community life	8.9 [6.5 – 10.0]	9.1 [7.1 – 10.0]*	10.0 [10.0 – 10.0]*	166.0	<0.001
Education #	10.0 [8.3 – 10.0]	8.9 [2.5 – 10.0]	10.0 [10.0 – 10.0]		
Employment	8.6 [6.7 – 10.0]	9.5 [7.3 – 10.0]	10.0 [8.7 – 10.0]	270.5	0.032
Recreation	7.1 [4.3 – 9.3]	8.9 [6.4 – 10.0]*	10.0 [10.0 – 10.0]*	189.5	<0.001
Total score	8.5 [7.4 – 9.3]	9.0 [8.2 – 9.6]*	9.9 [9.6 – 10.0]*	106.5	<0.001

	Satisfaction Range [-10 to +10]				
	CP Baseline	CP six-years follow-up	TD		
	Median [IQR]	Median [IQR]	Median [IQR]	U	p
Nutrition	8.8 [6.4 – 10.0]	8.8 [5.0 – 10.0]	10.0 [8.8 – 10.0]	285.5	0.074
Fitness	6.3 [5.0 – 9.7]	5.0 [5.0 – 10.0]	10.0 [6.6 – 10.0]	281.5	0.051
Personal care	8.6 [5.9 – 10.0]	5.0 [5.0 – 10.0]*	10.0 [10.0 – 10.0]*	175.0	<0.001
Communication	9.0 [5.2 – 10.0]	7.8 [5.0 – 10.0]	10.0 [10.0 – 10.0]	252.0	0.007
Housing	5.6 [5.0 – 9.8]	5.0 [5.0 – 10.0]*	10.0 [8.3 – 10.0]*	209.5	0.001
Mobility	5.0 [3.8 – 7.4]	5.0 [1.3 – 6.8]*	10.0 [8.2 – 10.0]*	95.5	<0.001
Responsibilities	8.5 [5.7 – 10.0]	6.3 [5.0 – 9.9]*	10.0 [9.0 – 10.0]*	198.0	0.001
Interp rel	6.5 [4.1 – 10.0]	7.5 [5.0 – 10.0]	10.0 [7.4 – 10.0]	289.0	0.054
Community life	5.6 [5.0 – 9.4]	5.0 [5.0 – 10.0]*	10.0 [8.4 – 10.0]*	203.0	0.001
Education #	10.0 [5.0 – 10.0]	5.0 [3.1 – 8.8]	10.0 [10.0 – 10.0]		
Employment	5.0 [2.6 – 9.4]	5.0 [3.3 – 10.0]	10.0 [5.5 – 10.0]	272.5	0.038
Recreation	6.4 [3.1 – 8.3]	5.0 [2.5 – 10.0]	10.0 [5.0 – 10.0]	244.5	0.011
Total score	7.1 [5.1 – 8.6]	5.1 [4.5 – 9.4]*	9.5 [8.2 – 10.0]*	178.0	<0.001

 # Differences in education scores were not tested since this was only applicable for a minority of participants (CP baseline: n=6; CP six-year follow-up: n=8; TD: n=15). Significance set at p < 0.002.

** Significant different: Adults with CP six-year follow-up versus TD adults. Abbreviations: TD, adults who typically developed; CP, adults with cerebral palsy and spastic diplegia; IQR, interquartile range; Interpersonal rel.; Interpersonal relationships.*

Functional Mobility Scale

FMS scores were significantly lower at six-year follow-up compared to baseline in participants with CP for 5m (Z=-2.33, p=0.020), 50m (Z=-2.51, p=0.012) and 500m (Z=-2.71, p=0.004). The percentage of adults with CP who could walk 5m independently or with assistive devices (FMS level 5 and 6) reduced 86% to 79% between baseline and the six-years follow-up, while it reduced from 64 to 46 for 50m and 500m. In addition, the percentage of adults with CP who used a crutch, cane or walker increased from 14% to 21% for 5m, 29% to 36% for 50m and 14% to 32% for 500m. None of the adults with CP was wheelchair dependent for 5m both at baseline and six-years follow-up, while this percentage increased from 7% to 18% for 50m. For 500m, 21% of the adults with CP was dependent both at baseline and six-year follow-up. Bar graphs of FMS scores for participants with CP are presented in **Figure 5.2**.

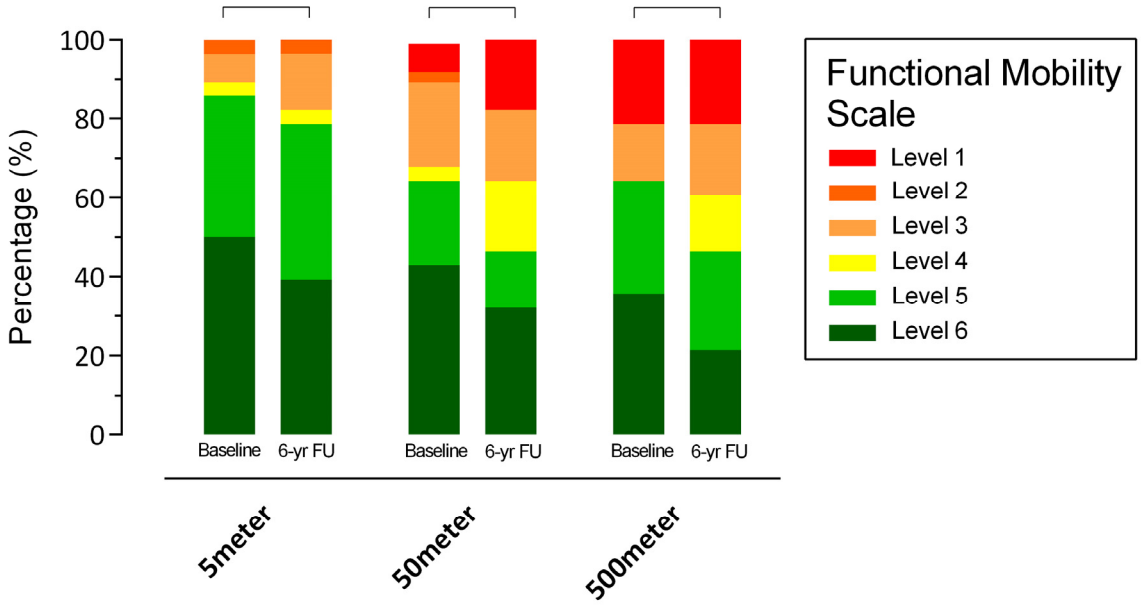

Figure 5.2. Bar graphs indicating the percentage of participants with CP classified in level 1 to 6 of the FMS at baseline and six-years follow-up. *Significance set at p < 0.05.*

Frequency of pain

Bar graphs of frequency of pain that adults with CP and TD adults experienced in their back, upper limb and lower limb are presented in **Figure 5.3**. No differences were observed between the frequency of pain participants with CP experienced at baseline and six-years follow-up. However, adults with CP experienced significantly more pain in their back, upper and lower limb compared to TD participants (back: U=224.00, p=0.003; upper limb: U=276.00, p=0.012; lower limb: U=252.00, p=0.008). At six-year follow-up, 75% of adults with CP reported to experience back pain, of which 18% reported daily pain.

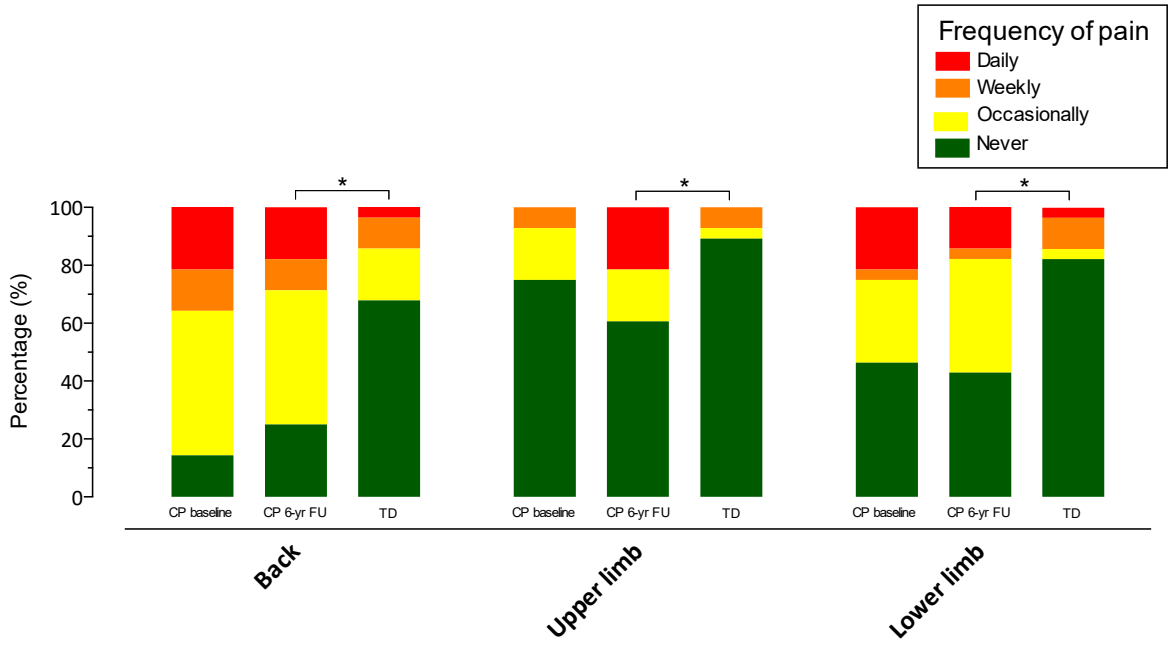

Figure 5.3. Bar graphs indicating percentages of pain on different locations by TD adults, adults with CP at baseline and six-years follow-up. *Significance set at p < 0.0167.*

Associations

Positive correlations were observed between Life-H total accomplishment score and FMS for 5m, 50m and 500m (**Table 5.3**). In addition, a negative correlation was observed between total satisfaction score and the frequency of pain participants with CP experienced in their back.

Table 5.3. Correlations between Life-H total scores and participant's characteristics, functional mobility and frequency of pain

	Total score accomplishment		Total score satisfaction	
	r	p	r	p
Participant's characteristics				
Age	-0.246	0.207	-0.263	0.177
SES	-0.116	0.558	0.014	0.942
BMI	-0.353	0.066	-0.083	0.675
FMS				
5m	0.532	0.004*	0.202	0.303
50m	0.560	0.002*	0.266	0.171
500m	0.604	0.001*	0.350	0.068
Pain frequency				
Back	-0.339	0.077	-0.467	0.012*
Upper limb	-0.168	0.394	-0.061	0.760
Lower limb	-0.233	0.233	-0.370	0.052

Abbreviations: SES, socio-economic status; BMI, body mass index; FMS, functional mobility scale.

** Significance set at p < 0.0167.*

DISCUSSION

To our knowledge, this is the first study that investigated changes in levels of accomplishment and satisfaction in daily activities and participation, functional mobility and pain in ambulant adults with CP who are living in a developing country. The results of this study showed that these levels of accomplishment and satisfaction were stable over a period of six years. Adults with CP did however show a reduction in functional mobility, while frequency of pain did not change.

The level of accomplishment and satisfaction in daily activities and participation in adults with CP were relatively high and in line with previous research among adults with CP who were living in developing[14] as well as developed countries.[30] In addition, the finding that levels of accomplishment and satisfaction were stable showed to be in line with a recent study by Tan et al., who showed that participation levels increased between the ages of 1 to 20, after which it seemed to stabilize.[31] Importantly, no associations between SES and accomplishment and satisfaction levels were found, suggesting that SES does not seem to influence participation levels in adults with CP who are living in a developing country. However, as hypothesized, accomplishment scores were considerably reduced compared to TD adults who were

matched for gender, age, BMI and SES. Particularly scores for life habits related to nutrition, personal care, housing, mobility, community life, recreation, and the total score were lower in adults with CP. These factors could be specifically targeted in rehabilitation programs. Despite these differences in accomplishing life habits, the adults with CP were overall as satisfied, though a very low percentage (7%) showed dissatisfaction in life habits regarding personal care, housing, mobility, responsibilities, community life and the total score than TD peers.

The level of functional mobility reduced over a period of six years in adults with CP. Overall, 21-32% showed a reduction in functional mobility for the distances over 5m, 50m, and 500m. This is in accordance with previous research, reporting that 25-40% of ambulant adults with CP experienced decline in walking function.[10,32–35] This reduction in functional mobility may be related to balance problems and potential falls, which are frequently cited as both causes and potential consequences of mobility decline in adults with CP.[32,36]

Not surprisingly, levels of accomplishment (total score) was strongly associated with the level of mobility (FMS), indicating that adults with CP who have more limitations in mobility showed more difficulties in the accomplishment of life habits. These findings suggest that adequate mobility is a prerequisite for good participation in daily life. In line with this, adults with CP who are more severely physically impaired are likely to experience more challenges in daily activities and participation in comparison to those with better mobility. This finding is in line with previous research in children and adolescents with CP.[31,37] Maintaining the ability to walk is therefore important and desirable for adults with CP. This is particular the case for adults living in developing countries, since accessibility is for those walking with assistive devices is difficult and areas often show a lack of wheelchair accessible transport.[38] Future research should investigate whether intervention programs specifically developed for adults with CP can prevent deterioration in functional mobility and to maintain social participation and retain independence.

The findings of this study show that the frequency of pain adults with CP experienced in their back, upper limbs or lower limbs did not change over a six-year period. Adults with CP did report to experience pain more frequently in their back, upper and lower limbs than TD adults. Percentages of adults that experienced pain in the different regions was slightly higher than reported by Jahnsen et al. (2004);[11] while 64% of adults with CP and spastic diplegia in the

study of Jahnsen et al. reported back pain 75% of adults with CP in current study reported back pain. In addition, in 35% and 41% of their cohort reported pain in the hip and knee, respectively, while 57% of the adults with CP in current study reported pain in lower limbs. Life-H satisfaction rates were negatively associated with the frequency of pain experienced in the back by adults with CP. This association indicates that those who experienced more often back pain were generally less satisfied with the accomplishment of daily life habits. No associations were however observed between pain and accomplishment scores, whereas previous research showed diverse findings. For the impact of pain on daily activities in CP, several studies found that adults with CP tended to report no to minor interference from pain on their activity level and social or work functioning,[9,39] whereas another study demonstrated that one-third of their CP sample reported a moderate to extreme impact of pain in daily life.[11] The discrepancy of previous and current results might be attributed to the specific age window included in the study and/or methodology to assess pain.

Unemployment rate was considerably higher in adults with CP (29%) than TD adults (14%), but similar to unemployment rates in adults with CP in South Africa who were treated with SDR.[14] The cause of this low employment rate is complex and can be explained by difficulties in finding a suitable job, but also by other factors such as receiving a disability grant, which might be the main family's income, especially in the adults with a low SES. Nearly 40% of adults with CP were dependent on a disability grant and applying for short-term employment position puts the adults with CP and the associated family of risk of losing a stable income source. This unfortunately discourages these adults to actively look for employment, which only seems to be worth pursuing in a long-term contract can be offered.

Limitations

Several limitations should be taken into account before implementing these results in clinical practice. Because of the inclusion of solely ambulant adults with CP and spastic diplegia who underwent orthopaedic interventions, current results may only be applicable for this homogenic subgroup. Adults with CP particularly underwent orthopaedic interventions following the ISA approach, which is still the standard in most developing countries such as South Africa. Hence, level of accomplishment and satisfaction presented in this study apply to large cohorts of adults with CP and spastic diplegia, who live in developing countries

worldwide. Second, although the overall sample size for this study was reasonable, a small number of adults with CP classified in GMFCS level III was included, and therefore this data should be interpreted with extra care. Future research should be aimed to set up a multi-center approach.

Conclusion

The results of the current study showed that the level of accomplishment and satisfaction of activities and participation was stable over a period of six years in ambulant adults with CP and spastic diplegia who are living in a developing country. SES showed not to influence the levels of accomplishment and satisfaction. Although levels of accomplishment were lower compared to TD adults, the overall levels of accomplishment and satisfaction were relatively high, and in correspondence with previous studies. Importantly, functional mobility deteriorated over the six-year period. Furthermore, adults with CP with reduced functional mobility experienced more difficulties in accomplishing daily activities and participation. No changes in the frequency of back pain or pain in upper and lower limbs were reported, although adults with CP experienced more frequently pain in the different areas compared to their peers. In addition, back pain showed to be associated with satisfaction levels in daily activities and participation. Thus, systematic screening and timely support should be implemented to develop and maintain optimal activities and participation of adults with CP.

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SUMMARY AND CONCLUSIONS

RATIONALE

The most common cause of major physical disability in childhood is cerebral palsy (CP). CP has been defined as "a group of permanent disorders of development of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. While limitation of activity may be the main concern, the motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behavior, by epilepsy, and by secondary musculoskeletal problems".[1]

Currently no cure is available for the non-progressive lesion in the immature brain which causes CP. A significant part of treatment approaches thus focuses on the progressive musculoskeletal manifestations and its sequela. Physicians primarily attempt to prevent and/or minimise secondary consequences of the upper motor neuron (UMN) syndrome in CP which causes a pathological neural and mechanical pathway which eventually results in irreversible musculoskeletal pathology.[2] A major factor contributing to the detrimental sequela on the musculoskeletal system is spasticity which often causes contractures and lever arm dysfunction consequently affecting locomotion, quality of life and healthy ageing.

In an effort to target secondary consequences of spasticity, individuals with CP often undergo orthopaedic surgery on the lower extremities.[3,4] Numerous studies have evaluated and demonstrated the benefits of orthopaedic surgery for individuals with CP. These studies, however, largely comprise relatively short or intermediate term follow-up assessments in children and adolescents.[5] Taking into consideration the increased life expectancy of individuals with CP,[6–8] follow-up studies which focus on this ageing population is needed. Colver et al. very eloquently stated in a review article that the primary focus of 21st century research on disabilities should be on evaluating and understanding the life course of adults who have grown up with a *paediatric condition* as well as the treatments they received in childhood.[9]

Although general agreement exists that the accepted gold standard of treatment for musculoskeletal abnormalities in children with CP is a multi-disciplinary approach with orthopaedic Single Event Multilevel Surgery (SEMLS) followed by intense rehabilitation,[10] the reality is that a large number of children with CP in the developing world are still treated according to the more traditional orthopaedic Interval Surgery Approach (ISA). The reason for this can be mainly ascribed to *a lack of*: infrastructure, appropriate multidisciplinary CP care

centres and the necessary expertise with financial constraints and inefficient rehabilitation services and facilities also playing a role.[11] It thus remains important to evaluate the long-term outcome/s of adults with CP living within these circumstances.

Given the concerns regarding ageing in adults with CP,[6–8] the aim of this thesis was to assess different aspects of ageing, within the ICF framework of adults with CP living in a developing country. Our cohort, who participated in six-year follow-up studies, presents an unique opportunity to evaluate the ambulant adult with CP and spastic diplegia. We focused on a homogenic cohort of ambulant adults with CP and spastic diplegia who received their first orthopaedic ISA surgery more than 25 years ago. It is important to highlight we aimed to focus on the ageing process, rather than investigating long-term effects of orthopaedic interventions (no pre-operative data). In addition, the aim was to further explore associations between the results yielded in the different The International Classification of Functioning, Disability and Health (ICF) -model domains along with individual characteristics. The outcomes of this research work will provide important clinical insights which will support adults with CP, parents, caregivers and clinicians in their decision-making processes.

ICF MODEL

The International Classification of Functioning, Disability and Health (ICF) model, developed by the World Health Organisation (WHO)[12] was applied to acquire a clear overview of the impairments, limitations and restrictions in daily life experienced by ambulant adults with CP. **Figure 6.1** presents an overview of the outcome measurements used in this thesis along with a reference to the corresponding chapter/s in which the results are described.

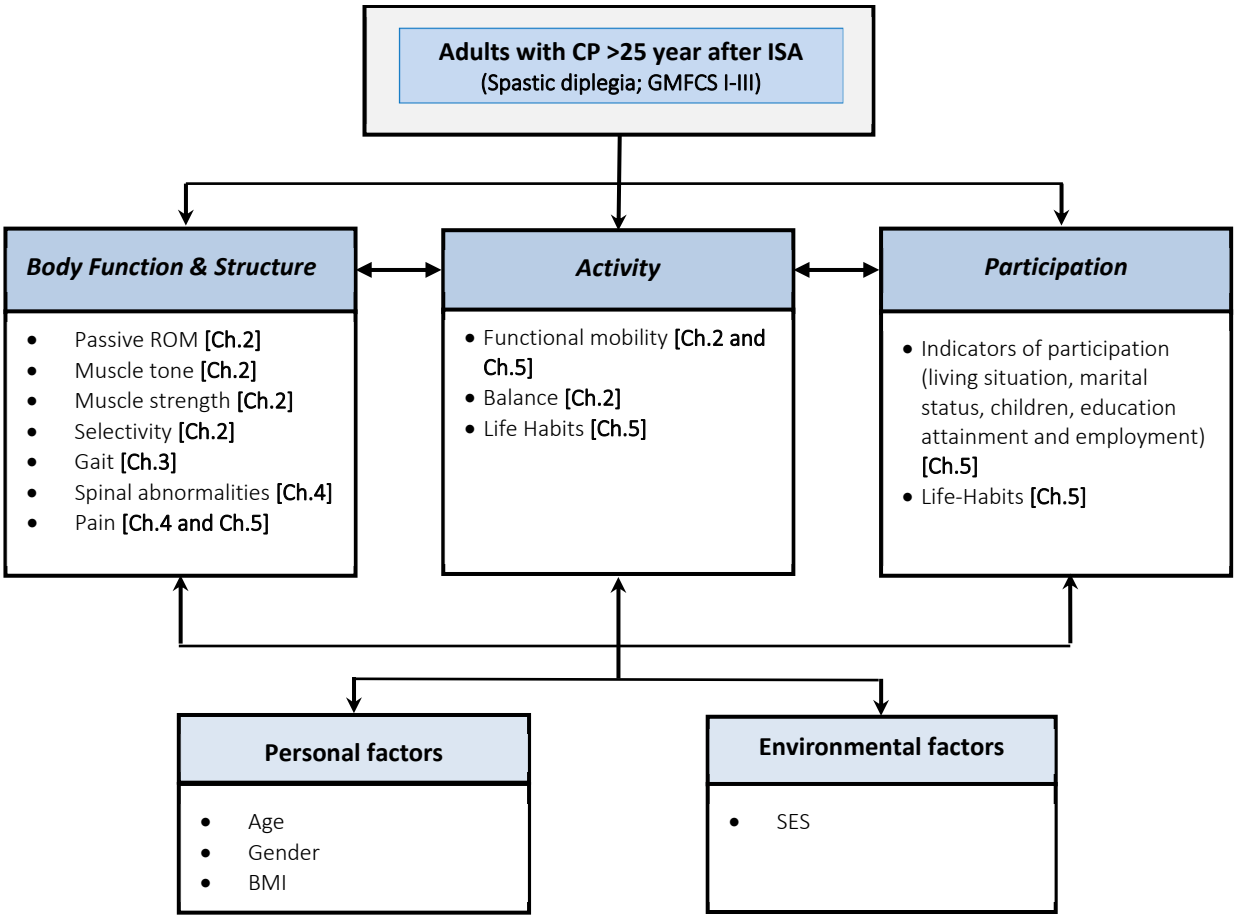

Figure 6.1. Overview of focus areas of objectives related to the International Classification of Functioning, Disability and Health (ICF)
Abbreviations: GMFCS, Gross Motor Function Classification System; Ch., Chapter; ROM, Range of Motion; BMI, Body Mass Index; and SES, Socio-Economic-Status.

Outcomes and Clinical Implications within the ICF framework

A summary of the main findings of this thesis are presented in **Table 6.1**. This summary includes results pertaining to:

i. Changes in participants' status during the six-year follow-up period (2011 CP versus 2017 CP)
ii. Differences in outcomes between adults with CP (2017 CP) and the reference group (TD)
iii. Associations between current status (2017 CP) versus individual characteristics

Table 6.1: Summary of results found in four thesis chapters for change during the six-year follow-up as well as differences between adults with CP and reference group

Chapters and main outcome measures	Change during six-year follow-up period (CP 2011 vs CP 2017)	Difference to reference values (CP 2017 versus TD)	Associations with individual characteristics
Chapter 2: Physical status, functional mobility and balance			
Physical exam PROM (goniometer: degrees) Strength (HHD: torque) Selectivity (selectivity scale) Muscle tone (Ashworth score)	No follow-up data	• PROM - Hip flexion, Hip abduction, Knee flexion, Dorsiflexion: CP < TD - Popliteal angles: CP > TD • Strength: CP < TD • Selectivity: CP < TD • Muscle tone: CP > TD	Muscle strength vs GMFCS, BMI and TUG
Functional mobility and balance Standing Balance (CTSIB) Functional mobility and dynamic balance (TUG)	No follow-up data	• CTSIB (on foam eyes closed): CP < TD • TUG: CP > TD	TUG vs GMFCS
Chapter 3: Gait			
Gait pattern (GDI)	No	CP < TD	GDI vs GMFCS and BMI
Waveforms (SPM stats, 3 planes) Pelvis Hip Knee Ankle	Yes, especially in sagittal plane: • Pelvic: anterior tilt ↑ • Knee: flexion ↓ • Ankle: dorsiflexion ↓	Not tested	Not tested
Kinematics (Angles, degrees)	Several parameters ↑ and ↓ *(NB Difference angle <10°: not clinically relevant)*	CP more flexed (pelvis, hip, knee and ankle) and stiff knee gait compared to TD adults	Not tested
ND spatiotemporal distance parameters Speed Cadence Time to Foot off	Yes, some ↑ and ↓ • Speed and cadence: ↓ • Time to Foot off: ↑ *(NB Difference not clinically relevant)*	• Speed and cadence: CP < TD • Time to Foot off: CP > TD	Not tested

Chapter 4: Spine and level of disability			
Spine curvature (x-rays, angles) Scoliosis Cobb Thoracic kyphosis Lumbar lordosis	No: • Scoliosis Cobb • Lumbar lordosis Yes: • Thoracic kyphosis: curve ↑ *(NB effect size: moderate)*	Different compared to norm values: • Scoliosis: 33% (mild: 29%; moderate: 4%) • Hyper lordosis: 15% • Hyper kyphosis: 0%	Lumbar lordosis vs Age
Level of disability due to back and/or leg pain (ODI score)	No	• Moderate disability: 26% • Severe disability: 11%	None
Chapter 5: Life-habits, functional mobility and pain			
Level of Activity and Participation (Life Habits Accomplishment level)	No	Life-habits domain scores: CP < TD (Nutrition, Personal care, Housing, Mobility, Community life, Recreation and Total score)	Accomplishment level vs FMS
Level of Activity and Participation (Life Habits Satisfaction level)	No	Life-habits domain scores: CP < TD (Personal care, Housing, Mobility, Responsibilities, Community life and Total score)	Satisfaction level vs back pain
Functional Mobility (FMS)	Yes, FMS ↓ for 5, 50 and 500m	-	FMS vs Accomplishment level
Pain (frequency)	No	Back, upper and lower limb pain: CP > TD	Back pain vs Satisfaction level

Abbreviations: CP, Cerebral Palsy; TD, Typical Developed; PROM, Passive Range of Motion; HHD, Hand Held Dynamometer; CTSIB, Clinical Test of Sensory Interaction on Balance; TUG, Time Up and Go; GDI, Gait Deviation Index; SPM, Spatial Parametric Mapping; 3D, three-dimensional; ND, non-dimensional; ODI, Oswestry Disability Index; FMS, Functional Mobility Score.

Body Function and Structure

Outcomes

Adults with spastic diplegic CP, classified in Gross Motor Function Classification System (GMFCS) Levels I - III, who underwent orthopaedic ISA interventions >25 years ago, showed considerable limitations in physical status compared to typically developed (TD) adults. Limitations within the ICF domain *Body Function and Structure* were particularly noted in passive range of movement (PROM), strength, selectivity and muscle tone (**Chapter 2**). Muscle strength profiles were consistent with findings in previous studies describing muscle weakness in individuals with CP compared to their TD peers.[13–16] In addition, the increased muscle tone was in line with expectations, based on the included adults with CP who did not undergo Selective Dorsal Rhizotomy (SDR) or who had received recent interventions aimed at reducing spasticity.

The gait pattern did not change over the six-year follow-up period and all the adults with CP remained ambulant. Although significant changes were observed for individual kinematic parameters, as well as spatiotemporal distance parameters, changes were relatively small and therefore were considered not clinically relevant. As expected, the Gait Deviation Index (GDI) and other gait parameters differed between adults with CP and TD adults. The gait pattern of adults with CP at the six-year follow-up consisted predominantly of a flexed gait pattern (pelvis, hip, knee and ankle) and a stiff knee gait (**Chapter 3**).

Spinal curves remained relatively stable over the six-year follow-up period. No changes were observed in scoliosis Cobb and lumbar lordosis angles. Although thoracic kyphosis curves increased in adults with CP, curves fell within normal ranges, and no changes were observed separately for the GMFCS levels. These findings are consistent with previous research which indicated that scoliosis Cobb, thoracic kyphosis and lumbar lordosis angles remain stable in individuals classified in GMFCS Levels I-III (in contrast to GMFCS Levels IV and V).[17] The 33% incidence of scoliosis found in the current study was confirmed to be considerably higher than that published for the TD population (8 - 9),[18,19] though the majority of the current cohort (29%) was diagnosed with *mild scoliosis.* Only a small portion of the cohort (37%) reported disability due to back pain at the six-year follow-up study (**Chapter 4**). In addition, based on a self-reported questionnaire, frequency of pain did not change over time, although back and (upper and lower) extremity pain were more commonly reported in adults with CP than their

TD peers (**Chapter 5**). It should be noted however that the frequency of pain that individuals report may not be associated with the disability that they experience due to pain. Future research should focus on the different aspects of pain and their associations.

With regards to associations tested, a relation was noted between GMFCS levels and muscle strength. In addition, increased restriction in physical status could also be observed between adults with CP with increasing GMFCS levels (from Level I to III) in PROM and selectivity. However, the severity of tone was similar across GMFCS levels. The findings regarding physical status and relation to GMFCS levels were consistent with previous research amongst children and adolescents with CP (**Chapter 2**).[20,21] Not surprisingly, the GMFCS level showed a strong correlation ($r = -0.83$, $p<0.0001$) with GDI (**Chapter 3**). In addition, age was also negatively associated with lumbar lordosis (**Chapter 4**) which underscores the findings reported in literature.[22]

Another individual characteristic explored for possible associations was participants' Body Mass Index (BMI). It was determined that this factor shows an association with muscle strength (**Chapter 2**) and GDI (**Chapter 3**). This association has been confirmed in previous research studies in children with CP where a negative correlation was noted between BMI and physical status, mobility and locomotion.[23]

Interestingly, contrary to our expectations, no relationships were found between the environmental factor *Socio-Economic-Status (SES)* and outcomes at the levels of Body Function and Structure.

Clinical Implications

This cohort of adults with CP exhibited decreased PROM, muscle strength and selectivity in comparison with their TD peers. In addition, negative associations were noted between muscle strength and GMFCS levels. These results highlight the importance of muscle strength training in rehabilitation programmes for ageing CP adults. This may inhibit the rate of physical status deterioration and thus possibly delay the secondary negative influences on Body Function and Structure as well as enhance the level of Activity and Participation in daily life.

The negative association of muscle strength, gait patterns and BMI, although not surprising, highlights the occurrence that adults with CP are often caught in a vicious cycle in which reduced muscle strength may lead to increased limitations in functional mobility and dynamic balance which, in turn, results in increased sedentary behaviour and an increase in BMI. Appropriate interventions, including muscle strength training as well as overall fitness and weight loss programmes, may delay or disrupt the cycle of association between *decreasing* muscle strength and *increasing* BMI.

Although there were some changes in gait over the last six years in our cohort of adults with CP, all of them remained ambulant. This important clinical information enhances our ability to council ambulant adults with CP on what they can expect in terms of future ambulation abilities. The abnormal gait patterns (flexed and stiff knee gait) could be related to numerous factors with possible causes being: decreased muscle strength and motor control as well as deficient spasticity management which resulted in a continued increase in muscle tone and contractures as well as lever arm dysfunction. It could also be that historically individuals with CP received less lever arm corrective surgery or that incorrect surgical choices were made. Addressing these factors in children with CP may result in better gait patterns in adulthood.

Spinal curves were relatively stable and remained within normal ranges in ambulant adults with CP and spastic diplegia classified in GMFCS I, II and III over a period of six years. Nevertheless, a high prevalence of spinal deformities warrants regular follow-up to monitor changes in spine curvature in adults with CP. This is emphasised in two participants (GMFCS II and III) who showed considerable increases in their scoliosis Cobb Angle (16° and 17°, respectively) and one participant who progressed from *mild* to *moderate* scoliosis (from 22° to 30°). These results may improve specialised clinical care and possibly aid in counselling regarding the progression of spinal disease in adults with CP.

Activity and Participation

Outcomes

The cohort of ambulant adults with CP showed a considerable deterioration in functional mobility based on the Functional Mobility Scale (FMS) over the six-year follow-up period (**Chapter 5**). In addition, they showed limitations in functional mobility and dynamic balance

relative to TD adults with more time needed to complete the Time Up and Go test (TUG) and increasing GMFCS level (**Chapter 2**). This is consistent with previous research done by Morgan et al.[24]

Accomplishment and satisfaction levels in daily activities and participation remained stable over the six-year period in ambulant adults with CP who live in a developing country. However, adults with CP experienced considerably more difficulties in accomplishing certain life habits and reported lower satisfaction levels compared to their TD peers (**Chapter 5**). This is consistent with the findings of a study which focused on adults with CP living in the Netherlands.[25]

As regards the associations investigated, functional mobility and dynamic balance (TUG) scored better for adults classified with a lower GMFCS level and thus more functionality (**Chapter 2**). In addition, it is important to note that functional mobility, based on FMS, was strongly associated with the accomplishment of life habits. This is an indication that adults with CP who had more limitations in mobility reported that they experienced more difficulties in the accomplishment of activities and participation in daily life. On the other hand, functional mobility was not related to satisfaction levels. However, this was negatively associated with the frequency of back pain experienced in the adults with CP. This association indicates that those who experienced back pain more often, were generally less satisfied with the accomplishment of daily life habits (**Chapter 5**). Lastly, no association could be drawn between any of the outcome measures related to the ICF-domain *Activities and Participation* and SES (**Chapters 2 and 5**).

Clinical Implications

Appropriately designed interventions may prevent further deterioration of functional mobility in adults with CP. Strong associations were observed between muscle strength levels and functional mobility and dynamic balance, suggesting that adults with CP may benefit from strength and/or resistance training. These findings suggest that adequate mobility is a prerequisite to maintain abilities and good participation in daily life. It highlights the importance of preventing further deterioration of functional mobility during ageing so that

adults with CP can maintain high levels of accomplishment of activities and participation in daily life.

With regards to SES, basic care levels and capacity in developing countries are limited by the poor availability of medical personnel with experience and expertise in managing CP.[11] One could expect that limited access to health care facilities and specialists, as well as a lack of adaptive equipment such as wheelchairs and other ambulation aids, may influence participation. In contrast to these expectations, no relationships were however found between SES and outcomes at the levels of activity or participation. This indicates that SES did not influence these levels - an important finding for individuals with CP living in a developing country. An underlying factor that could explain the lack of associations with SES is that only adults with CP, who were classified in GMFCS Levels I, II and III, were included in the study. Individuals who experience increased limitations in gross motor function (GMFCS Levels IV and V) may experience more difficulties in accessing health care facilities. An example of this is limited wheelchair access and lack of wheelchair accessible transport which, in turn, restricts the accomplishment of activity and participation. In addition, individuals who have more limitations may increasingly depend on regular therapy which could be less accessible for those with lower SES.

Lastly, although the frequency of pain in this cohort of adults with CP remained generally stable, those that experienced back pain were generally less satisfied with the accomplishment as measured by lower scores on daily life habits questions. Programmes directed at adequate pain management within the developing world setting may aid in increasing satisfaction with the accomplishment of daily life habits.

ICF interdisciplinary

Adults with CP showed major impairments on the levels body function and structure, activity and participation of the ICF model compared to TD adults. In addition, associations between outcomes at different levels highlight that adults with CP are prone to develop more restrictions during ageing. The results of this thesis showed that changes over the six-year ageing period in these adults with CP occurred mainly at the level of body function and structure and activity, i.e. in gait parameters, gross motor function and functional mobility.

These changes, however, did not seem to cause changes to occur on the level of participation and other outcomes of the level of activity, such as performing life habits. Though, it is important to note that a combination of individually changes may have occurred on the different levels, which could lead to major restrictions when these adults age.

LIMITATIONS

The results of this thesis should be considered within the context of certain limitations. Firstly, our cohort consisted of a homogenous group of adults with CP and spastic diplegia classified in GMFCS Levels I – III. Results may not be applicable to individuals who have been diagnosed with topographically different or another subtype of CP. In addition, a small sample of adults with CP classified in GMFCS Level III was included. This could have led to changes in the outcomes being underestimated. Secondly, only adults with CP who received orthopaedic surgery via ISA in childhood were assessed and these outcomes are thus not applicable when referring to individuals who received SEMLS or a neurosurgical intervention. However, the majority of adults with CP living in developing countries solely undergo orthopaedic interventions following ISA approach during childhood (>80), and therefore it would be suggested that current findings provide insight into the natural progression of CP during ageing in a developing country. Thirdly, there was no true control group or baseline data (pre-operative) available. Fourthly, the cohort was selected from an urban setting in one country in the developing world. The profile of adults with CP from rural areas within South Africa may differ. Lastly, the majority of the participants studied (baseline and six-year follow-up) ranged from age 25-45 years. The question remains whether outcomes and characteristics may change when older adults with CP age.

FUTURE RESEARCH

Future research is recommended to compare our long-term outcomes with other treatment groups, for example adults with CP who had received SEMLS, SDR or other non-operative treatment modalities. In addition, re-evaluating this cohort at a later period in time will yield valuable information about ageing with CP. Longitudinal studies are recommended to investigate the long-term effects of the different types of orthopaedic interventions. Based

on the associations noted in this thesis, future studies to evaluate the effectiveness of strength training and/or weight loss and fitness programmes on mobility, level of activity and participation in adults with CP are necessary. In addition, it needs to be investigated whether those adults with CP who were actively involved in childhood (rehabilitation) programmes have long-lasting beneficial outcomes during adulthood. Lastly, the current dataset which relates to our group of participants allows for further research regarding integral aspects of ageing such as bone health (bone mineral density), mental status and quality of life. This information can be used in future studies to appropriately design interventions and educational tools to prevent deterioration in functional capacity and to promote healthy ageing in adults with CP.

CONCLUSIONS

CLINICAL IMPLICATIONS AND TAKE HOME MESSAGES

- Lower extremity passive range of motion, strength, selectivity, muscle tone, functional mobility and balance of adults with CP and spastic diplegia were impaired compared to TD adults.
- Overall, adults with CP walked with a flexed and stiff knee gait pattern, though the GDI did not change during the six-year follow-up period.
- GDI seen in these adults with CP was associated with GMFCS level and BMI.
- Strength was associated with GMFCS level, BMI, level of functional mobility and dynamic balance (TUG).
- Functional mobility (FMS) deteriorated during the six-year follow-up and related to the level of accomplishing daily activities and participation in the community.
- Adults with CP were overall satisfied with their level of accomplishing daily activities and participation (only some dissatisfaction related to their personal care, mobility, employment and recreation) and was associated with back pain.
- Level of back pain (and also pain in the extremities) remained the same during the six-year follow-up period. The level of disability due to back pain also remained stable over time.
- Strength, balance, fitness and weight loss programmes may aid in delaying the cycle of muscle weakness, deteriorated walking ability, frequency of pain and subsequent difficulties in activities and participation in daily life.
- Per GMFCS level the spinal curves were stable during the six-year follow-up and no severe spinal deformities were formed during ageing.
- Regular follow-up is required to monitor changes in the spine curvature, but a conservative approach with respect to treating spinal abnormalities in adults with CP may be most appropriate.
- No relationships were, however, found between SES and outcomes at the ICF-model domains Body Function and Structure as well as Activity and Participation, which is an important finding for individuals with CP living in a developing country.

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