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CEREBRAL PALSY: STUDIES ON HEALTH AND SOCIAL OUTCOMES IN YOUNG ADULTHOOD, AND ON TREATMENTS FOR SPASTICITY AND PAIN

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Cerebral Palsy: Studies on Health and Social Outcomes in Young Adulthood, and on Treatments for Spasticity and Pain

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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This thesis is dedicated to all participants and their families for their invaluable contributions and for letting others benefit from this work in the future.

ABSTRACT

Cerebral palsy (CP) is a permanent disorder caused by a non-progressive brain injury or malformation that has occurred early in the development of the child's brain. The disorder is characterized by dysfunction of movement and posture, with frequent but variable occurrences of other dysfunctions in cognition, perception, sensation, communication, as well as of epilepsy, and pain. The movement dysfunctions are often what is most apparent for an outside observer and interventions have traditionally focused primarily on movement. Spasticity, a type of abnormal contraction of muscles, is common in CP and an aspect of movement that is often targeted for treatment. As CP is a life-long disorder it is important to understand the long-term effects of treatments, especially if they are performed early in life. It is also important to understand how the disorder and the consequences of the disorder evolve 'long-term' as the individual grows up. Our knowledge of CP after childhood has been limited. Concerns have been raised on the topics of integration into society for adults with CP, and on some emerging health issues; especially a high prevalence of chronic pain. Understanding these issues and finding ways to manage them is a priority.

This thesis focuses on the health and social situation of individuals with CP right after childhood, and on specific treatments for spasticity and pain. This was done using a few separate methods. Health and social situation were investigated cross-sectionally in 20-22-year-old young adults with CP. The long-term effects of the spasticity-reducing neurosurgical procedure selective dorsal rhizotomy (SDR) were investigated using a consecutive case series. And botulinum toxin-A (BoNT-A) was tested as a treatment for chronic muscle-related pain in adults with CP by means of a randomized, placebo-controlled, double-blinded clinical trial.

It was found that most young adults with CP still lived in their parental home; more so than in the general population. A majority of those without an intellectual disability had an occupation, but the risk of having no occupation at all was increased. Communication function classification level (CFCS), and intellectual disability were major determinants of the social outcomes, while gross motor function classification level (GMFCS) was not. The overall health-related quality of life (HRQoL) of young adults with CP was comparable to population norms. There were, however, significant sub-group differences across different levels of gross motor function. Pain and fatigue were prevalent across all levels of functioning.

The SDR procedure was effective in the long term in reducing spasticity, but this did not prevent contracture development, nor did it seem to improve functioning. Finally, BoNT-A was not superior to placebo in reducing pain in adults with CP at six weeks after treatment. Pain intensity did, however, trend downwards in the BoNT-A group at the last follow-up, suggesting that trials of longer duration are warranted.

LIST OF SCIENTIFIC PAPERS

I. Exploring social participation in young adults with cerebral palsy.

Jacobson D.N.O., Löwing K., Hjalmarsson E., Tedroff K.

J Rehabil Med. 2019 Mar 13;51(3):167-174.

II. Health-related quality of life, pain, and fatigue in young adults with cerebral palsy.

Jacobson D.N.O., Löwing K., Tedroff K.

Dev Med Child Neurol. 2020 Mar;62(3):372-378. Epub 2019 Nov 28.

III. Does loss of spasticity matter? A 10-year follow-up after selective dorsal rhizotomy in cerebral palsy.

Tedroff K., Löwing K., Jacobson D.N.O., Åström E.

Dev Med Child Neurol. 2011 Aug;53(8):724-9.

IV. A first randomized controlled trial on Botulinum toxin-A for chronic muscle-related pain in adults with cerebral palsy.

Jacobson D.N.O., Löwing K., Kullander K., Rydh B-M., Tedroff K.

Submitted

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
ANOVA	Analysis of Variance
BoNT-A	Botulinum toxin-A
BPI	Brief Pain Inventory
CFCS	Communication Function Classification System
CI	Confidence interval
CP	Cerebral palsy
CPUP	Cerebral Palsy Follow-up Program
DMC	Data Monitoring Committee
EADCS	Eating and Drinking Classification System
EMG	Electromyography
FMS	Functional Mobility Scale
FSS	Fatigue Severity Scale
GABA	Gamma-aminobutyric acid
GMFCS	Gross Motor Function Classification System
GMFCS-ER	Gross Motor Function Classification System – Extended and Revised
GMFM	Gross Motor Function Measurement
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
ID	Intellectual disability
ITB	Intrathecal baclofen
IQ	Intelligence quotient
MACS	Manual Ability Classification System
MAS	Modified Ashworth Scale
MCS	Mental Component Score
NBS	Norm Based Scores
NNT	Numbers needed to treat

NRS	Numerical Rating Scale
OT	Occupational therapy
PCS	Physical Component Score
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
RCT	Randomized controlled trial
ROM	Range of motion
SCPE	Surveillance of Cerebral Palsy in Europe collaboration
SD	Standard deviation
SDR	Selective dorsal rhizotomy
SF-36v2	Short Form-36 version 2
SGPALS	Saltin Grimby Physical Activity Level Scale
SMC	Selective motor control
VAS	Visual Analogue Scale
VFCS	Visual Function Classification System
WHO	World Health Organization
QoL	Quality of life

1 INTRODUCTION

1.1 CEREBRAL PALSY

1.1.1 Definition, etiology and prevalence

Cerebral palsy (CP) is defined as a group of permanent disorders of the development of movement and posture, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Rosenbaum et al., 2007). These non-progressive disturbances are most often transient destructive processes that injure the brain, most commonly identified as hypoxia-ischemia, infections or focal infarcts (Bax et al., 2006). Congenital causes (i. e. not injuries) such as malformations or purely molecular genetic disorders are less common (Bax et al., 2006; MacLennan et al., 2015). The etiology of the destructive process can be singular (such as a single cerebrovascular event) but is probably often a combination of precipitating events (such as prematurity, growth restriction and inflammation) (Leviton et al., 2013; McIntyre et al., 2013). Acute intrapartum hypoxia has historically been assumed to be the main cause of CP but has been estimated to account for less than 10% of cases (Ellenberg & Nelson, 2013; Nelson & Ellenberg, 1986).

An important prerequisite for the cerebral palsy diagnosis is that the non-progressive disturbance to the brain "occurred in the developing fetal or infant brain" (Rosenbaum et al., 2007), emphasizing that the disturbance resulting in CP happened before or during the development of the affected function (such as hand manipulation or walking) (Rosenbaum et al., 2007). There is no explicit age limit, but disturbances occurring after two years of age are generally not considered CP (Rosenbaum et al., 2007), and most national registries reporting on prevalence figures (see below) exclude post-neonatal cases (Galea et al., 2019; Hollung et al., 2018; Sellier et al., 2016).

The most recent reported birth prevalence of CP in western Europe is 1.77 per 1000 live births (or 0.17%) (Sellier et al., 2016), with a 99% confidence interval (CI) between 1.57-1.99. Similar figures have recently been reported from Australia (Galea et al., 2019). Both reports note that the prevalence of CP is decreasing when comparing more recent birth cohorts with birth cohorts from the 1980-1990's, where the prevalence was at or above 0.20% (Galea et al., 2019; Sellier et al., 2016). This decrease is thought to be due to improvements in prenatal and postnatal/neonatal care (Galea et al., 2019; Sellier et al., 2016).

1.1.2 Clinical characteristics and classifications

As the definition states, CP comprises a group of clinical disorders. Further delineation is necessary. The movement aspects of the disorder take precedence in the ensuing categorization. Other aspects of function are, however, gaining in importance, as discussed further on. The guidelines issued in 2000 by the Surveillance of Cerebral Palsy in Europe collaboration (SCPE) remain the gold standard in classifying the clinical sub-types of CP (Cans et al., 2000) (Figure 1). The clinical sub-types of CP are spastic bilateral, spastic unilateral, dyskinetic (with further sub-classification into dystonic and choreoathetoid),

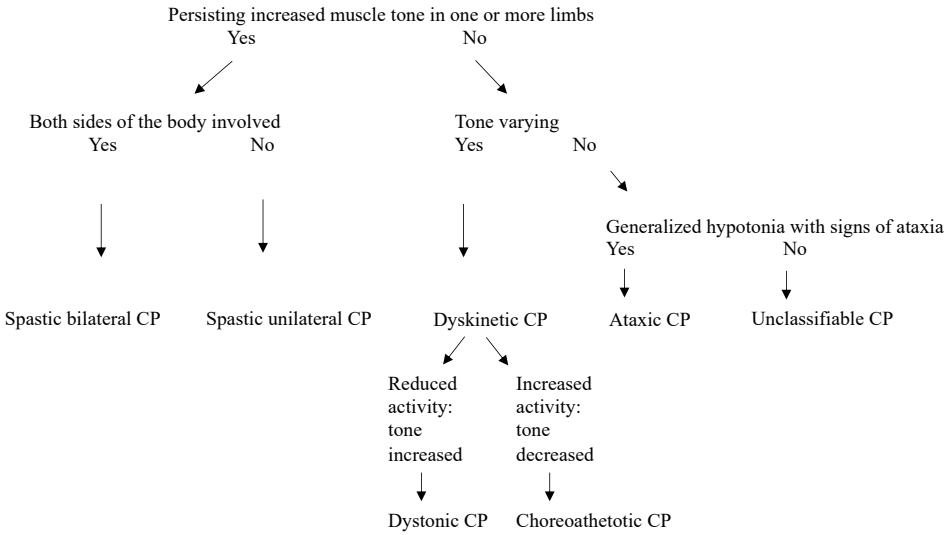

Figure 1. Hierarchical decision tree for classifying cerebral palsy sub-types. Adapted from Surveillance of Cerebral Palsy in Europe – Cans et al. (2000).

ataxic, and unclassifiable. Further distinctions are made using classification systems of functional abilities. These classification systems play a major role in this thesis. The Gross Motor Function Classification System (GMFCS) (Figure 2) (Palisano et al., 1997), revised in 2008 (Palisano et al., 2008) was the first classification system. It has since gained universal use clinically and in research as well as served as a model for subsequent classification systems. It classifies gross motor functioning into five levels ranging from high motor functioning in level I to low motor functioning in level V (Figure 2). The GMFCS has been shown to be valid, reliable, stable over time and predictive of long term motor functioning (Hanna et al., 2009; Palisano et al., 2006; Palisano et al., 2008; Palisano et al., 1997). Although developed for children, the updated version (GMFCS-ER) (Palisano et al., 2008) has been shown to be valid also for adults (Jahnsen et al., 2006). The GMFCS is associated with the presence and severity of accompanying impairments such as intellectual disability (ID), epilepsy, impairments of vision and hearing, and more (Delacy et al., 2016; Himmelmann et al., 2006). Thus, the clinical sub-type and the GMFCS, both descriptors of movement, have been established as the basis for classifying CP in an individual. The Manual Ability Classification System (MACS) (Eliasson et al., 2006) is constructed analogous to the GMFCS and classifies hand performance/manual ability on a five level scale. The MACS has equally gained widespread use in the clinical setting and in research (Rosenbaum et al., 2014).

Given that the basis for the disorder is any early non-progressive brain injury or malformation (be it large or small, well-defined or diffuse) that gives rise to motor signs and symptoms, it is only logical to assume that other central nervous system functions, besides movement, often are affected. This is indeed the case; intellectual disability is present in about half of individuals with CP, epilepsy in a third, with impairments of vision, hearing, communication,

behavior, amongst other co-morbidities, also being common (Novak et al., 2012). This has also been recognized in the latest definition of CP (Rosenbaum et al., 2007). The co-morbidities are, as mentioned above, not uniformly distributed in individuals with CP but more common when there is more motor activity limitation and less common (but not necessarily absent) when there is less motor activity limitation (Delacy et al., 2016; Himmelmann et al., 2006).

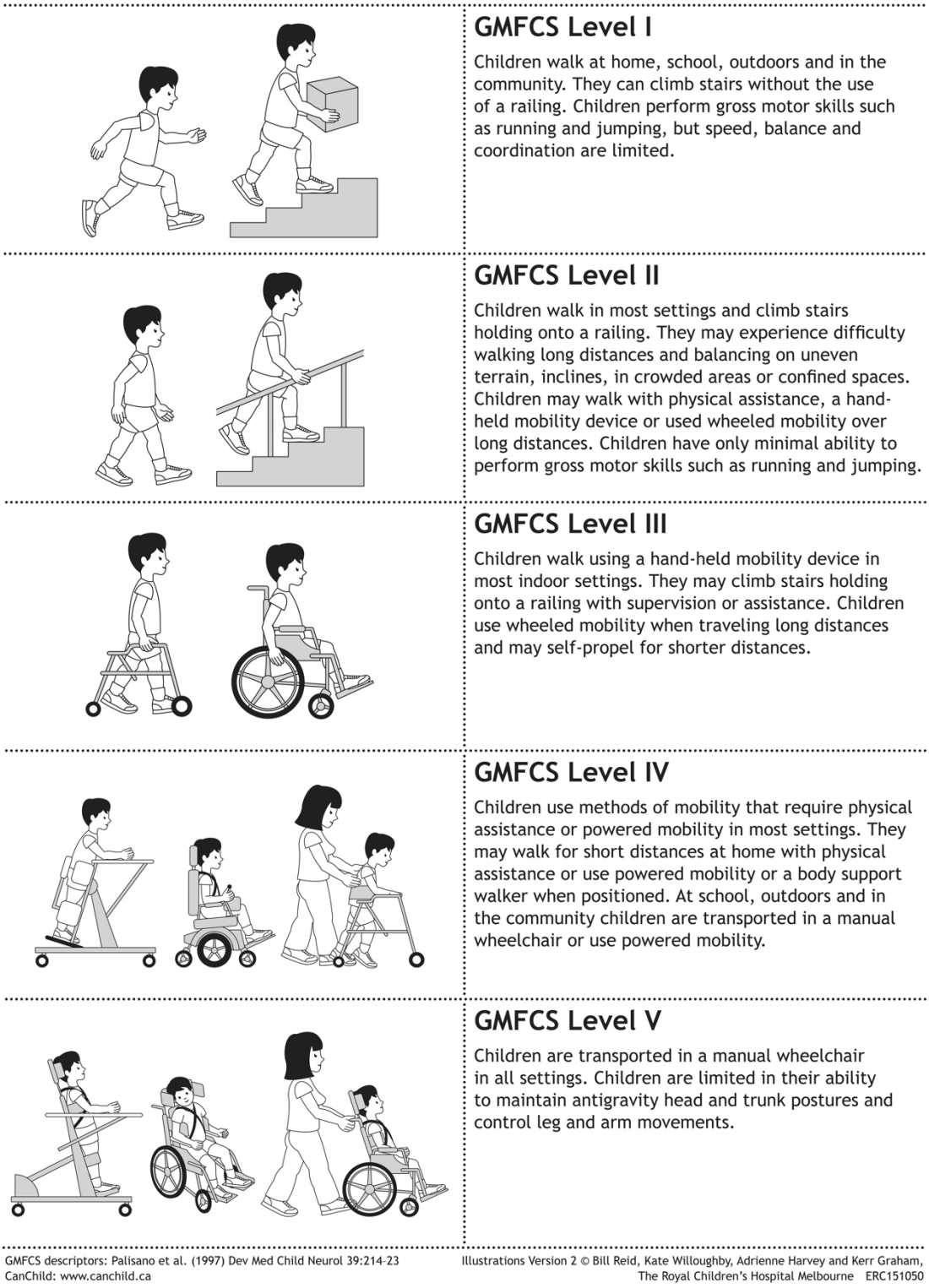

Figure 2. Illustrations of the five levels of the Gross Motor Function Classification System. Courtesy of Prof. K. Graham, The Royal Children's Hospital, Melbourne. Reprinted with permission.

Functional levels of communication have been formalized in the Communication Function Classification System (CFCS) (M. J. Hidecker et al., 2011). It similarly has five levels, and has been found to complement the GMFCS and the MACS in that the combination of the three systems gives a more comprehensive picture of functioning in children with CP (M. J. C. Hidecker et al., 2012). The impact and usefulness of these systems have resulted in additional classification systems being published, for example, the Eating And Drinking Classification System (EADCS) (Sellers et al., 2014) and the Visual Function Classification System (VFCS) (Baranello et al., 2020). The classification systems share a number of common features. Noteworthy are that the systems focus on what an individual *does* as opposed to their *difficulties* (i. e. achievement rather than deficit), and that the systems classify performance (children/adults' usual activity) as opposed to capacity (what an individual can do at their best) (Rosenbaum et al., 2014). The systems do not weigh how 'normally' an individual performs an activity (Rosenbaum et al., 2014).

1.2 HEALTH AND WELL-BEING IN CEREBRAL PALSY

1.2.1 The concept of health

In 1946, the World Health Organization (WHO) agreed upon a definition of health that is still in use, stating that "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 1946). Apparent to most but still an important reminder to some is that having a disability does not exclude enjoying good health. That social life is an integral part of overall health is another reminder.

1.2.2 Aspects of disability

Disability can be conceptualized as 1) a medical problem; a feature of the person directly caused by disease or trauma, where the solutions are medical treatments or other interventions aimed at 'normalizing' or correcting the feature, or 2) a socially created problem; that disability is not about the individual herself but instead caused by an unaccommodating environment, where solutions are interventions aimed at correcting the environment (World Health Organization, 2002). In reality, disability is a complex interplay between both concepts. Drawing upon these models and their complex interactions, the WHO has developed the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001) as a universal classification for health and disability and a framework for understanding this interplay. Whereas the International Classification of Diseases (ICD) (World Health Organization, 2004) helps in structuring diagnoses correctly, the ICF helps in structuring functioning correctly. A notable feature of the ICF framework is the division of human functioning into three levels: the level of body or body part, of the whole person, and the whole person in a social context (World Health Organization, 2002). Correspondingly, disability involves dysfunction at one or more of these three levels, namely as 'impairment' (body or body part), 'activity limitation' (whole person), or as 'participation restriction' (whole person in a social context). The framework is therefore two-sided: body structure and function, and activity and participation denote the "positive aspects": the health

or functioning of the individual. Impairment, activity limitation and participation restriction denote the "negative aspects": the disability(World Health Organization, 2013). Disability and functioning are regarded as outcomes of the interactions between these health conditions and the contextual factors; namely environmental factors (such as societal attitudes, legal and social structures, the physical structuring of public milieus) and personal factors (such as age, gender, social background, and coping style) (World Health Organization, 2002).

The concepts of the ICF have been part of a general shift in the way CP is approached clinically and scientifically (Rosenbaum & Gorter, 2012). It has helped to shift focus from body structure and function-oriented interventions to interventions instead directly aimed at improving activity and participation (Novak et al., 2013; Rosenbaum & Gorter, 2012). In other words – a shift from 'correcting' or 'normalizing' impairments to that of promoting activity, and achieving societal participation and self-set goals (Rosenbaum & Gorter, 2012).

1.2.3 Quality of life

Measuring well-being is the mission of quality of life (QoL) instruments. The WHO defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization, 1997). This has not been the only attempt to delineate and define the concept. Considerable uncertainty remains in separating the concepts of QoL, health-related quality of life (HRQoL), and health status (Karimi & Brazier, 2016). In an attempt to distinguish HRQoL from QoL the following definition has been presented: "Quality of life is an all-inclusive concept incorporating all factors that impact upon an individual's life. Health-related quality of life includes only those factors that are part of an individual's health" (Torrance, 1987), meaning that, for example, economic or political considerations should be omitted from the HRQoL concept. It has been argued that common HRQoL instruments in fact measure health, as per the WHO definition of health (World Health Organization, 1946), and should therefore be referred to as measures of 'health status' or 'self-perceived health' (Karimi & Brazier, 2016). In this thesis, the terms 'HRQoL', 'health status' and 'self-perceived health' will be used interchangeably.

1.2.4 Young adulthood

The period of life characterized by transition from childhood to adulthood is of interest when looking at a life-long childhood-onset disability such as CP. This is because information on health at this time can be used to inform 'up-stream' pediatric health services as well as 'down-stream' adult health services, between which there is often an inappropriate, sharp demarcation (Alriksson-Schmidt et al., 2014; Bjorquist et al., 2015; Nguyen et al., 2016; van Staa et al., 2011). Usually, there has been a multitude of measurements and interventions performed as part of the pediatric services for CP. Getting an overview of health and health problems right after the conclusion of childhood can help give feedback on the results of those actions. This information is also useful for adult health services, as identified emerging health issues can be addressed and managed early. The adult population with CP is very

large; while mortality is increased in individuals with CP with multimorbidity, most individuals will have a life expectancy similar to that of the general population (Himmelmann & Sundh, 2015; Reid et al., 2012; Touyama et al., 2013).

The terms 'adolescence' and 'young adulthood' share common elements and have not been conclusively defined (Sawyer et al., 2018). However, for reasons of consistency in this thesis adolescence will be defined as the period in life between puberty and legal adulthood, and young adulthood as the first years of legal adulthood.

1.2.4.1 Social aspects

Social well-being is an integral part of the WHO definition of health (World Health Organization, 1946). What constitutes well-being in this sense is a matter of personal and environmental factors, cultural standards, and expectations (World Health Organization, 1997). Qualitative research approaches have found that youth with CP and other chronic disorders rank social inclusion (Lindsay, 2016), relationships (Bjorquist et al., 2015), gaining independence from the parental family (Bjorquist et al., 2015; Nguyen et al., 2016) and moving away from the parental family (Tornbom et al., 2013) as desirable goals when transitioning from childhood to adulthood. Research has been scarce as to what degree goals such as these have been achieved, and perhaps more importantly, if there are particular factors that enable or disable the individual from reaching them.

One of the first available reports on this topic was, interestingly enough, from the Stockholm area and the Karolinska Hospital (Avignon & Gardestrom, 1958). Data on health and social situation were gathered on children and young adults with CP. One main conclusion was that many of the respondents risked social exclusion due to lack of employment opportunities. Subsequent later studies from Denmark, in the 2000's, found that adults of all ages with CP were to a lesser extent employed, in tertiary studies, living independently and/or cohabiting with partners, than the population as a whole (Michelsen et al., 2006; Michelsen et al., 2005). Findings along the same line were reported from clinic-based studies conducted in the Netherlands and the United States (Donkervoort et al., 2009; Murphy et al., 2000; van der Slot et al., 2010; Wiegerink et al., 2010). The studies found that cognitive function played a large part in determining social outcomes, while motor functioning appeared to have had a minor role. Conducted mainly on samples of individuals in wide age ranges, the specific situation in young adulthood remained to be further investigated, especially in a Swedish context[a].

[a] Please note that the studies, including from Sweden, which have been published on this subject *after* the start of the data collection for this part of the thesis (2013) will be reviewed under Results and Discussion.

1.2.4.2 Health status

Similar to social aspects, the health status of individuals with CP after childhood was to a large extent unknown due to limited attention in research. Reports emerging in the 1990's and 2000's on adults with CP of all ages noted that pain and fatigue were prevalent and that these issues appeared to become more troublesome in adulthood (Jahnsen, Villien, Aamodt, et al., 2004; Jahnsen et al., 2003; Murphy et al., 1995; Sandstrom et al., 2004; van der Slot et al., 2012). Fatigue can be described as experiencing feeling weak, tired, or lacking energy (McPhee et al., 2017). Fatigue has been recognized as a particularly debilitating co-morbidity in other conditions involving central nervous system dysfunction, such as adult stroke (Radman et al., 2012) and multiple sclerosis (Flachenecker et al., 2002). Overall health status (or HRQoL) for adults with CP has been reported as reduced in regards to physical functioning when compared to population norms, but not reduced in regards to self-reported mental health (Opheim et al., 2011; van der Slot et al., 2010). The situation specific to young adulthood remained inconclusive. Furthermore, it was noted that the health issues accompanying CP, such as pain and fatigue, were given too little attention (Baxter, 2013)[a].

1.2.4.3 Physical activity

Physical activity is considered generally beneficial for most health parameters and CP is no exception. A meta-analysis (Ryan et al., 2017) of studies on exercise programs for individuals with CP have shown that exercise, especially aerobic or mixed programs, can improve gross motor function and participation in individuals with CP. Level of physical activity has been found to be inversely related with GMFCS-level (Bjornson et al., 2007; Maher et al., 2007). However, physical activity is possible also for individuals with more severe motor limitations using techniques such as RaceRunning (Hjalmarsson et al., 2020) and aquatic therapy (Lai et al., 2015).

1.3 SPASTICITY, PAIN, AND ASSOCIATED TREATMENTS

1.3.1 Spasticity

The most common clinical sub-types of CP (Sellier et al., 2016); spastic unilateral CP and spastic bilateral CP (see Figure 1), are, from a movement-and-posture perspective, clinically characterized by elements of the so-called upper motor neuron syndrome (Kandel et al., 2013; Purves et al., 2004)[b]. The underlying pathology is typically injury or dysfunction of the neurons of primary motor cortex or of their corticobulbar or corticospinal projections (Sanger et al., 2003). Salient features of this concept are weakness, reduced selective motor control, spasticity, and secondary musculoskeletal changes. (Note that other dysfunctions are sometimes included, such as hyperreflexia, and retained developmental reflexes). *Weakness* is "the decreased ability of the muscle to generate voluntary force" (Sanger et al., 2006).

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[b] Although the term 'upper motor neuron syndrome' is often used; especially in medical training for matching clinical neurological signs to neuroanatomical lesions, some neuroscientists advise against its use, deeming it a too simplistic view of the primary motor cortex (see Kandel et al, 2013)

Reduced selective motor control is "the impaired ability to isolate the activation of muscles in a selected pattern in response to demands of a voluntary posture or movement" (Sanger et al., 2006). *Secondary musculoskeletal changes* involve alterations in the molecular and histological architecture of skeletal muscles, impaired muscle growth, and joint contracture development (Lieber et al., 2004; Mathewson & Lieber, 2015). *Spasticity* is, as apparent, only one component of the movement impairments but has been given a prominent role possibly due to it being a conspicuous feature. Although spasticity is a common clinical sign and symptom, there is no universally accepted definition (Malhotra et al., 2009). One of the most commonly used definitions is that of Lance (Lance, 1980): "a motor disorder characterized by a velocity-dependent increase in the tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex". A second definition, put forth by an interdisciplinary task force on the definition of childhood motor disorders include muscle hypertonia (itself defined as "resistance to passive stretch while the patient is attempting to maintain a relaxed state of muscle activity") together with one or both of the following signs: "1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle" (Sanger et al., 2003). Recurring themes of spasticity are (oversimplified for visualization purposes): 1) stiff muscles and 2) muscles that become stiffer when stretched quickly. How to actually measure this stiffness or resistance to passive stretch is a matter of considerable debate (Fleuren et al., 2010; Lin, 2011; Malhotra et al., 2009; Willerslev-Olsen et al., 2013).

Although spasticity is a conspicuous clinical feature of many individuals with CP, and although therapies and interventions aimed at alleviating spasticity have taken prominent positions in the management of individuals with CP, the actual effect of spasticity on functioning in individuals with CP has been estimated to be limited. The fact that the definition is debated and how to objectively measure spasticity is disputed adds complexity when trying to disentangle the relative contributions of, for example; weakness, reduced selective motor control and spasticity on the functioning of the individual. Gorter and colleagues found a very limited relationship between spasticity and gross motor development in toddlers with CP (J. W. Gorter et al., 2009). Kim and Park performed a path analysis study of data on muscle strength, spasticity, gross motor function and functional activity in children with CP and found that strength was more associated with gross motor function than spasticity, but that neither were associated with functional activity (Kim & Park, 2011). Damiano and colleagues studied the resistance to stretch as performed by a mechanical device (as a measurement of spasticity) and the relationships between this with gait parameters. They found no correlation between the amount of resistance with gait parameters, although a subset of children whom had undergone selective dorsal rhizotomy (SDR) to relieve spasticity had gait changes that could imply a causal relationship with spasticity (Damiano et al., 2006). Noble and colleagues investigated the relationship between selective motor control (SMC) and gross motor function and spasticity in youth with CP: SMC was more strongly linked to gross motor function than spasticity was (Noble et al., 2019). Earlier,

Lin and Brown found no relationship between clinically assessed spasticity with toe-walking in children with spastic unilateral CP (Lin & Brown, 1992). Thus, it appears that the connection between spasticity and function is far from strong.

Spasticity has traditionally often been implicated as the primary cause behind the development of contractures (Graham & Selber, 2003). Contractures appear when the muscle-tendon-complex length is shorter than needed for full range of motion of the joint it passes (Mathewson & Lieber, 2015). This can result from either the shortening of a previously adequately long muscle, or, as can be the case in a growing child, the inappropriate growth of a muscle. In CP, spasticity has been blamed for this, theorizing that stiff and over-reactive muscles kept the joints in question flexed and unrelaxed, thus inhibiting growth (Graham & Selber, 2003). This causality is still a widespread belief despite evidence of the contrary. In a long-term follow-up of children with CP treated with injections of botulinum toxin-A (BoNT-A) it was found that while spasticity was reduced, joint range of motion (ROM) continued to decline (Tedroff et al., 2009). Using a randomized controlled design, BoNT-A was used to reduce spasticity in the adductor muscles in an attempt to halt or slow progression of hip joint displacement in CP, also without success (Graham et al., 2008). Paper III of this thesis adds evidence that a completely different modality of spasticity reduction (selective dorsal rhizotomy) also fails to prevent contracture development (Tedroff et al., 2011). Cloodt and colleagues recently reported on the relative associations of age, GMFCS-level, hamstring and gastrocnemius muscle length, and spasticity of the knee and plantar flexors on the presence of knee contractures in a large sample of Swedish children with CP (Cloodt et al., 2018). They found that spasticity in the knee flexors, but not plantar flexors, was modestly associated with knee contractures. Research into properties of the skeletal muscles in individuals with spasticity has revealed that the muscle itself has significant changes in its molecular and histological composition, including changes to the extracellular matrix and the number of stem cell-like satellite cells it holds; changes that make the muscle stiffer and less likely to grow as expected (Dayanidhi et al., 2020; Lieber et al., 2004; Mathewson & Lieber, 2015). The radical change in neural activity to the muscle that occurs as a consequence of the brain injury or malformation is thought to set in motion these alterations in the muscle (Pingel et al., 2017), alterations which probably remain regardless of whether any clinically evident spasticity is treated or not.

1.3.2 Treatment of spasticity

The decision to treat spasticity is individualized and should be made on the basis of the extent to which it interferes with activities and participation, individual and family goals, and care, comfort and sleep, while keeping in mind the limitations stated in the previous section. Evidence-based treatment modalities that are often considered for spasticity in CP include the following (Novak et al., 2013):

- Botulinum toxin-A (BoNT-A). This neurotoxin is extracted from the anaerobic bacteria *Clostridium botulinum* (Mazzocchio & Caleo, 2014) [c] and given as intramuscular injections (Heinen et al., 2010). After uptake in the presynaptic terminal of the neuromuscular junction BoNT-A inhibits the release of acetylcholine causing dose-dependent paralysis of the target muscle with a transient effect (Mazzocchio & Caleo, 2014). It is a common first choice of therapy in focal spasticity (Blumetti et al., 2019). The therapeutic use and evidence base of BoNT-A are expanded on below.
- Baclofen. A selective agonist of the gamma-aminobutyric acid$(GABA)_B$-receptor (Rang et al., 2003) baclofen acts by inhibition of central nervous pathways, especially of interneurons in the spinal cord (Price et al., 1984). It is given either orally, or, as a continuous intrathecal infusion (intrathecal baclofen, ITB) by means of an implanted pump (Albright et al., 2006). It is mainly used to treat non-focal spasticity (Dan et al., 2010).
- Selective dorsal rhizotomy (SDR). This is an irreversible neurosurgical procedure where spinal dorsal rootlets containing afferent excitatory nerve fibers from the proprioceptors of the muscle spindles are sectioned before entry into the dorsal horn of the spinal cord (Park et al., 1993; Smyth & Peacock, 2000). The aim is to abolish or reduce the hyperexcitable stretch reflex of spasticity (Smyth & Peacock, 2000).
- Bensodiazepines. These substances potentiate the effect of GABA on $GABA_A$-receptors by binding to an accessory site on the receptor (Rang et al., 2003). The mechanism of action in spasticity is through inhibition of central nervous system pathways. Diazepam and clonazepam are examples of specific substances used for this purpose (Novak et al., 2013).

In this thesis, particular attention is given to SDR (as the treatment evaluated in paper III) and BoNT-A (as the treatment evaluated in paper IV).

1.3.2.1 Selective dorsal rhizotomy

The history of the SDR procedure goes back to classical experiments on the corticospinal tracts performed by Sherrington in the late 19th century. Muscle hypertonia in cats, induced by interrupting the cerebrospinal tracts, was relieved when the lumbosacral afferent dorsal roots were cut (Sherrington, 1898). The technique was used to treat spasticity in humans in a report from 1911 (Foerster, 1911) and subsequently intermittently but overall rarely used, with a variety of techniques (Fasano et al., 1978; Privat et al., 1976), until it was popularized in the 1980's (Enslin et al., 2019; Vaughan et al., 1991). It was popularized mainly for the treatment of lower-limb spasticity in CP; a feature of the clinical sub-type then referred to as

[c] Of academic interest, the bacterial genus *Clostridium* contains a number of well-known human pathogens: besides *C. botulinum* as the causative agent of botulism, *C. tetani* causes tetanus, and *C. perfringens* can cause food poisoning and gas gangrene. They induce disease primarily through the toxins they produce; the tetanus toxin is structurally very similar to the botulinum toxin.

spastic diplegia and now included in the sub-type spastic bilateral CP. Gaining widespread use, the procedure now most commonly involves selectively sectioning fascicles (or 'rootlets') of the dorsal roots, from lumbar myotome level 2 (L2) to sacral myotome level 1 (S1), based on the electromyographical (EMG) appearance of intraoperative stimulation of each fascicle (Enslin et al., 2019). The dorsal roots are accessed either by a laminotomy of spinal levels L2-L5 (the "Peacock technique" (Smyth & Peacock, 2000)) where the fascicles are manipulated and severed close to the foraminae, or through a narrow laminotomy exposing just the conus medullaris (the "Park technique" (Park et al., 1993)). The post-operative immobilization has varied between resumption of physical activities on postoperative day three, to being confined to six weeks in a spinal plaster (Enslin et al., 2019; Park et al., 1993). Adverse events in the short-to-intermediate term include sensory deficits and bladder control issues (McLaughlin et al., 1998; Nordmark et al., 2008; Park et al., 1993; Tedroff et al., 2011), unexpected falls (Grootveld et al., 2016) and a high frequency of spinal complications such as scoliosis, hyperlordosis and spondylolisthesis (Tedroff et al., 2020). There is also concern about the safety in the long-term given that so much sensory input, including proprioception, has been severed by the procedure.

As it was found that the procedure markedly reduced spasticity it was, by the nature of the assumptions that spasticity was the main culprit behind functional limitations and contracture development, assumed that the procedure would indirectly result in better functioning and prevent contracture development in individuals with CP. A meta-analysis from 2002 (McLaughlin et al., 2002) of three randomized controlled trials (RCT) (McLaughlin et al., 1998; Steinbok et al., 1997; Wright et al., 1998) in children with CP remain the primary evidence-base for the efficacy of the procedure. The meta-analysis found that SDR clearly reduced spasticity in the children in all three included studies (McLaughlin et al., 2002). However, the effect on gross motor function: a mean difference between groups of 4.5 percentage points on the Gross Motor Function Measurement, original version (GMFM-88) (Russell et al., 1989) and 2.7 points on the updated version (GMFM-66) (Russell et al., 2000) was less clear, with the authors stating that "these modest improvements in gross motor functioning are somewhat disappointing" and that "it is difficult to know the clinical importance of a mean difference in change score of 4 percentage points on the GMFM" (McLaughlin et al., 2002). The main limitation of the underlying RCTs was, from a clinical utility perspective, that they only had short-term follow-up (between 9 months and 2 years). The long-term effect on spasticity, gross motor function and contracture development needed further investigation.

1.3.2.2 Botulinum toxin-A use in cerebral palsy

The use of BoNT-A for spasticity in children with CP began in the 1990's and has since gained widespread use. It was noted early on that the implementation of the procedure quickly surpassed the scientific evidence-base supporting its use (Forssberg & Tedroff, 1997). Consensus papers on its use have since been published regarding children with CP (Heinen et al., 2010) and to some extent adults with CP (Esquenazi et al., 2010). There are

Cochrane Systematic Reviews that evaluate the effectiveness and evidence-base of BoNT-A use in the upper (Hoare et al., 2010) and lower extremities (Blumetti et al., 2019) in children with spastic CP. The 2010 review of its use in the upper extremities concluded that there was a high level of evidence that a combination of BoNT-A and occupational therapy (OT) was better than OT alone in reducing spasticity, improving activity level outcomes and goal achievement, but, that BoNT-A alone was ineffective (Hoare et al., 2010). The 2019 review of BoNT-A use in the lower extremities found that there was limited evidence that BoNT-A was more effective in reducing spasticity and improving gait, ROM and satisfaction as compared to placebo (Blumetti et al., 2019). Results on gross motor function were contradictory (Blumetti et al., 2019). Here, the quality of the evidence was considered low to very low, despite including 31 studies with a total of 1508 participants.

Botulinum toxin-A has also been used in the control of excessive drooling (Walshe et al., 2012), and has been tested as a treatment for pain in children with spastic CP in certain situations (Barwood et al., 2000; Lundy et al., 2009), which will be expanded on in the next section.

During much of its use, BoNT-A has been considered a safe and fully reversible treatment with the effect diminishing over a few months. However, there are advocates for a more cautious use of BoNT-A. Concerns have been raised regarding long-standing negative effects on muscle strength and muscle composition, which could be irreversible (Alexander et al., 2018; Gough et al., 2005; Multani et al., 2019).

1.3.3 Pain in cerebral palsy

As a co-morbidity of CP, pain has only fairly recently become a focus for systematic evaluation. In adults, in the US, Turk and colleagues performed a clinic-based survey in 1997 amongst women with cerebral palsy of all adult ages and found that 84% reported bodily pain (Turk et al., 1997). In 1999, Schwartz and colleagues conducted a face-to-face study interviewing adults in the state of Washington, focusing on pain and pain interference (Schwartz et al., 1999). Sixty-seven percent reported one or more areas of chronic pain, however the interference pain had on daily activities was low. In adults in Scandinavia, Andersson and Mattsson had items on pain in their Swedish mailed survey from 2001 where 48% reported muscle and joint pain at least once a month (Andersson & Mattsson, 2001). Jahnsen and colleagues highlighted the problem of persistent pain in their 2004 Norwegian survey of adults with spastic CP. They reported a prevalence rate of about 30% of the adults reporting chronic pain, with an increasing trend with age (Jahnsen, Villien, Aamodt, et al., 2004). Both overexertion and inactivity were common self-reported triggers and/or causes of pain. In follow-up studies on this Norwegian cohort of adults with CP, it was shown that pain and fatigue were correlated to deterioration in walking (Opheim et al., 2009) and that pain most commonly was located at the level of the neck, back and foot/ankle (Opheim et al., 2011).

Pain came even more into the spotlight in a 2012 systematic review on clinical issues accompanying CP (Novak et al., 2012). Their results were that 75% of the entire population with CP suffered from pain, which in turn triggered a debate on whether pain was under-diagnosed and under-treated in CP (Baxter, 2013). A systematic review on pain in children and young adults with CP from 2019 noted that pooling the data from existing studies was not easy due to sampling bias and differing methodology (McKinnon et al., 2019). Their results were that 14-76% in the study population had pain and that risk factors were female gender, increasing age, and being classified in GMFCS level V (McKinnon et al., 2019).

Different mechanisms causing pain have been proposed and these include over-use and excessive strain on disabled limbs (Murphy et al., 1995), pain worsening during certain aspects of physiotherapy (Parkinson et al., 2013), and pain caused by dystonia (Penner et al., 2013) and hip subluxation (Penner et al., 2013). Spasticity has often been implied as a cause of pain, both by clinicians and researchers and not least by individuals with CP themselves, but the systematic literature on this is fairly scarce (Blackman et al., 2018). Flanigan and colleagues recently found correlations between pain intensity with both spasm frequency and spasticity in adults with CP (Flanigan et al., 2020).

1.3.4 Treatment of pain in cerebral palsy

The evidence base for the management of pain in CP is poor. An attempt (2019) at a systematic review for pain management in children with CP had to resolve to narrative synthesis instead of meta-analysis due to a high risk of bias in included studies, and could only make recommendations for a few specific clinical situations (e. g. children whom were candidates for ITB, and postoperative situations) (Ostojic et al., 2019). The review stressed that further research was needed especially in the area of chronic pain (Ostojic et al., 2019). There are no published RCTs in adults with CP with pain reduction as the primary objective prior to our study. Finding treatments addressing chronic pain in adults with CP is a major priority, as pain appears to worsen with age (McKinnon et al., 2019).

1.3.4.1 The potential use of botulinum toxin-A

Botulinum toxin-A has been tried and reported in a few specific circumstances as an analgesic in children with CP. Lundy and colleagues reported a case series of children in GMFCS level V whom had spasticity and pain at the hip level. The children, all treated with BoNT-A, reported a decrease in pain (Lundy et al., 2009). Barwood and colleagues performed an RCT where BoNT-A was compared to placebo in children with spasticity at the hip level who underwent adductor tenotomy. They found significant pain reduction and reduction of hospital stay for the BoNT-A group (Barwood et al., 2000). Recently, however, Will and colleagues found no difference in pain when comparing BoNT-A to placebo in a similar perioperative setting but where the children underwent bony hip surgery (Will et al., 2019).

Botulinum toxin-A has found use in pain conditions that are unassociated with muscle overactivity. For example, it has a proven effect on chronic migraine (Herd et al., 2018), post-

herpetic neuralgia (Safarpour & Jabbari, 2018) and trigeminal neuralgia (Safarpour & Jabbari, 2018). Besides the direct actions BoNT-A has on muscle activity (reducing muscle tone and decreasing spasms) through the inhibition of presynaptic acetylcholine release, it also appears to block neurotransmitter and neuropeptide release from nociceptive nerve endings (Mazzocchio & Caleo, 2014; Ramachandran & Yaksh, 2014). This combined mode of action makes BoNT-A an interesting candidate for pain treatment in individuals with CP.

2 AIMS OF THE THESIS

The overall aim of this thesis was to better understand the health status and social situation of young adults with cerebral palsy and to evaluate specific treatments for spasticity and pain.

The specific aims of the studies were as follows:

I. To describe a set of social outcomes in young adults with CP and to explore associations between these outcomes and the young adults' level of gross motor function, manual ability, communication function, and presence of intellectual disability.

II. To describe health-related quality of life, pain, and fatigue in young adults with CP and to explore associations between these variables and the young adults' level of gross motor function and level of physical activity.

III. To describe the long-term outcome after selective dorsal rhizotomy in children with CP, with a focus on the effect on spasticity, gross motor function, and contracture development.

IV. To test if botulinum toxin-A is effective in reducing chronic muscle-related pain in adults with spastic cerebral palsy.

3 METHODS

3.1 GENERAL STUDY DESIGNS

The following methods were used in order to answer the research aims for each paper respectively:

- Papers I and II used a cross-sectional study design.
- Paper III used a case series study design.
- Paper IV used a randomized, double-blinded, placebo-controlled study design.

The different study designs carry with them different possibilities and limitations, which are worth a brief review.

3.1.1 Cross-sectional studies

A cross-sectional study describes a group of subjects at a particular point in time(Campbell, 2007). It can describe the proportion of individuals within the group with a particular characteristic and analyze how that characteristic varies by other variables in the group, such as age or gender. Cross-sectional studies allow hypothesis testing of whether different characteristics are positively associated (i. e. tend to be present together) or negatively associated (i. e. tend to not be present together) These associations can be quantified through for example correlational analyses, but the study design does not in itself permit establishing causality.

3.1.2 Case series

A case series is typically a study that follows a group of individuals with a similar exposure, such as a particular treatment, over time in order to describe their outcome (Dekkers et al., 2012). It can also refer to a group of individuals with a particular (and rare) diagnosis who are studied to determine the course of their disease. The method is one of the few ways to perform research on rare diagnoses or rare treatments. It is distinct from a cohort study, which starts with a sample of exposed and unexposed individuals and follows them over time to see which ones get the outcome, usually involving a very large sample (Dekkers et al., 2012). A case series is a type of descriptive study and not generally meant for hypothesis testing. Any change in the outcome over the course of the time can, however, be subjected to statistical testing to see whether the change could be attributed to random chance or not.

Consecutive case series are preferred over non-consecutive series as the latter involve the risk of excluding individuals with unfavorable outcomes (selection bias).

3.1.2.1 Note on Paper III

At the commencement of the SDR-study in 1993, it was intended as an RCT with three treatment arms: SDR + standard care, orthopedic surgery + standard care, or standard care

alone. As allocation to anything other than SDR proved difficult for families to accept, the study turned into a consecutive case series of children undergoing SDR.

3.1.3 Randomized controlled trials

The randomized controlled trial (RCT) is the study design which offers the best possibility to establish causality. By randomly allocating subjects to the different treatments under investigation much of the bias inherent to observational studies can be avoided, most notably the unmeasured or unknown bias (Campbell, 2007). Preferably, the allocation remains hidden to the patient and the investigator (double blinding) in order to avoid conscious or unconscious preconceptions. Positive expectations or negative expectations on a treatment will have powerful effects on the outcome as has been shown in many different scenarios in the field of placebo research (Benedetti et al., 2015; Benedetti et al., 2014; Jensen et al., 2012; Kaptchuk et al., 2006).

3.2 PARTICIPANTS

All four papers in this thesis exclusively include individuals with a diagnosis of CP. All participants have given informed oral and written consent, either themselves directly or through their legal proxies. All studies were approved by the appropriate Ethical Review Board. An overview of the participants is given in Table 1.

Table 1. An overview of participant characteristics

Paper	Number of participants, N	Age at inclusion, mean (SD)	Female sex, N (%)	Data collection period
I & II	61	21 y, 2 m (8 m)	27 (44)	2013-2016
III	19	4 y, 7 m (1 y, 7 m)	4 (21)	1993-2007
IV	16	32 y (13 y)	10 (63)	2015-2018

N: Number. SD: Standard deviation. y: years. m: months.

Papers I and II had joint data collection. There were only a few occasions where one individual participated in more than one data collection: three individuals whom had taken part in the SDR follow-up (Paper III) also participated in Papers I and II, and five individuals whom had participated in Papers I and II participated also in Paper IV.

Other than a diagnosis of CP, inclusion and exclusion criteria differed between data collections to accommodate the study aim. The criteria are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Paper	Inclusion criteria	Exclusion criteria
I & II	• Diagnosis of CP registered at a Stockholm county clinic • Age ~ 21 y (born 1992-1995)	• None
III	• Spastic diplegic CP • Age 2 – 9 y • Normal or only mildly impaired cognitive development • Some method of independent locomotion • Significant spasticity in the lower extremities with a slow increase or plateau in gross motor development ≥ 6 months	• Major rigidity, dystonia, dyskinesia, ataxia or hypotonia • Marked weakness in antigravity muscles • Fixed joint contractures • Previous surgery such as osteotomies, tendon lengthening or neurectomy

IV	• Age ≥ 18 y
	• Spastic sub-type of CP
	• Chronic pain related to spastic muscle
	  ○ ≥ 3 months duration
	  ○ ≥ 3 in pain intensity on NRS
		• Hypersensitivity to BoNT-A
		• Pregnancy or breastfeeding
		• Treatment with BoNT-A within the last 5 months
		• Changes in muscle tone altering drugs within the last 2 weeks
		• Degenerative pain etiology
		• Intellectual disability and/or communication limitation

BoNT-A: Botulinum toxin-A. CP: Cerebral palsy. NRS: Numerical rating scale. y: years.

3.2.1 Methods for inclusion

3.2.1.1 Papers I & II

The approach for finding and including participants in a cross-sectional study varies. The goal should however always be to try to include a sample of individuals whom truly represent the population of interest. The target population in this data collection was young adults, within a narrow age-span, with CP within a geographical area reasonably available to the research team. The individuals in this population were located based on a few assumptions: 1) they should have had at least one visit to any one of the clinics in the Stockholm county serving children and adolescents with CP within the last five years, 2) the medical record from the visit(s) should contain the ICD-10 diagnosis code for CP, and 3) they should hold a Swedish personal identity number. It was considered that this approach reasonably should include most if not all of the target population, and that the inclusion approach itself therefore could be referred to as population based.

3.2.1.2 Paper III

All children whom underwent SDR at the Karolinska University Hospital, Stockholm, Sweden from the time when the procedure was established (1993) to the time when the procedure was largely discontinued (after 1997) were invited to participate in the follow-up study.

3.2.1.3 Paper IV

Multiple ways of reaching adults with spastic CP and muscle-related pain were used. This was based on the knowledge that health care for adults with CP is mostly decentralized and uncoordinated in the Swedish health care system. It was assumed that potential participants could be found in various environments: in a few specialized clinics, in rehabilitation centers, in patient-advocacy groups, in the group of young adults participating in the first two studies of this thesis, and in society as a whole. Therefore, information was sent out to these health care institutions and advertisements were placed in journals and the general press.

3.3 SPECIFIC ASPECTS OF THE DESIGN AND THE DATA COLLECTION

The papers in this thesis share a characteristic in regards to the data collection: information was collected through direct contact with the study participants (as opposed to mailed surveys, or collection exclusively through chart reviews). For papers I, II and IV the author was the primary investigator.

3.3.1 The cross-sectional studies

The process of making contact with the young adults, arranging the visit, and collecting the data was laborious. The primary incentive for the young adults to participate was solely to contribute to the scientific knowledge within the field; the visit was not a formal health-care visit although any medical issues which arose were given appropriate evaluation and necessary referral. The visits had to be arranged as to not collide with other scheduled

activities for the young adult, and so that the appropriate proxy could attend in the case of communication limitations.

Image 1. Snapshot of the data collection. With permission from the participant.

The data collection took place as an on-site visit to the Astrid Lindgren's Children's Hospital at the Karolinska University Hospital, Solna (Image 1). Here, the young adult and any accompanying family members or personal assistants met with the author as the primary investigator and one of two specialized physiotherapists as co-investigators. The visit often lasted half a working day and included short breaks. Only a minority (20%) participated through telephone. Telephone participation required the same or more time to complete the data collection, as this required additional chart reviews to retrieve clinical data. The data collection was extensive and included more variables than those presented in this thesis.

All participants received a small gift of gratitude (the young adults' choice of movie theater vouchers or vouchers for a clothing store).

3.3.2 The selective dorsal rhizotomy case series

Follow-up of after the SDR procedure was performed at six months, twelve months, eighteen months and then yearly. As with the other data collections in this thesis, the visit took place as a specifically dedicated, on-site, multidisciplinary evaluation, lasting half a day. It is thus not a retrospective combination of chance visits to the center or other centers, but a specifically purpose-designed follow-up.

3.3.3 The randomized controlled trial

Paper IV is an academically initiated and academically funded randomized controlled trial free from involvement of any entity with a commercial interest in the pharmaceutical product. This means that all stages of the trial were managed by the authors; design, study protocol, case report forms, applications to regulatory authorities and ethical committees, clinical visits, hosting inspections, analysis of the data, and writing reports and the manuscript. While requiring considerably more time and effort than an industry-sponsored clinical trial, the risk of bias introduced by economic interests is avoided (Lundh et al., 2017). The study was continuously monitored (inspected) for adherence to the study protocol and all regulations by the independent organization Karolinska Trial Alliance.

3.3.3.1 Interim analysis

Paper IV included, by design, an interim analysis. This analysis was incorporated into the study for one main reason: to avoid exposing people to experimental treatments if it was shown to be unnecessary. The interim analysis was thus of the type called *stop for futility* and meant that it should be stopped if calculations performed roughly half-way through the study were to show that the probability to achieve success on the primary outcome was less than twenty percent. These evaluations were performed by an independent Data Monitoring Committee (DMC) consisting of hired statistical and medical expertise.

The use of such an interim analysis was motivated by the fact that there were no formal preceding pilot trials. It was therefore necessary to make assumptions regarding the expected efficacy of the active treatment as well as any placebo responses, as well as the expected time-to-effect of the treatment (see also Sample size below). Other than the obvious goal of protecting study participants from unnecessary experimental treatment, the interim analysis can also be said to serve a dual purpose in the usefulness of the study. In the primary scenario where the interim analysis *does not* recommend a termination of the trial, the study can run its course and fulfill the confirmatory purpose. In the scenario were the DMC recommends *stop for futility*, the study can serve as a pilot trial for future confirmatory trials.

3.4 SAMPLE SIZE

Papers I, II and III were all exploratory in their design and did not therefore involve prespecified differences to detect (in contrast to a confirmatory study). Hence, no formal sample size calculation was performed for these studies. For papers I and II, the aim for the sample size was to maximize inclusion within the limits of the inclusion criteria (as larger samples give more precise estimates) and to aim for good generalizability through the population-based inclusion approach.

For the case series in paper III the sample size itself was not the primary aim. It would be questionable to promote surgery for the sake of sample size. The primary aim concerning inclusion was to maintain a consecutive case series.

Paper IV was a hypothesis-testing study with a pre-specified primary endpoint and thus relied on sample size calculation. This requires determining what difference one wants to detect: if a very small difference in between groups is what you expect to find or are satisfied in finding, then you need a large sample size to detect it. If on the other hand you only consider a large difference to be meaningful to find, you only require a smaller sample. In the case of this study, with BoNT-A treatment being compared to placebo treatment, there are several arguments that point out that only a large difference is worth finding:

1) BoNT-A is expensive: both the drug itself and the fact that the administration of it requires clinic time and resources and skilled practicioners (as opposed to, for example, pills you take at home).
2) The treatment itself involves procedural pain. Soreness is not uncommon in the days following treatment.
3) The treatment goal is reduction of pain, which is a 'softer' endpoint than for example reduced mortality or a reduction of disability. For example: if a study shows that if you treat 67 patients with a drug you save the life of one individual (Shakur et al., 2010) (numbers needed to treat (NNT) = 67), it is likely to be considered a valuable treatment. However, a study where the outcome was that one in 67 patients experienced reduced pain is likely to be considered ineffective.
4) Established analgesics for chronic pain have NNT values somewhere around 2 – 10 (Derry et al., 2016; Finnerup et al., 2015). Given the relative inconvieniences of BoNT-A, the desired NNT should be in the lower part of that interval.

The primary endpoint was the proportion of treatment responders, defined as a reduction of pain intensity of ≥ 2 on the NRS as compared to baseline, at six weeks after treatment. The study was designed to detect a difference in the primary endpoint of 40%, i. e. a 70% proportion of responders in the BoNT-A group compared to a 30% proportion of responders in the placebo group. This corresponds to an NNT of 2.5.

Before determining a sample size, the appropriate level of risk for making a type 1 error and a type 2 error must be selected. A type 1 error is the rejection of a true null hypothesis; i. e. a false positive. A type 2 error is the non-rejection of a false null hypothesis; i. e. a false negative. False positives are generally considered more dangerous than false negatives. These risks are realities: eliminating them would require huge and impractical sample sizes. A common practice in medical research is therefore to set the risk of a type 1 error to 5% ($\alpha = 0.05$) and the risk of a type 2 error to 20% ($\beta = 0.20$) (Campbell, 2007). The power to detect a true difference (often referred to as the 'statistical power') is therefore often $1 - \beta$ or 80%.

With $\alpha = 0.05$ and $1 - \beta = 0.80$ the sample size for paper IV is calculated to be n=42, meaning 21 individuals per treatment arm.

3.5 VARIABLES AND OUTCOME MEASURES

This section will expand on the variables and outcome measures that were used in the papers. These are presented by the field of interest they relate to.

The common clinical descriptors of individuals with CP; the clinical sub-type and the GMFCS level (and the MACS level and CFCS level) are described in section 1.1.2 in the Introduction.

3.5.1 Social outcomes

This is one of the methodologically more challenging parts of the thesis. There is no universally accepted measurement for social outcomes or social participation. Most studies within this field have used in-house constructed items (Andersson & Mattsson, 2001; Benner, Hilberink, Veenis, van der Slot, et al., 2017; Michelsen et al., 2006; Michelsen et al., 2005; Reddihough et al., 2013) based on common themes of participation from the ICF concept (World Health Organization, 2002), while others have used specific surveys or instruments such as specific sections of the Vineland Adaptive Behavior Scales or the Life Habits questionnaire (Tan et al., 2016; van der Slot et al., 2010; van Wely et al., 2020). The social outcomes measured in paper I were in-house constructed items developed using a multi-modal approach. The choice was motivated in part by the fact that simple yes or no questions on easily understandable items, such as *Have you moved away from home,* are more intuitively informative than a 'participation score'. The first step in defining the outcomes was to scrutinize published literature on the social situation of adults with CP and to, if possible, use similar items as to be able to compare outcomes between different studies and populations. Questions which adolescents with CP and their families frequently asked in the clinic were also considered. Before implementation, volunteer pilot participants (young adults with CP known to the research group) were interviewed using drafts of the study protocol and gave feedback on the validity and categorization of the items.

The final items referred to whether the young adult had:

- Moved away from the parental home
- An intimate relationship, past or present
- Friends with whom they socialized with outside of the home including on evenings
- An occupation, specified as
    - Regular (competitive) employment
    - Higher education (university/college)
    - Vocational studies or adult high school
    - Wage-subsidised employment or activity programs
    - Activity programs for individuals with ID
    - No occupation or activity
- Personal finances that were
    - Independent
    - Dependent on the parental family

    - Dependent on government subsidies
- Need for support, by parental family members, with activities of daily living (ADL)

3.5.1.1 Comments on the social outcomes

There were originally more items on friends and socialization. However, many young adults reported difficulties in reliably answering many of the items. The remaining item as defined above about socialization outside of the home including on evenings could however be reliably answered as assessed both by the participants and the investigators (the author and co-authors). This item is also found in the TRACE-study by Canadian investigators (J. W. Gorter & Punthakee, 2012) and in the Rotterdam Transition Profile developed in the Netherlands (Donkervoort et al., 2009). A general observation is that items need to be adjusted to the changing patterns of socialization online and in social media.

The items mostly belong to the Participation component of the ICF (World Health Organization, 2013), while personal finances and family help with ADL can be sorted under Contextual factors. If instead the item on ADL was posed as "to what extent do you perform your ADL by yourself" it would belong to the Activities component. However, the intent was to explore the issue from the perspective of transition from parental-family-centered life to parental-family-independent life.

3.5.2 Health-related quality of life

The Short Form-36 version 2 (SF-36v2) (Optum, 2019; Ware & Sherbourne, 1992) was used to measure HRQoL. The SF-36v2 is a 36-item generic survey that is valid and reliable for the measurement of physical and mental health / HRQoL (Optum, 2019; Ware & Sherbourne, 1992). The survey is administered as a questionnaire. The results of the questionnaire are processed in a software which produces scores on different health domains.

The SF-36v2 software provides scores for eight health domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Two summary scores are also provided: The Physical Component Score (PCS) and the Mental Component Score (MCS). Norm-based scores (NBS) are most often used. These norms center on a score of 50, with 10 points corresponding to 1 SD.

3.5.2.1 Comments

The debate on the nomenclature for health status versus HRQoL (see Introduction, section 1.2.3) is evident also in regards to this instrument. While some of the original developers of the SF-36 refer to it as "a set of generic, coherent, and easily administered quality-of-life measures" (Rand Corporation, 2020), the current copyright holder of the SF-36v2 refers to it as a "measurement of physical and mental health" (Optum, 2019).

The EQ-5D is another generic instrument for measuring health status/HRQoL. The SF-36 and the EQ-5D are arguably the most common measurements for this purpose. The EQ-5D family of measurements include versions aimed at young respondents (Herdman et al., 2011; Wille

et al., 2010; Williams, 1990). The EQ-5D-3L is used in the Swedish Cerebral Palsy Follow-Up Program (CPUP) (Jarl et al., 2019) but had not been used in a peer-reviewed publication from the CPUP at the time of the design of this thesis. The SF-36v2 was chosen in part because it has been used in previous studies on adults with CP (Jahnsen, Villien, Egeland, et al., 2004; Opheim et al., 2011; van der Slot et al., 2010) (where it was, as a side note, referred to as a measurement of HRQoL), which would allow for comparisons across populations.

3.5.3 Fatigue

The severity of fatigue is, similar to HRQoL and pain, a subjective patient-reported outcome (PRO). In this thesis the Fatigue Severity Scale (FSS) (Krupp et al., 1989) was used. The FSS is a questionnaire consisting of 9 items where the respondent is asked to rate on a 1 – 7 ordinal scale the agreement with different statements regarding the personal experience of fatigue, for example (question 4): "Fatigue interferes with my physical functioning". The result of the questionnaire is most often reported as the mean rating on these items.

3.5.3.1 Comments

The FSS has been used in many studies in adults with CP (Opheim et al., 2009; Russchen et al., 2014; Slaman et al., 2015; van der Slot et al., 2012). It is also the fatigue measurement of choice in the Swedish CPUP program for adults. Other instruments that have been used in adults with CP but to a lesser extent include the Fatigue Questionnaire (Jahnsen et al., 2003; Opheim et al., 2009), the Fatigue Assessment Scale (Sienko, 2018) and the Fatigue Impact and Severity SelfAssessment (McPhee et al., 2017).

3.5.4 Pain

The main measurements of pain in this thesis were the Numerical Rating Scale (NRS), the Brief Pain Inventory – Short Form (BPI) (Keller et al., 2004) and the Bodily Pain domain on the SF-36v2.

The NRS is a simple 1-item question: "Please rate your pain by circling the one number that best describes your pain on the average in the last 24 hours" with the interval being 0 – no pain, to 10 – worst pain imaginable, with discrete single digit steps (Dworkin et al., 2005). The NRS can be a stand-alone item but it is also integrated in the BPI.

The BPI is a 2-page questionnaire with a 24-hour recall period. It includes a simple template of the human body where pain localizations can be marked. The questions are divided into pain intensity, current treatment and efficacy, and pain interference. The respondent is asked to rate the intensity of pain or the interference pain imposes on the different items on a 0 – 10 ordinal scale ranging from 0: no pain/no interference to 10: worst imaginable pain/completely interferes.

See the previous section for a description of the SF-36v2 measurements.

3.5.4.1 Comments

The NRS has been recommended as the preferred method to measure pain intensity in research rather than the Visual Analogue Scale (VAS) (Dworkin et al., 2005).

The BPI has been used in other studies involving individuals with CP (Flanigan et al., 2020; Sienko, 2018) and has been formally validated in this population (Tyler et al., 2002). The measure of pain interference is considered particularly useful and has made the BPI a recommended pain measure in clinical trials (Dworkin et al., 2005).

3.5.5 Physical activity

The Saltin-Grimby Physical Activity Level Scale (SGPALS) (Grimby et al., 2015) was used to measure habitual physical activity. It is a generic measure administered as a 1-item questionnaire. The scale is divided into four levels:

- Level 1: Sedentary lifestyle. Being almost completely physically inactive; reading, watching TV, using computers/iPads/similar or doing other sedentary activities.
- Level 2: Light-moderate physical activity. Some physical activity at least 4 hours per week as bicycling, walking, self-propelled mobility and similar.
- Level 3: Regular strenuous physical activity. At least 2-3 hours per week of physical activity or training such as running, swimming, raquet sports, race-running and similar markedly heart-rate increasing activities.
- Level 4: Regular hard physical activity for competition sports, several times per week.

The scale was only slightly modified by adding examples of activities that apply to individuals with physical disabilities.

3.5.5.1 Comments

There is no well-established standard for measuring habitual physical activity in individuals with CP across the whole spectrum of motor functioning, a problem which has been highlighted in systematic reviews (Bloemen et al., 2017; Reedman et al., 2017; Ryan et al., 2017). The SGPALS has a simple structure, which could be a strength, but it has with a few exceptions (Tedroff et al., 2015) not found wide use in CP. Wearable accelerometers are frequently used in research to measure habitual physical activity in ambulant individuals with CP. Accelerometers do however have limitations in measuring physical activity in individuals with limited ambulatory activity and cannot accurately measure, for example, swimming (Reedman et al., 2017).

3.5.6 Gross motor function and mobility

In paper III, the gross motor function was measured using the Gross Motor Function Measure (GMFM-88) (Russell et al., 1989). The GMFM-88 is a standardized observational assessment of motor capacity. Conducting a GMFM-88 measurement requires trained health professionals. It consists of 88 gross motor function items, which are scored on a four level ordinal scale (0 – does not initiate, 1 – initiates, 2 – partially completes, and 3 – completes) in

five areas of motor functioning: Lying and Rolling; Sitting; Crawling and Kneeling; Standing; and Walking, Running and Jumping. The results are reported as a percentage score on each gross motor area as well as a combined percentage score, where 100% is the expected capacity of a typically developed five-year-old child.

Paper III also included a mobility scale, the Wilson Mobility Scale, a 1-item assessment comprising nine discrete levels of mobility functioning (Astrom & Soderhall, 2002), with level 1 describing "functional walking without aids in all surroundings" and level 9 describing "sitting with support and no mobility".

3.5.6.1 Comments

Further development of the GMFM-88 has led to the shortened GMFM-66 (Russell et al., 2000) with derivatives.

Other functional mobility assessments that have been used in the field of CP include the Functional Mobility Scale (FMS) (Graham et al., 2004) and the Gillette Functional Assessment Questionnaire (Novacheck et al., 2000).

3.5.7 Spasticity

Table 3. The Modified Ashworth Scale (MAS) according to Bohannon & Smith

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (<50%) of the ROM
2	More marked increase in muscle tone through most of the ROM, but easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part rigid in flexion or extension

ROM: Range of motion.

In Papers I, II and IV in this thesis, the Modified Ashworth Scale (Bohannon & Smith, 1987) (Table 3) according to Bohannon and Smith was used to assess spasticity. In Paper III, the

Modified Ashworth Scale according to Peacock and Staudt (Peacock & Staudt, 1991) (see description under comments) was used.

The MAS is assessed with the person being examined lying on his/her back and resting. The joint in question is then extended from maximal flexion to maximal extension, with the motion taking place in one second.

3.5.7.1 Comments

The Ashworth scale as modified according to Peacock and Staudt differs mainly compared to Bohannon and Smith by including hypotonia (marked as '0') on the scale, with '1' signifying normal muscle tone. This scale ranges from 0 – 5 (Peacock & Staudt, 1991).

As expounded on in section 1.3.1 in the Introduction, there is considerable debate in regards to the definition and measurement of spasticity. The validity and reliability of the MAS has been questioned (Fleuren et al., 2010), particularly that presence of a contracture would confound the measurement (Patrick & Ada, 2006), but it nonetheless remains arguably the most common way of reporting spasticity. A recent systematic review and meta-analysis found satisfactory reliability (Meseguer-Henarejos et al., 2018). The MAS is the measurement used for spasticity in the Swedish CPUP program.

Another common measure is the Modified Tardieu scale (Boyd & Graham, 1999; Tardieu et al., 1954), which emphasizes testing the resistance to passive stretch at different velocities (Haugh et al., 2006). This scale has also been the subject of methodological critique (Yam & Leung, 2006).

3.5.8 Contractures

The presence of contractures can be described by measuring the maximal passive joint range of motion (ROM) and using cut-off values for when a large enough deficit in ROM results in a deformity and/or functional limitation. Because contractures are often treated with tendon-lengthening procedures in individuals with CP the extent of soft-tissue surgery can be used as a proxy measurement of contracture development.

3.6 STATISTICAL METHODS

The statistical methods for each part of the thesis are described in detail in the individual papers. Standard practices for descriptive statistics and analytical statistics were followed with consideration of whether the underlying data was nominal, ordinal, interval or ratio, and whether the assumptions for parametric or non-parametric tests were fulfilled. A conservative approach was used: if there was any doubt that the assumptions for a parametric test were not met, a more robust non-parametric test was used in its place.

Regression models were preferred over Analysis of Variance (ANOVA) calculations when estimating the effect of multiple variables on an outcome in order to report the individual significances of each included variable.

All analyses were performed with Stata IC (StataCorp LLC, TX, USA) and SPSS (SPSS Inc., IL, USA).

4 RESULTS AND DISCUSSION

In this section the results of the four papers are summarized and discussed.

4.1 HEALTH AND SOCIAL OUTCOMES IN YOUNG ADULTHOOD

4.1.1 Participant characteristics

There were 189 individuals whom met the inclusion criteria for the data collection for papers I and II. Only 138 responded to communication attempts by mail or telephone, of which 61 subsequently participated in the data collection. This corresponds to an inclusion of 32% of the target study population or 44% of those 138 whom could be reached. Table 4 outlines the proportions of levels of the GMFCS in this data collection with comparison populations.

Table 4. Distribution of GMFCS level categorizations for the current sample with comparison populations.

GMFCS level	Current sample, %	CPUP Adult, Sweden (Alriksson-Schmidt et al., 2014), %	ACPR, Australia (Delacy et al., 2016), %	CPRN, Norway (Hollung et al., 2018), %
I	41	37	34	67
II	13	14	25	
III	11	11	12	6
IV	15	8	13	27
V	20	15	16	

Note: Fifteen percent had unknown GMFCS classification level in the CPUP Adult Sweden population.
GMFCS: Gross Motor Function Classification System. CPUP: Cerebral Pares UppföljningsProgram. ACPR: Australian Cerebral Palsy Register. CPRN: Cerebrale pareseregistret i Norge.

The young adults in the current sample did not differ substantially from important comparison populations with regard to the distribution of GMFCS levels. The most important comparison is with the Swedish CPUP Adult population (Alriksson-Schmidt et al., 2014). The difference would be that the current sample includes a few more with lower motor

functioning. The distribution of sex (with a slight male predominance) is as expected (see paper I) and the prevalence of intellectual disability (46%) and epilepsy (34%) (Jacobson et al., 2019) is likewise not different from expected proportions (Novak et al., 2012). It can therefore be argued that the sample of young adults should be representative.

4.1.2 Social outcomes

Paper I gives a snapshot picture of social outcomes in young adults with CP, around 21 years of age, who have grown up in the larger Stockholm area. In summary:

- 20% had moved out of the parental home
- 20% were currently in an intimate relationship
    - 31% were not currently in a relationship, but had previously been so
- 70% socialized with friends, outside home, including on evenings
- 85% were in an occupation, whereof
    - 18% were in regular (competitive) employment
    - 16% were in higher education
    - 5% were in vocational studies or adult high school
    - 5% were in wage-subsidised employment or activity programs
    - 41% were in activity programs for individuals with intellectual disability
- Personal finances were classified as
    - 30% had independent personal finances
    - 39% were dependent of government subsidies
    - 31% were dependent on the parental family
- 43% needed support from parental family members, day and night, with ADL

Five of these variables were further analyzed to detect whether being in levels I-II or III-V on the GMFCS, MACS and CFCS respectively, or having ID, made any difference on the outcome. The variables were

1) Having moved away from the parental home
2) Presently being or previously having been in an intimate relationship
3) Being in regular employment and/or in higher education
4) Having independent personal finances
5) Socializing with friends, outside home, including on evenings

The results (Table 5) were that there were no associations between these variables and the GMFCS levels, with or without adjustment for ID. Being in levels III-V on the MACS was negatively associated with the outcomes of variables 3 & 4 when not adjusting for ID. Being in levels III-V on the CFCS was negatively associated with the outcomes of all variables except variable 1 when not adjusting for ID, and with variable 5 also when adjusting for ID.

Table 5. The association between the dichotomized levels of the GMFCS, MACS and CFCS, and ID on selected social outcomes. Statistically significant results in bold.

	Crude odds ratios (95 % CI)			
	GMFCS	MACS	CFCS	ID
Moved out	0.8 (0.2 – 3.4)	0.3 (0.03 – 1.6)	0.3 (0.03 – 1.5)	0.3 (0.1 – 1.5)
Intimate relationships	0.9 (0.3 – 2.9)	0.5 (0.2 – 1.8)	**0.2 (0.1 – 0.7)**	0.3 (0.1 – 1.0)
Employed and/or higher education	0.3 (0.1 – 1.1)	**0.1 (0.01 – 0.6)**	**0 (0 – 0.1)**	**0 (0 – 0.1)**
Independent personal finances	0.3 (0.1 – 1.2)	**0.1 (0.001 – 0.5)**	**0 (0 – 0.2)**	**0 (0 – 0.1)**
Socializing with friends, including on evenings	0.8 (0.2 – 2.8)	0.3 (0.1 – 1.1)	**0.1 (0.03 – 0.5)**	**0.1 (0.03 – 0.6)**
	Odds ratios adjusted for ID (95% CI)			
	GMFCS	MACS	CFCS	
Moved out	1.7 (0.4 – 7.9)	0.5 (0.1 – 3.8)	0.4 (0.03 – 5.3)	
Intimate relationships	2.5 (0.6 – 10.1)	1.4 (0.3 – 6.6)	**0.1 (0.01 – 0.95)**	
Employed and/or higher education	NA	NA	NA	
Independent personal finances	NA	NA	NA	
Socializing with friends, including on evenings	4.3 (0.8 – 24.2)	1.2 (0.2 – 5.5)	0.2 (0.02 – 2.0)	

CFCS: Communication Function Classification System.
CI: Confidence Interval. GMFCS: Gross Motor Function Classification System. MACS: Manual Ability Classification System. NA: Not available.
ID: Intellectual disability

It was impossible to delineate the association between the GMFCS and the MACS with adjustment for ID on variables 3 & 4 because both ID and the CFCS completely predicted the outcome on these variables, meaning that having ID and/or being in CFCS levels III-V meant that the young adult always (100%) answered *no* on these items.

To summarize, being in high functioning or low functioning gross motor classification levels did not make any detectable difference on these social outcomes. The manual ability categories had some impact, but the effect of communication function categories was very pronounced as was having intellectual disability.

These results can be approached from two perspectives. The descriptive results are absolute proportions. They are more informative if they can be compared to data on individuals without CP in order to gauge whether individuals with CP are disadvantaged on these outcomes. As this was a cross-sectional study without a dedicated control group this analysis was not the primary scientific value of this investigation. To evaluate and discuss the results of the association analyses are more important as these give hints on the impact that different dimensions of functioning have on social outcomes. Both aspects also need to be compared with the results from other studies.

Starting with the descriptive results, the item on housing can be compared to official Swedish statistics. Forty-four percent (Official Swedish Statistics, 2016a) of 21-year old young adults in Sweden had moved out from the parental home in the year 2016. This is more than twice as many as in the group of young adults with CP. Keeping in mind that the official statistics refer to Sweden as a whole, and that the capital of Stockholm tends to have a more difficult housing market, this would still indicate that young adults with CP remain in the parental home to a larger extent than typically developed peers. In a report from southern Sweden (Alriksson-Schmidt et al., 2014), 43% of young adults with CP in the age span 18 – 24 years had moved away from home. This figure would seem to be more in line with the general population and contradict the results. However, of the very few studies in this field two other studies on adults with CP have both demonstrated that housing independent of the parental families is more rare if you have CP: in Australia 35% vs 78% for typically developed (age span 20 – 30 years), and in Denmark 68% vs 92% (age span 29 – 35 years) (Michelsen et al., 2006; Reddihough et al., 2013). All in all, this would appear as an area in need of improvement as independent living has been highlighted as a particularly important goal by young adults with CP (Bjorquist et al., 2015; Nguyen et al., 2016; Tornbom et al., 2013). Our results did not show any significant effect of the domains of functioning on housing, but there were few individuals who had moved away from the parental home on this item and associations were therefore unlikely to appear. It is likely that the solutions that enable young

adults to move away from home are in the political and societal domain. On the one hand this requires housing that is accessible both physically and financially, on the other hand strengthened personal assistance that can replace the need for the parental family to perform day-and-night ADL for their young adults (which was the case amongst 43% in this material).

Occupation is another item where comparisons with the general population is possible. According to official Swedish statistics (Official Swedish Statistics, 2016b) 9% of the age-matched general population were neither employed or studying. In our sample 15% overall and 21% of young adults without ID had no activity. Similar proportions have been reported from studies performed in the Netherlands (Verhoef et al., 2014). This again would appear as an area where individuals with CP are disadvantaged and where active policy making is needed. There were some clear associations on this item with regards to the dimension of functioning. The levels in the MACS and the CFCS were both strongly associated with employment and/or higher education, as was ID. In fact, being in levels III-V on the CFCS or having ID equated to always answering *no* on this item in this sample of young adults.

4.1.2.1 Intellectual disability as a confounder

The results clearly show that the levels in the CFCS and ID are major determinants of social outcomes in young adults with CP. The levels in the MACS also show associations. The question arises if these are independent associations or if the results, especially the CFCS results, are confounded by ID (as being associated with both lower functioning levels on the classification systems as well as associated with the social outcomes).

Table 6. Correlations between the levels in the classification systems and intellectual disability

Classification system	Correlation coefficient with ID
GMFCS	0.688
MACS	0.648
CFCS	0.867

Spearman's correlation coefficient. ID: Intellectual disability

The correlation coefficients (Table 6) represent the strength with which the levels in the classification systems and ID are in this sample. This represents the first argument of why ID cannot explain the bulk of the association results. The GMFCS and the MACS display the same strength of association with ID, but the GMFCS was not associated with any of the social outcomes while the MACS was.

The correlation coefficient is high between the levels of the CFCS and ID. In non-technical terms: if a young adult was categorized within lower functioning levels in the CFCS, he or she was likely to also have ID, and vice versa. However, the CFCS displayed an independent result (Table 4) on the item of intimate relationships when the regression was adjusted for presence of ID – indicating a separate mechanism of participation restriction. As a more cautious and weak indication, it can be noted that the direction and magnitude of the other odds ratio estimates remained more or less the same when adjusting for ID, but that the estimates became less precise with non-significant confidence intervals.

4.1.2.2 The results in relation to the literature

The question is if other studies have seen the same results of the impact of ID and lower communication functioning – the answer is more or less affirmative. Comparisons are somewhat hampered by the use of different definitions and by different inclusion criteria. In their study on 20-30 year old adults with CP in Australia, Reddihough and colleagues found that "average intellect" was a predictor of independent living and living with a partner, and that "average intellect" and "lack of any speech impairment" both were independent predictors of secondary school completion(Reddihough et al., 2013). In the US, Murphy and colleagues noted that cognition affected employment status, but not physical impairment and interestingly also not "communicative impairment" (Murphy et al., 2000). In the Netherlands, Tan et al have found that epilepsy, "speech impairment" and intellectual disability had a negative influence on social participation (Tan et al., 2016; Tan et al., 2020).

It is also worth noting what dimension of functioning that did not have an impact on the social outcomes: the gross motor function classification. It did not seem to matter whether you were a habitual walker with or without aids or mainly used wheeled mobility when it comes to the studied social outcomes. In the study from southern Sweden (Alriksson-Schmidt et al., 2014), GMFCS and MACS levels correlated with living arrangements when these were separated into "independent living", "living with parents" and "special service housing". If you revisit the data and analyze the association between "living with parents" and the GMFCS-levels, there is however no association ($p=0.391$) (data not shown). This is in line with the findings in paper I. The question is also if the moderate associations found (Alriksson-Schmidt et al., 2014) between the GMFCS and MACS with regards to occupational status would remain significant if these were adjusted for ID. In the Danish study (Michelsen et al., 2006), an analysis of living arrangements in a large adult population with CP with adjustment for, amongst other things, IQ-levels, found that gross motor function only influenced the results marginally. Similar conclusions were made in the Australian study (Reddihough et al., 2013).

It would appear, if the goal is to maximize social integration in adults with CP, that emphasis should be on alleviating the negative effects of limitations in communication and cognition.

4.1.3 Health-related quality of life, pain, and fatigue

In summary, the results in paper II were as follows

- Overall HRQoL (or health status) of young adults with CP was similar to that of the norm population
    - Mental health status was reported as higher by young adults in GMFCS levels III-V as compared to levels I-II
    - Physical health status was reported as lower by young adults in GMFCS levels III-V as compared to levels I-II and as compared to the norm
    - Lower physical health status was associated with a sedentary lifestyle – but this finding can be explained by the fact that both were associated with being classified within GMFCS levels III-V
- Pain was reported by 33 % in the preceding 24 hours and by 49% in the preceding four weeks.
    - Pain prevalence showed little variance across GMFCS levels
    - Pain locations were similar to previous descriptions of individuals with CP
    - There were (surprisingly) few predictors of pain; female sex was independently associated with having more pain
- Being fatigued was reported by 41%
    - Prevalence of fatigue was fairly even across GMFCS levels I-IV with a higher (67%) prevalence in GMFCS level V
    - Mean fatigue severity decreased with increasing level of physical activity

It was also shown that

- Twenty-eight percent reported being physically inactive, while the remaining 72% reported engaging in various intensities of regular physical activity.
- Sleep problems were reported by 41% of participants, with a 70% prevalence in GMFCS level V
- Sixteen percent were using antidepressant pharmacotherapy
- Only 40% of young adults categorized as being in GMFCS level I were enrolled in specialized rehabilitation services

4.1.3.1 Health-related quality of life

The overall HRQoL (or health status) results are welcome findings. The results can help reassure patients and families with a general positive outlook on HRQoL. These findings align with the results of other recent studies. From the CPUP Adult registry in Sweden, Jarl and colleagues described EQ-5D results of primarily high motor functioning adults with CP and found a generally high HRQoL (Jarl et al., 2019). Results on QoL of adolescents with CP reported from pooled European data (Boldyreva et al., 2020) were equal to the general population. They also found that proxies (parents) rated QoL of the adolescents as lower compared to self-reporting, a phenomenon which has been previously described (Andresen et al., 2001; White-Koning et al., 2007) and which is of interest in the analysis of the sub-group

results in the current data set. Jiang and colleagues in Australia also found that proxies for young adults with CP reported significantly lower QoL than those whom were able to self-report. Interestingly, they also found that psychological well-being was good in young adults in lower-functioning gross motor levels. (Jiang et al., 2016)

The most striking difference in HRQoL across GMFCS levels was when the results were divided into the main component scores of the SF-36v2; the PCS and the MCS. Not unexpectedly, physical health status (PCS) was reported as poorer by individuals with more extensive motor limitations. However, limitations in movement is likely not the only cause; as described in the Introduction (section 1.1.2) individuals within lower motor functioning levels in the GMFCS are more likely to also have accompanying co-morbidities such as epilepsy and hearing and vision impairments. The results on mental health status (MCS) are somewhat more unexpected. Young adults in GMFCS levels III-V reported better mental health status than young adults in GMFCS levels I-II. The differences were not as pronounced as for PCS (where the association was the other way around), but still apparent. So, are these findings valid? First, young adults in GMFCS levels III-V are more often assisted by a proxy or represented by a proxy when reporting their HRQoL. The correlation is high between GMFCS levels and the use of proxies (Spearman's correlation coefficient 0.72, $p < 0.001$). If proxy-responders overestimate HRQoL it could explain the better mental health status. This could however only explain the present results if proxies differentially overestimate mental health status while not overestimating physical health status. This appears unlikely. Secondly, as described previously, other researchers have shown that proxies tend to underestimate HRQoL (Andresen et al., 2001; Boldyreva et al., 2020; White-Koning et al., 2007). If this apparently inherent bias of proxy-reporting is applied to the present results it would mean that physical health status is actually less poor and mental health status even better in young adults classified within levels III-V on the GMFCS. We can therefore assume that the better mental health status in young adults in GMFCS levels III-V is valid. This is a welcome finding in the sense that this can help reassure families with children classified within these levels.

It could be speculated that the result is due to frames of reference – what you as an individual compare yourself to. This is also what was generally perceived during the visits for the data collection. In this theory, youth with minor activity limitations have typically developed peers as their frame of reference, while youth with major activity limitations have other youth with major activity limitations as their frame of reference. High motor-functioning individuals are in the first instance at risk of underestimating their own abilities and capacities because the ruler by which they gauge their own performance is constantly that of peers without physical disability. This theory can however not fully explain the results. Although there was a substantial variance in MCS results (considerably more than for PCS) the group differences were primarily driven by the fact that young adults in GMFCS levels IV-V tended to score higher MCS results than the norm, and not that young adults in GMFCS levels I-II scored lower than the norm.

4.1.3.2 Pain

The results on pain in young adults with CP are for the most part congruent with what has now been reported within the field. The pain prevalence (33 – 49%) falls within the rather broad interval (14 – 76%) identified in the most recent systematic review (McKinnon et al., 2019) of studies on pain in children and young adults with CP. That female sex is a risk factor for pain is also in line with the literature (Jahnsen, Villien, Aamodt, et al., 2004; McKinnon et al., 2019). The results did not show any association between having severe spasticity (MAS ≥ 2 in any examined muscle group) and having pain and the results do not therefore support a general group-level relation between these two.

The present results come with norm comparisons. Percentages and prevalence aside, the result is that the combined pain intensity and pain interference (as assessed on the SF-36v2) was very similar to age and gender matched norm comparisons. This result is also a welcome finding. Would this then mean that pain is not more of an issue in CP than in the general population? The answer to that question is no, but it requires some explanation. First, pain in CP appears to be, in many cases, progressive with age (Alriksson-Schmidt & Hagglund, 2016; McKinnon et al., 2019), becoming a more pronounced problem for older adults with CP (Jahnsen, Villien, Aamodt, et al., 2004; Opheim et al., 2009). Secondly, the characteristics of pain in CP in youth with CP differ from comparison population. While adolescents in the general population typically report headaches as the most common complaint, adolescents with CP typically report lower extremity pain (McKinnon et al., 2019), and in paper II back pain. The approach and management are therefore different, and pain in CP requires special considerations. Being in GMFCS level V has been found to be a particular risk factor for having pain (McKinnon et al., 2019) (with pronounced musculoskeletal deformities as the mechanism) but this could not be confirmed in the present study, where pain severity was similar across GMFCS levels. Proxy-reports of pain have been found to underestimate the extent of pain (White-Koning et al., 2007). This bias could mean that the true pain severity was higher in GMFCS level V. However, all other studies on this population should suffer from the same bias and thus it is not apparent where this discrepancy stems from. Of interest is that the results highlight that young adults in higher functioning GMFCS levels are not pain free – it would appear to be just as much a problem in this group as in lower functioning GMFCS levels. This is of importance as it was uncommon for young adults in GMFCS level I to be connected to specialized services – leading to a higher risk that these issues go unmanaged and may have bigger consequences later on in life.

4.1.3.3 Fatigue, and physical activity

The cut-off for when you are considered to be fatigued has in different populations, including CP, been set at an FSS mean score of 4.0 or above (Russchen et al., 2014; Valko et al., 2008). Using this cut-off, a considerable proportion of the sample of young adults were fatigued. Fatigue has increasingly been recognized as an important co-morbidity of CP with important consequences for health and well-being (Benner, Hilberink, Veenis, Stam, et al., 2017; Brunton & Bartlett, 2017; Sienko, 2018; van der Slot et al., 2012; van Gorp et al.).

Interestingly, an association between higher and higher levels of physical activity and less and less fatigue was observed here, a finding reported also by McPhee and colleagues (McPhee et al., 2017) whom assessed physical activity using accelerometers. While both studies are cross-sectional and unable to give a causal explanation (it could be that being fatigued prevents being physically active as well as the other way around) the results open up for interventional studies – interventions based on further promoting physical activity. Pilot studies have shown positive results (Slaman et al., 2015; Vogtle et al., 2014) and should be followed on by confirmatory studies.

Young adults in the present sample were generally more physically active than was reported from southern Sweden (Waltersson & Rodby-Bousquet, 2017). Interestingly and somewhat disappointing was that physical activity showed no association with pain prevalence or severity, neither in the present sample nor in the study from southern Sweden (Waltersson & Rodby-Bousquet, 2017).

4.1.3.4 Sleep

A large proportion of the young adults reported sleep problems (41%), defined as difficulties in establishing and/or maintaining sleep to such an extent that it negatively impacts on daily life. This is similar to the 46% recently reported (Petersen et al., 2020) in school aged children in Australia and exactly the same proportion as found in another study from the neuropediatric unit at the Karolinska Institutet in children with CP (Löwing et al., 2020) but higher than the 23% reported by a systematic review including studies up to 2018 (Horwood et al., 2019). Sleep problems were in the present results particularly common in young adults in GMFCS level V, where also a majority used sleep medications regularly. This highlights that sleep issues should be actively sought and addressed when meeting young adults with CP in the clinical setting.

4.2 TREATMENTS FOR SPASTICITY AND PAIN

4.2.1 Long-term results after selective dorsal rhizotomy

The SDR procedure, as performed at the Karolinska University Hospital between the years 1993-1997, appeared to be relatively safe. Adverse events consisted of postoperative hypotonia in the lower extremities as well as calf spasms, which were transient complications in all children. Sensory complications in the form of hyperesthesia in the lower extremities did occur in a majority of the children, resolving over weeks to, in a few cases, several years after the procedure. One child had transient urinary incontinence in the immediate postoperative period.

With regards to the efficacy of the procedure, it was found that

- Spasticity was markedly reduced or normalized, with only a slight recurrence of spasticity in the knee flexors and plantar flexors in some children at the 10-year follow-up
- Gross motor function improved significantly between baseline and 18 months, and between 18 months and 3 years; it subsequently declined between 3 years and 10 years – still with a significant improvement compared to baseline status
- Mobility function was improved in 12 children, was unchanged in two, and worsened in five children at the 10-year follow-up compared to baseline
- After an initial increase in joint range of motion at the hip, knee and ankle level up to the 3 year follow-up ROM decreased, and all but three children underwent orthopedic surgeries (with tendon lengthening procedures being most common)

It can be safely concluded that the SDR-procedure produced a marked and near permanent reduction or normalization of muscle tone – very few children required additional tone management in the form of BoNT-A and none had received such treatment in conjunction with the follow-ups. It can also be safely concluded that the procedure, and the subsequent reduction of spasticity that it produced, did not prevent contracture development. It is not proven that it did not slow down contracture development (there was no direct comparison group), but it certainly did not prevent it.

But what about functional gains? In order to correctly interpret the results of the GMFM-88 it is important to understand the natural progression of gross motor function with age in children with CP. Figure 3 represents data (Hanna et al., 2009) on the predicted development of gross motor function (GMFM-66) as a function of age, by GMFCS levels. The study describes that, on group level, children in GMFCS level I reach a mean GMFM-66 (minimum 0 – maximum 100) score of 85-90 in the age span of 9-12 years of age. Children in GMFCS level II reach a mean GMFM-66 score of about 70 by the same age span of 9-12 years of age. Both groups then maintain a stable gross motor function into adolescence and young adulthood. Children in GMFCS levels III-V differ from this pattern in that they reach their maximum gross motor function somewhat earlier, followed by a decline in gross motor function into adolescence and young adulthood. This decline is most pronounced in GMFCS

level IV (Hanna et al., 2009). The existence of these distinct gross motor function trajectories has been confirmed in a separate population (Smits et al., 2013). However, in that study (Smits et al., 2013) no decline of function in GMFCS levels III-V was seen. The populations were however not entirely compatible. Young adults with ID were excluded, which the authors believe significantly skewed the subgroups in GMFCS III-V towards better motor prognosis (Smits et al., 2013).

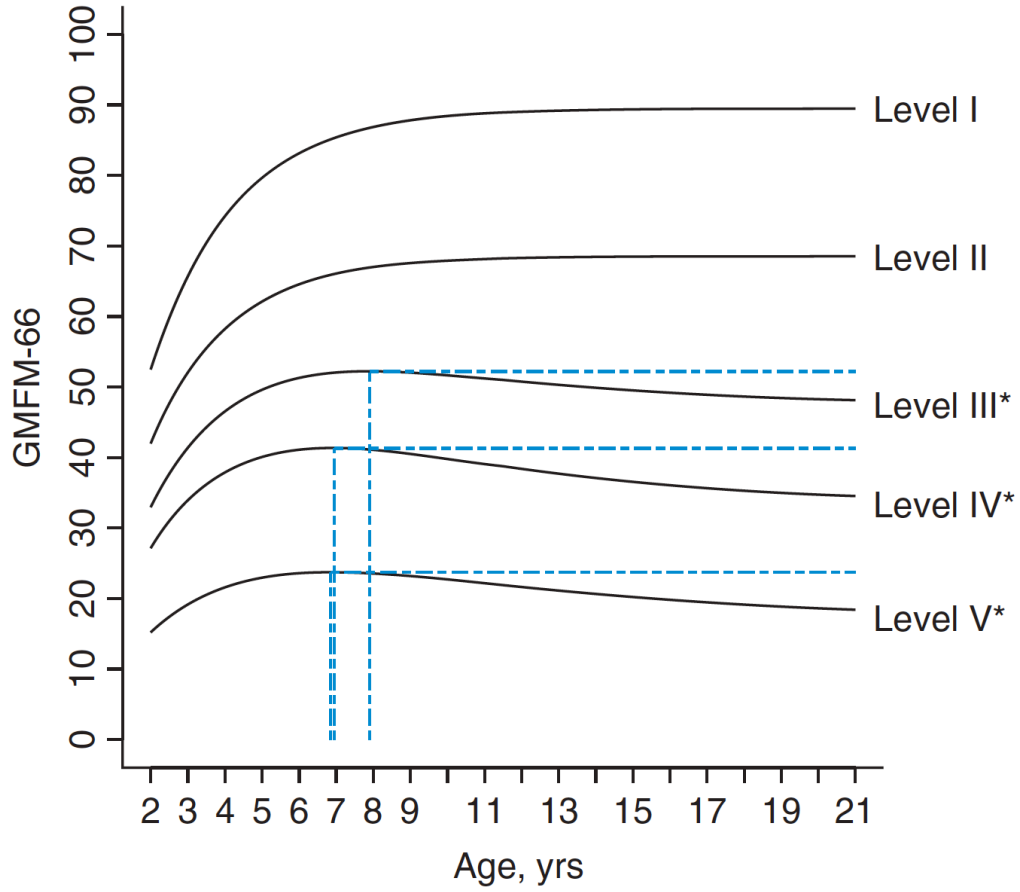

Figure 3. Gross motor function scores as a function of age by Gross Motor Function Classification (GMFCS) level. Dashed lines indicate peak gross motor function scores for levels III – V. From Hanna et al. 2009. Reprinted with permission.

Given that the mean age was 4 years and 7 months at surgery it is expected that the mean GMFM should increase substantially from the baseline examination to the 3-year follow-up. It is, likewise, given the large proportion of children in GMFCS level IV, expected that the GMFM should decrease at the 10-year follow-up. The results can therefore be said to mimic the typical expected development of gross motor function in these children. It cannot be safely concluded that the procedure resulted in better than expected gross motor function, nor that it worsened it.

It is unfortunately not possible to do more precise comparisons due to a couple of reasons. First, the development curves (Figure 3) appear appealing for direct comparisons (e. g. by plotting the GMFM-88 data from paper III onto the curves) but behind the curves is a

substantial variance in individual gross motor function within the different GMFCS levels (Hanna et al., 2009). The present sample would have to had been considerably larger for such statistical comparisons to be meaningful. Secondly, children whom are offered SDR do not represent average children with CP. As can be noted in the inclusion criteria children whom are offered SDR must have good cognition, good trunk control, adequate muscle strength, no dystonia, and be able to adhere to intensive pre- and post-operative training programs. The last variable is complex and probably involves high-functioning aspects of cognition, attention, and executive performance as well as a supportive and capable environment. These children are therefore a subgroup where all share positive predictors of particularly good motor development. Carefully selected control groups are needed for comparisons to be accurate – with so many factors to account for it is probably only achieved through prospective randomization to the procedure or to control.

Other studies have since found similar spasticity-reducing efficacy in long (≥ 10 years) follow-ups (Ailon et al., 2015; Josenby et al., 2012; Munger et al., 2017). It can be generally concluded that SDR reduces spasticity even though most studies do not have a control group. The natural progression of spasticity in the gastrosoleus muscles with age in children with CP has been reported from the Swedish CPUP program (Linden et al., 2019). In summary, spasticity increases in severity up to a peak at about 5-6 years of age, followed by a gradual reduction (not, however, to normal muscle tone on the group level). Although spasticity in the gastrosoleus muscles peak around the same time as many children undergo SDR (Linden et al., 2019), and the decline in spasticity therefore could be thought of as natural development with age, the magnitude of the rapid and sustained reduction/normalization of spasticity in children whom have had SDR performed is probably not explained by this natural progression alone.

So how about function? This is a subject of considerable debate (Park, 2020; Tedroff et al., 2020). Many long-term case series have expressed positive conclusions about the effect of SDR on gross motor function and activity (Bolster et al., 2013; Dudley et al., 2013; Hurvitz et al., 2013; Josenby et al., 2012; Langerak et al., 2009; Park et al., 2017; Romei et al., 2018). There are however methodological limitations to these case series with medium to high risks of biased results (Tedroff et al., 2020). Attrition of participants in the case series (making some significantly non-consecutive) is one major methodological limitation in many follow-ups. Notwithstanding these limitations, the trend is clear that most (but not all) children in the follow-ups have better gross motor function, in absolute percentages, at the long-term follow-up compared to pre-operative status. In this sense the present study data is not much different from that of other follow-ups at other centers. The main difference is in the interpretation of the data. The natural development of gross motor function and the selection process for SDR are major confounders, which need to be addressed before any assertion is made that SDR has resulted in long-term improvement. First, as expanded on previously it is expected that gross motor function should improve with age in childhood (followed by a probable decline in certain groups). Secondly, even those follow-ups that report better-than-expected gross motor function development (Bolster et al., 2013; Josenby et al., 2012) fail to acknowledge

the impact of the selection process for SDR. As mentioned before these children represent a subgroup of children with CP with particularly good positive predictors of motor development and particularly little occurrence of negative predictors. It could therefore be argued that children whom are candidates for SDR have a particularly good gross motor prognosis regardless of the intervention. Again, adequate control groups are crucial if you wish to conclude that SDR delivers superior results on gross motor function. Two case-control studies of long-term functioning have been published (Daunter et al., 2017; Munger et al., 2017). Daunter and colleagues concluded that SDR leads to superior long-term functioning compared to those whom have not been operated on (Daunter et al., 2017). However, the control group was not representative of the SDR-group. For example, the control group included individuals with subtypes of CP, and presence of impairments, that are exclusion criteria for SDR. Munger and colleagues went further methodologically to assign a representative control group, which was also confirmed using propensity matching modelling (Munger et al., 2017). They found that study outcomes were similar for both the SDR group and the non-SDR group, with gait quality actually better in the control group. Neither study have however shown that they have controlled and matched for cognition, selective motor control, presence of dystonia, and perhaps most importantly, the ability to participate in intensive training programs. So, addition of control groups in long-term follow-ups is a major step forward on the way to answering the role of SDR in long-term functioning. But until studies have been published where the control group has been matched also on these important parameters the author of this thesis would argue that the question on the effect on long-term functioning remains unanswered.

That contractures develop despite SDR has been seen in other follow-ups (Ailon et al., 2015; Munger et al., 2017) and has become more or less accepted as established knowledge, together with increased knowledge of the underlying mechanisms behind the progressive shortening of muscles in CP and the limited role of spasticity in this development (see section 1.3.1 of the Introduction). There is however debate as to whether SDR could *decrease* (not prevent) the extent of contractures. At least two studies (Josenby et al., 2012; Munger et al., 2017) argue that contractures appear less extensive in those whom have undergone SDR based mostly on frequency and type of add-on orthopedic interventions. Again, until comparisons have been made with fully representative control groups, the question of a partial effect of SDR on the extent of contracture development remains unanswered.

There are other possible beneficial effects of SDR. One is that a near-permanent reduction of spasticity could, in some cases, perhaps prevent later development of some types of pain. Low pain intensity and low pain interference were found in an even later follow-up of this particular cohort (Tedroff et al., 2015). The study by Munger and colleagues found similar results; that pain interference was markedly low in the SDR group long-term, however, the control group also reported low pain interference and there was no statistically significant difference between groups (Munger et al., 2017). The issue requires further exploration.

4.2.2 Botulinum toxin-A for muscle-related pain

The main results of paper IV are as follows.

Primary outcome:

- There was no difference in the proportion of responders on pain intensity (defined as a reduction of pain intensity ≥ 2 NRS compared to baseline, at six weeks after treatment) in the BoNT-A group (4 responders, 4 non-responders) and the placebo group (4 responders, 4 non-responders).

Secondary outcomes:

- There was no statistically significant difference in analgesics use between the BoNT-A group (5 decreased, 2 unchanged, 1 increased) and the placebo group (2 decreased, 4 unchanged, 2 increased).
- There was no difference in the proportion of responders on pain interference (defined as a reduction of mean pain interference of ≥ 1 on the BPI compared to baseline, at six weeks after treatment) in the BoNT-A group (4 responders) and the placebo group (4 responders).

Exploratory outcomes:

- The mean and median pain intensity continued to trend downwards in the BoNT-A group, while returning to baseline in the placebo group. At ten weeks after treatment (the last follow-up), the mean and median pain reduction was -2.0 NRS in the BoNT-A group and 0.0 NRS in the placebo group.
- Muscle spasticity was reduced in 80% of treated muscles in the BoNT-A group and 50% of treated muscles in the placebo group. There was an equal proportion (around 40% in both groups) of improvements in ROM.
- There were no significant differences in the change of fatigue severity, HRQoL or Patient's Global Impression of Change Scale in between groups. The SF-36v2 subdomain that showed the largest difference was that of an improvement in Bodily Pain in the BoNT-A group (+8.2, p=0.055).

The study was stopped at the interim analysis (see Methods, section 3.3.3.1) due to futility of the primary outcome when 16 participants had finished the study. At this point, there was an equal proportion of responders in the BoNT-A group as in the placebo group and the probability of achieving success on the primary outcome was assessed to be less than twenty percent.

The details of the recruitment process are described in paper IV, especially Figure 1. Fifty individuals were screened for eligibility: the most common reason for not being included in the study was that the individual presented with pain that could not be attributed to spasticity.

4.2.2.1 Interpretation of the results – the recruitment process

The recruitment process shows that only a fraction of adults with spastic CP with chronic pain referred for study screening did indeed have pain that could be attributed to spastic muscle. Other pain mechanisms that were commonly seen included arthralgia, idiopathic lower back pain and neuropathic pain. This finding highlights the need to further study the specific clinical characteristics of chronic pain in adults with CP – spasticity is but one of many possible mechanisms.

4.2.2.2 The results on pain intensity

The trial can conclude, with reasonable power[d], that BoNT-A was not superior to placebo at six weeks after treatment.

Given the results, it would however appear that our initial assumption that pain reduction following BoNT-A would be most pronounced around six weeks after treatment was incorrect. Will and colleagues had the same preconception in their RCT on preoperative BoNT-A vs placebo in bony hip surgery with the primary outcome at six weeks after treatment (Will et al., 2019). The results suggest that pain reduction after BoNT-A comes later, at least for muscle-related pain, whereas the effect of placebo injections wane off quicker. This has implications for future studies on this subject.

4.2.2.3 Assessment of the justification for further trials on this treatment

Results supporting that further trials are warranted

- The trend of a continuous reduction of pain intensity at the last follow up in the BoNT-A group.
- The trend that more participants reduced their concomitant use of analgesics in the BoNT-A group.
- The trend that Bodily Pain in the SF-36v2 measurement was reduced in the BoNT-A group.
- The appearance of individual sustained pain reduction responses in the BoNT-A group compared to mixed transient results in the placebo group (Figure 3b in paper IV).

Results that speak against further trials

- There were no appreciable group differences on pain interference (i. e. how much pain interferes with ADL), which has been argued to be an endpoint at least as important as pain intensity(Dworkin et al., 2005).
- There were no appreciable group differences on HRQoL.

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[d] The study had an original power (1-ß) of 0.8 (80%), which after the interim analysis (<20% probability of a positive primary endpoint) produces a post hoc power of 0.8 x 0.8 = 0.64 or better (>64%).

- The size of the final study, in terms of number of study participants, was small, which increases the risk of chance findings.

Taken together with the fact that there is a fairly widespread off-label use of BoNT-A on this indication, which needs to become evidence-based, the overall conclusion is that it appears to be justification for further trials of longer duration.

4.3 METHODOLOGICAL CONSIDERATIONS AND RISK OF BIAS

4.3.1 General comment on patient reported outcomes

The last few years have seen the development and implementation of PROMIS (Patient-Reported Outcomes Measurement Information System), which is an initiative by the US National Institute of Health (NIH). The goal was to develop a "psychometrically validated, dynamic system to measure patient reported outcomes efficiently in study participants with a wide range of chronic diseases and demographic characteristics"(HealthMeasures, 2020). PROMIS measures cover physical, mental, and social health. These measurements have now found use in research in cerebral palsy and should be considered for future studies with aims similar to the ones presented in this thesis.

4.3.2 Papers I & II

A mailed survey would have been a more typical approach to data collection in papers I and II. Benefits with a mailed survey would possibly, but not definitely, include a higher inclusion rate because of the relative ease of answering the questions at home instead of together with the examiner. The benefits of having a data collection through direct contact with one or a few investigators include that items that the participant feel are unclear can be clarified (increasing accuracy), that the same approach to the items is used consistently (increasing accuracy and decreasing differential misclassifications) and that incongruent responses from the participant can be addressed (again, increasing accuracy).

While the recruitment approach targeted an age-specific total population, the final sample was a lesser proportion: 32% of the entire target population or 44% of those where contact could be made. Distribution of sex, GMFCS-levels, and prevalence of epilepsy and ID all matched expected proportions, which gives strong evidence of a representative sample. There is however still the possibility that those who agreed to participate differ in some respects compared to those who did not. The main concern is that of selection bias(Hernan et al., 2004), i. e. that the possibility of being included in the study is associated with the outcome. To put it in an example: that those who participate tend to have higher or lower HRQoL, or better or worse social outcomes, than those who did not participate. This is a particularly high risk in convenience samples. The fact that the present sample of young adults, which was not a convenience sample, had expected frequencies on the most central variables and comorbidities down-plays this risk but does not eliminate it. There are examples where it has been shown that more pronounced disease severity is coupled with an increased willingness to participate in cross-sectional studies (Apfelbacher et al., 2009). If this bias is present in this

data collection it would mean that the direction of the bias is that of overestimation of 'disease severity', in this study translated into that health status, pain, fatigue and social outcomes are in fact better in young adults with CP than what the present results show.

The use of proxy-responders enabled the study to include young adults with CP within all levels of functioning. This was a strength of the study. However, the use of proxies introduces risks of bias. As discussed in section 4.1.3.1, proxies tend to underestimate HRQoL. This could mean that HRQoL could be even higher than reported in those who were assisted by proxies. And as discussed in section 4.1.3.2, proxies tend to underestimate pain. This could mean that pain actually is more of an issue in those who were assisted by proxies.

The instruments used to assess HRQoL, pain, fatigue, physical activity etc. were not disease-specific and not specifically tailored to individuals with childhood-onset disability. This introduces some likely degree of measurement error. This measurement error was likely non-systematic (apart from that stated about proxy responses above) and therefore probably resulted in some decreased accuracy. Habitual physical activity is difficult to evaluate in individuals in GMFCS levels IV-V and is overall probably better evaluated using wearable accelerometers (Clanchy et al., 2011) and perhaps wearable heart rate monitors.

The studies lacked data on bullying and ostracism. These are common burdens in individuals with disabilities (Holmberg, 2010; Twyman et al., 2010), including CP (Lindsay & McPherson, 2012), which have negative effects on health status (Holmberg, 2010; Whitney et al., 2019). There is not much research done on bullying and social exclusion in CP and the effects they have on health and well-being. It is unfortunate that this was not included in the data collection as it has the potential to add additional clarity to the results and associations that were found. Future studies should incorporate these aspects.

4.3.2.1 External validity

The overall results should be generalizable to young adults about 21 years of age with CP living in societies with similar health-care systems and social support structures as in Sweden. Some findings, which are less environment-dependent, such as the association between less fatigue and more physical activity can probably be generalized even more broadly.

4.3.3 Paper III

The internal validity of the study should be considered adequate. The core outcome measure of gross motor function (GMFM-88) has largely been superseded by the GMFM-66 but it is still a valid and reliable gross motor measure. The use of the MAS to measure spasticity has its shortcomings (see Introduction section 1.3.1 and Methods section 3.5.7) but it remains the most widespread method, including most studies on SDR. A risk that has been reported is that the MAS has the potential to systematically misclassify contracture as spasticity when contractures are present (Patrick & Ada, 2006). Given that the MAS measurements were high preoperatively (before the development of contractures) and low at the long-term follow-up

(after contractures developed) means that any such misclassification, if present, had a minimal influence on study conclusions. For mobility, the Wilson Gait (Mobility) Scale has found little use in CP, where mobility more often is measured using the Function Mobility Scale (Graham et al., 2004). The FMS includes more options on wheeled mobility devices. It is possible that the results on mobility would have been different if the FMS was used.

The operations were performed with largely the same techniques as reported by other centers regarding intraoperative neurophysiology and percentage of rootlets cut.

Unfortunately, the follow-up did not include systematic radiography of the spine. Spinal complications are thus not systematically captured.

The Karolinska cohort of children whom had SDR had a similar distribution of GMFCS levels as the Lund cohort (Josenby et al., 2012) and the Vancouver cohort (Ailon et al., 2015) but more participants in GMFCS level IV compared to the Gillette cohort (Munger et al., 2017) and the Dutch cohort (Bolster et al., 2013), which has implications for the interpretation of the development of gross motor function at the group level.

4.3.3.1 External validity

The inclusion and exclusion criteria are in line with those previously and currently practiced for SDR and the general results should be generalizable to children undergoing SDR at most centers where strict selection criteria are implemented. The SDR method produces a significant and lasting reduction of spasticity without direct manipulation of the joint or muscle and therefore serves as a good experimental model for the study of spasticity reduction on contracture development. That contractures develop despite reduction or removal of spasticity, as measured using the MAS, can be generalized.

4.3.4 Paper IV

The paper can be argued to have good to excellent internal validity, mainly due to adherence to international consensus on methodology for randomized, placebo-controlled, double-blinded clinical trials. The blinding process was however not through delivery of coded vials from an external study pharmacy, which would be considered gold standard. At the time, in Stockholm, this turned out to be financially completely unfeasible. The process of blinding where the study nurse prepared coded syringes did however work well in that the blinding of the allocation remained intact with regards to both the treating team, the patient and the evaluating team.

From the perspective of the PRO's, future studies should consider using PROMIS measurements for added comparability with other studies, as well as longer registrations of baseline pain intensity and interference and perhaps pain follow-ups at shorter intervals using smartphone applications.

The main limitation of the study is however the small number of study participants; the sample size. This increases the risk of chance findings. It is however not definite that forty-

two participants would have made any major difference on the study conclusions compared to the present sixteen. This is because the primary outcome (proportion of responders at six weeks) was very likely to fail (probability of failure >80%) even if recruitment continued. The interesting results and trends presented in paper IV are exploratory, i. e. found by chance, and not pre-specified. And these results would remain exploratory even with a larger sample. The exploratory results would have less uncertainty, but they would still be exploratory. The conclusion from such a study (conducted with the same protocol but a larger sample) would be that there seems to be cause for trials of longer duration with the primary outcome later than six weeks after treatment. The author of this thesis would argue that we already have reached these very same conclusions, and this without exposing unnecessarily many human beings to experimental treatment.

4.3.4.1 External validity

As with most RCT's, the generalizability of the results is restricted to those who conform to the strict inclusion and exclusion criteria (which are strict in order to maintain internal validity in the study). The results are generalizable to adults with spastic CP where the dominant pain mechanism is that of spasticity in the muscle: cramping, pulling, tenseness or other mechanical discomfort that can be linked to the presence and/or exacerbation of spasticity.

5 CONCLUSIONS

Eighty percent of young adults with CP were still living in the parental home; fewer had moved out compared to the general population. Many were still dependent on their parental family financially (31%), and for support with ADL on a day-and-night basis (43%). A majority (79%) of young adults without intellectual disability were in an occupation. There was however an overall increased risk of having no occupation at all. Communication function classification level, and presence of intellectual disability, were major determinants of the social outcomes. Interventions aimed at alleviating the effect of these particular disabilities should be prioritized.

Overall health-related quality of life, or health status, of young adults with CP was comparable to population norms. There were however significant subgroup differences. Physical health status was reported as worse in young adults in GMFCS levels III-V, both compared to norms and compared to young adults in GMFCS levels I-II. Mental health status was however better in young adults in GMFCS levels III-V compared to those in levels I-II. Pain prevalence (33-49%) was in line with that of other studies. Female sex, but not spasticity nor GMFCS level, was a risk factor for having more pain. Fatigue and sleep problems were prevalent, particularly in GMFCS level V. Physical activity could have a protective effect on fatigue severity.

Selective dorsal rhizotomy was a relatively safe procedure at this center. It resulted in a markedly reduced or normalized muscle tone. However, contractures continued to form during the long-term follow-up and there were no clear positive effects on functioning. The results rule out spasticity as the main culprit behind contracture development in CP.

Botulinum toxin-A was not superior to placebo in reducing chronic muscle-related pain in adults with spastic CP when assessed six weeks after a single treatment cycle. There was however a trend for a continuing reduction of pain at the last follow-up for the botulinum toxin-A group not seen in the placebo group. There is motivation for trials of longer duration with the primary endpoint later in the study timeline.

6 FUTURE DIRECTIONS

So, is communication function the major determining factor in activity limitations and participation restriction in CP? First of all, the results need to be confirmed in other populations of young adults with CP, preferably also in larger samples in order to get more precise estimates. But what if these exploratory findings were to be confirmed? The question then is if it is purely the sending and receiving of information that is the deciding factor, or if it is some other variable that is correlated to communication function. Perhaps it is cognition after all? It would be intriguing to try to discern, with the help of extensive neuropsychological and communicative test batteries, the main cognitive and/or communicative factor associated with participation restriction in CP.
However, this would be looking at the problem from an impairment approach (with the hope of finding something that could be 'fixed'), which is an approach that historically has met limited success. The proposed studies should nonetheless be performed, and the results integrated with those from studies focusing on identifying environmental barriers for participation. It is probable that such an approach, which integrates health conditions with contextual factors, would have the best chances of finding ways to improve participation in young adults with CP.

The encouraging overall findings on self-perceived health status (or HRQoL) in young adults with CP is, as discussed, in line with recent studies. It would be of value to confirm these findings by pooling information from population-based registries that include young adults with CP across the globe, using standardized measurements, perhaps PROMIS-measurements, and applying hypothesis-testing methodology (possibly so-called non-inferiority design).
It would also be of value to perform a rigorous randomized controlled trial on physical activity interventions with fatigue as a primary outcome. The proposed RCT should probably be multi-center given the challenges in reaching an adequate inclusion rate in single-center set-ups.

The long-term effects, including adverse outcomes, of selective dorsal rhizotomy need to be further investigated in order to properly determine whether the procedure is beneficial or not. Assigning a representative control group is perhaps the most challenging methodological aspect (see section 4.2.1). Randomization is essentially what is necessary given the myriad of confounders associated with the selection process for SDR. However, maintaining such long-term randomization is not feasible in the real clinical world. The alternative is therefore to conduct case-control studies where the control group has been meticulously matched so that only the exposure (in this case, SDR) is what sets the two groups apart.

Finally, there is an obvious need for evidence-based treatments for chronic pain in CP. There is justification for a follow-on RCT on BoNT-A for muscle-related pain in spastic CP. The primary endpoint of pain reduction should be set at ≥10 weeks after the treatment; multiple treatment cycles could also be considered. The proposed trial should be multi-center to ensure

an adequate inclusion rate. In addition, there is a need to learn more about the different types of chronic pain presenting in individuals with CP. Spasticity-related pain is but one of many mechanisms encountered in adults with CP.

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8 SAMMANFATTNING PÅ SVENSKA

Cerebral pares (CP) är en diagnos innefattande varaktig funktionsnedsättning orsakad av en icke fortskridande skada eller malformation som har inträffat tidigt i utvecklingen av barnets hjärna. Diagnosen kännetecknas av nedsatt rörelseförmåga och hållning med varierande grad av samtidig nedsatt funktion inom kognition, perception, sensorik, kommunikation, samt av epilepsi och smärta. Rörelsestörningarna är ofta den mest framträdande komponenten och behandlingar har oftast riktats mot just dessa. Behandlingar för att försöka minska spasticitet, en typ av abnorm muskelspänning som är vanlig vid CP, förekommer ofta. Då CP är ett livslångt tillstånd är det viktigt att förstå de långsiktiga effekterna av behandlingarna, särskilt om de genomförs tidigt i livet. Det är också viktigt att förstå hur CP utvecklas över tid och förstå vilka delar av funktionsnedsättningen som spelar störst roll när individen växer upp och går in i vuxenlivet. Vår kunskap om CP efter barndomen har varit begränsad. Det har uppkommit oro kring att individer med CP inte integreras i samhället så väl som man kunnat hoppas, samt att nya former av samsjuklighet uppkommer i vuxenlivet, särskilt kronisk smärta. Att förstå denna samsjuklighet och att hitta bra behandlingar är ett prioriterat område.

Denna avhandling fokuserar på hälsa och social situation hos individer med CP i ung vuxen ålder, och på behandlingar för spasticitet och smärta. Detta gjordes med hjälp av några olika metoder. Hälsa och social situation undersöktes med en tvärsnittsstudie av 20 – 22 åringar med CP inom Stockholmsregionen. Långtidseffekterna av den spasticitetsreducerande operationen selektiv dorsal rhizotomi (SDR) undersöktes i form av en konsekutiv fallserie. Och botulinumtoxin-A (BoNT-A) testades som en behandling för kronisk muskelrelaterad smärta hos vuxna med CP i en randomiserad, placebokontrollerad, dubbelblindad klinisk studie.

Resultaten visar att de flesta unga vuxna med CP bodde kvar hemma, fler än i jämförelsebefolkningen. Majoriteten av de som inte hade intellektuell funktionsnedsättning hade någon form av sysselsättning, men risken för att inte ha någon sysselsättning alls var ökad. Den unga vuxnes kommunikativa funktionsnivå, och huruvida det förelåg intellektuell funktionsnedsättning, hade avgörande inverkan på den sociala situationen. Den motoriska funktionsnivån var av mindre betydelse. Den övergripande hälsorelaterade livskvaliteten var på samma nivå som för jämförelsebefolkningen, men det fanns signifikanta gruppskillnader. Unga vuxna med uttalad motorisk aktivitetsbegränsning skattade sin fysiska hälsa som låg, men tvärtom sin mentala hälsa som god. Unga vuxna med lindrig motorisk aktivitetsbegränsning skattade sin fysiska hälsa som god, men sin mentala hälsa som sämre. Smärta och fatigue (sjuklig trötthet eller brist på energi) förekom i alla funktionsnivåer. Selektiv dorsal rhizotomi hade en varaktigt god effekt på spasticitet, men detta förhindrade inte utvecklingen av kontrakturer och inte heller tycktes det ha gett någon avgörande positiv effekt på den grovmotoriska funktionen. Botulinumtoxin-A var inte bättre än placeboinjektioner på att minska muskelrelaterad smärta hos vuxna med CP vid huvudmätningen sex veckor efter behandlingen. Smärtintensiteten fortsatte dock nedåt i BoNT-A-gruppen vid den sista uppföljningen vilket motiverar nya, längre, studier.

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