AUTISM AND ADHD IN CHILDREN WITH CEREBRAL PALSY

Magnus Påhlman

UNIVERSITY OF GOTHENBURG

Gillberg Neuropsychiatry Centre

Institute of Neuroscience and Physiology

Sahlgrenska Academy, University of Gothenburg

Gothenburg 2020

Cover illustration: Thesis synopsis in the shape of an area-proportional Euler diagram created in RStudio with the package eulerr.

Autism and ADHD in children with cerebral palsy

magnus.pahlman@gnc.gu.se

ISBN 978-91-8009-030-8 (print)
ISBN 978-91-8009-031-5 (pdf)
http://hdl.handle.net/2077/65148

Printed by Stema Specialtryck AB, Borås 2020

Oftast man tingen ställer
i ett prosaiskt antingen/eller
Nu förenas vi i motpolernas krock
i ett poetiskt både/och

Jonas Hellström 1982

Matters of things you usually put
in a prosaic 'either or'
Now we unite in the opposites' collision
in a poetic 'both is more'

Translation Per Josefsson 2020

ABSTRACT

BACKGROUND: Autism spectrum disorder (autism) and attention-deficit/hyperactivity disorder (ADHD) are likely underdiagnosed in children with cerebral palsy (CP). Early identification of impairments is important for adequate understanding and support.

AIMS: To estimate the prevalence of autism and ADHD in CP in a total population of school-aged children with CP. To describe the associations between autism/ADHD and sex, gestational age, CP type, motor function, intellectual disability (ID), other associated impairments, epilepsy and neuroimaging findings in children with CP.

METHODS: A well-defined total population of 264 children with CP from the CP register of western Sweden was examined. All available medical records were scrutinised for diagnosed impairments. Parents to all children were invited to complete a comprehensive questionnaire to detect signs of autism and ADHD. Further, children without full concordance between clinical diagnoses and screening outcome for autism/ADHD were assessed. Results were merged with existing information about already assessed children. Neuroimaging findings were compared in regard to the presence of autism and/or ADHD.

RESULTS: One third of the 264 children were already diagnosed with autism and/or ADHD (autism 18%, ADHD 21%). Screening was positive to a much higher extent (autism 35%, ADHD 50%). Further neuropsychiatric assessments revealed additionally 19 children meeting diagnostic criteria for autism and/or ADHD. The group that completed screening and assessment comprised 200 children. In total 90 of these 200 children (45%) were diagnosed with autism and/or ADHD; 15% with autism only, 15% with ADHD only and 15% with both autism and ADHD. ID, present in 51%, was the main predictor of autism and ADHD, while both autism and ADHD were mainly independent of gross motor severity and CP type. Autism and ADHD were common in all neuroimaging patterns. However, autism was more prevalent in children with white matter injury, and ADHD in children having sustained middle cerebral artery infarction.

CONCLUSION: Autism and ADHD are very common in children with CP and should be regarded as two main associated impairments in CP. The high prevalence of autism and ADHD emphasises the need to screen and, if indicated, further assess all children with CP for these impairments. Further studies, including neuroimaging, may help us better understand the strong association between CP and autism/ADHD.

KEYWORDS: cerebral palsy, children, autism spectrum disorder, attention-deficit/hyperactivity disorder, impairments, screening, prevalence, neuroimaging

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Cerebral pares (CP) är den vanligaste orsaken till rörelsehinder hos barn, och 2 av 1000 levande födda barn får denna diagnos med varierande grad av funktionsnedsättning. Ofta är andra funktionsnedsättningar mer begränsande än själva rörelsehindret. Nedsatt syn, hörsel, kommunikation, intellektuell funktionsnedsättning och epilepsi är vanliga hos barn med CP, ju svårare rörelsehindret är desto vanligare. Autism och ADHD är också vanliga vid CP, men vår hypotes var att dessa tillstånd ofta är underdiagnostiserade.

Syfte

Målet med forskningsprojektet var att bestämma förekomsten av autism och ADHD i en hel population av barn med CP, samt att beskriva sambanden mellan autism/ADHD och kön, graviditetslängd, CP-typ, motorisk funktion, intellektuell nivå, andra funktionsnedsättningar, epilepsi och typ av hjärnskada. Det västsvenska CP-registret ger goda möjligheter till forskning om barn med CP. Vi valde att undersöka barn i skolåldern för att lättare och säkrare kunna urskilja autism och ADHD. Gruppen bestod av alla barn med CP, totalt 264, födda 1999-2006 i Västra Götaland.

Delarbete I

För att få veta vilka funktionsnedsättningar barnen hade gick vi igenom samtliga tillgängliga journaler. Tre fjärdedelar hade minst en annan funktionsnedsättning utöver själva rörelsehindret, vanligast var intellektuell funktionsnedsättning och epilepsi. Autism och ADHD var diagnostiserat hos nästan en tredjedel (autism 18%, ADHD 21%), vilket var mer än dubbelt så vanligt som när samma barn var i förskoleåldern.

Delarbete II

Föräldrar till alla 264 barn erbjöds att delta i screening för att identifiera tecken till autism och ADHD. De fick fylla i ett omfattande frågeformulär med tre skalor för autism och tre för ADHD, riktade såväl till barn med normal begåvning som barn med intellektuell funktionsnedsättning. Svarsfrekvensen var hög, 88% (232 barn). Screeningen gick inte att bedöma för 19 av barnen med svårast rörelsehinder och svår eller mycket svår intellektuell funktionsnedsättning. För

återstående 213 barn visade screeningen betydligt oftare misstanke om autism (35%) och ADHD (50%) än vad som redan diagnostiserats.

Delarbete III

I nästa steg jämförde vi redan ställda diagnoser med resultat från screeningen: autism, ADHD, autism + ADHD eller varken eller. För 110 barn med full överensstämmelse mellan diagnoser och screeningresultat bedömdes inte ytterligare utredning nödvändig. Av resterande 103 barn utreddes 90 neuropsykiatriskt. Tvåhundra av 264 barn genomgick alltså processen med både screening och utredning. Nya autism- och/eller ADHD-diagnoser ställdes på 19 barn utan tidigare diagnos, medan 9 barn med en tidigare diagnos fick ytterligare en.

Sammantaget hade 90 av 200 barn (45%) autism och/eller ADHD; 30 (15%) enbart autism, 31 (15%) enbart ADHD och 29 (15%) både autism och ADHD. Intellektuell funktionsnedsättning, diagnostiserad hos hälften av barnen, var den faktor som bäst kunde förutsäga risk för både autism och ADHD. Både autism och ADHD förekom huvudsakligen oberoende av rörelsehindrets svårighetsgrad och CP-typ. För tidig födsel ökade risken för autism.

Delarbete IV

Hjärnavbildning med MR (magnetkameraundersökning) eller datortomografi hade genomförts på 184 av de 200 barnen. Resultaten klassificerades enligt MRI Classification System, och relaterades till diagnostiserad autism och ADHD. Både autism och ADHD var vanliga vid alla typer av skademönster i hjärnan, även vid normal bild. Autism var vanligare hos barn med vitsubstansskada, som uppkommer tidigt under graviditeten och är den typiska skadan hos för tidigt födda barn. ADHD var vanligare hos barn efter arteria cerebri media-infarkt, vilket ofta sker runt fullgången tid.

Slutsats

Autism och ADHD är mycket vanligt hos barn med CP. I denna populationsbaserade undersökning av barn i skolåldern fanns autism hos 3 av 10 och ADHD hos 3 av 10. Intellektuell funktionsnedsättning fanns hos 5 av 10 och samvarierade ofta med autism och/eller ADHD. Två tredjedelar av barnen hade autism, ADHD och/eller intellektuell funktionsnedsättning. Att dessa svårigheter ofta förekommer samtidigt och överlappar varandra belyses av begreppet ESSENCE (early symptomatic syndromes eliciting neurodevelopmental clinical examinations).

Betydelse

Autism och ADHD bör betraktas som vanliga funktionsnedsättningar hos barn med CP, med liknande förekomst som intellektuell funktionsnedsättning och epilepsi. Vi rekommenderar därför att alla barn med CP genomgår screening för tecken till autism eller ADHD, och vid misstanke genomgår en fördjupad utredning. En tidig diagnos möjliggör att ge rätt stöd i rätt tid till rätt barn, vilket kan leda till förbättrad funktion och livskvalitet. Tidig diagnos hjälper också familjer och förskola/skola att bättre förstå och kunna stötta barnen. Mer forskning, inklusive neuroradiologi, behövs för att bättre förstå varför det är så vanligt med autism och ADHD hos barn med CP.

LIST OF PAPERS

This thesis is based on the following studies,
referred to in the text by their Roman numerals.

I

Påhlman M, Gillberg C, Himmelmann K.
One third of school-aged children with cerebral palsy have neuropsychiatric impairments in a population-based study.
Acta Paediatrica 2019; 108: 2048-2055.

II

Påhlman M, Gillberg C, Wentz E, Himmelmann K.
Autism spectrum disorder and attention-deficit/hyperactivity disorder in children with cerebral palsy: results from screening in a population-based group.
European Child & Adolescent Psychiatry 2020 Jan 11. Epub ahead of print.

III

Påhlman M, Gillberg C, Himmelmann K.
Autism and attention-deficit/hyperactivity disorder in children with cerebral palsy: high prevalence rates in a population-based study.
Developmental Medicine & Child Neurology 2020 Oct 12. Accepted.

IV

Påhlman M, Gillberg C, Himmelmann K.
Neuroimaging findings in children with cerebral palsy with autism and/or attention-deficit/hyperactivity disorder: a population-based study.
Submitted.

CONTENT

ABBREVIATIONS

AAC	Augmentative and Alternative Communication
ABC	Autism Behavior Checklist
ADHD	Attention-Deficit/Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
ASSQ	Autism Spectrum Screening Questionnaire
BFMF	Bimanual Fine Motor Function
BSCP	Bilateral Spastic Cerebral Palsy
CARS	Childhood Autism Rating Scale
CFCS	Communication Function Classification System
CI	Confidence Interval
CP	Cerebral Palsy
CT	Computed Tomography
DBC	Developmental Behaviour Checklist
DBC-ASA	DBC Autism Screening Algorithm
DBC-HI	DBC Hyperactivity Index
DISCO	Diagnostic Interview for Social and COmmunication disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
GMFCS	Gross Motor Function Classification System
ICD	International Statistical Classification of Diseases and Related Health Problems
ID	Intellectual Disability
IQ	Intelligence Quotient
MACS	Manual Ability Classification System
MRI	Magnetic Resonance Imaging
MRICS	MRI Classification System
OR	Odds Ratio
SCPE	Surveillance of Cerebral Palsy in Europe
SDQ	Strengths and Difficulties Questionnaire
SNAP	Swanson, Nolan And Pelham
USCP	Unilateral Spastic Cerebral Palsy
VABS	Vineland Adaptive Behavior Checklist
VSS	Viking Speech Scale

THESIS AT A GLANCE

Paper	Aims	Methods	Results	Conclusions
I Diagnoses	To describe motor function and associated impairments, particularly autism and ADHD, in school-aged children with CP.	Retrospective study of a total population of children with CP from the CP register of western Sweden, where all available medical records were scrutinised to retrieve updated information. n=264	One third of the children had been diagnosed with autism and/or ADHD (autism 18% and ADHD 21%). Three out of four had at least one associated impairment, the most common ID and epilepsy.	Autism and ADHD are common in children with CP, but may still be underdiagnosed. Every child with CP needs to be assessed broadly.
II Screening	To estimate the prevalence of autism and ADHD screening positivity in children with CP, and to compare with already identified diagnoses of autism and ADHD.	Parent-completed questionnaires with three different scales to detect signs of autism and ADHD, respectively. Response rate 88% (n=232), but not all were possible to evaluate. n=213	More than half (56%) of the children were screening positive; 35% for autism and 50% for ADHD, which was about twice as often as identified diagnoses of autism/ADHD. ID was often associated with screening positive autism and ADHD.	The very high screening positivity for autism and ADHD indicate that the prevalence of autism and ADHD most likely are underestimated in children with CP.
III Assessment	To assess a total population of school-aged children with CP for autism and ADHD with a view to determining the prevalence, and to relate findings to CP type, motor function, intellectual level and other associated impairments.	Results from comprehensive clinical assessments of 90 children without full concordance between clinical diagnoses and screening outcome for autism/ADHD, were merged with existing information about 110 children with full concordance between diagnoses and screening. n=200	Ninety children (45%) were diagnosed with autism and/or ADHD; 30% with autism and 30% with ADHD. ID was present in 51%. Two thirds had autism, ADHD and/or ID. ID was the main predictor of autism and ADHD, while both were mainly independent of gross motor severity and CP type.	Autism and ADHD are, among other already well-known associated impairments, very common in children with CP. The high prevalence of autism and ADHD emphasises the need to screen and assess all children with CP for these impairments.
IV Neuroimaging	To describe and compare the neuroimaging patterns according to MRICS in children with CP with and without autism and/or ADHD.	Neuroimaging was performed in the majority of children, and the findings were classified according to the MRICS. n=184	Autism and ADHD were common in all MRICS patterns, but autism was more prevalent in children with white matter injury, and ADHD in children having sustained middle cerebral artery infarction.	Neuroimaging findings may give useful prognostic information regarding autism and ADHD for the child with CP. Further studies may help us better understand the strong association between CP and autism/ADHD.

INTRODUCTION

CEREBRAL PALSY

Some historical notes

Cerebral palsy (CP) is the most common cause of motor disability in childhood. CP was probably identified already by the Father of Medicine, Hippocrates (460-390 B.C.). In his work "Of the Eight-Month Foetus" he discusses the association of preterm birth, congenital infection and prenatal stress in relation to the origin of brain damage and refers to children with "intra-uterine disease". Also, in later manuscripts he describes a clinical picture well consistent with CP (Panteliadis et al 2013).

In the 19th century, contributions by several clinicians and researchers increased the knowledge in the field, four of whom will be mentioned.

The first person known to be more intensely engaged in CP was William John Little (1810-1894), regarded as the founder of orthopaedic surgery in England. In the mid-19th century he suggested a causal relationship between birth complications and disorders of mental and physical development after birth. In 1862 he summarised this topic in probably one of the most commonly cited articles on CP (Little 1862). At the end of the 19th century, the condition of spastic diplegia ascribed to prematurity and birth asphyxia was named Little's Disease.

The first woman to write a thesis on cerebral palsy was Sarah McNutt (1839-1930), a physician in New York working mainly in the field of paediatrics and neurology. She became the first female member of the American Neurological Association in 1884. In her inaugural address she presented her thesis entitled "Double Infantile Spastic Hemiplegia" (McNutt 1885).

Another great person dedicated to CP was William Osler (1849-1919), a Canadian professor of clinical medicine in Pennsylvania. He was the first to use the term cerebral palsy, although in plural, in his monograph entitled "The Cerebral Palsies of Childhood", describing a specific group of non-progressive neuromuscular disabilities in children (Osler 1889). Later he wrote concerning the pathology: "we

are impressed, on the one hand, with the extent of which sclerotic and other changes may exist without symptoms if the motor areas are spared, and, on the other hand, with the degree of permanent disability which may exist with even the slightest affliction of this region". Osler was also the first to mention neonatal jaundice as a possible aetiology.

A fourth person in the field was Sigmund Freud (1856-1939) publishing volumes entitled "Cerebral Palsy" in the 1890s. His contribution was the concept of infantile CP, formulated somewhat broader than by others before him. Freud combined all infantile motor deficits of cerebral origin, except those rapidly progressive, into one entity, a concept still valid. He was also the first to classify the causes as congenital (antepartum), acquired during birth (intrapartum), and acquired postnatally (postpartum). Freud finished his extensive work in this field with a monograph in 1897, and then moved on to the field of psychoanalysis (Freud 1897, Kavcic and Vodusek 2005).

Definition

The definitions of CP have differed somewhat over the years. The most recent definition was generated internationally for a variety of reasons. Modern neuroimaging techniques and new neurobiological insights have increased the understanding of different aetiologies. Another important reason was to give more prominence to the non-motor neurodevelopmental disabilities of performance and behaviour that commonly accompany CP. The concept CP had been challenged but was retained at an international consensus meeting in Bethesda in 2004, and in 2006 the new definition was agreed upon (Rosenbaum et al 2007).

"Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.

The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour; by epilepsy, and by secondary musculoskeletal problems."

Aetiology

CP is an "umbrella term" including different pathologies of different timing to the developing brain; from maldevelopments early during gestation, lesions associated with preterm birth, perinatal factors at term birth further to post-neonatal causes up to two years of age. Aetiology is heterogeneous, often multifactorial. Different pathologies may cause similar brain lesions, by affecting the same chain of events, a model known as causal pathways (Stanley et al 2000). Furthermore, pathologies may have different impact depending on gestational age, with varying susceptibility in the immature brain during early development. Genetic factors may also contribute to part of the aetiology, which has been more in focus in recent years (MacLennan et al 2019).

Although CP is heterogeneous in aetiology and severity, the disturbances affecting the immature, developing brain may often give common expressions of difficulties in children with CP. Aetiology is important to determine, if possible, since it may enable prevention of risk factors for CP at a population level, as well as information at an individual level for the child with CP.

The CP register of western Sweden

CP has been studied since half a century in western Sweden through the CP panorama study, started and carried out over decades by Bengt and Gudrun Hagberg. It is the longest series of studies of CP (Hagberg et al 1975, 1975, 1976, 1984, 1989, 1993, 1996, 2001, Himmelmann et al 2005, 2010, Himmelmann and Uvebrant 2014, 2018). The CP register of western Sweden was established in 1971. It includes children with CP born from 1954 to date in the counties of Västra Götaland, Halland and Jönköping. There are 2.4 million inhabitants in the area today, and approximately 28000 births per year. This longitudinal study is ongoing. Data are presented in four-year cohorts, and the latest published report concerns children with CP born in 2007-2010. Many papers and several dissertations have originated from this unique register.

Prevalence

The prevalence of CP has varied over the years between 1.5 and 2.5/1000 live births in the CP register of western Sweden (Figure 1), a picture essentially

confirmed from other long-standing CP registers in high income countries (Colver et al 2014, Himmelmann and Uvebrant 2018, Galea et al 2019). In low- and middle-income countries there is a great variation in prevalence between 2 and 10/1000 live births, depending on other aetiological profiles as well as difficulties and differences in data collection (Khandaker et al 2015). There seems to be a decreasing trend in the last reports from CP registers both in Europe and Australia (Sellier et al 2016, Galea et al 2019).

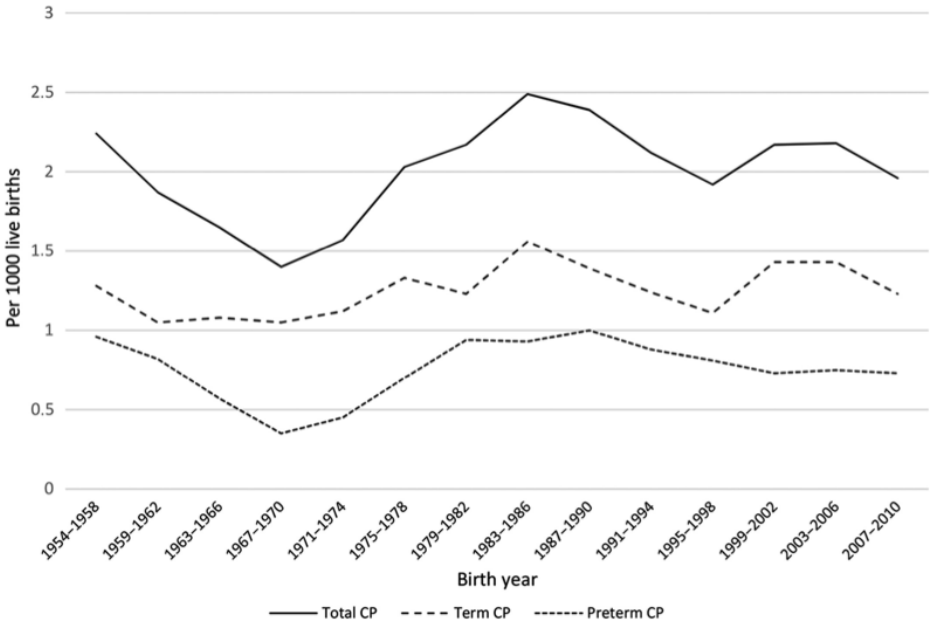

Figure 1. Crude prevalence of cerebral palsy (CP) per 1000 live births, in the birth years 1954–2010 in western Sweden. From the most recent report on the panorama of CP in western Sweden in Acta Paediatrica (Himmelmann and Uvebrant 2018), printed with permission.

Classification

CP is classified into different subtypes based on neurological findings. The Swedish and internationally recognised classification developed by Bengt Hagberg and co-workers has been used in the CP register of western Sweden (Hagberg et al 1975). It classifies CP into spastic hemiplegia, diplegia and tetraplegia, and ataxic and dyskinetic subtypes. Due to differences between countries, especially in terms of the spastic subtypes, and to meet the need for standardised and harmonised data between registers, a common classification was developed in the network of CP registers across Europe – Surveillance of Cerebral Palsy in Europe (SCPE)

(SCPE 2000). Furthermore, a decision and a classification tree were developed as support. Three main subtypes are defined: spastic, dyskinetic and ataxic CP. Spastic CP, the most common subtype, is further divided into unilateral and bilateral spastic CP. Bilateral spastic CP corresponds to diplegia and tetraplegia in the Swedish classification.

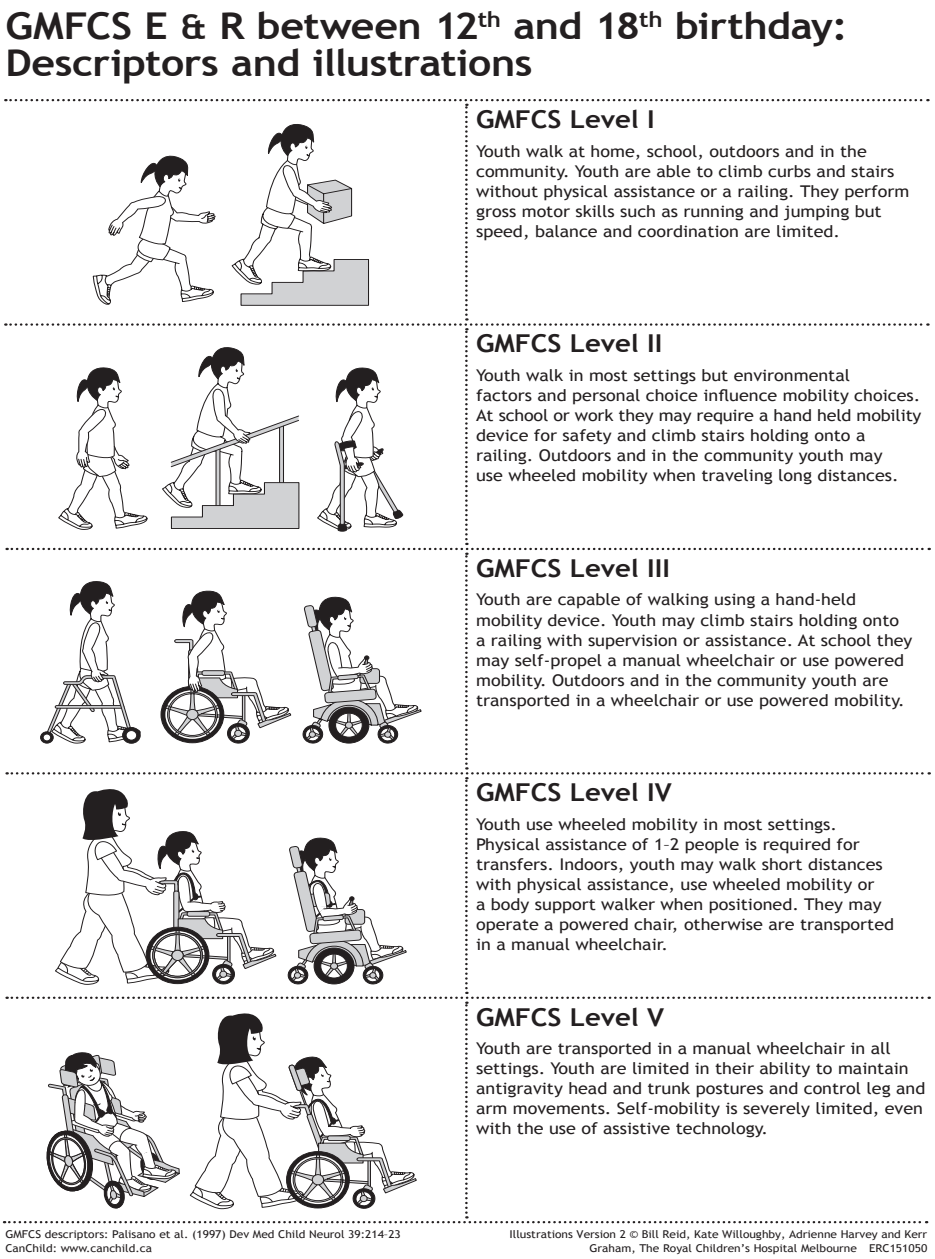

Figure 2. Illustration of the Gross Motor Function Classification System (GMFCS) levels between 12 and 18 years of age. From www.canchild.ca. Descriptions by Palisano et al 1997, illustrations by Reid, Willoughby, Harvey and Graham. Printed with permission.

Function

For more than two decades functional aspects have been in focus, with emerging ways of ascertaining and measuring functions in a valid way. The development of the Gross Motor Function Classification System (GMFCS) was the first and most important of these classification systems, developed at McMaster University in Canada (Palisano et al 1997, 2008, Rosenbaum et al 2008). The GMFCS has been widely used and adopted worldwide. It consists of five levels of gross motor functional abilities and limitations, which are specified for different age bands during childhood. (Figure 2 and Table 1)

Table 1. Gross Motor Function Classification System (GMFCS) levels with general headings. The title for each level is the method of mobility that is most characteristic of performance after 6 years of age.

I	Walks without limitations
II	Walks with limitations
III	Walks using a hand-held mobility device
IV	Self-mobility with limitations; may use powered mobility
V	Transported in a manual wheelchair

With time, more classification systems have been developed:

Fine motor function

- Bimanual Fine Motor Function (BFMF) (Beckung and Hagberg 2002, Elvrum et al 2017)
- Manual Ability Classification System (MACS) (Eliasson et al 2006)

Speech

- Viking Speech Scale (VSS) (Pennington et al 2013)

Communication

- Communication Function Classification System (CFCS) (Hidecker et al 2011)
- Functional Communication Classification System (FCCS) (Barty et al 2016)

Eating and swallowing

- Eating and Drinking Ability Classification System (EDACS) (Sellers et al 2014)

Vision

- Visual Function Classification System (VFCS) (Baranello et al 2020)

All of these systems have five levels except the Viking Speech Scale with four.

Associated impairments

As is pointed out in the CP definition, the motor disorder is often accompanied by other impairments, which have been said to affect more than half of all children with CP (Novak et al 2012, Delacy and Reid 2016, Horber et al 2020). The term "associated impairments" does not include all comorbidities which may occur in CP, but mainly those mentioned in the definition; "disturbances of sensation, perception, cognition, communication, and behaviour" and by epilepsy (Hollung et al 2020). Most associated impairments increase with more severe gross motor impairment (Himmelmann et al 2006, Andersen et al 2008, Sigurdardottir et al 2009, Himmelmann and Uvebrant 2011).

Epilepsy

Epilepsy is reported in 25-40% of all children with CP. The occurrence varies with CP type and gross motor function and increases with severity of the motor impairment. Children with CP due to maldevelopments and grey matter injury more often have epilepsy, than children with white matter injury (Carlsson et al 2003, Himmelmann et al 2006, Himmelmann and Uvebrant 2011, Sellier et al 2012, Gabis et al 2015). Epilepsy in children with CP may remit with time but is mostly life-long (Tsubouchi et al 2019).

Sensation

Visual impairment is common in children with CP, including problems with visual acuity, perception and eye motility. Although the definition varies between studies, visual impairment is often defined as an acuity of not more than 0.3 in the best eye with correction, and severe visual impairment defined as an acuity of not more than 0.1 in the best eye with correction or the presence of functional blindness. The prevalence is reported to be 15-35%, with severe visual impairment in 10-20% (Himmelmann et al 2006, Sigurdardottir et al 2009, Himmelmann and Uvebrant 2011, Delacy and Reid 2016). Problems with visual perception may affect nearly half of all children with CP, especially those with white matter injuries often born preterm (Ego et al 2015). A classification of visual function in children with CP has recently been proposed (Baranello et al 2020).

Hearing may also be impaired in children with CP, but there are few studies about hearing in CP. Severe sensorineural hearing impairment, defined as deafness or need of hearing aid, is reported in 3% (Sigurdardottir et al 2009, Himmelmann and Uvebrant 2011, Dufresne et al 2014). A recent study included hearing loss of all types in children with CP, reporting the severity of hearing loss to be correlated with the degree of motor impairment (Weir et al 2018). Children with CP after neonatal hyperbilirubinemia are at particular risk of hearing impairment.

Cognition

Intellectual disability (ID) defined as an intelligence quotient (IQ) <70 (International Statistical Classification of Diseases and Related Health Problems - Tenth Revision, ICD-10, World Health Organization WHO 2007) occurs in between 30 and 50% in most register-based studies (Himmelmann et al 2006, Sigurdardottir et al 2009, Himmelmann and Uvebrant 2011, Reid et al 2018). The prevalence of ID depends on the age of assessment, becoming more common with increasing age. Some intellectual abilities develop later in childhood and cannot be assessed until school age. Furthermore, the brain lesion causing CP may affect the cognitive development compared to typically developing children (Smits et al 2011, Stadskleiv 2020). Accurate testing is difficult in children at the lowest levels of ID, and the level may instead be estimated. For children with speech, visual or hearing impairments, tests have to be adapted (Ballester-Plané et al 2018, Stadskleiv et al 2018). The prevalence of ID increases with the severity of gross motor impairment and with the presence of epilepsy.

Communication

Communication includes the sending and receiving of messages, and communication has several modalities, one of which is speech. Around half of the children have no speech problems and around one third are non-verbal. Dysarthria is also common (Sigurdardottir and Vik 2011, Nordberg et al 2013). Communication problems have come more into focus during the last decade with development of classifications for speech as well as for communication (Hidecker et al 2011, Pennington et al 2013, Barty et al 2016). Communication classified according to the CFCS correlates to gross and fine motor function and cognitive function (Himmelmann et al 2013). However, communication is more complex

to classify than motor function. A recent Swedish study pointed out some rating problems with the CFCS (Kristoffersson et al 2020).

Speech disorder is strongly associated with gross motor severity and ID. Many children with CP need augmentative and alternative communication (AAC) and many are dependent on other persons.

Language disorder is another communication disorder, with difficulties in the use of language across modalities due to deficits in the comprehension and production, not better explained by motor dysfunction or intellectual level (American Psychiatric Association, APA 2013). Hence, language disorder can only be considered in children with CP at higher levels of language ability.

Behaviour

Behaviour is a wide concept influenced by both intrinsic and extrinsic factors and can be affected by psychopathology of different kinds. There is a mixed terminology partly covering the same difficulties – behavioural, mental, emotional, psychological and/or psychiatric. These difficulties and disorders may be examined in different ways, on population basis often through screening. The occurrence of behavioural problems is reported in 25-60% of children with CP (Carlsson et al 2008, Parkes et al 2008, Sigurdardottir et al 2010, Brossard-Racine et al 2012, Rackauskaite et al 2016, Weber et al 2016, Downs et al 2018, Bjorgaas et al 2020).

Behaviour problems are common in neuropsychiatric disorders, such as autism spectrum disorder (autism) and attention-deficit/hyperactivity disorder (ADHD).

AUTISM SPECTRUM DISORDER (AUTISM)

Definition and diagnostic criteria

Autism is a neurodevelopmental disorder, characterised by persistent deficits in social communication and interaction, together with presence of restricted and repetitive patterns of behaviour, interests and activities. Autism is a pervasive clinically impairing disorder with symptoms presenting early during development. The aetiology of autism is multifactorial, and the diagnosis is made on the basis of the behavioural phenotype. The currently most often used autism diagnostic criteria are those of the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th ed) released in 2013, which replaced the former DSM-IV from 1994. (Table 2)

Table 2. Diagnostic criteria for autism according to DSM-5, without examples.

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity.
   2. Deficits in nonverbal communicative behaviors used for social interaction.
   3. Deficits in developing, maintaining, and understanding relationships.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech.
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.
   4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability or global developmental delay.

Prevalence

The prevalence of autism has been reported to be about 1% of the general population, most often a bit lower in preschool children (Nygren et al 2012). This prevalence of registered autism has increased substantially during the last decades, and in some recent reports the prevalence has been reported at 2-4% (Kogan et al 2018, Delobel-Ayoub et al 2020, May et al 2020).

Autism in children often co-exists with ID, language disorder, developmental coordination disorder, anxiety disorder and ADHD (APA 2013).

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Definition and diagnostic criteria

ADHD is a neurodevelopmental disorder defined by impairing levels of inattention and/or hyperactivity/impulsivity; levels excessive for chronological age and developmental age. An ADHD diagnosis requires substantial and impairing symptoms during childhood, presenting in more than one setting. ADHD is, like autism, a phenotype of different origins. The criteria currently most used are those of the DSM-5 (APA 2013), very similar to those of the DSM-IV (APA 1994). (Table 3)

Prevalence

The prevalence of ADHD has been reported to be around 5% in the general population worldwide, with different levels of severity (Rydell et al 2018).

Children with ADHD often have "comorbid" oppositional defiant disorder, conduct disorder, ID or specific learning disorder, anxiety disorder and autism (APA 2013).

Table 3. Diagnostic criteria for ADHD according to DSM-5, without examples.

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities.
   b. Often has difficulty sustaining attention in tasks or play activities.
   c. Often does not seem to listen when spoken to directly.
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.
   e. Often has difficulty organizing tasks and activities.
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
   g. Often loses things necessary for tasks or activities.
   h. Is often easily distracted by extraneous stimuli.
   i. Is often forgetful in daily activities.
2. Hyperactivity and impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected.
   c. Often runs about or climbs in situations where it is inappropriate.
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor".
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed.
   h. Often has difficulty waiting his or her turn.
   i. Often interrupts or intrudes on others.

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings.

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder.

ESSENCE

Autism, ADHD and other neurodevelopmental disorders, such as ID, language disorder and tic disorder, often co-exist. Sharing of symptoms across diagnostic categories is the rule rather than the exception in these disorders, and in early years it can be hard to make specific diagnoses. In 2010, Christopher Gillberg coined the term ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) to draw attention to this overlap and co-existence and the need for early intervention for children with these difficulties. There is always a need for broad clinical assessment and follow-up of children with symptoms within this area (Gillberg 2010).

Having one neurodevelopmental impairment is a strong risk factor for having other impairments. This way of thinking may be applied also for children with CP. The second part of the definition of CP emphasises the risk of also having other neurodevelopmental impairments. Early diagnosis and support have been proven to give a better prognosis for children with autism as well as ADHD (Epstein et al 2010, Nygren et al 2012).

CEREBRAL PALSY AND AUTISM

There are several studies on autism in children with CP, with different study designs, using different methods and instruments. The cohorts of children with CP studied have seldom been population-based, in some cases the primary study inclusion has not been CP, and in other studies the groups studied had CP with some added impairment. With those reservations, the prevalence of autism found in children with CP have been indisputably higher than in the general population, ranging from 3 to 16% (Craig et al 2019). However, there has so far been no report actively assessing a total population of children with CP for autism.

Goodman and Graham were first to report autism to be more common in children with CP. In 1996, they reported psychiatric problems in children with hemiplegia at the age of 6-10 years. They used both questionnaires and clinical assessment for diagnosis. Autism was diagnosed in 4 out of 149 children (2.7%), while substantial emotional or behavioural difficulties affected half of all children with hemiplegia, with no difference whether right or left side was affected. The

main predictor of difficulties was lower IQ, possibly a marker for underlying neurobiological abnormalities (Goodman and Graham 1996).

Nordin and Gillberg studied autism in children known to habilitation services due to physical and mental disabilities, using the screening and diagnostic instruments Autism Behavior Checklist (ABC) and Childhood Autism Rating Scale (CARS). Of a total of 177 children, 38 had concurrent CP. Four of these 38 children also had autism (10.5%) (Nordin and Gillberg 1996). Another Swedish study reported on 90 children with a combination of epilepsy and learning disability, representing more severely disabled children. Thirty-seven of these had CP, 6 of whom also had autism (16.2%) (Steffenburg et al 2003). The covariation between epilepsy, ID and autism has been described in several other studies (Reilly et al 2014).

A Turkish study from a tertiary hospital found autism in 19 of 126 children with CP (15.1%) using the ABC and the CARS. Autism was more common in children with epilepsy, learning disability and no speech ability (Kilincaslan and Mukaddes 2009).

The Autism and Developmental Disabilities Monitoring Network in the US studied children identified administratively for service provision in areas in four states reporting autism in 6.9-8.2% of 8-year-old children with CP (Kirby et al 2011, Christensen et al 2014).

Other record-based studies report autism prevalence in the same range. A previous study from the CP register of western Sweden reported a prevalence of autism of 4.8% in a total population of CP (Himmelmann and Uvebrant 2011). A genetic study on CP reported autism in 6.6% (McMichael et al 2015).

A multi-centre study from five CP registers in Europe in the SCPE network, reported an overall autism prevalence of 8.7%, with considerable differences across registers. Registers in South East France, South West France and North East England reported in the same range as above; 4.0%, 7.0% and 6.6% respectively, while registers in western Sweden and Iceland reported higher prevalence rates of autism; 14.8% and 16.7% respectively. Male sex, epilepsy, ID and better walking ability were factors associated with autism (Delobel-Ayoub et al 2017).

The results from Iceland and western Sweden indicated that autism may be more common in preterm born children, while this was not the case for the other

registers. However, a study on extremely preterm children (less than 28 gestational weeks) in the US also reported a high prevalence of autism in the children with CP, 8 of 40 (20.0%) (Hirschberger et al 2018).

Bjorgaas et al investigated psychiatric disorders in a population of children with CP at GMFCS level I-IV. The screening instrument ASSQ was used for autism. Results showed 19% of the children scoring above the 98th percentile, strongly suggesting ASD to be more common in CP than previously known (Bjorgaas et al 2014).

A recent study from Norway on comorbidities in CP used ICD-10 codes in the national patient registry. Autism prevalence was reported to be 4.3% (Hollung et al 2020). A similar study from Denmark on mental disorders reported autism in 3.4% (Rackauskaite et al 2020). In the Danish study ID was associated with gross motor severity, while autism was not.

Thus, autism prevalence is reported to be considerably higher than in the general population, rates ranging from 3 to 19% depending on method and studied cohort. There also seems to be a trend over time with more diagnoses of autism. This is in line with the stronger trend of increase in the number of autism diagnoses found in the general population (Lundström et al 2015).

It is not surprising that studies based on medical records, depending on the documentation of autism diagnoses, find a lower frequency of co-occurring autism compared with studies that performed more systematic screening and diagnoses (Christensen et al 2014). In more recent data from national patient registries, even fewer diagnoses were captured suggesting that perhaps disorders may not have been appropriately coded by health care professionals.

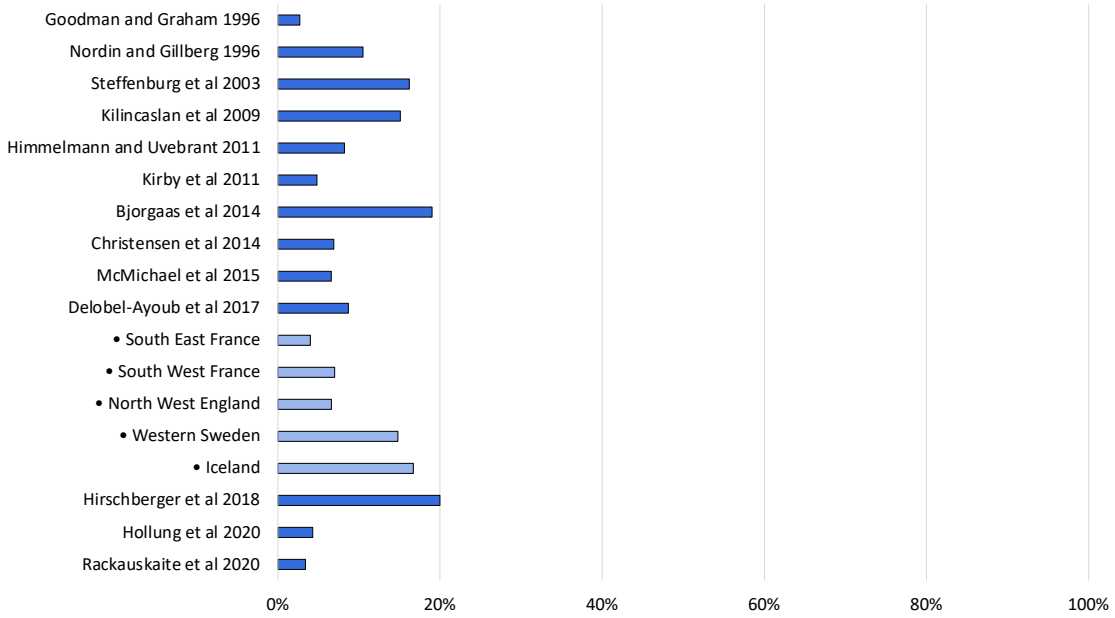

Figure 3. Autism prevalence in children with cerebral palsy in studies of different cohorts and with different methods. The multi-centre study by Delobel-Ayoub et al is presented both in total and by centre.

CEREBRAL PALSY AND ADHD

There are few studies on ADHD symptoms in children with CP, and studies on ADHD as a diagnostic category are even fewer. Inattention and hyperactivity are often viewed in a broader context of behavioural problems using screening questionnaires. Nevertheless, problems with attention and activity regulation are reported to be at high rates in children with CP (Craig et al 2019). To date no study actively assessing a total population with CP for ADHD diagnosis has been published.

In an older study reporting on parent-identified behavioural problems in children with CP, 25.5% had hyperactive problems and/or concentration difficulties. Behavioural problems were more common in the children who also had ID (McDermott et al 1996).

An Israeli study of participation of children with CP, all at GMFCS level II-IV and attending mainstream schools, reported ADHD in 18.9%. ADHD did not influence these children's participation, measured with a school function instrument (Schenker et al 2005).

A European multi-centre study on psychological problems in children with CP from nine centres in Europe, the SPARCLE (Study of Participation of Children with Cerebral Palsy Living in Europe) study (Colver 2006), used the Strengths and Difficulties Questionnaire (SDQ) which was completed by parents when the children were 8-12 years. The hyperactivity subscale on the SDQ was above cut-off in 222 of 806 children (27.5%), and borderline in a further 95 children (11.8%), suggesting that moderate to severe ADHD symptoms were present in almost 40% (Parkes et al 2008).

In an Icelandic study on children with CP at 4-6 years of age, parents and preschool teachers completed questionnaires about behavioural and emotional problems. Attention difficulties were common in children with CP, both with and without ID, with scores significantly higher than in a comparison group with typically developing children. In the 33 children, two (6.1%) were already diagnosed with ADHD. No child at GMFCS level V was included in the study (Sigurdardottir et al 2010).

A representative sample of school-aged children with CP was studied in a Canadian study, also using the SDQ completed by parents. Hyperactivity problems were found in 30.3%. The authors pointed out that SDQ is not a diagnostic test for ADHD but reflects parental perceptions of their child's behaviour (Brossard-Racine et al 2012).

In their studies of psychiatric disorders in children with CP in Norway, Bjorgaas et al evaluated attention deficits through parental interviews at school starting age. Half of the children (50%) at GMFCS level I-IV were found to meet diagnostic criteria for ADHD. At that time 15% of the children had already been clinically diagnosed with ADHD (Bjorgaas et al 2012). A recent follow-up when the children were 11 years of age reported a stable prevalence of ADHD but a significant increase of emotional disorders (Bjorgaas et al 2020).

An Israeli study of comorbidities in a more impaired cohort of children with CP (more than half of the children at GMFCS level IV-V) found ADHD in 22.5% of the children. Intellectual level was higher in children with ADHD, than children with no ADHD diagnosis, and the authors claimed it was plausible that ADHD was underestimated in more impaired children (Gabis et al 2015).

The previously mentioned studies on comorbidities in children with CP found in national patient registries in Norway and Denmark, reported ADHD in 8.4% and

4.1% respectively (Hollung et al 2020, Rackauskaite et al 2020). An American cross-sectional study using a national survey showed children with CP susceptible to mental health disorders. ADHD was more prevalent in children with CP (OR 3.2) (Whitney et al 2019).

Some studies have included neuropsychological testing of attention and executive functions in children with CP. A Danish study tested a group of 33 children with spastic CP with "normal" cognitive function and found impaired attention and executive function compared with test norms. No difference was seen between unilateral and bilateral spastic CP (Bottcher et al 2010). Another study of 34 children with CP reported significantly slower processing speed at testing and more symptoms of inattention and hyperactivity at parent rating than typically developing controls (Shank et al 2010).

While there are several studies on behavioural problems including inattention and hyperactivity, there are few studies reporting ADHD diagnosed through systematic clinical assessment. The problems of inattention and hyperactivity/impulsivity are more difficult to discern from other impairments, from epilepsy, or from the impact of other factors such as pain. The DSM-5 diagnostic criteria for ADHD may also be hard to apply in children with severe motor impairment and ID. Even taking these difficulties in diagnosing ADHD into account, inattention and hyperactivity seem overrepresented in children with CP.

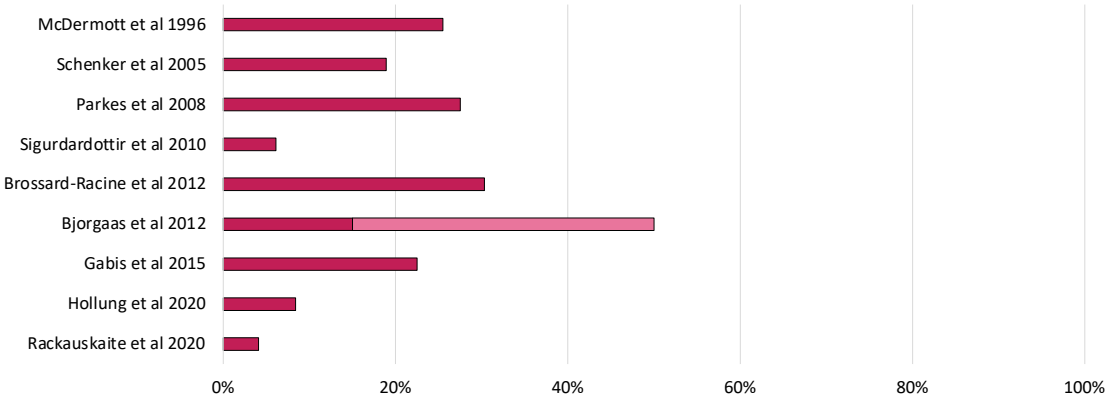

Figure 4. Occurrence of inattention and hyperactivity in children with cerebral palsy from studies of different cohorts and using different methods. The results from Bjorgaas et al are divided to represent both already diagnosed ADHD and outcome of the parental interviews.

NEUROIMAGING

Cerebral palsy

Neuroimaging is of great importance, although not mandatory, for the diagnosis of CP. MRI of the brain shows abnormal patterns in almost 90% of children with CP. These findings may reveal something about aetiology and timing of the origin of the pathology, as well as the relationships between structure and functioning (Krägeloh-Mann and Horber 2007, Himmelmann and Uvebrant 2011, Fiori et al 2014, Horber et al 2020).

The MRI Classification System (MRICS) was developed by the SCPE to harmonise the classification of MRI findings associated with CP, related to timing of insult (Himmelmann and Horber et al 2017). In the MRICS, findings are classified in clear pathogenic patterns; maldevelopments (early in gestation), predominant white matter injury (late in the second trimester or early in the third trimester), and predominant grey matter injury (late in the third trimester and around birth). There are also categories for miscellaneous findings and normal findings. (See Table 5) Bilateral lesions have been reported to often be associated with more considerable functional deficits than unilateral lesions. (Krägeloh-Mann et al 2017).

Autism and ADHD

MRI, both structural and functional, as well as other imaging techniques have been used to increase the understanding of brain function in relation to autism and ADHD. Since both autism and ADHD are heterogeneous disorders it is no surprise that findings of structural basis often have been inconsistent.

Autism is often associated with increased brain volume, especially in childhood, involvement of the frontal and temporal lobes, reduced cerebellar volume, reduced corpus callosum thickness and involvement of the basal ganglia and amygdala. There are also reports of affected volume differences in the white matter and involvement of hippocampus and the brainstem (Stigler et al 2011, Pagnozzi et al 2018, Sarovic et al 2020). ADHD is also often associated with abnormalities in the prefrontal cortex, the basal ganglia, the cerebellum and the corpus callosum, although there are reports of widespread regions of the brain associated with ADHD (Albajara Sáenz et al 2019).

AIMS

The overall aim was to find out how common autism and ADHD really are in children with CP. Our hypothesis was that autism and ADHD are underdiagnosed in children with CP. Given that early identification of all impairments is important for adequate understanding and support, it would be essential to estimate the rate of autism and ADHD in children with CP.

More specifically, the aims were:

- To estimate the prevalence of autism and ADHD in CP through medical records, screening and assessment in a total population of school-aged children with CP.
- To compare the occurrence of associated impairments in children with CP from preschool age to school age.
- To describe the associations between autism/ADHD and sex, gestational age, CP type, motor function, intellectual level, other associated impairments, epilepsy and neuroimaging findings in children with CP.

PARTICIPANTS AND METHODS

PARTICIPANTS

The CP register of western Sweden was – given its high quality and ascertainment – the appropriate basis for this population-based research. With the main aim of finding the prevalence of autism and ADHD we wanted to assess children at school-age up to adolescence, before becoming "adults" at 18 years of age. Therefore, we included children from the CP register born 1999-2006 (Himmelmann et al 2010, Himmelmann and Uvebrant 2014), i.e. eight birth-year cohorts.

The study was restricted to children from the county of Västra Götaland, the primary catchment area of the tertiary centre for children with impairments where this research project took place. Västra Götaland is the largest county of three in the CP register and comprises almost three quarters of the children reported originally. Of the 281 children identified from the CP register, eleven had died, three had moved abroad and three children were no longer considered having CP. Thus, the study group comprised 264 children. (See flowchart in Figure 5.) The Roman numerals I-IV refer to the four papers in this thesis.

I Diagnoses

The total target population of CP, 264 children (141 boys, 123 girls), participated in the retrospective study on CP type, motor function and associated impairments, particularly autism and ADHD, when they were 10 years 0 months - 17 years 11 months of age (median 13 years 8 months). Data were collected from the CP register and all available medical and habilitation records were scrutinised to retrieve updated information.

II Screening

All parents of the 264 children were invited to participate in screening, primarily focusing on autism and ADHD, by completing a comprehensive combined questionnaire (see Methods). The parents of 101 children were asked at a visit to

the regional centre, 156 were contacted through telephone, while the parents of seven children were not possible to reach in person or by telephone, and therefore only received a written invitation. The parents of eight children declined to participate. Thus, 256 questionnaires were sent out. The parents of 232 responded, while 24 questionnaires were not returned despite reminders (17 despite accepting participation, and all seven with written contact only). The age at screening was 8 years 4 months - 17 years 10 months (median age 12 years 11 months).

The questionnaires for 19 children were not possible to assess due to too few completed items (see Methods). They were all among the most disabled children at the most severe GMFCS levels and ID levels. Therefore these 19 children were excluded in the following, leaving 213 children (115 boys, 98 girls).

III Assessment

The results from the screening study were compared with already identified diagnoses of autism and ADHD, reported in the diagnoses study, see flowchart. The 28 children with screening positive results fully concordant with already identified diagnoses of autism and/or ADHD, were not further assessed, since all diagnoses had been made by clinically experienced teams. Similarly, the 82 screening negative children with no diagnoses of autism or ADHD, were not further assessed. They had repeatedly been evaluated by multi-professional habilitation teams throughout childhood and several years at school without identified need for neuropsychiatric assessment. It was therefore concluded that no further assessment would be needed for these 110 children.

The remaining 103 children were approached for clinical assessment. Twelve families of children screening positive for autism and/or ADHD declined further participation in the study, and one child had died. The remaining 90 children participated in neuropsychiatric examinations at the age 7 years 3 months – 17 years 11 months (median age 14 years 5 months). The results from the 90 newly clinically assessed children were then added to the results of the 110 previously screened and assessed 110 children resulting in a total study group of 200 children (109 boys, 91 girls).

IV Neuroimaging

Data on neuroimaging for the assessed children was retrieved from the CP register, and in addition the radiology records were scrutinised for more current neuroimaging investigations. MRI had been performed in 144 of the 200 children. In addition, CT had been performed in 48 children. In 40 children the CT showed clear pathogenic patterns, and these children were included in the study, while the eight children with a normal CT were excluded together with eight children without any neuroimaging data. Hence, the study group comprised 184 children (97 boys, 87 girls). Neuroimaging data derived from the neonatal period in 18 children, and before the age of 18 months in further 50 children. All MRIs classified as normal had been performed after the age of 18 months.

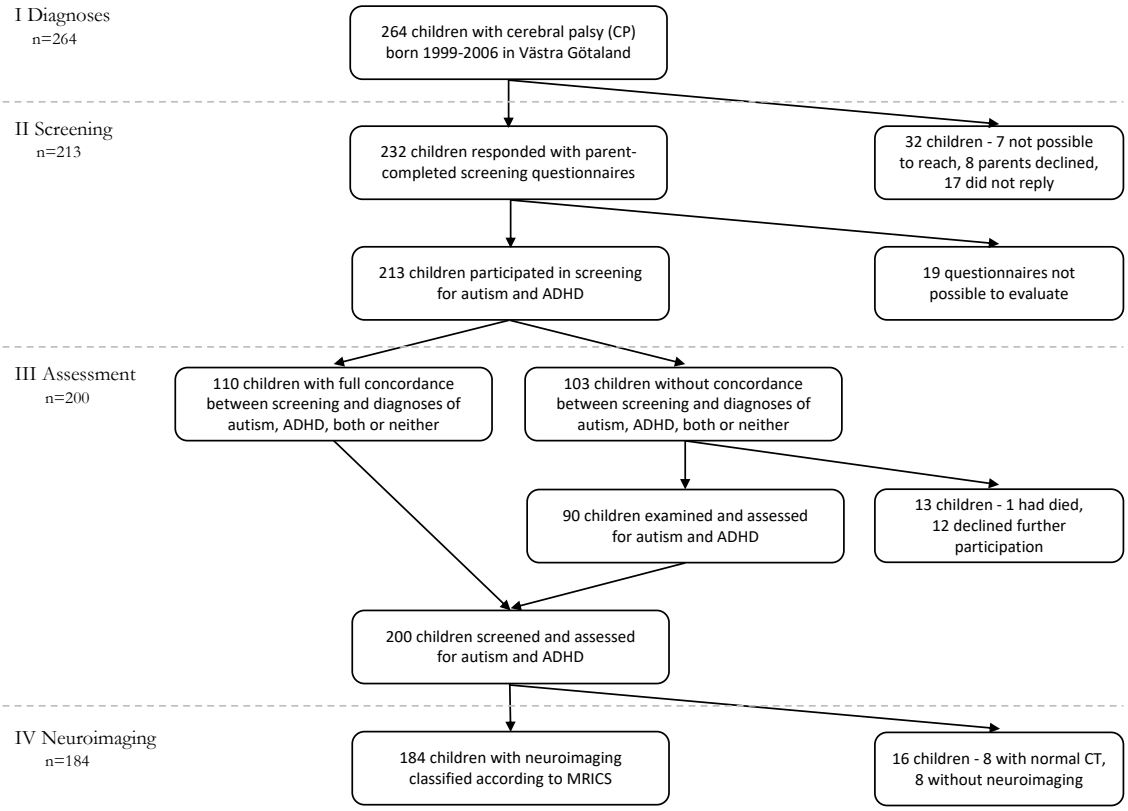

Figure 5. Flowchart of the participants in the four studies in the project about autism and ADHD in children with cerebral palsy.

METHODS

Definitions

Gestational age groups were considered: extremely preterm (birth occurring at less than 28 completed gestational weeks), very preterm (28–31 weeks), moderately preterm (32–36 weeks) and term (more than 36 weeks).

CP types were classified according to the SCPE; into unilateral spastic CP (USCP), bilateral spastic CP (BSCP), dyskinetic CP and ataxic CP (SCPE 2000).

Gross and fine motor function was classified with the GMFCS, the BFMF and the MACS, respectively (Palisano et al 2008, Elvrum et al 2017, Eliasson et al 2006).

Intellectual level was defined as normal if intelligence quotient (IQ) was ≥85, and borderline intellectual functioning if IQ was 70–84. ID (term according to DSM-5), was defined according to ICD-10; mild (IQ 50–69), moderate (IQ 35–49), severe (IQ 20–34) and profound (IQ < 20). IQ, or developmental quotient, had been measured by Wechsler scales or Griffiths developmental scales or estimated on the basis of clinical observation. The results from psychological tests had been complemented with results from adaptive behaviour scales.

Visual impairment was defined as an acuity of not more than 0.3 in the best eye with correction, and severe visual impairment was defined as an acuity of not more than 0.1 in the best eye with correction or the presence of functional blindness.

Hearing impairment included sensorineural impairment or deafness, unilateral or bilateral.

Epilepsy was defined as epilepsy under treatment according to the medical records.

Speech was classified with the Viking Speech Scale (VSS) (Pennington et al 2013); level I not affected speech, II imprecise speech, III unclear speech and IV no understandable speech. Children at level III and IV were regarded as having a severe speech impairment.

I Diagnoses

Retrospective study of the total population of children with CP as a basis for the project. Information about sex, gestational age, CP type, gross and fine motor function, and associated impairments at the age of 4-7 years was taken from the CP register. All available medical and habilitation records were scrutinised to retrieve updated and additional information about associated impairments – vision, hearing, intellectual level, speech ability, epilepsy, language disorder, autism and ADHD. Data up until 31 December 2016 were collected when the children were 10-17 years old.

Information was collected regarding assessments and diagnoses, codes according to the ICD-10 (WHO 2007). Three autism spectrum diagnoses were found; autistic disorder, atypical autism and Asperger syndrome, and they are all included in the term autism. The diagnoses of autism and ADHD had all been made by child psychiatrists or paediatric neurologists.

II Screening

Screening of all children aimed at finding children with considerable symptoms of autism and/or ADHD, and to evaluate the screening procedure for autism and ADHD in children with CP. Screening was performed by inviting parents of all the 264 children with CP to complete a comprehensive combined questionnaire. The parents were asked either in person at a visit to the regional centre (n=101), by telephone (n=156), or if not possible to reach other than by written invitation (n=7). In total 232 questionnaires were received, answered by either the mother (n=131), the father (n=31), both parents (n=69), or the foster mother (n=1).

The screening questionnaire was composed of validated screening tools. As a basis we used the same instruments as in the population-based Norwegian Bergen Child Study (Heiervang et al 2007), which included SDQ (Strengths and Difficulties Questionnaire), ASSQ (Autism Spectrum Screening Questionnaire), and SNAP-IV (Swanson, Nolan and Pelham). We added two further instruments covering questions pertaining to children with ID: DBC (Developmental Behaviour Checklist) and ABC (Autism Behavior Checklist). (References see below.) The composite questionnaire consisted of altogether 282 items. The lowest established cut-off levels for each scale within the 282-item questionnaire were used to ensure high sensitivity and to compensate for single items, most

commonly pertaining to motor function or speech, which were impossible to evaluate for some parents of some children. There were also two open questions at the end about the child's greatest difficulty and strength. (Table 4) See Appendix for the questionnaire in Swedish.

Instruments

The SDQ is a brief emotional and behavioural screening questionnaire for children and adolescents (Goodman 1999). The version for parents of 4-17 years old children was used. For the study the hyperactivity/inattention subscale consisting of 5 items was used with 6 as a cut-off level for screening positivity for ADHD (Ullebø et al 2012).

The ASSQ is a widely used autism spectrum screening instrument and consists of 27 items (Ehlers et al 1999). Also, the 18 items in the extended version (ASSQ-REV) (Kopp and Gillberg 2011) were included in the questionnaires, but not reported in this paper due to lack of a validated cut-off level. For ASSQ a cut-off level of 15 (of a possible maximum of 54) was used (Posserud et al 2006).

The SNAP-IV includes the diagnostic symptoms for ADHD (inattention on the one hand, hyperactivity on the other) and oppositional defiant disorder (ODD) (Swanson et al 2001). The scale was adapted in the same way as in the Bergen Child Study from four to three levels. We defined the cut-off as 6/9 items scored as "somewhat true" or "certainly true" in the two sub-scales of inattention and hyperactivity/impulsivity, respectively (Ullebø et al 2012).

The DBC is a suite of instruments for the assessment of behavioural and emotional problems in developmental and intellectual disabilities (Einfeld and Tonge 1995). The DBC Autism Screening Algorithm (DBC-ASA) is a 29-item subscale with a cut-off level of 17 (Brereton et al 2002). The DBC Hyperactivity Index (DBC-HI) is a 6-item subscale for hyperactivity described in a pilot study (Gargaro et al 2014), and we decided to use 7 as a cut-off level for ADHD. The DBC was present in a Swedish translation, but after our experiences from the first sent questionnaires we initiated a revision of the translation to a more modern Swedish.

The ABC was developed to measure levels of autistic behaviour in individuals with severe disabilities (Krug et al 1980). The 57 items were weighted as originally between 1 and 4 points, and a total score of 45 was used as cut-off level (Nordin and Gillberg 1996), higher scores indicating more autism type symptoms.

In summary three scales were used to define autism screening positivity (ASSQ, DBC-ASA and ABC) and three scales were used to define screening positivity for ADHD (SDQ hyperactivity/impulsivity, SNAP-IV and DBC-HI). Since the scales are targeting children at different intellectual levels, a child was considered screening positive if at least one out of three scales for autism and ADHD, respectively, reached cut-off levels. A child was considered screening negative if all three scales for autism and ADHD, respectively, were below cut-off. Not all items had been completed in all questionnaires. If less than 75% of all items were completed in all three scales for autism and ADHD, respectively, and no scale reached cut-off level, the questionnaire was considered not possible to evaluate.

Table 4. Screening instruments in the study questionnaire for screening of autism and ADHD in children with cerebral palsy.

	Items	Cut-off	Scores
Autism			
ASSQ	27	15	not true 0/somewhat true 1/certainly true 2
DBC-ASA	29	17	not true 0/somewhat true 1/certainly true 2
ABC	57	45	not true/true, scoring according to algorithm (Krug et al 1980)
ADHD			
SDQ hyp/imp	5	6	not true 0/somewhat true 1/certainly true 2
SNAP-IV	9+9	6/9 scored as 1 or 2 in the two subscales	not true 0/somewhat true 1/certainly true 2
DBC-HI	6	7	not true 0/somewhat true 1/certainly true 2

III Assessment

Ninety children without full concordance between screening results and previous diagnoses of autism and ADHD were clinically examined at the regional centre for children with impairments. They were assessed by professionals experienced in the field, either in one day by a child neurologist (this author), a neuropsychologist and a speech and language pathologist, or as part of a comprehensive clinically requested examination by a multi-professional team during one week. Some complementing parental interviews were also made by telephone (n=10).

Instruments used for autism diagnosis were the Diagnostic Interview for Social and COmmunication disorders (DISCO), the Childhood Autism Rating Scale (CARS), and, when applicable, the Autism Diagnostic Observation Schedule 2nd edition (ADOS-2). For ADHD diagnosis the Swanson, Nolan and Pelham scale (SNAP-IV) was used, by parents and complemented by teachers if further clarification was needed regarding the diagnosis. Adaptive behaviour was assessed through parental interview with Vineland Adaptive Behavior Scales-II (VABS-II) and intellectual level was tested with Wechsler scales, if not done in the last year.

Instruments

The DISCO is a standardised, semi-structured interview with a primary purpose of eliciting information relevant to the autism spectrum. It collects information in a systematic way to give a broad picture of the individual's skills, impairments and behaviour, and can therefore assist also in identifying other conditions associated with autism. It is dimensional in its approach and has been designed to assist in the diagnosis of individuals of all ages and all levels of ability. The DISCO is useful in different aspects of clinical work and has been adapted for research purposes (Wing et al 2002, Nygren et al 2009).

The CARS is a much used and documented autism instrument. It is a combination of observation schedule and interview, developed for distinguishing autism from other developmental disabilities. It comprises 15 domains, rated on a nominal scale of severity, yielding a summary score with cut-offs indicating mild autism and severe autism, respectively (Schopler et al 1980).

The ADOS-2 is an instrument used for diagnosing autism and consists of a series of standardised tasks that involve social interaction between the examiner and the child, with behaviours scored according to a protocol. Research-determined cut-offs identify potential diagnosis of autism. There are modules for different levels of speech (Gotham et al 2007).

The SNAP-IV is an extensively used instrument where the diagnostic symptoms of ADHD are scored. The original four level scale was used for diagnostic purpose. There are cut-offs for both parents and teachers indicating ADHD diagnoses. It is also validated for children with ID (Swanson et al 2001, Miller et al 2004, Bussing et al 2008).

The VABS-II assesses adaptive behaviour through a semi-structured interview and gives a composite score as well as scores for domains as communication, daily living skills and socialisation (Sparrow et al 2005).

The Wechsler intelligence scales measure IQ and contain different versions for different ages – WPPSI (Wechsler Preschool & Primary Scale of Intelligence), WISC (Wechsler Intelligence Scale for Children), WAIS (Wechsler Adult Intelligence Scale). The appropriate test was administered to the individual child, sometimes with adaptations due to associated impairments affecting vision, hearing or speech, to find the intellectual level (Wechsler 2003).

Intellectual level was decided on the basis of clinical examination, individualised standardised cognitive testing and assessment of adaptive functioning, according to the DSM-5 criteria (APA 2013). Children at an intellectual level of less than 1 year were not considered further for autism diagnostics, and children at an intellectual level of less than 3 years were not considered further for ADHD diagnostics. At these low developmental ages symptoms of autism and ADHD, respectively, are not possible to distinguish from symptoms related to the low intellectual level. Nor is it meaningful for the child with another diagnosis at too low an intellectual level.

Clinical diagnoses of autism and ADHD were made on the basis of relevant DSM-5 criteria (APA 2013) by the multi-professional assessment team in consensus. The diagnoses were based on the developmental and medical history, results of administered instruments, clinical observations and examinations.

Evaluation was made with special consideration to the intellectual level, way of communication, other impairments e.g. epilepsy, pain and environmental factors.

In cases of uncertainty, the children (n=25) were further evaluated with the final decision made by consensus in a case conference with two child neurologists and a very experienced child and adolescent psychiatrist.

The results from these 90 newly clinically assessed children were added to the existing results of the 110 previously screened and assessed children, resulting in the total study group of 200 children.

IV Neuroimaging

Neuroimaging findings were classified according to the MRICS (Himmelmann and Horber et al 2017) in maldevelopments (A), predominant white matter injury (B), predominant grey matter injury (C), miscellaneous (D) and normal (E) (Table 5). The group with predominant grey matter injury was further classified at the subgroup level into basal ganglia/thalamus lesions (C1), cortical-subcortical lesions only (C2), and arterial infarctions (C3). The abnormal findings were also recorded as bilateral or unilateral.

If several imaging studies had been performed, the latest one was considered. Neuroimaging data were from the neonatal period in 18 children. Further 50 children had their neuroimaging before the age of 18 months. All children classified as normal (E) had an MRI after the age of 18 months. The 40 children included having performed a CT were classified as A in 3 children, B in 22 and C in 15. No difference was found between children having performed MRI or CT regarding, sex, gestational age, CP type, gross motor function or associated impairments in each MRICS group, respectively.

Table 5. The harmonised classification of magnetic resonance imaging (MRI) based on pathogenic patterns (MRI classification system) proposed by the SCPE (Surveillance of Cerebral Palsy in Europe) network.

A. Maldevelopments
A1. Disorders of cortical formation (proliferation and/or migration and/or organisation)
A2. Other maldevelopments (examples: holoprosencephaly, Dandy–Walker malformation, corpus callosum agenesis, cerebellar hypoplasia)
B. Predominant white matter injury
B1. PVL (mild/severe)
B2. Sequelae of IVH or periventricular haemorrhagic infarction
B3. Combination of PVL and IVH sequelae
C. Predominant grey matter injury
C1. Basal ganglia/thalamus lesions (mild/moderate/severe)
C2. Cortico-subcortical lesions only (watershed lesions in parasagittal distribution/multicystic encephalomalacia) not covered under C3
C3. Arterial infarctions (middle cerebral artery/other)
D. Miscellaneous (examples: cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, haemorrhage not covered under B, brainstem lesions, calcifications)
E. Normal

PVL, periventricular leukomalacia, IVH, intraventricular haemorrhage.
Table from the original article on MRICS in Developmental Medicine & Child Neurology 2017 (Himmelmann and Horber et al 2017), printed with permission.

STATISTICS

Descriptive statistics were used in this primarily descriptive research. To compare groups regarding the association between categorical variables, the $\chi 2$ test for independence was used, and for the comparison in a group with an ordinal scale, the Cochran–Armitage $\chi 2$ test for trends was used. Spearman's rank correlation (rho) was used to analyse the relationship between classification scales. A p-value of <0.05 was regarded as statistically significant.

Analysis of the total population after assessments (study III) was made to estimate the relationships between variables. The outcome of autism and ADHD respectively was analysed using a multiple regression model including dichotomised variables; sex, preterm/term born, mild (GMFCS I-II) or moderate to severe (GMFCS III-V) impaired gross motor function, and the associated impairments as no or some impairment. The recommendation of Bursac was used (Bursac et al 2008). The first step was bivariate analysis retaining variables with a p-value <0.25. The second step was a multiple model with the remaining variables, in which we removed the variables with a p-value >0.10, but not those defined as confounders, i.e. changing the estimates more than 15%. In the third and final step we refitted the multiple model, adding the previously abolished variables stepwise, keeping those with a p-value <0.10. Odds ratios (OR) with 95% confidence intervals (CI) were then calculated for the remaining variables associated with autism or ADHD in the models.

The screening sensitivity and specificity were calculated by comparing the diagnoses of autism and ADHD after assessments (study III) with the screening results (study II) for that group of 200 children.

Analyses of the $\chi 2$ tests were conducted in Excel, and analyses for the multiple regression were conducted in R version 3.6.2. (R Foundation 2019), and the Euler diagram was produced in RStudio using the package eulerr (Larsson 2019).

ETHICS

The study was approved by The Regional Ethical Review Board in Gothenburg, ref 145-07 and 398-12. Study I and IV were implemented from the CP register. Consent for participating in the screening in study II was obtained through parents completing and returning the questionnaires. Written consent was obtained from parents of all the participating children in the assessment in study III.

RESULTS

CHARACTERISTICS (I)

The total population of 264 children comprised slightly more boys than girls. A majority was born at term. Spastic CP was found in 201 children (76%), dyskinetic in 45 (17%) and ataxic in 18 (7%). Unilateral spastic CP was right-sided in 47 and left-sided in 56 children.

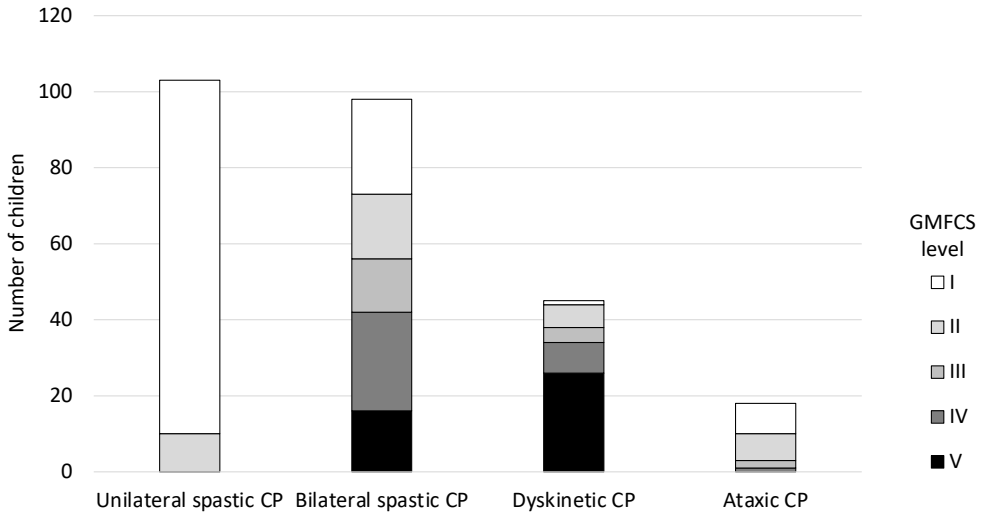

Figure 6. Cerebral palsy (CP) types with levels of gross motor function according to the GMFCS in a total population of 264 children with CP from the CP register of western Sweden.

Nearly two thirds of the children (63%) were independent walkers, i.e. at GMFCS level I-II. The distribution of GMFCS levels varied between CP types. (Figure 6) All children with USCP had a mild gross motor impairment. Children with dyskinetic CP had the most severe gross motor impairment with 76% at GMFCS level IV or V. Children with BSCP were at all GMFCS levels. The severity of gross motor impairment did not differ between children born at term and preterm, while the distribution of CP types did; BSCP was more common in children born preterm, while dyskinetic CP was most prevalent in those born at term.

Table 6. Characteristics and associated impairments of the participants through the project with its four studies. The dotted line indicates that some children in the assessment had performed at another intellectual level than previously described.

		I Diagnoses	Response	II Screening	III Assessment	IV Neuroimaging
All		264	232	213	200	184
Sex	male	141	126	115	109	97
	female	123	106	98	91	87
Gestational age	week 23-27	26	21	20	20	19
	week 28-31	30	23	22	22	17
	week 32-36	45	40	37	35	32
	week 37-42	163	148	134	123	116
CP type	USCP	103	89	89	82	72
	BSCP	98	83	76	73	70
	Dyskinetic CP	45	44	32	31	30
	Ataxic CP	18	16	16	14	12
GMFCS	I	127	110	110	101	87
	II	40	33	33	33	32
	III	20	19	19	18	17
	IV	35	31	30	29	29
	V	42	39	21	19	19
BFMF	I	97	76	76	74	62
	II	67	64	64	57	54
	III	41	39	39	37	36
	IV	24	21	18	17	17
	V	35	32	16	15	15
MACS	I	93	74	74	72	60
	II	59	54	54	48	45
	III	35	34	34	31	30
	IV	33	31	29	29	29
	V	44	39	22	20	20
Visual impairment	No	213	189	183	170	155
	Not severe	18	15	15	15	14
	Severe	33	28	15	15	15
Hearing impairment	No	243	214	198	186	170
	Sensorineural	21	18	15	14	14
Intellectual level	Normal	98	90	90	79	66
	Borderline	26	19	19	20	18
	Mild ID	57	47	47	45	45
	Moderate ID	19	19	19	20	19
	Severe ID	32	29	26	20	20
	Profound ID	32	28	12	16	16
Viking Speech Scale (VSS)	I	122	104	104	97	86
	II	58	51	51	49	45
	III	17	17	17	16	15
	IV	67	60	41	38	38
Epilepsy	No	155	133	132	125	111
	Active	109	99	81	75	73

Fine motor function according to the BFMF and MACS was at corresponding levels in 75% (rho=0.91; p<0.001). Fine motor function corresponded with GMFCS levels in 55% using BFMF (rho=0.77; p<0.001), and 61% using MACS (rho=0.82; p<0.001).

For participants distribution regarding sex, gestational age, motor function and associated impairments in all studies in the project see Table 6.

ASSOCIATED IMPAIRMENTS (I)

Associated impairments had been described for the total population of 264 children in the original reports when the children were 4-7 years of age (preschool age) (Himmelmann et al 2010, Himmelmann and Uvebrant 2014). We repeated the data extraction procedure when the children were 10-17 years of age (school age) and found that 182 children (69%) had one or several of the following impairments: visual impairment, hearing impairment, ID, severe speech impairment or epilepsy. The occurrence of these impairments all increased with more severe gross motor function. (Figure 7)

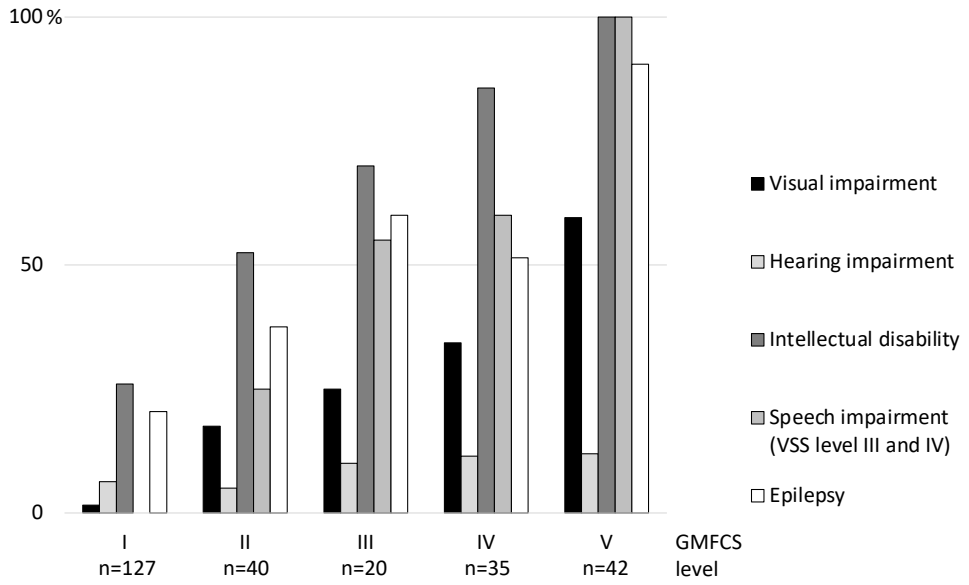

Figure 7. Proportion of associated impairments in a population-based group of 264 children with cerebral palsy at the age of 10-17 years presented by GMFCS level.

Visual impairment was found in 51 children (19%) at school age and was severe in 33 children (12%). The occurrence of severe visual impairment had not changed since preschool age. Twenty-nine of the 33 children with severe visual impairment were at GMFCS level IV or V.

Hearing impairment was rare at both ages and found in 22 children (8%) at school age.

ID was the most common associated impairment in both age groups and diagnosed ID had increased from preschool age to school age ($\chi 2=6.84$; $p=0.009$). At 4-7 years of age 110 children (42%) had ID, while there were 140 children (53%) with ID at 10-17 years of age. The intellectual level had been tested in 204 children, and was estimated in 60 children, either as normal in 36 children or as severe or profound ID in 24 children.

Severe speech impairment (VSS level III or IV) was found in 84 children (32%) and was more common in dyskinetic CP (39 of 45 children). More severe ID also correlated with less speech ability (rho=0.72; $p<0.001$).

Language disorder was diagnosed in 27 children (10%); generalised type was most common (16 of 27). Of these 27 children, 17 had USCP (right-sided in ten and left-sided in seven), and five had ataxic CP. All 27 children were at GMFCS level I and II; and none had more than mild ID.

Epilepsy was found in 108 children (41%) at preschool age, compared to 109 children (41%) at school age. Twelve children no longer had epilepsy, while in 13 children epilepsy had started after preschool age. The occurrence of epilepsy increased with the severity of ID ($\chi 2_{trend}=103.59$; $p<0.001$). Epilepsy was more common in dyskinetic CP (32 of 45 children) than in other CP types.

Hence, some associated impairments - visual impairment and epilepsy - did not increase with age, while other associated impairments did - ID and, as we will come to, autism and ADHD. (Figure 8) In the following, hearing impairment and language disorder are not addressed further.

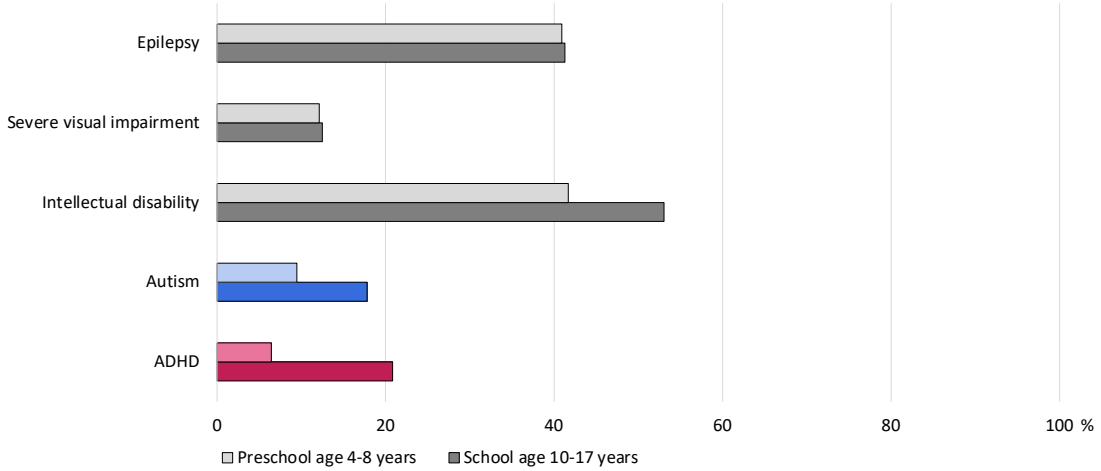

Figure 8. Associated impairments at preschool age (4-7 years) and school age (10-17 years) in a population-based group of 264 children with cerebral palsy.

AUTISM AND ADHD (I)

At preschool age autism was diagnosed in 25 children (9%) and ADHD in 17 children (6%), four of these children had both diagnoses; in total 38 children (14%) were diagnosed with autism and/or ADHD. At school age children with diagnosed autism and/or ADHD had more than doubled to 84 children (32%); autism in 47 children (18%) and ADHD in 55 children (21%), hence both diagnoses in 18 children (7%). (Figure 9)

Thus, autism diagnoses had almost doubled from 9% to 18% ($\chi 2=7.78$; $p=0.005$) and ADHD diagnoses had increased more than three times from 6% to 21% ($\chi 2=23.22$; $p<0.001$) from preschool age to school age.

Mean age at autism diagnosis was 8 years 3 months (range 3-15 years), and at ADHD diagnosis 9 years 5 months (range 4-15 years). No differences of age at diagnosis of autism nor ADHD were seen related to sex, CP type, GMFCS level, intellectual level, speech ability and epilepsy.

The majority of children with autism as well as ADHD were at GMFCS level I or II, in total 62 of the 84 children. The occurrence of autism as well as ADHD decreased with increasing gross motor severity, from GMFCS level II to V. The

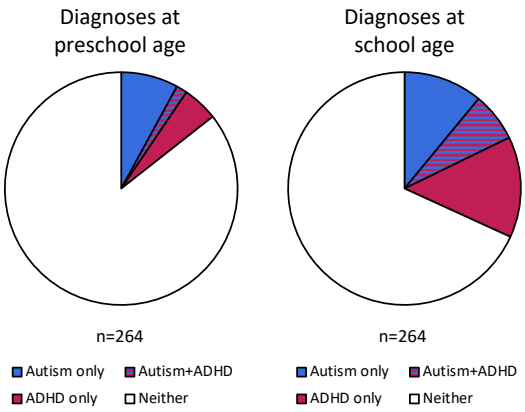

Figure 9. Autism and ADHD in 264 children with cerebral palsy at preschool age (4-7 years) and school age (10-17 years).

pattern of autism and ADHD in relation to GMFCS levels was reverse from the other associated impairments.

In total, 199 children (75%) had autism, ADHD or any of the earlier described associated impairments alone or in combination at age 10-17 years.

SCREENING (II)

Parents of all the 264 children were asked to complete extensive questionnaires, aiming to find the children with autism or ADHD not identified and diagnosed. Response rate was 88%; 232 questionnaires out of 264 were returned. The responders were representative of the whole group of children. No major differences were found between the responders and the non-responders. (Table 6)

However, the questionnaires of 19 children were not possible to evaluate due to too few completed items. They represented the most disabled children; 12 with dyskinetic CP and seven with BSCP at the most severe GMFCS levels and ID levels. (Table 6) They accounted for more than two thirds of all uncompleted items in the returned questionnaires. These 19 children were therefore excluded, leaving 213 children.

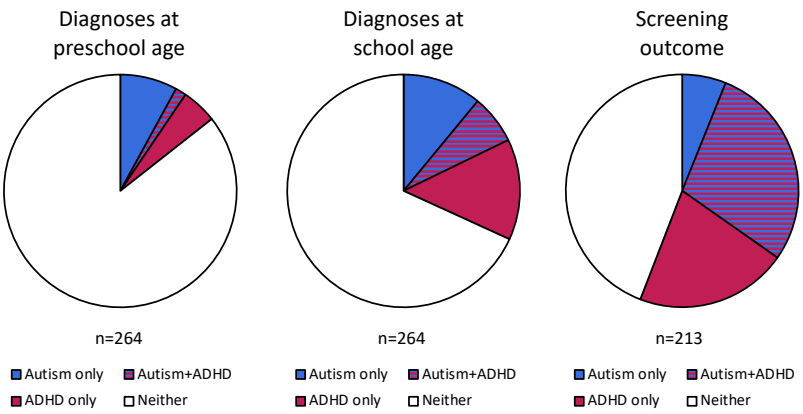

Figure 10. Proportion of screening outcome for autism and ADHD in 213 children with cerebral palsy (CP) compared with diagnoses of autism and ADHD in the original population of 264 children with CP.

Overall, 119 of the 213 children (56%) were screening positive for autism and/or ADHD. Seventy-four children (35%) were screening positive for autism, and 106 children (50%) for ADHD. The group screening positive for both autism and ADHD constituted nearly one third; 61 children (29%). (Figure 10)

The outcome of the different screening instruments is seen in Table 7. Most children screening positive for autism were positive on the ASSQ, and most children screening positive for ADHD were positive on the SNAP. The number of screening positive instruments (one, two or three) for autism did not correlate to previously diagnosed autism. Nor was there a correlation between the number of screening positive instruments for ADHD and previously diagnosed ADHD.

Table 7. Screening positive outcome in 213 children with cerebral palsy.

Screening positive	
Autism	74 children (35%)
ASSQ	68
DBC-ASA	34
ABC	26
ADHD	106 children (50%)
SDQ hyp/imp	58
SNAP-IV	91
DBC-HI	28
	213 children

Of the 213 screened children, almost twice as many were screening positive for autism than were previously diagnosed (74 compared to 42 children), and more than twice as many were screening positive for ADHD than were already diagnosed (106 compared to 49 children). Of the 42 children with a previous autism diagnosis, 33 were screening positive for autism (sensitivity 79%), and of the 49 children with an ADHD diagnosis, 42 were screening positive for ADHD (sensitivity 86%). The children with autism or ADHD diagnoses screening negative did not differ from the children screening positive regarding sex, gestational age, CP type, GMFCS level or other associated impairments.

Occurrence of positive autism screening increased by severity of motor impairment ($\chi 2_{trend}$=9.09; p=0.003), while no association was seen between ADHD screening positivity and GMFCS levels ($\chi 2_{trend}$=0.04; p=0.84). This was in contrast to already identified diagnoses of both autism and ADHD, which decreased from GMFCS level II to V. (Figure 11)

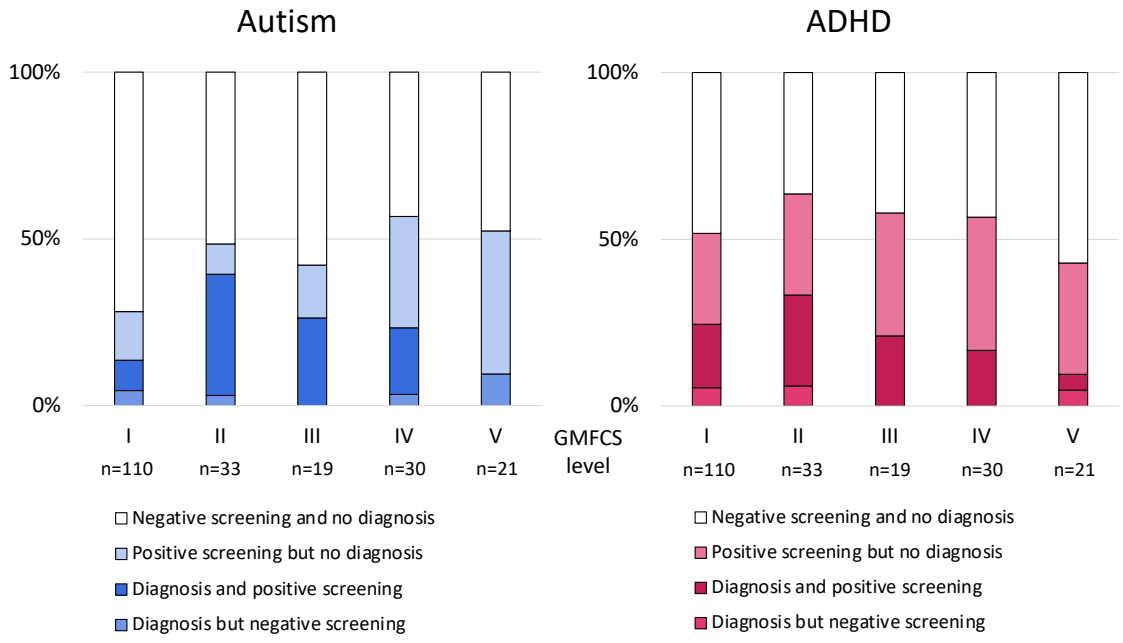

Figure 11. Results of screening for autism and ADHD in relation to already identified diagnoses in the same 213 children with cerebral palsy. The darkest parts of the bars represent the proportion screening positive with diagnosed autism and ADHD respectively. The lighter parts above show the proportion screening positive without diagnoses. In the bottom the few children screening negative but with already identified diagnoses are shown.

SCREENING IN RELATION TO PREVIOUS DIAGNOSES (II AND III)

The screening results from the 213 children were compared with the already identified diagnoses of autism and ADHD (Figure 12). The 28 children with screening positive results fully concordant with already identified diagnoses of autism and/or ADHD, were not assessed further, since all diagnoses had been made by clinically experienced teams. The 82 screening negative children with no diagnoses of autism or ADHD, were not assessed further either. They had repeatedly been evaluated by multi-professional habilitation teams throughout childhood and several years at school without identified need for neuropsychiatric assessment. It was concluded that no further assessment would be needed for these 110 children.

The remaining 103 children were approached for clinical assessment. Twelve screening positive children declined further participation in the study, and one had died. The remaining 90 children participated in neuropsychiatric examinations.

ASSESSMENTS (III)

Of the 90 children examined, seven performed at too low an intellectual level for further evaluation of autism or ADHD; four below an intellectual level of 1 year with no diagnoses of autism, and three children at an intellectual level between 1 and 3 years already diagnosed with autism but not ADHD.

Of the remaining 83 children, 40 had previously been diagnosed with autism and/or ADHD. All those diagnoses (23 autism and 21 ADHD) were found to meet current DSM-5 criteria. Additional diagnoses were identified in nine of these children: five with autism and four with ADHD.

Of the 43 children with no previous diagnoses of autism and ADHD, 19 were found to meet diagnostic criteria; 10 with autism, seven with ADHD and two with both autism and ADHD. In other words, 12 new autism diagnoses and nine new ADHD diagnoses were made in this group.

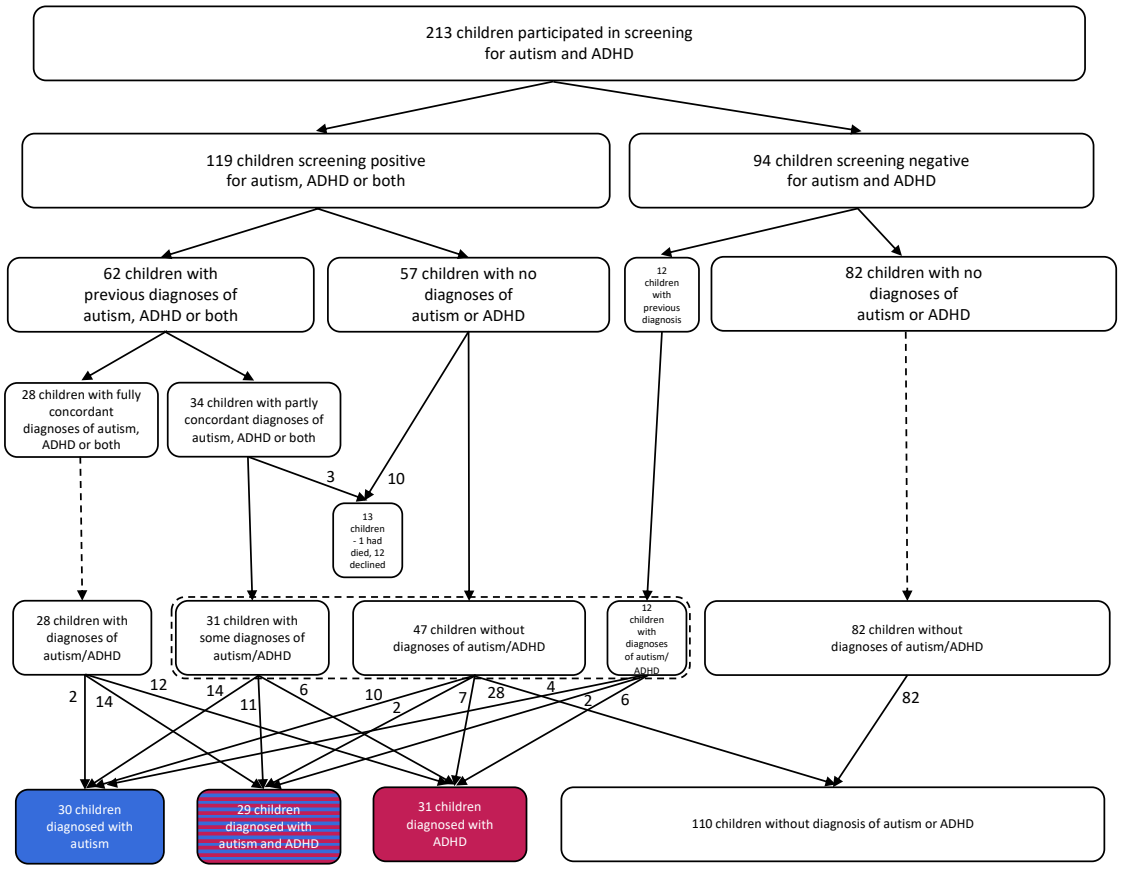

Figure 12. Flowchart of study III from screening results, through assessments to final diagnoses of autism and/or ADHD in 200 children with cerebral palsy. The areas of the boxes are proportional to the numbers of children. Children in the dashed box were examined in study III.

All in all, 17 new diagnoses of autism and 13 new diagnoses of ADHD were identified in 28 of the 90 children. There were another nine children with obvious autistic traits not meeting full diagnostic criteria for autism, and there were also several children with attention-deficits not meeting full criteria for an ADHD diagnosis.

The 17 children with new autism diagnoses were more often at GMFCS level IV-V (9 of 17), had more often mild to severe ID (12 of 17), and had a higher proportion of dyskinetic CP (6 of 17). The proportion of new versus previous diagnoses are presented in Figure 14.

The 13 children with new ADHD diagnoses more often had mild to moderate ID (8 of 13). A higher proportion were at GMFCS level III-IV (5 of 13), while in

absolute numbers most children with new ADHD diagnoses were at GMFCS level I. In extremely preterm born children, five of 20 received new ADHD diagnoses. Four of these five children also had autism.

Nineteen of the 90 children assessed performed at another intellectual level than previously described, all but one at a lower level. Seven children earlier regarded at normal intellectual level or borderline intellectual functioning were diagnosed with mild ID. Eleven other children altered level either from normal to borderline intellectual functioning, or at a lower level of ID than previously diagnosed. One child earlier at borderline intellectual functioning was found at a normal intellectual level.

TOTAL POPULATION (III)

The group completing the comprehensive procedure with screening and assessment comprised 200 children, constituting 76% of the original population of 264 children.

Of these 200 children, 90 (45%) were found to have autism and/or ADHD. Fifty-nine children (30%) had autism and 60 children (30%) had ADHD, overlapping with both diagnoses in 29 children. (Figure 13) The associations with sex, gestational age, CP type, motor function, ID and other associated impairments are presented in Table 8.

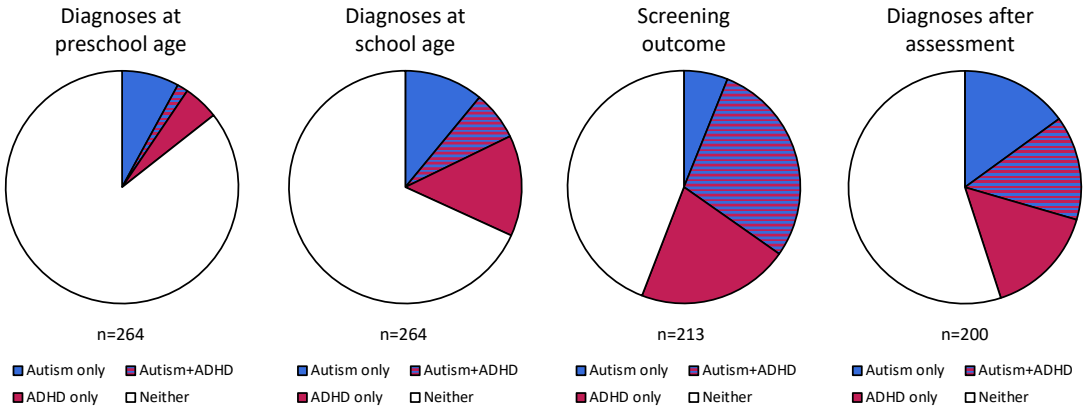

Figure 13. Autism and ADHD in school-aged children with cerebral palsy in the project. The last circle represents the outcome after screening and assessment in 200 children.

Table 8. Diagnoses of autism and ADHD in the population of 200 school-aged children with cerebral palsy (CP). The results are shown in relation to sex, gestational age, CP type, motor function and other associated impairments.

		Total	Autism only n (%)	Autism+ ADHD n (%)	ADHD only n (%)	None n (%)	Autism in total n (%)	ADHD in total n (%)
All		200	30 (15)	29 (14)	31 (16)	110 (55)	59 (30)	60 (30)
Sex	male	109	20 (18)	17 (16)	16 (15)	56 (51)	37 (34)	33 (30)
	female	91	10 (11)	12 (13)	15 (17)	54 (59)	22 (24)	27 (30)
Gestational age	week 23-27	20	4 (20)	7 (35)	4 (20)	5 (25)	11 (55)	11 (55)
	week 28-31	22	5 (23)	2 (9)	2 (9)	13 (59)	7 (32)	4 (18)
	week 32-36	35	6 (17)	4 (11)	3 (9)	22 (63)	10 (29)	7 (20)
	week 37-42	123	15 (12)	16 (13)	22 (18)	70 (57)	31 (25)	38 (31)
CP type	USCP	82	7 (9)	11 (13)	17 (21)	47 (57)	18 (22)	28 (34)
	BSCP	73	16 (22)	9 (12)	7 (10)	41 (56)	25 (34)	16 (22)
	Dyskinetic CP	31	6 (19)	3 (10)	5 (16)	17 (55)	9 (29)	8 (26)
	Ataxic CP	14	1 (7)	6 (43)	2 (14)	5 (36)	7 (50)	8 (57)
GMFCS	I	101	9 (9)	11 (11)	20 (20)	61 (60)	20 (20)	31 (31)
	II	33	5 (15)	10 (30)	3 (9)	15 (46)	15 (45)	13 (39)
	III	18	3 (17)	3 (17)	4 (22)	8 (44)	6 (33)	7 (39)
	IV	29	8 (28)	4 (14)	3 (10)	14 (48)	12 (41)	7 (24)
	V	19	5 (27)	1 (5)	1 (5)	12 (63)	6 (32)	2 (11)
BFMF	I	74	10 (14)	8 (11)	10 (14)	46 (62)	18 (24)	18 (24)
	II	57	7 (12)	10 (18)	11 (19)	29 (51)	17 (30)	21 (37)
	III	37	6 (16)	8 (22)	6 (16)	17 (46)	14 (38)	14 (38)
	IV	17	5 (29)	2 (12)	3 (18)	7 (41)	7 (41)	5 (29)
	V	15	2 (13)	1 (7)	1 (7)	11 (73)	3 (20)	2 (13)
MACS	I	72	7 (10)	8 (11)	12 (17)	45 (63)	15 (21)	20 (28)
	II	48	5 (10)	9 (19)	9 (19)	25 (52)	14 (29)	18 (38)
	III	31	5 (16)	7 (23)	6 (19)	13 (42)	12 (39)	13 (42)
	IV	29	8 (28)	4 (14)	3 (10)	14 (48)	12 (41)	7 (24)
	V	20	5 (25)	1 (5)	1 (5)	13 (65)	6 (30)	2 10)
Visual impairment	No	170	20 (12)	26 (15)	31 (18)	93 (55)	46 (27)	57 (34)
	Not severe	15	6 (40)	1 (7)	0 (0)	8 (53)	7 (47)	1 (7)
	Severe	15	4 (27)	2 (13)	0 (0)	9 (60)	6 (40)	2 (13)
Hearing impairment	No	186	28 (15)	26 (14)	29 (16)	103 (55)	54 (29)	55 (30)
	Sensorineural	14	2 (14)	3 (21)	2 (14)	7 (50)	5 (36)	5 (36)
Intellectual level	Normal	79	6 (8)	3 (4)	13 (16)	57 (72)	9 (11)	16 (20)
	Borderline	20	2 (10)	4 (20)	3 (15)	11 (55)	6 (30)	7 (35)
	Mild ID	45	5 (11)	12 (27)	11 (24)	17 (38)	17 (38)	23 (51)
	Moderate ID	20	4 (20)	6 (30)	4 (20)	6 (30)	10 (50)	10 (50)
	Severe ID	20	7 (35)	4 (20)	0 (0)	9 (45)	11 (55)	4 (20)
	Profound ID	16	6 (37)	0 (0)	0 (0)	10 (63)	6 (38)	0 (0)
Viking Speech Scale (VSS)	I	97	10 (10)	12 (12)	16 (17)	59 (61)	22 (23)	28 (29)
	II	49	8 (16)	9 (19)	8 (16)	24 (49)	17 (35)	17 (35)
	III	16	0 (0)	2 (12)	6 (38)	8 (50)	2 (13)	8 (50)
	IV	38	12 (31)	6 (16)	1 (3)	19 (50)	18 (47)	7 (18)
Epilepsy	No	125	14 (11)	14 (11)	20 (16)	77 (62)	28 (22)	34 (27)
	Active	75	16 (21)	15 (20)	11 (15)	33 (44)	31 (41)	26 (35)

There was no significant difference in sex distribution either for autism ($\chi 2$=2.28; p=0.13) or ADHD ($\chi 2$=0.01; p=0.93).

Extremely preterm children more often had autism ($\chi 2$=6.95; p=0.008) and ADHD ($\chi 2$=6.61; p=0.010), compared with those born after 27 gestational weeks. (Figure 14)

Autism and ADHD were found in all CP types. Children with ataxic CP (n=14) often had the combination of autism and ADHD, but the prevalence of autism was not significantly higher ($\chi 2$=3.04; p=0.081), whereas the prevalence of ADHD was ($\chi 2$=5.28; p=0.022). There was a non-significant trend for spastic CP with autism being more common in BSCP, and ADHD being more common in USCP (p=0.088 and p=0.092 respectively). (Figure 14)

Autism was less prevalent at GMFCS level I than at level II-V ($\chi 2$=15.03; p<0.001), while the prevalence of ADHD was lower at GMFCS level IV-V, although not significantly compared to level I-III ($\chi 2$=3.81; p=0.051). (Figure 14)

Fine motor function according to BFMF correlated well with GMFCS for the 200 children (rho=0.72; p<0.001). An increase in prevalence of autism and/or ADHD was seen from BFMF I-IV ($\chi 2_{trend}$=4.03; p=0.045).

ID was found in 101 of the 200 children (51%). The autism prevalence increased with lower intellectual level ($\chi 2_{trend}$=18.84; p<0.001). ADHD was also more prevalent with lower intellectual level ($\chi 2_{trend}$=3.86; p=0.049), profound ID excluded due to no ADHD per definition at this intellectual level. (Figure 14)

Speech ability classified according to the Viking Speech Scale was associated with GMFCS (rho=0.75; p<0.001) as well as intellectual level (rho=0.67; p<0.001), but speech impairment was not significantly associated with autism, nor with ADHD.

Autism was more prevalent in children with epilepsy ($\chi 2$=8.08; p=0.004), but epilepsy was not associated with ADHD ($\chi 2$=1.24; p=0.26).

Mean age at autism diagnosis was 10 years 4 months (range 3-18 years), and mean age at ADHD diagnosis was 10 years 7 months (range 4-18 years). The age at autism diagnosis, as well as ADHD diagnosis, was unrelated to sex, CP type, gross motor function, intellectual level, speech ability and epilepsy.

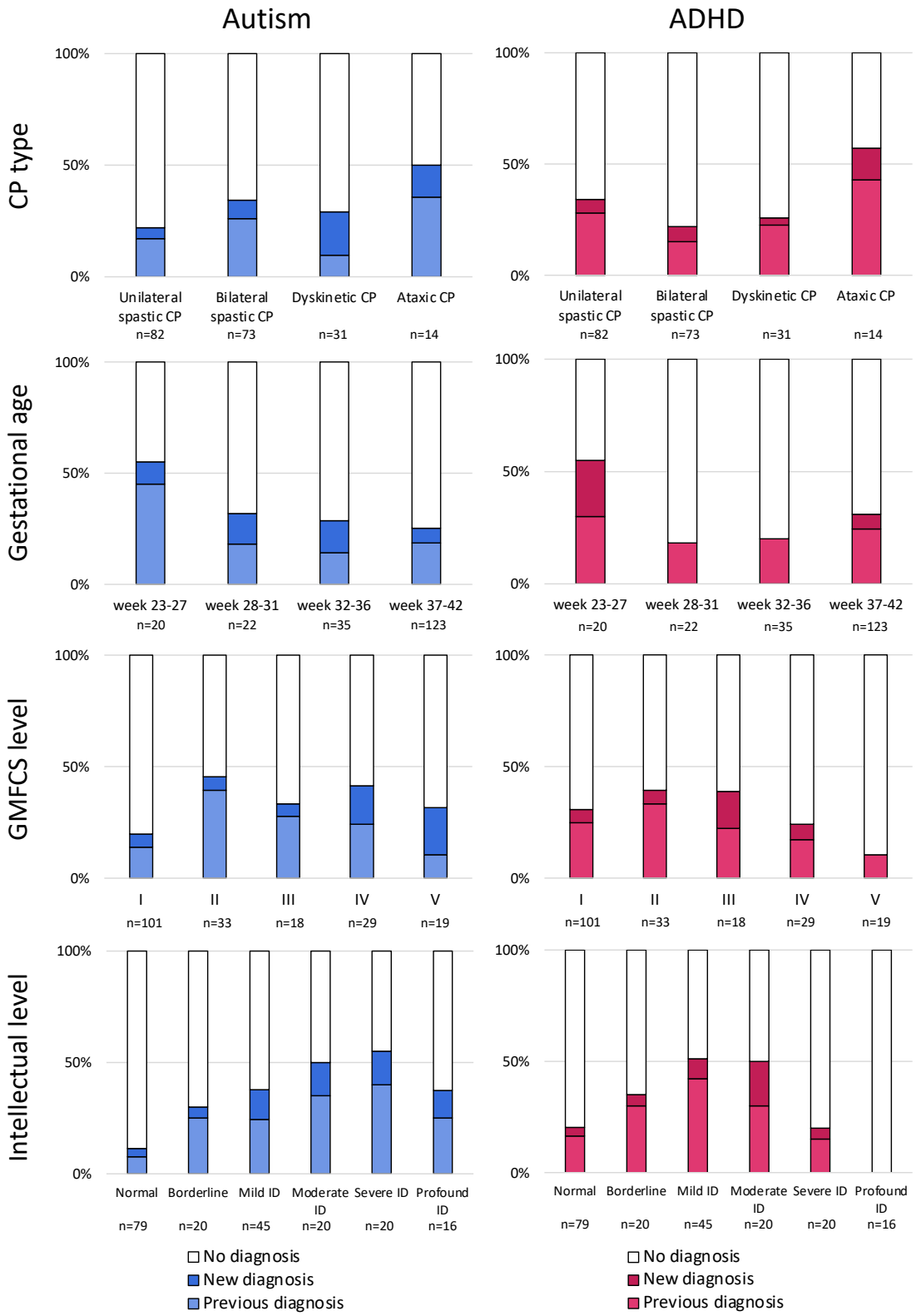

Figure 14. Diagnoses of autism and ADHD in the population-based group of 200 children with cerebral palsy (CP). Results are presented in relation to CP type, gestational age, gross motor function (GMFCS) and intellectual level (ID Intellectual Disability). New diagnoses identified through the assessment study are represented by the darker parts of the bars.

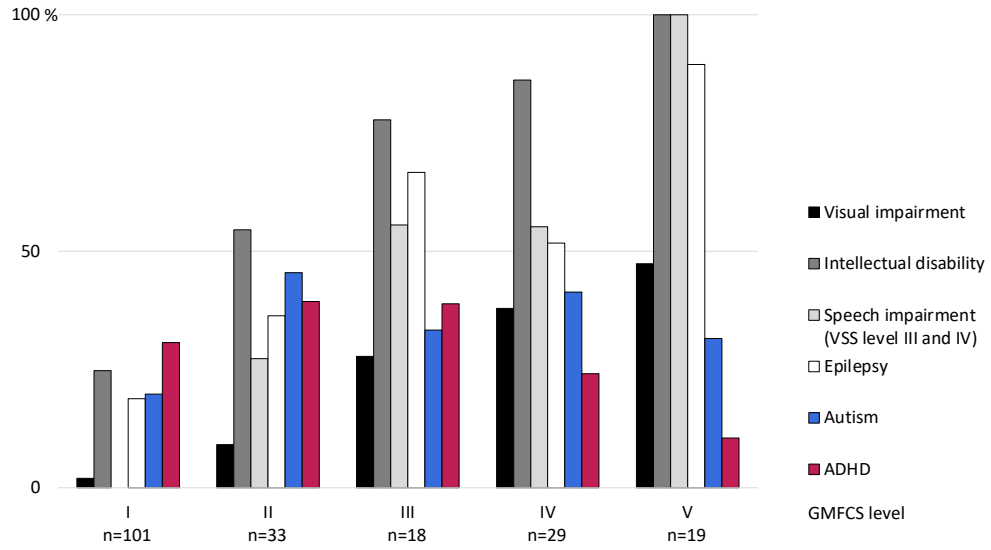

Figure 15. Proportion of associated impairments in a population-based group of 200 children with cerebral palsy in relation to gross motor function (GMFCS level).

The prevalence of visual impairment, ID, speech impairment and epilepsy all increased with more severe gross motor function for the 200 children, but the same pattern was not seen for autism and ADHD. (Figure 15)

Children with unilateral spastic CP had the lowest proportion of associated impairments, while the other CP types had higher proportions but with different patterns of single impairments. (Figure 16)

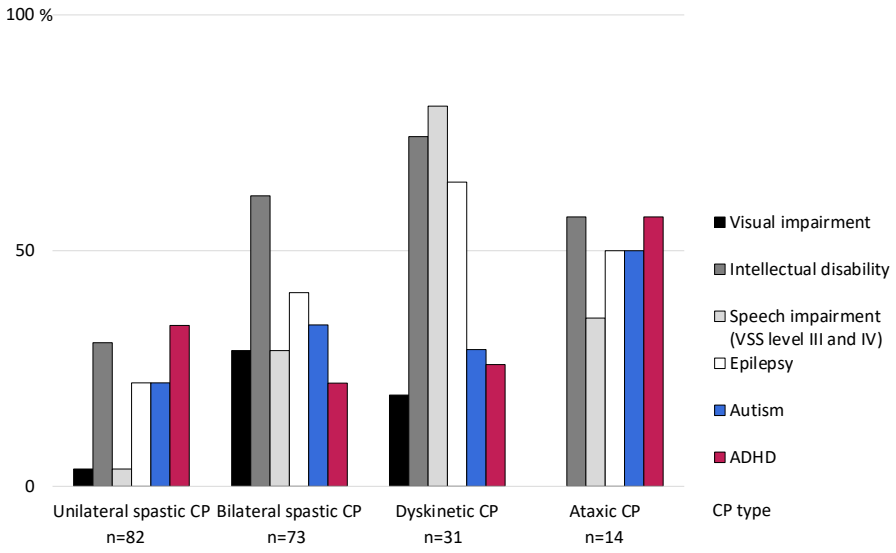

Figure 16. Proportion of associated impairments in a population-based group of 200 children with cerebral palsy (CP) in relation to CP type.

Multiple regression

The relationships between variables with autism and ADHD as outcomes were estimated using a multiple regression model.

Autism was predicted by three variables: ID, ADHD and preterm birth, while CP type, gross motor function, sex, speech ability and epilepsy did not add any extra information. The odds ratios for the outcome of autism were 4.1 for ID (95% CI 2.1-8.6), 3.2 for ADHD (95% CI 1.6-6.5), and 2.0 for preterm birth (95% CI 1.0-3.9).

ADHD was also predicted by three variables: ID, autism and a mild gross motor impairment. CP type, sex, preterm birth, speech ability and epilepsy did not add any extra information. The odds ratios for the outcome of ADHD were 2.3 for ID (95% CI 1.0-4.9), 3.0 for autism (95% CI 1.5-6.1), and 2.8 for mild gross motor impairment (95% CI 1.3-6.3).

Hence, autism, ADHD and ID were associated with each other. (Figure 17) Two thirds of the children had one or several of these three diagnoses – 33% had one, 22% had two and 11% had all three of autism, ADHD and ID. Half of the children with autism had ADHD, and half of the children with ADHD had autism.

The screening procedure was evaluated against the final diagnoses of autism and ADHD in the 200 children. The screening for autism showed a sensitivity of 83% and a specificity of 87%, while the screening for ADHD showed a sensitivity of 87% and a specificity of 69%. No significant differences of sensitivity and specificity in relation to GMFCS level were seen. The positive predictive value was 73% for autism and 55% for ADHD, while the negative predictive value was 92% for both autism and ADHD.

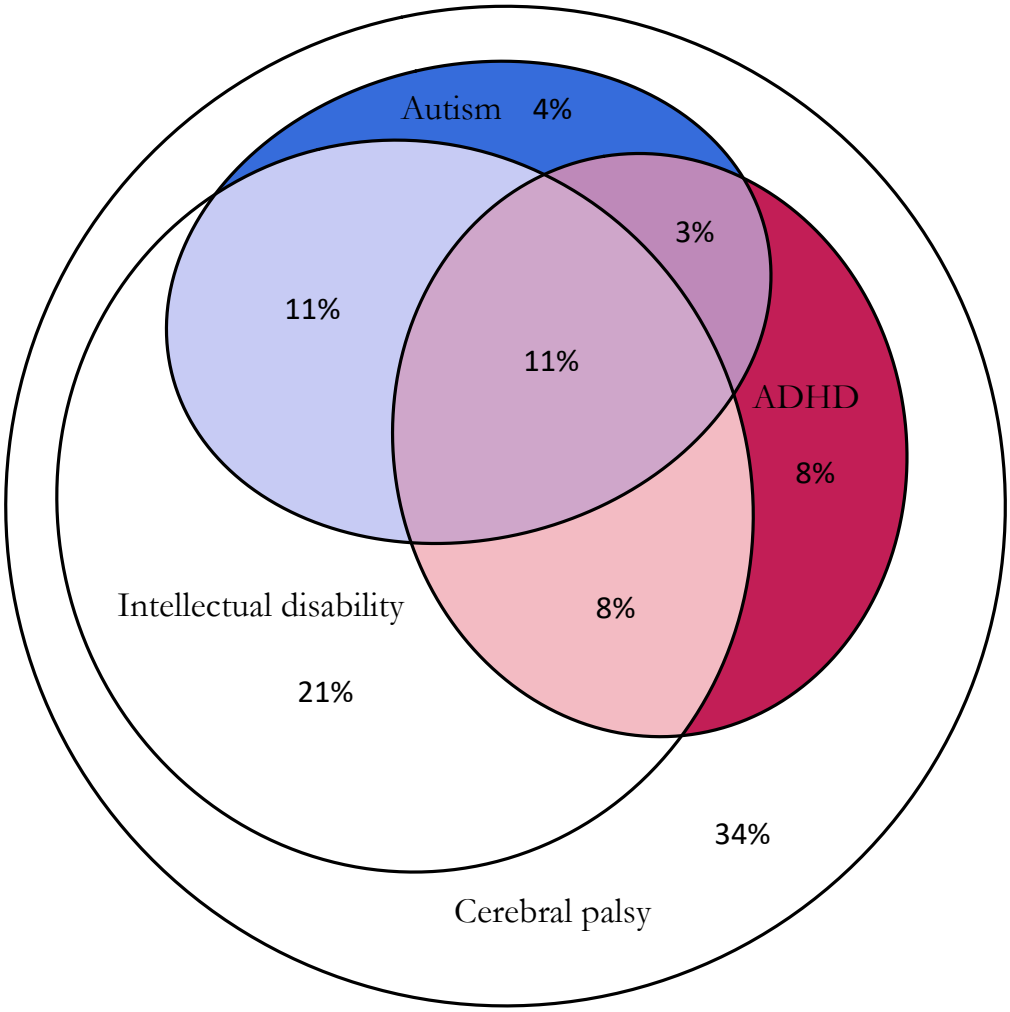

Figure 17. Autism and ADHD and intellectual disability diagnosed in the population-based group of 200 school-aged children with cerebral palsy. Illustration area-proportional in an Euler diagram (created in RStudio using the package eulerr).

Clinical characteristics

Children with CP without associated impairments were few. Forty-eight of the 200 children (24%) had CP without autism, ADHD, ID, speech/language disorder, visual/hearing impairment, or epilepsy. There was an equal number of boys and girls in this group. USCP was the most common CP type (41 of 48 children). Motor impairment was most often mild; 41 children were at GMFCS level I. Twenty-nine of the 48 children were at level I in all three gross and fine motor classifications, which was half of all children with this mildest motor impairment (60 of the 200 children).

Clinical characteristics of children with autism were often ID, ADHD, epilepsy, speech impairment, more severe gross motor impairment, and preterm (especially extremely preterm) birth. Autism was present in 59% of the children with ID + ADHD (22 of 37), in 55% with ID + preterm birth (21 of 38) and 80% with ID + extremely preterm birth (8 of 10). In children with ADHD + epilepsy nearly 60% had autism, regardless of ID or not.

Clinical characteristics of children with ADHD were often mild to severe ID, autism, less severe gross motor impairment, and extremely preterm birth. ADHD was present in 58% of the children with ID (profound excluded) + autism (22 of 38) and in 67% with ID (profound excluded) + extremely preterm birth (6 of 9).

The whole group of non-participants comprised 64 children. They were more often the most severely disabled at the lowest levels; GMFCS V, BFMF V, MACS V, VSS IV, and more often had visual impairment and epilepsy. The difference emanated from the 19 children for whom the screening had not been sufficiently completed for an evaluation to be made. In other aspects as sex, gestational age, CP type, ID and other levels of motor function no differences were seen between the 200 participants and the 64 non-participants.

Diagnoses of autism and ADHD recorded in study I were at that time equally common between the 200 final participants and the 64 non-participants regarding diagnosed autism ($\chi 2=2.98$; p=0.084) or diagnosed ADHD ($\chi 2=2.58$; p=0.108).

NEUROIMAGING (IV)

The 184 children with available neuroimaging classification did not differ regarding sex, gestational age, CP type, gross motor function, intellectual level or epilepsy, regardless of whether or not they were compared with the total original population of 264 children or with the 200 children who completed screening and assessment for autism and ADHD.

In the neuroimaging group of 184 children, 86 (47%) had autism and/or ADHD – 56 (30%) had autism and 57 (31%) had ADHD, meaning 27 (15%) had both autism and ADHD. ID was present in 100 children (54%) and epilepsy in 73 (40%).

Abnormal neuroimaging patterns were found in 164 children (MRICS A,B,C,D), and 20 had a normal MRI (E). The lesions were bilateral in 113 children and unilateral in 51. The children with bilateral lesions more often had visual impairment ($\chi 2=11.94$; $p=0.001$), intellectual disability ($\chi 2=25.87$; $p<0.001$), severe speech impairment ($\chi 2=24.65$; $p<0.001$) and epilepsy ($\chi 2=7.02$; $p=0.008$), while neither autism ($\chi 2=2.29$; $p=0.13$) nor ADHD ($\chi 2=1.05$; $p=0.31$) differed between the groups. (Figure 18)

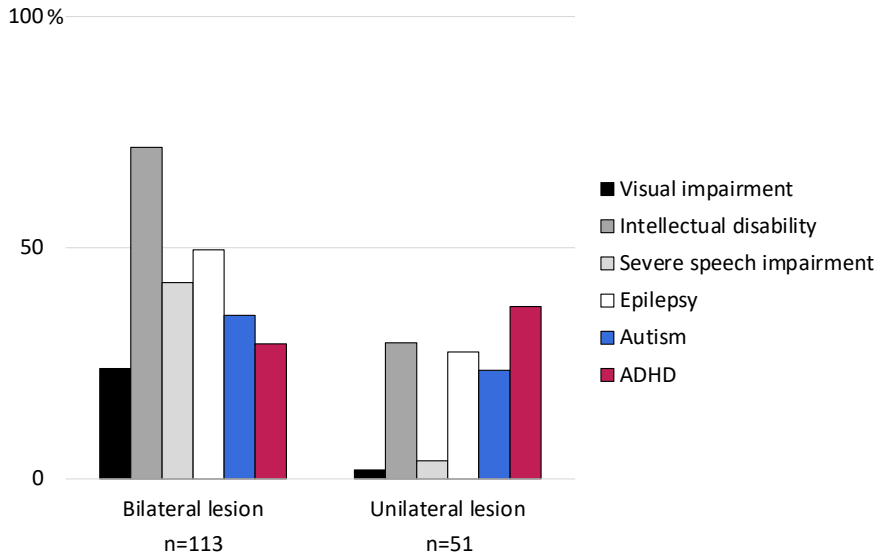

Figure 18. Associated impairments in 164 children with cerebral palsy with abnormal neuroimaging findings depending on bilateral or unilateral brain lesions.

Twenty children had a normal MRI (E). ID was less common in this group ($\chi 2=10.67$; $p=0.001$), while there was no significant difference in the prevalence of autism ($\chi 2=1.15$; $p=0.28$) and ADHD ($\chi 2=0.38$; $p=0.54$), compared to the children with abnormal neuroimaging findings.

Children with autism and ADHD were found in all groups of MRICS patterns. (Figure 19) Autism was more common in children with predominant white matter injury (B, 40%) than children with other MRICS patterns (25%) ($\chi 2=4.38$; $p=0.037$). ADHD was more common in children having sustained a middle cerebral artery infarction (C3, 63%) than in other MRICS patterns (28%) ($\chi 2=8.14$; $p=0.004$). No further significant differences in prevalence rates of autism or ADHD related to MRICS patterns were found.

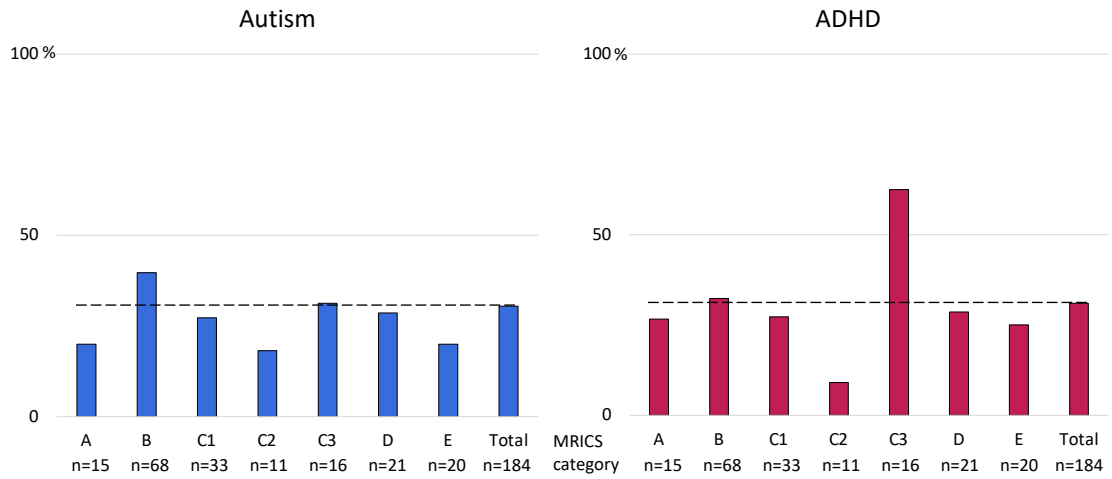

Figure 19. Autism and ADHD prevalence in MRI classification system (MRICS) patterns in a population-based group of 184 school-aged children with cerebral palsy.

In the children with USCP the most common MRICS patterns were predominant white matter injury (B, 30 of 72 children) and middle cerebral artery infarction (C3, 16 of 72 children). The two groups did not show any significant differences regarding gross motor function (χ^2_{trend}=3.12; p=0.077) or distribution of gestational age (χ^2_{trend}=3.22; p=0.073). Autism and ADHD did not differ significantly between children with predominant white matter injury (B) and middle cerebral artery infarction (C3), while ID (χ^2=4.44; p=0.035) and epilepsy (χ^2=5.01; p=0.025) were more common in children having sustained middle cerebral artery infarction (C3).

In the children with BSCP predominant white matter injury (B) was found in half (35 of 70 children). Autism was more common in BSCP with white matter injury (20 of 35 children) than with other MRICS patterns (4 of 35 children) (χ^2=16.23; p<0.001). No difference regarding ADHD, ID or distribution of gross motor function was seen between the groups.

Children with dyskinetic CP most commonly had basal ganglia/thalamus lesions (C1, 20 of 30 children). Autism, ADHD and ID were equally common in children with dyskinetic CP regardless of MRICS pattern. Children with dyskinetic CP showed a high prevalence of restricted and repetitive behaviour even if not fulfilling diagnostic criteria for autism.

DISCUSSION

GENERAL FINDINGS

This thesis is based on the population-based CP register of western Sweden enabling studies on CP with high quality. The combination with the leading expertise on children with autism and ADHD at Gillberg Neuropsychiatry Centre has provided a unique opportunity for studies on neuropsychiatric impairments in children with CP. The project has also relied on long clinical experience at the regional centre for children with CP and other disabilities. A majority of the 264 children with CP had previously attended the regional centre for different clinical needs.

CP is a group of disorders with a variety of expressions both regarding motor function and associated impairments. The focus has historically been the motor impairment, as it is the common and core symptom in CP. However, over the last decades focus has changed more to the often occurring associated impairments, something that was emphasised in the most recent CP definition from 2007.

Autism and ADHD were very common in this population-based group children with CP. Forty-five percent had autism, ADHD or autism plus ADHD, which is higher than previously reported. Thirty percent had autism and thirty percent had ADHD. The findings of the project are discussed below, starting with already identified diagnoses through screening to clinical assessments and association with neuroimaging findings.

ASSOCIATED IMPAIRMENTS AND DIAGNOSES (I)

Associated impairments are common in children with CP. How common depends of course on which impairments you consider and what definitions you use.

In our first study we looked at impairments affecting all the areas mentioned in the CP definition, and found more than 75% of the children affected by one or several associated impairments. This occurrence was higher than previously described (Shevell et al 2009, Delacy and Reid 2016, Horber et al 2020), most

probably due to the fact that the previous studies reported on children at preschool age.

The children in our study group were all at school age, 10-17 years, and we had information about the same children at preschool age, 4-7 years (Himmelmann et al 2010, Himmelmann and Uvebrant 2014). From preschool to school age the children with severe visual impairment and epilepsy had not increased. The early onset of epilepsy has been reported in earlier studies (Carlsson et al 2003, Reid et al 2018), and severe visual impairment is also detected early in life.

In contrast, diagnoses of ID, autism and ADHD had increased substantially from preschool to school age. The increase in ID can be attributed to several explanations. More children had been tested over time, and testing is usually easier and more reliable after the first years of life. Some abilities, such as reading (Dahlgren Sandberg 2006), develop later in childhood and cannot be assessed until school age. The brain lesion itself may also hamper the intellectual development, leading to a greater discrepancy compared to typically developing children with age (Smits et al 2011, Fluss and Lidzba 2020).

AUTISM AND ADHD (I)

Autism had doubled and ADHD more than tripled from preschool to school age. This is partly in line with the trend for diagnosed ID. Nonetheless, the trend with a higher occurrence of diagnosed autism and ADHD was stronger. The increase could also be attributed to the parallel trend of increasing diagnoses of autism and ADHD in the general population during this time (Lundström et al 2015, Rydell et al 2018). The occurrence of diagnosed autism and ADHD in our study was higher than earlier reported; nearly one third had autism and/or ADHD. This may have been influenced by the fact that many child neurologists at the habilitation units in the region have had part of their clinical training at the Child Neuropsychiatry Clinic connected to the Gillberg Neuropsychiatry Centre. The present research project alone could also have affected the numbers of referrals for assessment sent to our Regional Rehabilitation Centre.

At group level, there is a strong association between gross motor severity and the occurrence of associated impairments, first described by Himmelmann et al in

2006. Since then, this has been confirmed by several other centres (Andersen et al 2008, Shevell et al 2009, Sigurdardottir et al 2009, Delacy and Reid 2016).

However, the strong correlation between higher GMFCS level and visual impairment, ID, speech impairment and epilepsy was not reproduced for autism and ADHD. There was almost an opposite trend; both autism and ADHD decreased in children from GMFCS level II to level V. The rates of at least autism may be expected to increase in children with more severe gross motor impairment, similar to epilepsy and ID, both known to be associated with autism (Reilly et al 2014). Therefore, we speculated that autism and ADHD were not identified particularly in children at GMFCS level III and IV. In the most severely disabled children at GMFCS level V several other impairments may hamper neuropsychiatric diagnostics and these children may also be at too low an intellectual level for neuropsychiatric diagnoses to be made.

Even though our results through this record-based study showed high occurrence of autism and ADHD in children with CP, there were indications suggesting that not all neuropsychiatric impairments were identified by this more passive approach. Our main hypothesis that autism and ADHD were underdiagnosed was supported by our findings and a need for more active assessment was identified.

SCREENING (II)

Screening the total group was the next and more active step in the project, aiming to identify the children in need of a comprehensive neuropsychiatric examination. An additional aim was evaluating how screening worked in a population of children with CP.

Our starting point was finding a well-validated screening method applicable to all the children with CP, from the least to the more severely impaired. We opted to use the same screening instruments as in the large Bergen Child Study (Heiervang et al 2007), and added two other instruments developed for children with ID. Since our aim was to find all children with autism and ADHD, we wanted high sensitivity and chose the lowest established cut-off levels. The parents of almost

all children in the group gave a positive response and we had indications from many parents that they also regarded this project as important.

The screening outcome showed that a very large proportion of children with CP were screening positive for autism and/or ADHD (56%), suggesting that neuropsychiatric difficulties were very common. The rates were even higher than we had expected, with one third screening positive for autism and half for ADHD, altogether about twice the already identified diagnoses of autism and ADHD.

Screening positive outcome was more common than identified diagnoses of autism and ADHD in all types and functional levels of CP, although the excess was higher in children with more severe gross motor function and in children with mild to severe ID. These results supported our hypothesis that the occurrence of autism and ADHD in children with CP was underestimated especially in these children.

In spite of adding screening instruments developed for children with ID, the screening was not appropriate for the most severely disabled children, i.e. children at GMFCS level V and profound ID. Children with very severe impairments may not have enough abilities or expressions for the questionnaires to be feasible. In the remaining questionnaires regarding the children at GMFCS level V, fewer were screening positive than in the less disabled children. The same problem was encountered by Bjorgaas et al, hence all children at GMFCS level V were excluded in that study (Bjorgaas et al 2012). Screening is obviously not suitable for these most severely disabled children with their limitations. Adapted clinical assessments are needed to identify autism and ADHD in this group.

The overlap of screening positive outcome for both autism and ADHD was considerable with most children screening positive for autism also screening positive for ADHD. Children with autism, especially with ID, often show considerable levels of hyperactivity symptoms, although not meeting diagnostic criteria for ADHD (Gargaro et al 2014). The DBC subscales for autism (DBC-ASA) and hyperactivity (DBC-HI) have three items in common, further underlining common symptoms in neuropsychiatric disorders (Gillberg 2010, Bjorgaas et al 2013).

The screening procedure worked properly for the vast majority of children with CP. Earlier studies with screening for autism or ADHD in children with CP have

almost always used just one instrument or scale (Parkes et al 2008, Brossard-Racine et al 2012, Bjorgaas et al 2012, 2014). With regard to the heterogeneity in the group children with CP we used three scales for autism and ADHD respectively for better coverage of the children's varying abilities. The disadvantage is that the questionnaire then had to consist of more items.

Another issue is whether the screening really does capture the children who are in need of a broader assessment for autism and ADHD. Screening may be harder in children with several impairments with partly overlapping symptoms, and there may be problems capturing the often occurring complexity (Bjorgaas et al 2013).

ASSESSMENTS (III)

After comparing the screening results with already identified diagnoses of autism and ADHD it was concluded that no further assessment would be needed for around half of the children, as 110 were concordant between diagnoses and screening results. The majority of the 103 children approached for further clinical examination participated (90 of 103).

The examination consisted of several well-validated instruments and in most cases all of them were applied, ADOS when feasible in relation to the degree of other impairments. The DISCO gave a broad picture of the children's abilities and difficulties but did not add much information in the most severely impaired children. For those children, the information from the CARS and the clinical assessment was often enough. On the other hand, the CARS did not give much useful information about the children with milder impairment. The SNAP had limitations in children with several impairments because some items were not possible to evaluate. In these cases, the mean result from the completed items was used.

However, it is important to remember that the vast majority of children in the study, which also applies in general to children with CP, had a mild to moderate gross motor impairment and most children had understandable speech and sufficient vision. Hence, most children were examined and assessed the standard way for neuropsychiatric investigations in the general population.

The group of children with a more complex picture of different and often more severe impairments was small but required more thorough evaluation. The final decisions for both autism and ADHD were made taking all different factors in consideration, such as ID, co-existing autism or ADHD, respectively, communication ability, epilepsy, pain and environmental factors. Neither autism nor ADHD should be ruled out too quickly in children with complex and severe impairments, because the most affected children are often the ones also having autism and ADHD. (APA 2013)

There are of course grey areas where neuropsychiatric disorders are hard to diagnose due to a complexity in the clinical picture of a child, and our basic principle was to be cautious and make assured diagnoses only. In the end, autism and ADHD are clinical diagnoses based upon agreed clinical criteria (APA 2013). The aspect of categorical and dimensional approach is also important (Craig et al 2019). Diagnoses are binary, while impairments can be described as a continuum of abilities.

TOTAL POPULATION (III)

In summary, 200 children completed the comprehensive procedure with screening and assessment, i.e. 76% of the total population of 264 children. We knew that autism and ADHD are common in children with CP, however, with this active assessment we found prevalence rates higher than previously reported from other population-based studies (Sigurdardottir et al 2010, Bjorgaas et al 2014, Delobel-Ayoub et al 2017, Hollung et al 2020, Rackauskaite et al 2020). Altogether 45% had autism, ADHD or both autism and ADHD. Three children out of ten had autism and three children out of ten had ADHD, while half of the children with autism also had ADHD and vice versa.

For autism, several other studies have reported a prevalence of around 15% (Kilincaslan et al 2009, Bjorgaas et al 2014, Delobel-Ayoub et al 2017 - Icelandic data), which is slightly lower than our first study reporting already identified diagnoses. This prevalence level seems common for areas with a higher awareness of neuropsychiatric disorders. The prevalence rates reported tend to be lower the more register-based and the less clinical the studies are designed. The American studies on children identified for service provision reported a rate of 6.9-8.2%

(Kirby et al 2011, Christensen et al 2014), while reports based on national patient registers reported even lower rates 3.4-4.3% (Rackauskaite et al 2020, Hollung et al 2020). The trend over time with increasing autism diagnoses in the general population (Lundström et al 2015) may also have influenced diagnoses in children with CP. Comparisons between different samples of children with CP and population-based studies are more difficult.

Children with more severe CP are reported to be diagnosed with autism at older age than other children, often not until school age (Dahl et al 2014). In contrast, we could not find any difference in age at autism diagnoses related to gross motor severity in our studies.

For ADHD, population-based studies are scarce. There are some reports on increased levels of inattention and hyperactivity, however, often based only on parent-completed questionnaires (McDermott et al 1996, Parkes et al 2008, Brossard-Racine et al 2010) or neuropsychological testing (Bottcher et al 2010, Shank et al 2010). ADHD diagnoses require taking other co-existing impairments in consideration. Gabis et al reported a high prevalence of ADHD (22%) in a more impaired group of children with CP (Gabis et al 2015), while Bjorgaas et al reported clear ADHD symptoms in as much as 50% of children at GMFCS level I-IV through parental interviews (Bjorgaas et al 2012). Neither autism nor ADHD have up to now been actively assessed in a total population of children with CP.

Interestingly, a study of autism and ADHD in children with Down syndrome with similar design including screening and assessment, reported prevalence rates slightly higher but in the same order that we found in children with CP; autism in 42% and ADHD 34%. There was also an overlap of autism and ADHD, and in total 54% had autism and/or ADHD (Oxelgren et al 2017).

The final outcome of total autism and ADHD prevalence in children with CP was 45%, which was between the already reported diagnoses (32%) in the first study and the screening positive outcome (56%) in the second study. The final prevalence rates of both autism and ADHD were about 1.5 times higher than in our first study reporting already identified diagnoses. However, the screening positive outcome was considerably higher for ADHD than for autism (50% vs 35%). Hence, the screening for ADHD turned out to be too inclusive with a positive predictive value of 55%, compared to 73% for autism. Our interpretation is that the cut-offs for ADHD, especially for the SNAP, should have been higher. The screening method used was clearly more suitable for autism than for ADHD.

ASSOCIATIONS OF IMPAIRMENTS (III)

The association between more severe gross motor impairment and increased occurrence of associated impairments in children with CP has previously been mentioned. The different pattern for autism and ADHD in our first study was seen as an indication of not identified neuropsychiatric diagnoses especially in children at GMFCS level III-IV. Indeed, we found a high proportion of new diagnoses of autism and ADHD at these GMFCS levels. However, autism did not increase by GMFCS level in the same way as other associated impairments, and ADHD prevalence even decreased in children at GMFCS level V. Most likely ADHD in particular, but also autism, were still underdiagnosed due to diagnostic limitations in children with a complex clinical picture or at a too low an intellectual level (Thurm et al 2019).

Different CP types were not significantly associated with autism or ADHD, except for the small ataxic group where ADHD was significantly more common. Almost two thirds of children with ataxic CP had autism and/or ADHD. This has been pointed out earlier by Åhsgren et al, finding high rates of autism and hyperactivity disorder in children with non-progressive ataxia (Åhsgren et al 2005).

No significant differences in the prevalence of autism and ADHD were seen between boys and girls, suggesting that the brain lesion per se is involved in the pathogenesis, rather than genetic causes (Coleman and Gillberg 2012).

The strongest association with both autism and ADHD was seen with ID. The multiple regression models showed a covariation between autism, ADHD and ID, with little added extra information from other factors. The associations with other factors, like epilepsy and speech ability, were explained by their correlation to ID. ID was a predictor of both autism and ADHD, and autism and ADHD often co-occurred.

In addition, preterm birth was associated with autism in the multiple regression models. In particular extremely preterm born children have been reported to be at higher risk of both autism and ADHD (Hafström et al 2018, Hirschberger et al 2018, Montagna et al 2020).

The main findings of this project are the high prevalence of both autism and ADHD in children with CP, together with the strong associations between

autism, ADHD and ID. Two thirds of all children with CP have one, two or three of these impairments. However, gross motor function does not a predict autism and ADHD in the same obvious way as it is associated with ID and other associated impairments. Interestingly enough, this was one of the conclusions in the Danish national patient register study, although they showed a much lower prevalence of autism and ADHD (Rackauskaite et al 2020). High occurrence of ID was also reported in a study of ambulatory children with CP with co-existing autism (Smile et al 2013).

This co-existence and overlap across neurodevelopmental disorders are the essence of the concept of ESSENCE, underlining the need for broad clinical assessment in children with symptoms of impaired neurodevelopment (Gillberg 2010). Children with CP are at high risk of associated impairments, as pointed out in the second paragraph of the CP definition, and should be assessed and evaluated for neurodevelopmental disorders early in life and followed onwards.

We may speculate over reasons why autism and ADHD are not identified. It may be hard to recognise early signs of neurodevelopmental disorders in children with CP as something else beyond the symptoms and signs of the motor disorder. There may also be denial or reluctance from the environment to see signs of autism and ADHD. We often tend to explain everything from one perspective. CP is a concept comprising different clinical pictures, although with important features in common. Moreover, ID, autism and ADHD are not either completely separate, but often share symptoms, and may be regarded as sides of the same coin. In this context the common finding is the brain disturbance manifesting in a motor disorder, and very often also in other impairments.

NEUROIMAGING (IV)

Neuroimaging is important, although not mandatory, in the diagnostic work-up of CP. It often reveals information about aetiology and timing of insult and may contribute to better understanding and prognosis of associated impairments.

Autism and ADHD were common in all types of MRICS patterns, even in children with a normal MRI. Both autism and ADHD are associated with several different brain regions and networks reflecting the complexity of these higher

brain functions (Stigler et al 2011, Pagnozzi et al 2018, Albajara Sáenz et al 2019). Brain lesions early in life, especially before 3 years of age, have been found to give a more "general" effect on the development (Spencer-Smith et al 2011, Anderson et al 2014), giving an increased risk for autism and ADHD.

Autism was more common in children with predominant white matter injury. Such injuries occur late in the second trimester or early in the third trimester and are more likely the more preterm the child is born. This period has earlier been identified as a vulnerable period for autism (Croen et al 2005, Coleman and Gillberg 2012). A review about periventricular white matter lesions in children born preterm emphasised the association with both cognitive and social deficits (Pavlova and Krägeloh-Mann 2013). Regarding white matter volume in autism there are inconsistent findings. Reduced cerebellar volume has been found in children with autism (Pagnozzi et al 2018) and has also been described in extremely and very preterm born children (Kobayashi et al 2015). Organisation of the white matter, particularly in the corpus callosum, has been associated with both autistic traits and inattention symptoms (Aoki et al 2017).

ADHD was more common in children who had sustained a middle cerebral artery infarction. This is an injury often occurring around birth, suggesting a later timing. It is previously described that children with a perinatal ischemic stroke are at risk for attention deficits (Bosenbark et al 2017). However, basal ganglia are often involved in middle cerebral artery infarction and have been associated with both autism and ADHD (Stigler et al 2011, Pagnozzi et al 2018).

Children with both autism and ADHD did not differ in neuroimaging findings from children with autism or ADHD only, which was in line with a neuroimaging study in children with autism and ADHD showing no specific patterns (Mizuno et al 2019).

Neuroimaging studies have reported that children with CP with bilateral lesions had more functional deficits than children with unilateral lesions (Krägeloh-Mann et al 2017). We could confirm this for all registered associated impairments, except for autism and ADHD which were equally common. The extent of the brain lesion was not clearly related to the prevalence of autism and ADHD, which partly is in line with our previous findings of autism and ADHD not being associated with the severity of gross motor impairment (GMFCS level).

There are interesting associations between neuroimaging findings in CP and findings in autism and ADHD. Probably, there are affected brain regions in children with CP, also involved in the pathogenesis of autism and ADHD. We need to learn more about these common features through further in-depth studies on neuroimaging.

STRENGTHS AND LIMITATIONS

This project of assessing autism and ADHD in children with CP is based on solid ground, originating from a long-running well-maintained population-based CP register. The population of children with CP was well-defined, and the majority had been attending the clinical centre. The group was assessed at school-age, when autism and ADHD, as well as ID, were more likely to be recognised, than in lower age. We had good access to medical records.

Throughout the project, we had a high participation rate; from screening response to participating in clinical examinations, and having performed sufficient neuroimaging. The whole process was completed by 70% of the children in the original population. And there were no significant differences between the participating children and the 30% non-participating children regarding sex, gestational age, CP type, gross motor function, intellectual level or epilepsy.

The screening questionnaire was designed to include children both with and without ID, not least important since more than half of all children turned out to have ID.

The assessments for autism and ADHD were made with commonly used and validated instruments by experienced multi-professional teams working in the field of CP and associated impairments for many years. It made it easier to evaluate the findings in relation to other impairments affecting vision, hearing, speech, communication, epilepsy and pain.

This is to our knowledge the first study actively assessing a total population of children with CP for autism and ADHD.

A main limitation is of course that not all children participated in the study. Although as many as 76% completed the screening and assessment, 24% did not. There was a higher proportion of children at GMFCS level V and with profound

ID who did not participate, for the most part because the parents could not complete the screening study. The children with several and severe associated impairments were also difficult to examine and assess in a standardised way. Methods and instruments were not applicable without adaptation for this group.

In the screening study information about the children came only from one source, the parents. Additional teacher ratings would have been valuable. Screening is also coloured by the informants, which may influence the results in both directions. There may be some parents under-rating their children's impairments, due to difficulties to see and accept them. Conversely, some parents may look for impairments that a more "objective" assessment would not pick up.

Not all children were personally examined in the assessment study, with some of the data being retrospective in nature. However, the children for whom we concluded that a further assessment was not needed, had been diagnosed in a very similar way albeit by different multi-professional teams.

Neuroimaging was performed in most children, however, not MRI in all cases. Most children with CT belonged to the earlier birth-year cohorts in the total population. MRI gives more information than CT. Therefore, we excluded the children with a normal CT, since these data was not reliable in excluding all abnormalities. MRI had been performed at different ages with a considerable group before the age of 18 months, when MRI in children with CP is recommended in the current guidelines. Quality of classification of the MRI investigations would have benefitted from a blinded review by only one neuroradiologist.

CLINICAL IMPLICATIONS

There are several reasons for identifying autism and ADHD in children with CP. The children will benefit from early diagnosis and adapted support for all their impairments, hopefully leading to a better function and participation in the future. Early diagnosis is a key factor for better prognosis for children with autism and ADHD (Epstein et al 2010, Nygren et al 2012, Smile et al 2013). Parents and families will benefit from better possibilities to understand and meet their children's behaviour. The society may benefit from realising the extent of autism

and ADHD in children with CP, through adapting an appropriate organisation and better planning of service and support.

Autism and ADHD should be regarded as two of the main associated impairments in children with CP. There are good possibilities to implement this new knowledge into clinical practice. An active approach, similar to the present study's with screening and examination, could be recommended. Assessment for autism and ADHD is clearly warranted as part of evaluation in all children with CP. An increased awareness is eligible when the behaviour of a child is not sufficiently explained by identified impairments such as ID.

There are clinical guidelines for children with CP in Sweden where the need for assessments at different key ages are listed (Regionalt vårdprogram 2014, CPUP Uppföljningsprogram för cerebral pares). Assessment of autism and ADHD are included in this programme, but should have a larger focus, since autism and ADHD most likely are more prevalent than earlier known.

Screening at 5 years of age, before school start, in connection with cognitive assessment may be appropriate. However, there should be a high awareness of signs of autism and ADHD from early age with a low threshold for neuropsychiatric assessment. Follow-up evaluation at school age is important, since autism and ADHD may be more difficult to identify in children with other impairments.

CONCLUSIONS

Our first and main aim was to estimate the prevalence of autism and ADHD in children with CP. The results through this population-based active-approach project show that autism and ADHD are very common in children with CP, with prevalence rates higher than earlier reported. Three out of ten children with CP had autism, and three out of ten had ADHD. Since autism and ADHD co-occurred in half of the children respectively, altogether 45% had autism, ADHD or autism plus ADHD.

In addition, half of the children with CP had ID, often co-occurring with autism as well as with ADHD. In total, two thirds of the children had one, two or all three of these impairments. Autism and ADHD were not correlated to motor impairment severity, in contrast to ID and other associated impairments.

Autism and ADHD are common in children with CP almost regardless of CP type, gross motor impairment or neuroimaging findings. The brain involvement per se seems to increase the risk of autism and ADHD no matter the severity. However, neuroimaging may reveal prognostic information with timing of insult appearing to be of importance for the occurrence of autism and ADHD.

It is relevant to apply the ESSENCE concept of one neurodevelopmental disorder as a strong risk factor for other neurodevelopmental disorders, on children with CP. The importance of the second part of the CP definition should be emphasised and broadened to include autism and ADHD. Autism and ADHD should be regarded as two of the main associated impairments in children with CP. The focus in children with CP should not just be the "palsy" but the "cerebral" origin and impact.

FUTURE PERSPECTIVES

There is a need for further research about autism and ADHD in children with CP. We need to deepen our knowledge about the early signs and presentations, enabling earlier detection. Follow-up studies are important to learn more about effect of interventions and treatment as well as outcome in adult age.

The brain disturbance in itself is most likely the main explanation for the high prevalence of autism and ADHD. Autism and ADHD genetic causes are assumed to be as common in CP as in the general population. However, one cannot rule out that there could be common genes predisposing to CP and autism and ADHD. Furthermore, there may also be other factors, perhaps preventable at least to some extent, affecting the brain development during childhood, e.g. insufficient nutrition and lack of communication possibilities. The question if and to what extent restricted motor function may hamper the social development is also important.

Further research and development of the screening questionnaire is planned. The cut-offs especially for ADHD were too low and will have to be better adapted. There is an obvious need for a much shorter condensed questionnaire. A next step will be to try to identify the most important and decisive items. One additional important matter is if there is a need for more than one questionnaire, depending on for example GMFCS level, to have useful screening instruments.

The questionnaire administered contains much more information than used for the purpose to identify autism and ADHD. Only about half of the items (139 of 282) were included in the screening. The remaining items include information about mental health in a broader perspective, including emotional symptoms and anxiety, a field with increased awareness. The SDQ, the DBC and part of the SNAP-IV will be interesting to analyse further. At the end of the questionnaire we added two open questions about the child's main difficulty/limitation and the main resource/strength, which will be analysed with qualitative methods.

New questions have emerged during the project, especially in areas where data were insufficient for deeper analyses. Communication ability and methods ought to be subject to further in-depth studies.

Neuroimaging in children with CP is a field where our study with retrospective data gave interesting results raising new questions and interesting ideas. Further in-depth studies focusing on brain regions and networks associated with autism and ADHD are needed for better understanding, both at population level and individual level.

With research, answering one question raises more questions.

ACKNOWLEDGEMENTS

First, my great gratitude to all the children and their families participating in the project, sharing their time and narratives. I have learnt so much from you. You are the heroes.

Kate Himmelmann, my main supervisor, clinical mentor and colleague. You have the greatest pathos and devotion for children with disabilities, in particular children with cerebral palsy. Thank you for inspiring and guiding me on the way to this thesis.

Christopher Gillberg, my co-supervisor. Thank you for sharing your amazing expertise and wisdom in the field of neuropsychiatry. Your ideas and contributions have been invaluable.

Elisabet Wentz, my former co-supervisor. Thank you for your enthusiastic encouragement in the first half of the project.

All colleagues at Gillberg Neuropsychiatry Centre. Your inspiration and helpful curiosity have added more quality to this thesis. A special thanks to *Ingrid Vinsa* and *Anna Spyrou* for excellent support, always in good humour.

Agneta Rubensson, speech and language pathologist, and *Lee de Salazar*, neuropsychologist, my clinical co-workers in the assessment of the children. Your clinical experience and cooperation have been essential.

Berit Askljung, paediatric nurse and research assistant in the CP register. You always have the best in mind for the children and their parents. It is a true pleasure to work together with you, and very fun to. *Meta Nyström-Eek*, physiotherapist at the spasticity team. Through our collaboration you have taught me so much about children with cerebral palsy.

Colleagues and staff at the Regional Rehabilitation Centre for Children and Adolescents at Queen Silvia Children's Hospital. Working together for the sake of the children is so important for the families and at the same time so developing.

My teachers in paediatric neurology at Queen Silvia Children's Hospital, in particular *Ingrid Olsson*.

All my interested and encouraging friends.

My parents, *Lena* and *Bengt*. Thank you for always believing in me. You have supported me in so many ways.

My brother *Lennart* with family. I know I can always trust in you.

My wonderful daughters *Helena*, *Susanna* and *Sofia*, my son-in-law *Daniel* and my granddaughter *Liv*. You always remind me of what is important in life.

My wife *Ulrika*. Thank you for your love and patience, not least during the writing of this thesis. Thank you for sharing your life with me. You are my better half.

Giver of Life.

This thesis was financially supported by grants from the Linnea and Josef Carlsson Foundation, the Gothenburg Society of Medicine, the Foundation Sunnerdahl Disability Fund, the Torbjörn Jebner Foundation for Neuropaediatric Research, the Bertha and Felix Neubergh Memorial Foundation, the RBU Research Foundation, the Sahlgrenska University Hospital Foundations, the Queen Silvia Jubilee Foundation, the Petter Silfverskiöld Memorial Foundation, and the Swedish state under the agreement between Swedish government and the country councils, the ALF-agreement.

The CP register was additionally supported by grants from the Norrbacka-Eugenia Foundation, the AnnMari and Per Ahlqvist Foundation, the Region Västra Götaland and the Folke Bernadotte Foundation.

Gillberg Neuropsychiatry Centre received grants from the AnnMari and Per Ahlqvist Foundation and the Swedish Research Council.

REFERENCES

Albajara Sáenz A, Villemonteix T, Massat I. Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. *Developmental Medicine & Child Neurology* 2019; 61: 399-405.

American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) 1994; 4th ed. Washington, DC: APA, 1994.

American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5) 2013; 5th ed. Washington, DC: APA, 2013.

Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. *European Journal of Paediatric Neurology* 2008; 12: 4-13.

Anderson VA, Spencer-Smith MM, Coleman L, Anderson PJ, Greenham M, Jacobs R, Lee KJ, Leventer RJ. Predicting neurocognitive and behavioural outcome after early brain insult. *Developmental Medicine & Child Neurology* 2014; 56: 329-336.

Aoki Y, Yoncheva YN, Chen B, Nath T, Sharp D, Lazar M, Velasco P, Milham MP, Di Martino A. Association of white matter structure with autism spectrum disorder and attention-deficit/hyperactivity disorder. *JAMA Psychiatry* 2017; 74: 1120-1128.

Ballester-Plané J, Laporta-Hoyos O, Macaya A, Póo P, Meléndez-Plumed M, Toro-Tamargo E, Gimeno F, Narberhaus A, Segarra D, Pueyo R. Cognitive functioning in dyskinetic cerebral palsy: Its relation to motor function, communication and epilepsy. *European Journal of Paediatric Neurology* 2018; 22: 102-112.

Baranello G, Signorini S, Tinelli F, Guzzetta A, Pagliano E, Rossi A, Foscan M, Tramacere I, Romeo DMM, Ricci D; VFCS Study Group. Visual Function Classification System for children with cerebral palsy: development and validation *Developmental Medicine & Child Neurology* 2020; 62: 104-110.

Barty E, Caynes K, Johnston LM. Development and reliability of the Functional Communication Classification System for children with cerebral palsy. *Developmental Medicine & Child Neurology* 2016; 58: 1036-1041.

Beckung E, Hagberg G. Neuroimpairments, activity limitations, and participation restrictions in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2002; 44: 309-316.

Bjorgaas HM, Hysing M, Elgen I. Psychiatric disorders among children with cerebral palsy at school starting age. *Research in Developmental Disabilities* 2012; 33: 1287-1293.

Bjorgaas HM, Elgen I, Boe T, Hysing M. Mental health in children with cerebral palsy: does screening capture the complexity? *Scientific World Journal* 2013; 2013: 468402.

Bjorgaas HM, Elgen I, Ryland HK, Hysing M. Autism spectrum symptoms in children with cerebral palsy: prevalence and co-occurring conditions. *Research in Autism Spectrum Disorders* 2014; 8: 581-588.

Bjorgaas HM, Elgen IB, Hysing M. Trajectories of psychiatric disorders in a cohort of children with cerebral palsy across four years. *Disability and Health Journal* 2020 Sep 11: 100992. Epub ahead of print.

Bosenbark DD, Krivitzky L, Ichord R, Vossough A, Bhatia A, Jastrzab LE, Billinghurst L. Clinical Predictors of Attention and Executive Functioning Outcomes in Children After Perinatal Arterial Ischemic Stroke. *Pediatric Neurology* 2017; 69: 79-86.

Bottcher L, Flachs EM, Uldall P. Attentional and executive impairments in children with spastic cerebral palsy. *Developmental Medicine & Child Neurology* 2010; 52: e42-e47.

Brereton AV, Tonge BJ, Mackinnon AJ, Einfeld SL. Screening young people for autism with the developmental behavior checklist. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002; 41: 1369-1375.

Brossard-Racine M, Hall N, Majnemer A, Shevell MI, Law M, Poulin C, Rosenbaum P. Behavioural problems in school age children with cerebral palsy. *European Journal of Paediatric Neurology* 2012; 16: 35-41.

Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code for Biology and Medicine* 2008; 3: 17.

Bussing R, Fernandez M, Harwood M, Hou W, Garvan CW, Eyberg SM, Swanson JM. Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: psychometric properties and normative ratings from a school district sample. *Assessment* 2008; 15: 317-328.

Carlsson M, Hagberg G, Olsson I. Clinical and aetiological aspects of epilepsy in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2003; 45: 371-376.

Carlsson M, Olsson I, Hagberg G, Beckung E. Behaviour in children with cerebral palsy with and without epilepsy. *Developmental Medicine & Child Neurology* 2008; 50: 784-789.

Christensen D, Van Naarden Braun K, Doernberg NS, Maenner MJ, Arneson CL, Durkin MS, Benedict RE, Kirby RS, Wingate MS, Fitzgerald R, Yeargin-Allsopp M. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning - Autism and Developmental Disabilities Monitoring Network, USA, 2008. *Developmental Medicine & Child Neurology* 2014; 56: 59-65.

Coleman M, Gillberg C. The autisms. 4th ed. Oxford, UK: Oxford University Press, 2012.

Colver A; SPARCLE Group. Study protocol: SPARCLE - a multi-centre European study of the relationship of environment to participation and quality of life in children with cerebral palsy. *BMC Public Health* 2006; 6: 105.

Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. *Lancet* 2014; 383: 1240-1249.

CPUP Uppföljningsprogram för cerebral pares. [Follow-up surveillance programme for people with cerebral palsy – A national quality register in Sweden since 2005]. www.cpup.se.

Craig F, Savino R, Trabacca A. A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder. *European Journal of Paediatric Neurology* 2019; 23: 31-42.

Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Archives of Pediatrics and Adolescent Medicine* 2005; 159: 151-157.

Dahl M, Bergsten C, Hammarberg A, Sandström M, Strinnholm M. Autismspektrumtillstånd vid svår CP upptäcks ofta sent. Retrospektiv genomgång av 10 års journaler [Autism spectrum disorders in severe cerebral palsy often discovered late. Retrospective review of 10 years of medical records]. *Läkartidningen* 2014; 111: 1296-1298.

Dahlgren Sandberg A. Reading and spelling abilities in children with severe speech impairments and cerebral palsy at 6, 9, and 12 years of age in relation to cognitive development: a longitudinal study. *Developmental Medicine & Child Neurology* 2006; 48: 629-634.

Delacy MJ, Reid SM; Australian Cerebral Palsy Register Group. Profile of associated impairments at age 5 years in Australia by cerebral palsy subtype and Gross Motor Function Classification System level for birth years 1996 to 2005. *Developmental Medicine & Child Neurology* 2016; 58 *Supplement* 2: 50-56.

Delobel-Ayoub M, Klapouszczak D, van Bakel MME, Horridge K, Sigurdardottir S, Himmelmann K, Arnaud C. Prevalence and characteristics of autism spectrum disorders in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2017; 59: 738-742.

Delobel-Ayoub M, Saemundsen E, Gissler M, Ego A, Moilanen I, Ebeling H, Rafnsson V, Klapouszczak D, Thorsteinsson E, Arnaldsdóttir KM, Roge B, Arnaud C, Schendel D. Prevalence of autism spectrum disorder in 7-9-year-old children in Denmark, Finland, France and Iceland: a population-based registries approach within the ASDEU project. *Journal of Autism and Developmental Disorders* 2020; 50: 949-959.

Downs J, Blackmore AM, Epstein A, Skoss R, Langdon K, Jacoby P, Whitehouse AJO, Leonard H, Rowe PW, Glasson EJ; Cerebral Palsy Mental Health Group. The prevalence of mental health disorders and symptoms in children and adolescents with cerebral palsy: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology* 2018; 60: 30-38.

Dufresne D, Dagenais L, Shevell MI; REPACQ Consortium. Epidemiology of severe hearing impairment in a population-based cerebral palsy cohort. *Pediatric Neurology* 2014; 51: 641-644.

Ego A, Lidzba K, Brovedani P, Belmonti V, Gonzalez-Monge S, Boudia B, Ritz A, Cans C. Visual-perceptual impairment in children with cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology* 2015; 57 *Supplement* 2: 46-51.

Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *Journal of Autism and Developmental Disorders* 1999; 29: 129-141.

Einfeld SL, Tonge BJ. The Developmental Behavior Checklist: the development and validation of an instrument to assess behavioral and emotional disturbance in children and adolescents with mental retardation. *Journal of Autism and Developmental Disorders* 1995; 25: 81-104.

Eliasson AC, Krumlinde-Sundholm L, Rösblad B, Beckung E, Arner M, Ohrvall AM, Rosenbaum P. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Developmental Medicine & Child Neurology* 2006; 48: 549-554.

Elvrum AG, Beckung E, Sæther R, Lydersen S, Vik T, Himmelmann K. Bimanual capacity of children with cerebral palsy: intra- and interrater reliability of a revised edition of the bimanual fine motor function classification. *Physical & Occupational Therapy in Pediatrics* 2017; 37: 239-251.

Epstein JN, Langberg JM, Lichtenstein PK, Altaye M, Brinkman WB, House K, Stark LJ. Attention-deficit/hyperactivity dis- order outcomes for children treated in community-based pediatric settings. *Archives of Pediatrics and Adolescent Medicine* 2010; 164: 160-165.

Fiori S, Cioni G, Klingels K, Ortibus E, Van Gestel L, Rose S, Boyd RN, Feys H, Guzzetta A. Reliability of a novel, semi-quantitative scale for classification of structural brain magnetic resonance imaging in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2014; 56: 839-845.

Fluss J, Lidzba K. Cognitive and academic profiles in children with cerebral palsy: A narrative review. *Annals of Physical & Rehabilitation Medicine* 2020; S1877-0657(20)30036-1. Epub ahead of print.

Freud S. Die infantile Cerebrallähmungen. In: Nothnagel H, editor. Nothnagel's Specielle Pthologie und Therapie Wien. Hölder; 1897. [Infantile Cerebral Paralysis. University of Miami Press, Coral Gables, FL, USA; 1968].

Gabis LV, Tsubary NM, Leon O, Ashkenasi A, Shefer S. Assessment of abilities and comorbidities in children with cerebral palsy. *Journal of Child Neurology* 2015; 30: 1640-1645.

Galea C, Mcintyre S, Smithers-Sheedy H, Reid SM, Gibson C, Delacy M, Watson L, Goldsmith S, Badawi N, Blair E; Australian Cerebral Palsy Register Group. Cerebral palsy trends in Australia (1995-2009): a population-based observational study. *Developmental Medicine & Child Neurology* 2019; 61: 186-193.

Gargaro BA, May T, Tonge BJ, Sheppard DM, Bradshaw JL, Rinehart NJ. Using the DBC-P Hyperactivity Index to screen for ADHD in young people with autism and ADHD: a pilot study. *Research in Autism Spectrum Disorders* 2014; 8: 1008-1015.

Gillberg C. The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. *Research in Developmental Disabilities* 2010; 31: 1543-1551.

Goodman R, Graham P. Psychiatric problems in children with hemiplegia: cross sectional epidemiological survey. *BMJ* 1996; 312: 1065-1069.

Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *The Journal of Child Psychology and Psychiatry* 1999; 40: 791-799.

Gotham K, Risi S, Pickles A, Lord C. The Autism Diagnostic Observation Schedule: revised algorithms for improved diagnostic validity. *Journal of Autism and Developmental Disorders* 2007; 37: 613-627.

Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, Ådén U, Farooqi A, Thorngren-Jerneck K, Strömberg B. Cerebral palsy in extremely preterm infants. *Pediatrics* 2018; 141: e20171433.

Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. I. Analysis of the general changes. *Acta Paediatrica Scandinavica* 1975; 64: 187-192.

Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden. IV. Epidemiological trends 1959-78. *Acta Paediatrica Scandinavica* 1984; 73: 433-440.

Hagberg B, Hagberg G, Olow I, von Wendt L. The changing panorama of cerebral palsy in Sweden. V. The birth year period 1979-82. *Acta Paediatrica Scandinavica* 1989; 78: 283-290.

Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden. VI. Prevalence and origin during the birth year period 1983-1986. *Acta Paediatrica* 1993; 82: 387-393.

Hagberg B, Hagberg G, Olow I, von Wendt L. The changing panorama of cerebral palsy in Sweden. VII. Prevalence and origin in the birth year period 1987-90. *Acta Paediatrica* 1996; 85: 954-960.

Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. *Acta Paediatrica* 2001; 90: 271-277.

Hagberg G, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. II. Analysis of the various syndromes. *Acta Paediatrica Scandinavica* 1975; 64: 193-200.

Hagberg G, Hagberg B, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. III. The importance of foetal deprivation of supply. *Acta Paediatrica Scandinavica* 1976; 65: 403-408.

Heiervang E, Stormark KM, Lundervold AJ, Heimann M, Goodman R, Posserud MB, Ullebø AK, Plessen KJ, Bjelland I, Lie SA, Gillberg C. Psychiatric disorders in Norwegian 8- to 10-year-olds: an epidemiological survey of prevalence, risk factors, and service use. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007; 46: 438-447.

Hidecker MJ, Paneth N, Rosenbaum PL, Kent RD, Lillie J, Eulenberg JB, Chester K Jr, Johnson B, Michalsen L, Evatt M, Taylor K. Developing and validating the Communication Function Classification System for individuals with cerebral palsy. *Developmental Medicine & Child Neurology* 2011; 53: 704-710.

Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatrica* 2005; 94: 287-294.

Himmelmann K, Beckung E, Hagberg G, Uvebrant P. Gross and fine motor function and accompanying impairments in cerebral palsy. *Developmental Medicine & Child Neurology* 2006; 48: 417-423.

Himmelmann K, Hagberg G, Uvebrant P. The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999–2002. *Acta Paediatrica* 2010; 99: 1337-1343.

Himmelmann K, Uvebrant P. Function and neuroimaging in cerebral palsy: a population-based study. *Developmental Medicine & Child Neurology* 2011; 53: 516-521.

Himmelmann K, Lindh K, Hidecker MJ. Communication ability in cerebral palsy: a study from the CP register of western Sweden. *European Journal of Paediatric Neurology* 2013; 17: 568-574.

Himmelmann K, Uvebrant P. The panorama of cerebral palsy in Sweden. XI. Changing patterns in the birth-year period 2003–2006. *Acta Paediatrica* 2014; 103: 618-624.

Himmelmann K, Horber V, De La Cruz J, Horridge K, Mejaski-Bosnjak V, Hollody K, Krägeloh-Mann I; SCPE Working Group. MRI classification system (MRICS) for children with cerebral palsy: development, reliability, and recommendations. *Developmental Medicine & Child Neurology* 2017; 59: 57-64.

Himmelmann K, Uvebrant P. The panorama of cerebral palsy in Sweden part XII shows that patterns changed in the birth years 2007-2010. *Acta Paediatrica* 2018; 107: 462-468.

Hirschberger RG, Kuban KCK, O'Shea TM, Joseph RM, Heeren T, Douglass LM, Stafstrom CE, Jara H, Frazier JA, Hirtz D, Rollins JV, Paneth N; ELGAN Study Investigators. Co-occurrence and severity of neurodevelopmental burden (cognitive impairment, cerebral palsy, autism spectrum disorder, and epilepsy) at age ten years in children born extremely preterm. *Pediatric Neurology* 2018; 79: 45-52.

Hollung SJ, Bakken IJ, Vik T, Lydersen S, Wiik R, Aaberg KM, Andersen GL. Comorbidities in cerebral palsy: a patient registry study. *Developmental Medicine & Child Neurology* 2020; 62: 97-103.

Horber V, Sellier E, Horridge K, Rackauskaite G, Andersen GL, Virella D, Ortibus E, Dakovic I, Hensey O, Radsel A, Papavasiliou A, Cruz De la J, Arnaud C, Krägeloh-Mann I, Himmelmann K. The origin of the cerebral palsies: contribution of population-based neuroimaging data. *Neuropediatrics* 2020; 51: 113-119.

Horber V, Fares A, Platt MJ, Arnaud C, Krägeloh-Mann I, Sellier E. Severity of cerebral palsy - the impact of associated impairments. *Neuropediatrics* 2020; 51: 120-128.

Kavcic A, Vodusek DB. A historical perspective on cerebral palsy as a concept and a diagnosis. *European Journal of Neurology* 2005; 12: 582-587.

Khandaker G, Smithers-Sheedy H, Islam J, Alam M, Jung J, Novak I, Booy R, Jones C, Badawi N, Muhit M. Bangladesh Cerebral Palsy Register (BCPR): a pilot study to develop a national cerebral palsy (CP) register with surveillance of children for CP. *BMC Neurology* 2015; 15: 173.

Kilincaslan A, Mukaddes NM. Pervasive developmental disorders in individuals with cerebral palsy. *Developmental Medicine & Child Neurology* 2009; 51: 289-294.

Kirby RS, Wingate MS, Van Naarden Braun K, Doernberg NS, Arneson CL, Benedict RE, Mulvihill B, Durkin MS, Fitzgerald RT, Maenner MJ, Patz JA, Yeargin-Allsopp M. Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. *Research in Developmental Disabilities* 2011; 32: 462-469.

Kobayashi S, Wakusawa K, Inui T, Tanaka S, Kobayashi Y, Onuma A, Haginoya K. The neurological outcomes of cerebellar injury in premature infants. *Brain & Development* 2015; 37: 858-863.

Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, Perrin JM, Shattuck P, Kuhlthau KA, Harwood RL, Lu MC. The prevalence of parent-reported autism spectrum disorder among US children. *Pediatrics* 2018; 142: e20174161.

Kopp S, Gillberg C. The Autism Spectrum Screening Questionnaire (ASSQ)-Revised Extended Version (ASSQ-REV): an instrument for better capturing the autism phenotype in girls? A preliminary study involving 191 clinical cases and community controls. *Research in Developmental Disabilities* 2011; 32: 2875-2888.

Kristoffersson E, Dahlgren Sandberg A, Holck P. Communication ability and communication methods in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2020; 62: 933-938.

Krug DA, Arick J, Almond P. Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *The Journal of Child Psychology and Psychiatry* 1980; 21: 221-229.

Krägeloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology* 2007; 49: 144-151.

Krägeloh-Mann I, Lidzba K, Pavlova MA, Wilke M, Staudt M. Plasticity during Early Brain Development Is Determined by Ontogenetic Potential. *Neuropediatrics* 2017; 48: 66-71.

Larsson J. eulerr: Area-Proportional Euler and Venn Diagrams with Ellipses. R package version 6.1.0, 2020. https://cran.r-project.org/package=eulerr.

Little WJ. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities. *Transactions Obstetric Society of London* 1862; 3: 293-344.

Lundström S, Reichenberg A, Anckarsäter H, Lichtenstein P, Gillberg C. Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *BMJ* 2015; 350: h1961.

MacLennan AH, Lewis S, Moreno-De-Luca A, Fahey M, Leventer RJ, McIntyre S, Ben-Pazi H, Corbett M, Wang X, Baynam G, Fehlings D, Kurian MA, Zhu C, Himmelmann K, Smithers-Sheedy H, Wilson Y, Ocaña CS, van Eyk C, Badawi N, Wintle RF, Jacobsson B, Amor DJ, Mallard C, Pérez-Jurado LA, Hallman M, Rosenbaum PJ, Kruer MC, Gecz J. Genetic or other causation should not change the clinical diagnosis of cerebral palsy. *Journal of Child Neurology* 2019; 34: 472-476.

May T, Brignell A, Williams K. Autism spectrum disorder prevalence in children aged 12-13 years from the longitudinal study of Australian children. *Autism Research* 2020; 13: 821-827.

McDermott S, Coker AL, Mani S, Krishnaswami S, Nagle RJ, Barnett-Queen LL, Wuori DF. A population-based analysis of behavior problems in children with cerebral palsy. *Journal of Pediatric Psychology* 1996; 21: 447-463.

McMichael G, Bainbridge MN, Haan E, Corbett M, Gardner A, Thompson S, van Bon BW, van Eyk CL, Broadbent J, Reynolds C, O'Callaghan ME, Nguyen LS, Adelson DL, Russo R, Jhangiani S, Doddapaneni H, Muzny DM, Gibbs RA, Gecz J, MacLennan AH. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. *Molecular Psychiatry* 2015; 20: 176-182.

McNutt SJ. Double Infantile Spastic Hemiplegia. *The Journal of Nervous and Mental Disease* 1885; 12: 225-228.

Miller ML, Fee VE, Netterville AK. Psychometric properties of ADHD rating scales among children with mental retardation I: reliability. *Research in Developmental Disabilities* 2004; 25: 459-476.

Mizuno Y, Kagitani-Shimono K, Jung M, Makita K, Takiguchi S, Fujisawa TX, Tachibana M, Nakanishi M, Mohri I, Taniike M, Tomoda A. Structural brain abnormalities in children and adolescents with comorbid autism spectrum disorder and attention-deficit/hyperactivity disorder. *Translational Psychiatry* 2019; 9: 332.

Montagna A, Karolis V, Batalle D, Counsell S, Rutherford M, Arulkumaran S, Happe F, Edwards D, Nosarti C. ADHD symptoms and their neurodevelopmental correlates in children born very preterm. *PLoS One* 2020; 15: e0224343.

Nordberg A, Miniscalco C, Lohmander A, Himmelmann K. Speech problems affect more than one in two children with cerebral palsy: Swedish population-based study. *Acta Paediatrica* 2013; 102: 161-166.

Nordin V, Gillberg C. Autism spectrum disorders in children with physical or mental disability or both. I: Clinical and epidemiological aspects. *Developmental Medicine & Child Neurology* 1996; 38: 297-313.

Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics* 2012; 130: e1285-e1312.

Nygren G, Hagberg B, Billstedt E, Skoglund A, Gillberg C, Johansson M. The Swedish version of the Diagnostic Interview for Social and Communication Disorders (DISCO-10). Psychometric properties. *Journal of Autism and Developmental Disorders* 2009; 39: 730-741.

Nygren G, Cederlund M, Sandberg E, Gillstedt F, Arvidsson T, Carina Gillberg I, Westman Andersson G, Gillberg C. The prevalence of autism spectrum disorders in toddlers: a population study of 2-year-old Swedish children. *Journal of Autism and Developmental Disorders* 2012; 42: 1491-1497.

Osler W. The cerebral palsies of childhood: a clinical study from the infirmary for nervous diseases. Philadelphia: Blakiston P; 1889.

Oxelgren UW, Myrelid Å, Annerén G, Ekstam B, Göransson C, Holmbom A, Isaksson A, Åberg M, Gustafsson J, Fernell E. Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. *Developmental Medicine & Child Neurology* 2017; 59: 276-283.

Pagnozzi AM, Conti E, Calderoni S, Fripp J, Rose SE. A systematic review of structural MRI biomarkers in autism spectrum disorder: A machine learning perspective. *International Journal of Developmental Neuroscience* 2018; 71: 68-82.

Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology* 1997; 39: 214-223.

Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. *Developmental Medicine & Child Neurology* 2008; 50: 744-750.

Panteliadis C, Panteliadis P, Vassilyadi F. Hallmarks in the history of cerebral palsy: From antiquity to mid-20th century. *Brain & Development* 2013; 35: 285-292.

Parkes J, White-Koning M, Dickinson HO, Thyen U, Arnaud C, Beckung E, Fauconnier J, Marcelli M, McManus V, Michelsen SI, Parkinson K, Colver A. Psychological problems in children with cerebral palsy: a cross-sectional European study. *The Journal of Child Psychology and Psychiatry* 2008; 49: 405-413.

Pavlova MA, Krägeloh-Mann I. Limitations on the developing preterm brain: impact of periventricular white matter lesions on brain connectivity and cognition. *Brain* 2013; 136: 998-1011.

Pennington L, Virella D, Mjøen T, da Graça Andrada M, Murray J, Colver A, Himmelmann K, Rackauskaite G, Greitane A, Prasauskiene A, Andersen G, de la Cruz J. Development of The Viking Speech Scale to classify the speech of children with cerebral palsy. *Research in Developmental Disabilities* 2013; 34: 3202-3210.

Posserud MB, Lundervold AJ, Gillberg C. Autistic features in a total population of 7–9-year-old children assessed by the ASSQ (Autism Spectrum Screening Questionnaire). *The Journal of Child Psychology and Psychiatry* 2006; 47: 167-175.

R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2019. https://www.R-project.org/.

Rackauskaite G, Bilenberg N, Bech BH, Uldall P, Østergaard JR. Screening for psychopathology in a national cohort of 8- to 15-year-old children with cerebral palsy. *Research in Developmental Disabilities* 2016; 49-50: 171-180.

Rackauskaite G, Bilenberg N, Uldall P, Bech BH, Østergaard J. Prevalence of mental disorders in children and adolescents with cerebral palsy: Danish nationwide follow-up study. *European Journal of Paediatric Neurology* 2020; 27: 98-103.

Regionalt vårdprogram Cerebral pares hos barn och ungdom. [Regional medical program Cerebral palsy in children and adolescents]. Stockholms läns landsting 2014.

Reid SM, Meehan EM, Arnup SJ, Reddihough DS. Intellectual disability in cerebral palsy: a population-based retrospective study. *Developmental Medicine & Child Neurology* 2018; 60: 687-694.

Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, Gillberg C, Scott RC, Neville BG. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics* 2014; 133: 1586-1593.

Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson B. A report: The definition and classification of cerebral palsy April 2006. *Developmental Medicine & Child Neurology Supplement* 2007; 109: 8-14. Erratum in: *Developmental Medicine & Child Neurology* 2007; 49: 480.

Rosenbaum PL, Palisano RJ, Bartlett DJ, Galuppi BE, Russell DJ. Development of the Gross Motor Function Classification System for cerebral palsy. *Developmental Medicine & Child Neurology* 2008; 50: 249-253.

Rydell M, Lundström S, Gillberg C, Lichtenstein P, Larsson H. Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample. *The Journal of Child Psychology and Psychiatry* 2018; 59: 863-871.

Sarovic D, Hadjikhani N, Schneiderman J, Lundström S, Gillberg C. Autism classified by magnetic resonance imaging: a pilot study of a potential diagnostic tool. International *Journal of Methods in Psychiatric Research* 2020; 18: e1846. Epub ahead of print.

Schenker R, Coster WJ, Parush S. Neuroimpairments, activity performance, and participation in children with cerebral palsy mainstreamed in elementary schools. *Developmental Medicine & Child Neurology* 2005; 47: 808-814.

Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *Journal of Autism and Developmental Disorders* 1980; 10: 91-103.

Sellers D, Mandy A, Pennington L, Hankins M, Morris C. Development and reliability of a system to classify the eating and drinking ability of people with cerebral palsy. *Developmental Medicine & Child Neurology* 2014; 56: 245-251.

Sellier E, Uldall P, Calado E, Sigurdardottir S, Torrioli MG, Platt MJ, Cans C. Epilepsy and cerebral palsy: characteristics and trends in children born in 1976-1998. *European Journal of Paediatric Neurology* 2012; 16: 48-55.

Sellier E, Platt MJ, Andersen GL, Krägeloh-Mann I, De La Cruz J, Cans C; Surveillance of Cerebral Palsy Network. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. *Developmental Medicine & Child Neurology* 2016; 58: 85-92.

Shank LK, Kaufman J, Leffard S, Warschausky S. Inspection time and attention-deficit/hyperactivity disorder symptoms in children with cerebral palsy. *Rehabilitation Psychology* 2010; 55: 188-193.

Shevell MI, Dagenais L, Hall N; REPACQ Consortium. Comorbidities in cerebral palsy and their relationship to neurologic subtype and GMFCS level. *Neurology* 2009; 72: 2090-2096.

Sigurdardottir S, Thorkelsson T, Halldorsdottir M, Thorarensen O, Vik T. Trends in prevalence and characteristics of cerebral palsy among Icelandic children born 1990 to 2003. *Developmental Medicine & Child Neurology* 2009; 51: 356-363.

Sigurdardottir S, Indredavik MS, Eiriksdottir A, Einarsdottir K, Gudmundsson HS, Vik T. Behavioural and emotional symptoms of preschool children with cerebral palsy: a population-based study. *Developmental Medicine & Child Neurology* 2010; 52: 1056-1061.

Sigurdardottir S, Vik T. Speech, expressive language, and verbal cognition of preschool children with cerebral palsy in Iceland. *Developmental Medicine & Child Neurology* 2011; 53: 74-80.

Smile S, Dupuis A, MacArthur C, Roberts W, Fehlings D. Autism spectrum disorder phenotype in children with ambulatory cerebral palsy: A descriptive cross-sectional study. *Research in Autism Spectrum Disorders* 2013; 7: 391-397.

Smits DW, Ketelaar M, Gorter JW, van Schie PE, Becher JG, Lindeman E, Jongmans MJ. Development of non-verbal intellectual capacity in school-age children with cerebral palsy. *Journal of Intellectual Disabilities Research* 2011; 55: 550-562.

Sparrow SS, Cicchetti DV, Balla DA. Vineland Adaptive Behavior Scales, Second edition (Vineland-II). Circle Pines, MN: American Guidance Service, 2005.

Spencer-Smith M, Anderson P, Jacobs R, Coleman L, Long B, Anderson V. Does timing of brain lesion have an impact on children's attention? *Developmental Neuropsychology* 2011; 36: 353-366.

Stadskleiv K, Jahnsen R, Andersen GL, von Tetzchner S. Neuropsychological profiles of children with cerebral palsy. *Developmental Neurorehabilitation* 2018; 21: 108-120.

Stadskleiv K. Cognitive functioning in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2020; 62: 283-289.

Stanley F, Blair E, Alberman E. Cerebral palsies: epidemiology & causal pathways. London, UK: Mac Keith Press, 2000.

Steffenburg S, Steffenburg U, Gillberg C. Autism spectrum disorders in children with active epilepsy and learning disability: comorbidity, pre- and perinatal background, and seizure characteristics. *Developmental Medicine & Child Neurology* 2003; 45: 724-730.

Stigler KA, McDonald BC, Anand A, Saykin AJ, McDougle CJ. Structural and functional magnetic resonance imaging of autism spectrum disorders. *Brain Research* 2011; 22: 146-161.

Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Developmental Medicine & Child Neurology* 2000; 42: 816-824.

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child & Adolescent Psychiatry* 2001; 40: 168-179.

Thurm A, Farmer C, Salzman E, Lord C, Bishop S. State of the field: differentiating intellectual disability from autism spectrum disorder. *Frontiers in Psychiatry* 2019; 10: 526.

Tsubouchi Y, Tanabe A, Saito Y, Noma H, Maegaki Y. Long-term prognosis of epilepsy in patients with cerebral palsy. *Developmental Medicine & Child Neurology* 2019; 61: 1067-1073.

Ullebø AK, Posserud MB, Heiervang E, Obel C, Gillberg C. Prevalence of the ADHD phenotype in 7- to 9-year-old children: effects of informant, gender and non-participation. *Social Psychiatry and Psychiatric Epidemiology* 2012; 47: 763-769.

Weber P, Bolli P, Heimgartner N, Merlo P, Zehnder T, Kätterer C. Behavioral and emotional problems in children and adults with cerebral palsy. *European Journal of Paediatric Neurology* 2016; 20: 270-274.

Wechsler D. Wechsler Intelligence Scale for Children, 4th edition, San Antonio, TX, Psychological Corporation, 2003.

Weir FW, Hatch JL, McRackan TR, Wallace SA, Meyer TA. Hearing loss in pediatric patients with cerebral palsy. *Otology & Neurotology* 2018; 39: 59-64.

Whitney DG, Warschausky SA, Peterson MD. Mental health disorders and physical risk factors in children with cerebral palsy: a cross-sectional study. *Developmental Medicine & Child Neurology* 2019; 61: 579-585.

Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M. The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use. *The Journal of Child Psychology and Psychiatry* 2002; 43: 307-325.

World Health Organization (WHO) International classification of diseases and health related problems (ICD-10), 10th ed Genève, Switzerland, 2007.

Åhsgren I, Baldwin I, Goetzinger-Falk C, Eriksson A, Flodmark O, Gillberg C. Ataxia, autism, and the cerebellum: a clinical study of 32 individuals with congenital ataxia. *Developmental Medicine & Child Neurology* 2005; 47: 193-198.

APPENDIX

The questionnaire (Frågeformulär) in Swedish.