Antecedents of Cerebral Palsy in children born at term

according to subtype, motor severity and accompanying impairments

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”There is no easy walk to freedom anywhere, and many of us will have to pass through the valley of the shadow of death again and again before we reach the mountaintop of our desires.”

— Nelson Mandela

ABSTRACT

Aims: To explore antecedents of cerebral palsy (CP) according to subtype, severity of motor impairment and accompanying impairments (epilepsy and/or cognitive impairments) in relation to neuroimaging patterns.

Material and methods: Case control studies were performed in a population-based serie of children with CP born at term (n=309), matched with a control group (n=618). The cases and the matched controls were divided into CP subtype; spastic hemiplegia, spastic diplegia or tetraplegia and dyskinetic CP and into severity of motor impairment; mild, moderate or severe. Obstetric records and the CP register of western Sweden were reviewed and 88 antecedents to CP were analyzed for their associations to different subtypes, severity of motor impairment, associated impairments in CP as well as to neuroimaging pattern. Binary logistic regression, the Cochran-Armitage Chi-squared test for trends, interaction analyses and interrelationship analyses were used. Both univariable and adjusted analyzes were performed.

Results: Paper I: The antecedent pattern differed by CP subtype. All subtypes shared a mix of prepartal, intrapartal and postpartal antecedents, except for dyskinetic CP, for which intra- and postpartal events played a major role. Paper II: Maternal infections were associated only with the subgroup spastic hemiplegia whereas neonatal infection was associated with the subgroups of spastic diplegia or tetraplegia. Paper III: The antecedent pattern differed by severity of motor impairment in CP. Timing of antecedents corresponded to identified neuroimaging patterns. Paper IV: The accompanying impairments epilepsy and cognitive impairment in CP were associated with poor intrauterine growth, maldevelopment, and neonatal infections. Accompanying impairments in CP are more often associated with abnormal neuroimaging than motor impairment alone.

Conclusions: The antecedent pattern differed by CP subtype, severity of motor impairment and by presence of accompanying impairments in CP. Our results might illustrate some of the causal pathways to CP, namely hypoxia, malformations and infection.

Keywords: cerebral palsy, spastic hemiplegia, spastic diplegia, spastic tetraplegia, dyskinetic, motor impairment, motor function, accompanying impairments, epilspsy, cognitive impairment, antecedents, risk factors

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SAMMANFATTNING PÅ SVENSKA

CP drabbar ungefär två barn per 1000 levande födda och är det vanligaste motoriska funktionsnedsättningen hos barn. CP är ett samlingsnamn för en grupp av tillstånd där kroppens rörelser, balans och kroppshållning är påverkad. Cirka 50 % av barn med CP har även andra funktionsnedsättningar såsom intellektuell funktionsnedsättning och epilepsi. CP klassificeras baserat på dominerande neurologiska symtom och delas in i olika subtyper; spastisk, dyskinetisk och ataktisk typ. Ett annat sätt att klassificera är efter motorisk svårighetsgrad.

Avhandlingen syftade till att ge svar på följande frågeställningar:
I Vilka föregående händelser är förknippade med de olika subtyperna av CP?
II Är infektioner under graviditet och förlossning associerade med en ökad risk för CP? Ser associationsmönstren olika ut för de olika subtyperna av CP?
III Skiljer sig associationsmönstren och hjärnavbildningsmönstren åt för de olika svårighetsgraderna av CP?
IV Vilka antecedenter och hjärnavbildningsmönster är förknippade med utvecklingen av CP med samtidigt förekommande epilepsi och intellektuell funktionsnedsättning?

Populationsbaserade fall-kontrollstudier genomfördes med barn födda i fullgången tid mellan år 1983-1994. Sammanlagt studerades 309 barn med CP samt 618 kontroller. Kontrollerna matchades för kön, förlossningsklinik, graviditetslängd och flerbörd. 88 variabler från varje förlossningsjournal, inkluderande moderns egenskaper, faktorer under graviditeten, faktorer under förlossningen samt under de närmaste dagarna efter förlossningen dokumenterades.

Vi ser att associationsmönstret skiljer sig åt mellan de olika typerna och svårighetsgraderna av CP samt för dem som har epilepsi och intellektuell funktionsnedsättning i tillägg till det motoriska funktionshindret. Mönstren av associationer för de olika typerna och svårighetsgraderna visar också på möjliga mekanismer för, samt olika tidpunkter för, hur och när skadan kan ha uppkommit. Fynden bekräftades av resultaten ifrån bilddiagnostik av hjärnan. Studierna indikerar tre olika möjliga gemensamma vägar till cerebral pares, hypoxi (syrebrist hos barnet), infektion och missbildning.

LIST OF PAPERS

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

I. Ahlin K, Himmelmann K, Hagberg G, Kacerovsky M, Cobo T, Wennerholm UB, Jacobsson B. Non-infectious risk factors for different types of cerebral palsy in term-born babies: a population-based, case-control study. BJOG. 2013;120:724-731.

II. Ahlin K, Himmelmann K, Hagberg G, Kacerovsky M, Cobo T, Wennerholm, UB, Jacobsson B. Cerebral palsy and perinatal infection in children born at term. Obstet Gynecol. 2013;122:41-9.

III. Ahlin K, Himmelmann K, Nilsson S, Sengpiel V, Jacobsson B. Antecedents of cerebral palsy according to severity of motor impairment. Accepted for publication in Acta Obstet Gynecol Scand.

IV. Ahlin K, Jacobsson B, Nilsson S, Himmelmann K. Antecedents and neuroimaging patterns in cerebral palsy with accompanying impairments: a population-based study in children born at term. Submitted.

CONTENT

ABBREVIATIONS

BMI	Body Mass Index
CNS	Central Nervous System
CP	Cerebral Palsy
CT	Computed Tomograph
GMFCS	Gross Motor Function Classification System
IQ	Intelligence Quotient
LGA	Large for Gestational Age
MMR	Mild cognitive impairment (Mental Retardation)
MRI	Magnetic Resonance Imaging
NE	Neonatal Encephalopathy
SGA	Small for Gestational Age
SMR	Severe cognitive impairment (Mental Retardation)
WMI	White-Matter Injury

DEFINITIONS IN SHORT

Aetiology	The cause or origin.
Antecedents	One that precedes another. A preceding occurrence or event.
Apgar score	A method, introduced by Virginia Apgar, of assessing the condition of new-born babies. Appearance (colour); Pulse (heart rate), Grimace (response to suction), Activity (tone), and Respiration are assessed usually at one minute, five minutes and if low at ten minutes after birth.
Association	Denotes that the probability of the occurrence of one factor varies with the occurrence of a second factor.
Ataxia	Loss of orderly muscular coordination. Movement with abnormal force, rhytm and accuracy.
Bias	Deviation of results or inferences from the truth, or any factor or process that causes such a deviation.
Causal pathways	A causal pathway is a sequence of events or conditions culminating in the outcome or disease in interest, in which the effect of any step is dependent on the presence of other steps.

Cerebral palsy	CP was diagnosed according to the definition by Mutch et al. as a group of non-progressive, but often changing, motor impairment syndromes that are secondary to lesions or abnormalities of the brain arising in the early stages of development.
Developmental plasticity	Changes in neural connections during development as a result of environmental interactions as well as neural changes induced by learning.
Dyskinesia	Involuntary, uncontrolled, recurring occasionally stereotyped movements. Primitive reflexe patterns predominate, muscle tone is varying
Interaction	A situation where two or more factors modify their separate effect on a given outcome.
Intrapartal	Occurring during childbirth.
Lesion	Any abnormality in the tissue of an organism usually caused by disease or trauma.
MMR	Mild cognitive impairment was defined as an IQ between 50 and 69.
Pathogenesis	The pathogenesis of a disease is the mechanism that causes the disease. The term can also describe the origin and development of the disease.
Perinatal	Pertaining to the period immediately before and after birth.

Periventricular	Periventricular means around the ventricle.
Postpartal	Occurring after childbirth.
Prepartal	Starts before childbirth.
Risk	The probability of occurrence of an outcome.
Risk factor	A factor associated with the outcome of interest. It does not necessarily imply that the association is causal.
SMR	Severe cognitive impairment was defined as an IQ below 50.
Spastic/spacticity	Velocity-dependent increase in muscle tone or hypertonia usually associated with increased reflexes.
Term birth	Birth occurring between 37 weeks and 0 days and 41 weeks and 6 days.
Trimester	A period of three months or about three months. A pregnancy comprises first, second and third trimester.
Type I error	A type I error is detecting an effect that is not present (a "false positive").
Type II error	A type II error is failing to detect an effect that is present (a "false negative").

1 INTRODUCTION

Cerebral palsy (CP), first described by William Little in the 1840s (1), is a group of disorders that affects a person's ability to voluntary movement and posture. The condition is caused by damage to the developing brain sometime before birth, during birth, or after birth (2). Symptoms varies widely depending on the area of the CNS compromised (3).

Simply stated, “cerebral” refers to the brain, and “palsy” refers to muscle weakness and poor control. Although the brain injury itself is stationary, the symtoms of CP may change over time due to growth, developmental plasticity and maturation of the CNS (2).

CP is the commonest cause of physical disability in childhood and a life-long disability with need for services (4-6). Term-born children account for 50 to 65 % of children with CP, and they tend to be more severely impaired than children with CP born preterm (7).

Although the brain injury resulting in CP may have occured during gestation, the problems with control of movement and posture may not be noticed until a child’s motor abilities develop to the extent to identify the condition. Moreover, due to developmental plasticity, initial symtoms may disappear. Thus, many children with CP are not diagnosed until the child is 3-4 years of age (8).

Today, there is no cure for CP, but treatment, therapy, medications, special equipment, and, in some cases, surgery can help a child who is living with the condition. By taking advantage of these treatments, people with CP can improve their function, minimize risk of secondary complications and optimize life expectancy and the quality of life (2, 9).

1.1 Definition

CP is primarily a disorder of voluntary movement and co-ordination. However, it has always been a challenge to define ‘cerebral palsy’, because the term cerebral palsy comprises a collection of syndromes which vary by type, severity, aetiology and pathology (10).

A classic and commonly cited definition of CP was proposed by Bax 1964 (11) who described it as “a disorder of movement and posture due to a defect or lesion of the immature brain”.

In 1992, because of the heterogeneity of disorders covered by the term CP, as well as progress in understanding of development in infants with early brain damage, an international meeting of experts in the field of CP was held to modify the definition of CP. The new definition, reported by Mutch et al (12) read; CP is "an umbrella term covering a group of non-progressive but often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development". This definition continued to emphasize the motor impairment and acknowledged its variability, it also excluded progressive disease. The definition by Mutch et al was the definition used in the western Sweden CP project and in the western Sweden CP register during the birth year cohorts studied (12).

The most recent definition of CP is that by Rosenbaum et al., emphasizing that the motor disorder often is accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder (13, 14).

1.2 Prevalence

CP is the commonest physical disability in childhood, occurring in 2.0 to 2.5 per 1000 live births (4-6).

The fetal and infant mortality declined across the Western world during the last forty to fifty years (15). Socio-economic factors as well as advances in medical technology including the development of neonatal intensive care have been described as causes of this decline (16). It was assumed that the nature and timing of events leading to prepartal and intrapartal death were the same as those involved in CP. Therefore, with a decline in fetal and infant mortality death rates, it was expected that rates of CP would make a concomitant decrease (17). Prevalence rates of CP were used as outcome measures of obstetric practice and neonatal care (18, 19). However, the prevalence of CP remained relatively stable (4, 5, 20, 21).

What did change markedly during this time was the contribution made by different gestational-age groups. The proportion of preterm born infants increased (22-25). Increases in the prevalence of CP in the 1970s and 1980s was partly due to the increasing survival of extremely premature born infants that occurred without a concurrent improvement of neurological outcome. Figures from multiple population samples now show that this trend was reversed in the mid to late 1990s. Similar changes was seen in infants born at term (25).

According to the western CP register of western Sweden, a reduction in the prevalence of total CP observed since the 1980s stalled in the birth-year period from 1999 to 2002 (1). There was an increase in children born full-term, while the prevalence of children born preterm continued to decrease. The overall prevalence of CP in western Sweden remained unchanged during the birth years 2003-2006. However, the distribution of CP types changed and children with CP were born extremely premature, ie born before 28 weeks increased (26).

There is now a general consensus among epidemiologists and clinicians that there are probably many causal pathways that lead to the development of CP (2). Moreover, the mechanisms and timing of events leading to CP in children born at term infants are thought to be different from those that lead to CP in preterm born infants (2).

1.3 Classification

Because the clinical picture of CP can be very different in type, severity and distribution (2), clinicians have tried to develop ways of describing the individual child's symptoms for easier communication among health professionals and to ensure consistency when reporting the various clinical and functional presentations (5, 13, 27). The ability to group together people with similar clinical subtypes of CP is also essential in order to conduct large-scale, multicenter investigations into the epidemiology of CP and its prevention and treatment (5, 28).

Traditionally, CP has been classified by the neurologic symptom (subtypes), the areas of the body that are affected (distribution), and the severity of the impairment (mild, moderate and severe) (13).

A widely used classification system was described by Hagberg et al in 1975 (29), commonly referred to as the 'Swedish classification'. Hagberg and colleagues outlined three main syndromes, or CP subtypes - spastic, ataxic and dyskinetic.

The Surveillance of CP in Europe (SCPE), a network of CP research and registers has provided a harmonized of classification of CP that is widely accepted (5).

1.3.1 Subtypes

All CP subtypes have in common an abnormal pattern of movement and posture. The following descriptions are based on the predominant patterns of disability observed in populations of people with CP (5).

Spastic CP or spasticity refers to increased muscle tone and increased reflexes that are evident through observation or examination or both.
The Swedish classification further divides the spastic forms of CP, according to the extremities involved, into spastic hemiplegia, diplegia and tetraplegia (29, 30).

Hemiplegia refers to individuals where one side of the body is affected.

Diplegia refers to involvement predominantly of the legs although children with diplegia always have involvement in the arms to a lesser extent.

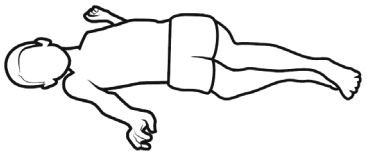
Tetraplegia refers to individuals where all four limbs are affected. Tetraplegia is the most severe of the three anatomically divided subgroups.

Illustrations by: Jan Funke

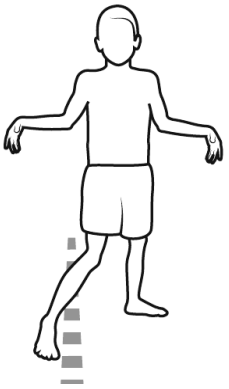
The SCPE classification divides spastic CP into bilateral and unilateral spastic CP (5).

Spastic bilateral CP is diagnosed if limbs on both sides of the body are involved.

Spastic unilateral CP is diagnosed if limbs on one side of the body are involved.



Dyskinetic CP or dyskinesia is characterized by involuntary, uncontrolled, recurring occasionally stereotyped movements. Muscle tone is fluctuating and persistent primitive reflex patterns predominate. Dyskinetic CP is divided into two subgroups; Dystonic CP and Choreo-athetotic CP. Dystonic CP is dominated by abnormal postures and incrased tone. Involuntary movements, distorted voluntary movements and abnormal postures due to sustained muscle contractions are characteristic. Choreo-athetotic CP is dominated by hyperkinesias and fluctuating, but mainly decreased tone. Chorea means rapid involuntary, jerky, often fragmented movements. Athetosis means slower, constantly changing, writhing or contorting movements. Both types of dyskinesia may occur in the same child (30).



Ataxic CP or ataxia refers to disordered movements characterised by loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy. Typical features are trunk and gait ataxia, resulting in disturbed balance and past pointing, resulting in over- or undershooting of goal directed movements. Tremor is another common sign as well as low tone (30).

Many children have mixed presentations. It is recommended that classification is made by the dominant type of tone or movement abnormality (13).

Illustrations by: Jan Funke

1.3.2 Severity of motor impairment

There is a severity continuum in CP ranging from severe global brain damage resulting in multiple and profound impairments to slight cerebral damage/ dysfunction resulting in barely detectable impairment (31). A variety of tools have been developed to describe a child's clinical picture (27). Since 1991 the Gross Motor Function Classification System (GMFCS) for cerebral CP is used (32). This is a five level classification system based on function, mobility inside and outdoors and the need for assistive technology or devices to achieve mobility such as walkers, crutches, and canes and wheel mobility devices. The purpose of the classification system is to understand a child's current function and mobility to plan interventions to help them be more independent in their lives.

GMFCS for children 6-12 years

Level 1: Walks Without Limitations
Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed, balance and coordination are limited.

Level 2: Walks With Limitations
Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces. Children may walk with physical assistance, a hand-held mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such as running and jumping.

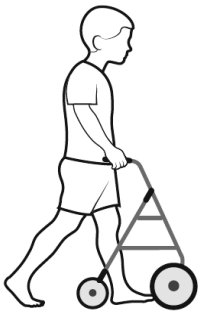
Level 3: Walks Using a Hand-Held Mobility Device
Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children use wheeled mobility when traveling long distances and may self-propel for shorter distances.

Level 4: Self-Mobility with Limitations; May Use Powered Mobility
Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned. At school, outdoors and in the community children are transported in a manual wheelchair or use powered mobility.

Level 5: Transported in a Manual Wheelchair
Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control leg and arm movements (30).

Before the introduction of GMFCS and in the CP register of western Sweden, the children have been labelled according to severity of motor impairment as

Mild (able to walk without aids)



Moderate (walks with aids)

Severe (depends on wheelchair ambulation)

Illustrations by: Jan Funke

According to the GMFCS scores, mild motor impairment corresponds to GMFCS level I and II, moderate motor impairment to GMFCS level III and severe motor impairment to GMFSC level IV and V (33).

1.3.3 Accompanying impairments

The motor disorders seldom appear alone in CP. Several other neurologic disabilities often accompany CP (13). The presence of additional impairments such as learning disability or seizures can contribute to the overall level of severity experienced (34) as well as affect quality of life (35).

The prevalence of accompanying impairments in CP varies between subtypes and level of gross motor function (20, 36, 37).

Epilepsy

Epilepsy is a condition characterised by recurrent and unprovoked seizures. The seizures are transient signs and symptoms of excessive, abnormal cortical nerve cell activity. An epileptic seizure occurs when the seizure threshold is low and/or in a lesion where nerve cells are hyperactive (38-41).

Epilepsy occurs in 0.5 % in the general population (40). Epilepsy is a significant comorbidity in children with CP reported to occur in 15 to more than 60 % of children with CP (20, 22, 37, 38, 42). Variation in occurrence owes much to the age at which the comorbidity is noted (38).

By definition the seizures occur spontaneously and without an immediate cause such as acute illness (43). In concurrence with the SCPE recommendation, the presence or absence of epilepsy (defined as two or more afebrile, non-neonatal seizures) is noted in CP registers (13).

The aetiology of epilepsy is genetic (where seizures are the core symtom of the disorder), structural/metabolic (another condition coexists that are associated with an increased risk of epilepsy), or unknown (44, 45). Epilepsy among people with CP is often of a structural cause, but a genetic predisposition to epilepsy is not uncommon among children with CP and epilepsy (46).

The seizures may be controllable with medication. In those whose seizures do not respond to medication, surgery, neurostimulation or dietary changes may be considered (47). Epilepsy can have adverse effects on social and psychological well-being (48).

Cognitive impairment

A cognitive impairment, also referred to as learning disability is a term used when a person has certain limitations in intellectual functioning and in skills such as communition, self-help, and social skills. These limitations will cause

a child to learn and develop more slowly than the average for a child of his chronological age (49).

Level of cognitive impairment can be established through the use of standardized tests of intelligence and adaptive behavior, scales such as Wechsler scales or, if standardized test could not be applied, based on observation (20, 22, 42, 50). In children with CP, an intelligene quotation (IQ) <70 is noted as cognitive impairment in the CP registers.

Cognitive impairment can be caused by a number of factors. Many instances of cognitive impairment are the result of genetic or chromosomal disorders. Cognitive impairment can also be attributed to injuries or illnesses that occur during pregnancy or early infancy (51, 52).

The prevalence of cognitive impairment is approximately 6.2 per 1000 individuals (53). Approximately 60 % of individuals with CP exhibit cognitive impairment (20, 22, 42, 54).

1.4 Pathophysiology, timing of events and brain imaging

Understanding the regional vulnerability of the immature brain to injury during various periods of brain development is helpful in the understanding of the possible pathogenesis of CP (55). Insults at different stages of development lead to different locations of the CNS impairment and to specific clinical symptoms (56-58). According to the definition of CP, the brain injury causing CP arises in the early stages of its development (13). The normal functioning of the brain is dependent on adequate oxygen and glucose supply. Acute reduction in cerebral oxygen will lead to breakdown of the neuronal energy metabolism within a few minutes (59). Through a series of chain rections, activation of enzymes initiates processes eventually leading to cell death. The nature of the lesions depends on the stage of brain development when such a pathogenic event takes place (60).

During the first and second trimester, cortical neurogenesis, characterized by proliferation, migration and organization takes place. Brain pathology at this stage is characterized by maldevelopments caused by genetic or acquired impairments. From about 20 weeks gestation, the ”gross architecture” of the brain is established and growth and differentiation events are predominant. Disturbances of brain development during this period predominantely result in lesions. Pathogenesis is mainly inflammatory-ischemic and/or infectious. During the early third trimester, the area most susceptible to damage is the

periventricular white matter. However, by full term, if an insult occurs at this stage, it is initially in the cells that have the highest metabolic need, which at this point is the cortex, the grey matter, the basal ganglia and thalamus (60).

Brain imaging such as ultrasound, Computed Tomography (CT) and MRI (MRI) has a potential to visualize lesions or maldevelopments of the brain. The ability to image the newborn brain during development has provided a new source of information regarding the effects of injury on brain development at different vulnerable time periods and allows us to match structure and function (3, 57, 58, 60-65).

1.5 Aetiology

When Little first described CP, he ascribed birth trauma as the cause of CP and this view was maintained for several decades. Freud had a converse view that intrauterine developmental abnormality was responsible, but received no recognition (66, 67). For over a century, most cases of CP was considered to be caused by lack of oxygen (asphyxia) during either labor or the period immediately afterwards (68, 69). Rates of CP was often used as a measure of the quality of obstetric care and intensive care units for newborns (18, 19) and it was anticipated that improvements in these areas would lead to a lower prevalence of CP (70, 71). As a result, there was increased use of interventions such as electronic fetal monitoring and caesarean section. However, the role of intrapartal and postpartal asphyxia in the aetiology of CP was challenged when the fetal and infant and mortality declined but the prevalence of CP remained constant (2, 71). Furthermore, the increased use of caesarean section and continuous cardiotocography during labor did not affect the prevalence of CP (72-74). However, continuous cardiotocography was associated with an increase in caesarean sections and instrumental vaginal births (75, 76). CP rates have remained approximately the same for 50 years despite a 6-fold increase in cesarean birth (74).

According to Blair, it was estimated that in only about 8 % of CP was caused by intrapartum asphyxia (68) and 10-13 % according to Himmelmann (6, 26). Over the last 20 years, new development in CP research has led to radical changes in our understanding of aetiological factors. The prevailing view is now that the aetiology of CP is multifactorial and that factors during the pre-, intra- as well as the postpartal period, or combined are all important and involved in the aetiology of CP (2, 77, 78).

The multifactorial and complex aetiology of CP make interpretation and description of research analysis in the area difficult. The difficulty lies in

evaluating and giving the associated factors discovered in the research the relevant significance. Events that happen during pregnancy, such as infections in the mother may in one context act as a primary cause of CP, in another only be one event in a chain of events that ultimately leads to CP. Other factors, such as growth retardation in the fetus or newborn baby, may not cause CP, but may be a sign of a previous injury or of that an incident such as a maternal infection occurred. Finally, other factors that are strongly associated with CP, as instrumental delivery and need of admission to neonatal intensive care unit (NICU), may have no causal or aetiological significance but are predictive of future outcomes (79, 80) and are indirect early signs of the child not doing well. Therefore, the terminology used when describing events associated with CP needs clarification and need to be handled with care.

1.5.1 Causality

A cause is any factor that contributes to the occurrence of a disease, without necessarily being sufficient cause in itself (2). The difficulty lies in identifying this causal factor reliably, accurately, and independent of other causal factors. In other words, does the exposure make a difference to the manifestation of the disease? The scientific method of investigating causality is to obeserve the effects of the exposure under a systematically planned series of experimental conditions. In epidemiological research in humans it is often not ethical to carry out such experiments. Instead, we must observe naturally occuring events, over which we have little control. Under these conditions, noncausal associations may arise, either systematically or by chance (81).

1.5.2 Risk factors

Case-control studies are often used to identify factors that may contribute to a medical condition by comparing those who have that condition/disease (the "cases") with those who do not have the condition/disease but are otherwise similar (the "controls"). The associated variables are often named risk factors.

A number of risk factors are associated with CP. It does not necessarily mean that the associations are causal. Even if a child does have a risk factor for CP; it does not mean that the child will develop CP. It just means that the risk of the child having CP is increased. Identifying risk factors guide researchers in the understanding of mechanisms involved in a disorder. Moreover, if a risk factor is present, it serves to alert parents and physicians to be very attentive to an infant’s development.

To provide an overview of current research on risk factors for CP in children born at term and as part of the process in deciding which risk factors explore, a systematic search in PubMed for original articles, published from 2000 to 2010, regarding risk factors for CP was conducted by the author of this thesis and Dr. Himmelmann. Full text review was made of 266 articles of which sixty-two articles meeting inclusion/exclusion criteria were examined. Consistent and significant risk factors from before and during pregnancy (prepartal), during labor and birth (intrapartal), and in the period shortly after birth (postpartal) were identified (77).

Prepregnancy risk factors

Factors occurring before the onset of pregnancy that were shown to be associated with CP were genetic factors (82-93), social deprivation, area of residence and socioeconomic status (94-96).

Prepartal risk factors

Chorioamnionitis, maternal urinary tract infection, neurotropic virus infection and cytomegalovirus infection (97-100), intrauterine growth restriction (101-103), maldevelopment (52, 104-106), gender (107-109), maternal trauma (110), maternal hypertension, high maternal body mass index (BMI), pre-eclampsia (111, 112), severe placental vascular lesions (113, 114) and multiple gestation (115-119) were shown to be associated with a higher risk of CP.

Intrapartal risk factors

Meconium stained amniotic fluid (120, 121), placental abruption (122-124) cord complications (114, 120, 125), emergency caesarean section (120, 123-126), birth asphyxia or hypoxic event (123, 125, 127), rupture of membranes (125, 127) and low Apgar score (124, 128-131) correlated with CP according to severeal studies.

Postpartal risk factors

Infections like meningitis, encephalitis and sepsis (120, 122, 123, 132, 133), seizures (109, 134) as well as meconium aspiration syndrome (135), and hyperbilirubinemia occurring during the first days in life (136, 137) were shown to be postpartal risk factors for CP.

1.5.3 Causal pathways

It is increasingly apparent that CP can have many aetiologies and that few consists of single events responsible for the motor damage. A single factor, unless it is of an overwhelming degree, can often be insufficient to lead to cerebral injury, while two or three interacting pathogenic events can

overwhelm the natural defenses and cause irreversible brain injury (138). This has led to the concept of "causal pathways" – a sequence of interdependent events that culminate in disease (2).

1.5.4 Antecedents

The term "antecedent" is used epidemiologically to refer to a factor that confers an increased probability of subsequent disease if it is present. Use of the term does not imply why or how the factor confers a greater probability of disease. Specifically, while a cause of a disease must be an antecedent, an antecedent may not always be a cause (2).

To avoid any misconceptions, the term "antecedent" will be used to describe events/factors associated with CP throughout the thesis.

1.6 CP registers

CP registers are confidential research population databases of information about people with CP. People with CP and their families are asked to register. There are several CP registers worldwide. In Europe alone, there are at least 18 centers that collect demographic data on CP. Data collection on CP is also carried out in Australia, the United States and Canada. A research network, Surveillance of Cerebral Palsy in Europe (SCPE), is a collaboration between CP registers with the purpose to standardize information collected, including a common definition and classification of CP (6).
The CP Register of western Sweden was started in 1971 by Bengt and Gudrun Hagberg and comprises birth-year cohorts from 1954 an onward. Dr. Kate Himmelmann is responsible for the register today. The main aims of the registers are to: monitor trends of CP, gain further understanding about the causes of CP, develop and evaluate preventative strategies and assist in planning services for people who have CP (25).

Using the CP register of western Sweden, all children with CP in western Sweden born at term between January 1, 1983 and December 31, 1994 were included in the studies described in this thesis.

1.7 Life expectancy for people with CP

It is believed that the majority of people with CP have a similar life expectancy to the rest of the population (139, 140). However, most researchers studying the area have reported differences in survival rates among different subgroups of CP (139-142). Himmelmann showed in 2015 that tetraplegia and dyskinetic CP is associated with decreased survival rates. Children with more severe forms of motor impairment, in particular those who can not walk, also has a higher risk of reduced survival. The presence of severe cognitive impairment and epilepsy have also been associated with reduced survival (139-142). Moreover, differences in survival has been noted for boys with CP (which was poorer than for girls with CP) and full-term infants with CP (whose survival was poorer than preterm infants (139). Still, survival estimates suggest that 87 % of people with CP survive to 30 years (141) and half of the most severe cases of CP survive to adulthood. However, there is no empirical experience of their life expectancy past middle age since this longevity is relatively recent. Socio-political determinants are not considered to influence the incidence of CP (143), however, they might be involved in the prevention of secondary complications that lead to an early death (142). There have been significant developments in the management of persons with CP during the last 2 decades, which involves specialist services from many different disciplines (144).

2 AIM

The overall aim of this thesis was to identify antecedents from the prepartal, intrapartal and postpartal period and their associations to CP subtype, severity of motor impairment and to accompanying impairments in CP for children born at term.

By classifying the various types of CP according to their clinical features, it may be possible to determine factors unique to particular CP subtypes and with different severity of motor impairment, as well as different load of accompanying impairment.

2.1 Specific aims of this thesis

The specific aims of this thesis were:

Study I:

To identify non-infectious antecedents of CP and its subtypes in children born at term.

Study II:

To analyse infection-related antecedents during pregnancy, delivery and the neonatal period and its relation to CP subtypes in children born at term.

Study III:

To examine pre-, intra- and postpartal variables and neuroimaging patterns and their association with different severities of motor impairment in children with CP born at term.

Study IV:

To analyse the association between a large set of pre-, intra- and postpartal variables and neuroimaging patterns, collected from mothers and children, and epilepsy and cognitive impairment in children with CP born at term.

3 METHODS

This thesis is part of the population-based ”Panorama of Cerebral Palsy in western Sweden study”. Previously published studies have reported on prevalence, aetiology and accompanying impairments in the study area every four years. There have also been a large number of other publications emerging from the same study population (20, 22, 38, 42, 145). The new approach in the studies described in this thesis are the case-control design, the large number of antecedents analysed and relating these to CP subtypes, severity of motor impairment, accompanying impairments in CP and neuroimaging patterns.

3.1 Study population

The study population described in this thesis was recruited from the western health care region of Sweden with a population of 1.7 million inhabitants. During the study period 1983-1994 282 351 live births occured in the area and 265 061 was born at term (≥37 weeks gestation). A total of 356 children were diagnosed with CP. Children with spinal malformation (n=1) and postnatal causes of CP (n=21) were excluded because the etiology of those cases is considered different from what the study intended to investigate. Children diagnosed with the subtype ataxic CP (n=25), a small group difficult to distinguish from other non-CP syndromes (29), were also excluded for the purpose of this study. Finally, 309 children with CP were selected, 309 of whom were singleton pregnancies and 2 of whom were twin pregnancies. Information about the selection process is shown in Figure 1.

Each case of CP was then matched with 2 control participants, n=618. Using a random sample would result in substantial confounding. To overcome confounding in the design and sampling stage the controls were matched for known confounding factors (sex, gestational age, place of birth, and multiple births).
The control participants were selected by identifying the child born immediately before and after the index case in each hospital and matched for singleton/twin, gestational age and sex. Matching for gestational age, multiple birth and sex was complete in all cases, whereas matching with regard to delivery ward was complete in 93 %, as controls could not always be recruited from small units. Controls were then recruited from units of similar level and size. The matched controls followed their respective case in the subgroup analyses.

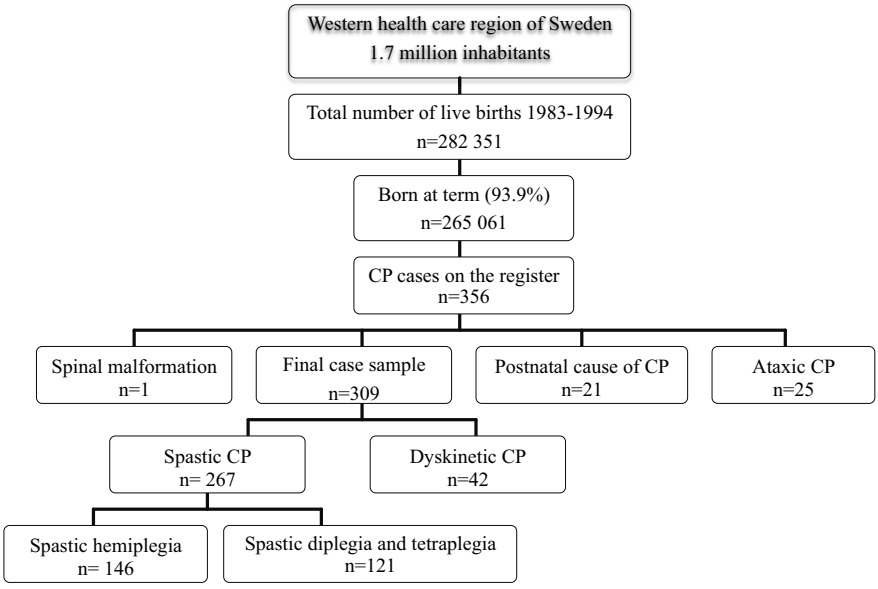


Figure 1. The Figure shows the selection process of the 309 cases of CP.

Data on diagnose of CP, information on subtype of CP, severity of motor impairment, occurrens of accompanying impairments epilepsy and cognitive impairment as well as data on mortality and neuroimaging patterns were obtained from the CP register of western Sweden during the period 1983-1994. Cases of CP in the register were validated based on review of the child's physical findings recorded in medical records verified at four to eight years of age and information is registered in a standard form. Children were included in the register if they have CP, as defined according to Mutch as " an umbrella term covering a group of non-progressive but often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development" (12).

3.2 Study design

Case control study was the design used for all studies described in this thesis, but study IV. A case-control study is an observational epidemiological study of persons with the disease (CP) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and nondiseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and nondiseased) (25).

These were population based (study I-IV) case control studies (study I-III) based on information recorded in the CP register of western Sweden. By dividing the various types of CP according to their clinical features, it was possible to determine factors unique to particular motor disorders, severity of motor impairment and where epilepsy and cognitive impairment accompany CP.

In study I and II the cases with CP were divided into CP subtypes according to the internationally accepted Swedish classification by Hagberg et al. (29, 42), spastic CP and dyskinetic CP. The spastic CP group was also further divided into spastic hemiplegia and spastic diplegia and tetraplegia.

For the purposes of study III, severity of motor impairment was defined as mild (walking without aids), moderate (walking with aids) and severe. (depending on wheelchair ambulation). These categories can generally be equated to the Gross Motor Function Classification (GMFCS) as follows: mild motor impairment corresponds to GMFCS level I and II, moderate motor impairment to GMFCS level III and severe motor impairment to GMFSC level IV and V.

The accompanying impairments documented in study IV were defined as follows: Cognitive impairment was when there was an IQ of less than 70. Mild cognitive impairment in children was when the IQ was 50-70 and severe cognitive impairment if the IQ was less than 50 (according to Wechslers scales or based on observation (20, 22, 42, 50). Epilepsy was defined as a diagnosis of active epilepsy at four to eight years of age. The child received this diagnose if two or more afebrile, non-neonatal seizures had occurred.

3.3 Data collection

Medical and obstetric records and charts from care in the NICU were reviewed by the author and supervisor, Professor Bo Jacobsson, unaware of the outcome. Variables (n=80) from the time periods, prepartal (during pregnancy), intrapartal (during labor) and postpartal (after labor) period were recorded.

3.4 The variables assessed

Table 1. Antecedents studied.

Maternal characteristics and prepartal variables		Intrapartal variables	Postpartal variables
Maternal age	**Pregnancy complications:**	**Mode of delivery:**	**Maternal:**
Maternal BMI	Preeclampsia	Vacuum extraction	Endometritis
Maternal weight week 34	Gestational hypertension/chronic	Cesarean section	Antibiotic therapy
Non-cohabitation with baby's father	hypertension	Instrumental delivery	Temp 38, unknown etiology
Smoking during early pregnancy	Bleeding during pregnancy (during first,		
Alcohol consumption during early	second and third trimester and separately)	**Type of cesarean section:**	**Neonatal:**
pregnancy	Gestational diabetes	Elective	Admission to NICU
Infertility	Suspected SGA	Acute	
In vitro fertilization	Intrauterine fetal death of one twin	Emergency	**Neonatal diagnoses from NICU:**
Ovulation induction	Prepartal diagnosis of CNS anomaly		NE
Miscarriage	External cephalic version	Obstetric catastrophe	Neonatal infection
Termination of pregnancy	Decreased fetal movements	Blood-stained amniotic fluid	Congenital infection
Nulliparity	Trauma during pregnancy	Meconium-stained amniotic fluid	Meconium aspiration
Previous cesarean section	Maldevelopment known at birth	Foul-smelling amniotic fluid	
Previous preterm birth		Neonatal diagnoses from NICU:	
Bad obstetric history	**Factors related to infection:**	Breech presentation	
	Any infectious disease	Umbilical cord complications	
Intercurrent disease:	Severe infection	Placental abruption	
Diabetes	Escherichia coli bacteriuria	Placental weight (g)	
Polycystic ovarian syndrome	Group B Streptococcus (GBS) in urine	Temp 38 degrees before onset of delivery	
Previous deep vein thrombosis	Bacterial growth in urine, unknown organism	Temp 38 degrees during delivery	
Epilepsy	Antibiotic therapy	Antibiotic therapy before onset of	
Rheumatic disorder		delivery	
Thyroid disorder	**Intrauterine growth:**	Antibiotic therapy during delivery	
Lung disease	SGA	Pre-hospital delivery	
Allergy	LGA		
Psychiatric disorder, e.g.	Birth length	**Neonatal characteristics:**	
psychosis or depression	Birthweight	Apgar at 5 minutes <7	
Sexually transmitted disease	Head circumference at birth		

A systematic search in PubMed for original articles, published from 2000 to 2010, regarding risk factors for CP was conducted by the author of this thesis and Dr. Himmelmann as part of the process in deciding which risk factors to explore. Full text review was made of 266 articles of which sixty-two articles meeting inclusion/exclusion criteria were examined. Consistent and significant risk factors from before and during pregnancy (prepartal), during labor and birth (intrapartal), and in the period shortly after birth (postpartal) were identified (77).

3.4.1 Definitions

Bad obstetric history: > 3 subsequent spontaneous abortions, one spontaneous abortion after 20 weeks of gestation, intrauterine fetal death or perinatal death

Alcohol consumption during early pregnancy: occasional or more frequent consumption of alcohol reported at prenatal care registration. Same definition for **smoking.**

Maternal BMI (kg/m^2) was calculated at prenatal care registration.

Maternal disease: diagnosis, prior to pregnancy, of any of the following: hypertensive disease, pulmonary disease, dysplasia, diabetes, psychiatric disorder, polycystic ovarian syndrome, epilepsy, rheumatic disorder or thyroid disorder

Sexually transmitted disease: a history of chlamydia, gonorrhea, syphilis, HIV, herpes simplex, trichomonas vaginalis or condyloma acuminatum

Preeclampsia: blood pressure (BP) ≥140/90 mmHg and ≥ 0.3g protein in urine after 20 weeks of gestation.

Gestational hypertension: BP ≥140/90 mmHg after 20 weeks of gestation

Chronic hypertension: BP >140/90 mm Hg before pregnancy or at < 20 weeks of gestation. **Birth weight** was standardized according to gestational age and sex, based on a Swedish ultrasonically derived fetal growth curve (146).

SGA: > - 24 % weight deviation from the ultrasound-estimated weight for a given gestational age and sex, corresponding to < - 2 standard deviations (SD) from the mean; the latter is a more common definition in pediatric contexts (146)

Calculation of **gestational age** was based on ultrasound at 16-19 gestational weeks (97%), although 3% were dated by last menstrual period

Prepartal diagnosis of CNS anomaly referred to diagnosis by ultrasound during pregnancy. **Maldevelopment diagnosed at birth:** CNS maldevelopment diagnosed at birth and reported in the child's discharge reports. **Severe infectious disease:** pyelonephritis and/or clinical chorioamnionitis, as previous studies have implied that severe infection in close relation to the genital tract may be associated with brain injury (147)

Clinical chorioamnionitis: fever (≥ 38°C recorded on two occasions ≥ 4 h apart) and/or uterine tenderness and/or fetal tachycardia and/or foul-smelling discharge in the absence of other foci of infection (148)

Umbilical cord complication: true knot, cord wrapped several times around the neonate's neck or prolapse

Fever at onset of delivery: temperature ≥ 38 °C prior to regular contractions, rupture of membranes or cervical dilation

Pre-hospital delivery: home delivery or delivery before arrival at hospital.

Obstetric catastrophe: a sudden major adverse incident during labor (e.g. uterine rupture, placental abruption or umbilical cord prolapse)
Instrumental delivery: caesarean section or vaccum extraction
Postpartum endometritis: temperature ≥ 38°C recorded on two occasions ≥ 4 h apart and uterine tenderness or foul-smelling cervico-vaginal discharge
Information on pediatric diagnoses was retrieved from discharge reports from the neonatal intensive care unit (NICU). **NICU** care was not restricted to specific diagnoses or conditions and included all neonates requiring observation or treatment.
NE: defined according to Badawi et al, seizures within the first 72 hours *or* any of the following lasting for longer than 24 hours: altered consciousness, difficulty maintaining respiration (of presumed central nervous origin), difficulty feeding (of presumed central nervous origin) or abnormal tone or reflexes (149)
Neonatal infection: verified infection during the NICU stay and any of the following: pneumonia, septicemia, meningitis, encephalitis, neonatal urinary tract infection (UTI) or ventriculitis
Congenital infection: cytomegalovirus, toxoplasmosis or varicella

3.5 Neuroimaging

Neuroimaging findings were classified into five categories: brain maldevelopment, white-matter injury (WMI), cortical and deep grey-matter lesions, miscellaneous and normal finding, according to Krägeloh-Mann (58).

3.6 Ethics

Ethical approval was obtained from the Regional Ethical Review Board in Gothenburg for study I-III (Ö 173-01) and for study IV (432-13). We also achieved approval from the Swedish Data Inspectorate.

3.7 Statistical analyses

The chisquare test or Fisher's exact test were used to analyse differences in proportions between groups and the Mann-Whitney U-test was used for continuous variables. All significance tests were two-tailed and a significance level of 0.05 was chosen. Separate analyses were done in subgroups of CP subtype (study I and II), severity of motor impairment (study III) and in the groups with CP together with accompanying impairments (study IV). The logistic regression model was used in both univariable and multivariable analyses. The aim with the logistic regression model is to find the best model

to describe the relationshiop between the outcome and possible independent (predictor or explanatory) variables. Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated.

Study I - The multivariable analysis was performed in study I using a stepwise multiple logistic regression analysis. Antecedents included in the initial model were those identified with a p-value <0.10 in the univariable analysis.

Study II – The multivariable models were used to adjust simultaneously for potential confounders. Adjustments were made, for the following characteristics: maternal age, maternal BMI*, parity, smoking*, non cohabitation with the father of the child*, SGA* and instrumental delivery* The confounders were selected based upon theoretical considerations, and/or had been added as standard covariates in previous similar studies (maternal age, parity) as well as upon if they reached significance, i.e., p<0.05 (* variables) in univariable statistical analyses.

Study III – Binary logistic regression with forward selection was used for multivariable analyses, including interaction analyses. Multivariable analyses were performed in two steps. Antecedents were selected for inclusion in the multivariable analyses if univariable analyses (analysis model A) had yielded $p < 0.1$. In analysis model B, the antecedents Apgar score < 7 at 5 min, meconium-stained amniotic fluid, mode of delivery parameters, NE and admission to NICU were excluded, as these excluded antecedents are not in themselves regarded as potential etiological factors, but instead either are markers of vitality or may be intermediates between exposure and outcome, and when related to the exposure, they may prevent earlier antecedent from becoming significant in the final model. The Cochran-Armitage Chi-squared Test for trends was also performed.

Reporting on as many variables that we have done, the question of their interrelationship is very important. We performed analyses on all CP cases and the correlation between the significant antecedents found. Correlation analyses was performed using Spearman's rank correlation. The two multivariable models were developed taking into account the results of the correlations found.

Study IV – In study IV, the odds ratios for a child with CP of being diagnosed with epilepsy, cognitive impairment and both respectively was calculated for every study variable and neuroimaging pattern. In the latter analysis children without epilepsy and cognitive impairment were used as

references. Multivariable analyses, using logistic regression, forward selection, were performed to investigate the influence of confounding factors. As in study III, we performed logistic regression using two different sets of inclusion variables. Multivariable analysis A included all variables with $p<0.1$ from univariable analyses. Analysis B included all variables from A, except Apgar score, admittance to NICU, mode of delivery parameters, meconium stained amniotic fluid and NE.

4 RESULTS

4.1 Summary of results

The antecedent and neuroimaging pattern differed by CP subtype, severity of motor impairment and by presence of accompanying impairments in CP.

The results from the studies presented in this thesis contributes to the understanding of the multifokal aetiology of CP and the diversity of causation as well as timing of causal events and its relation to different CP subtypes and severities of motor impairment.

Moreover, our results illustrate some of the causal pathways to CP, namely hypoxia, malformations and infection.

Validation on data collection

An independent researcher independently reviewed 20 of the obstetric records and compared the files to the recorded data in the database looking for any inconsistencies. No major inconsistencies were found. The number of recorded data variables in the database was 206. Studying 20 records with 206 details in each record, a total of 4120 details were reviewed. Twentyone inconsistencies were found (0.5 %). The majority of these data (12/21) was not used in the analysis, since these were data on surname, occupation etc. All other information in the obstetric records and diagnostic charts from the neonatal intensive care unit were consistent with the previously recorded data in the database.

Calculation on missing data was also performed. There was very little missing data on variables, less than 4 %, except for the variables antibiotic therapy during delivery (5.4 %), head circumference at birth (6.3 %), smoking during early pregnancy (6.9 %), alcohol consumption during early pregnancy (7.4 %), meconium-stained amniotic fluid (12.7 %), blood-stained amniotic fluid (12.7 %), foul-smelling amniotic fluid (12.7 %), birth length (16.2 %) and placental weight (23.5 %).

4.2 Results of papers included in the thesis

4.2.1 Paper I: Non-infectious risk factors for different types of cerebral palsy in term-born babies: a population-based case-control study

Of the 309 children with CP born in the birth years 1983-1994 267 children had spastic CP, of whom 121 children had spastic diplegia and tetraplegia and 146 children had spastic hemiplegia. 42 children had dyskinetic CP.

Prepartal antecedents

Demonstrated in Table 2 and 3, in the analysis of all CP cases and in spastic CP, intrauterine growth measurements, such as birth length, birthweight, head circumference at birth, suspition of being born SGA and SGA, were shown to be significantly associated with poor outcome. Likewise, maternal weight showed to be significantly associated with the same CP subtypes.

Non cohabitation with the baby's father were associated with the total CP group and with the group with spastic diplegia and tetraplegia.

Maternal smoking was associated with CP, when all cases were analysed together. 35 % of mothers to children who developed CP were smokers compared to 27 % among control mothers.

Evident in the analysis of prepartal antecedents to different CP subtypes is the absence of statistical significant prepartal antecedents in the dyskinetic group. Not a single significant relation was found between dyskinetic CP and prepartal antecedents. Likewise, newborn growth measurements birthweight, length and circumference of the head were equal to that of control children.

Table 2. Statistically significant prepartal antecedents according to CP subtype.

Variable	All CP				Spastic CP				Dyskinetic CP			
	Case (n=309)	Control (n=618)	p-value	OR (95% CI)	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)
Birth length (cm)	50.1 (2.7)*	50.6 (2.1)	0.003	0.9 (0.9-0.96)	49.9 (2.6)*	50.6 (2.1)	0.0009	0.9 (0.8-0.9)	51.6 (2.9)*	50.7 (2.1)	0.37	1.2 (0.97-1.5)
Birthweight (kg)	3.43 (0.60)*	3.61 (0.50)	<0.0001	0.5 (0.4-0.7)	3.40 (0.59)*	3.60 (0.50)	<0.0001	0.5 (0.4-0.7)	3.62 (0.61)*	3.70 (0.47)	0.28	0.7 (0.4-1.5)
Decreased fetal movements	12 (4 %)	13 (2 %)	0.18	1.9 (0.9-4.2)	11 (4 %)	10 (2 %)	0.11	2.3 (0.9-5.4)	1 (2 %)	3 4%)	1.00	0.7 (0.07-6.5)
Hypertension	16 (5 %)	26 (4 %)	0.61	1.2 (0.7-2.4)	14 (5 %)	22 (4 %)	0.58	1.3 (0.7-2.6)	2 (5 %)	4 (5 %)	1.00	1.0 (0.2-5.7)
Head circumference at birth (cm)	34.6 (1.9)	35.2 (2.1)	<0.0001	0.8 (0.8-0.9)	34.6 (1.9)*	35.2 (2.2)	0.0002	0.8 (0.8-0.9)	35.2 (1.6)*	35.4 (1.7)	0.36	0.9 (0.7-1.2)
Maternal BMI (kg/cm2)	23.9 (3.8)*	23.0 (3.6)	0.0004	1.1 (1.03-1.1)	24.0 (4.0)*	23.0 (3.6)	0.0004	1.1 (1.0-1.1)	23.6 (3.1)*	23.1 (3.1)	0.60	1.1 (0.9-1.2)
Maternal weight week 34 (kg)	65.7 (11.7)*	63.7 (10.6)	0.02	1.0 (1.0-1.03)	65.7 (11.9)*	63.6 (10.8)	0.01	1.02 (1.0-1.03)	65.4 (10.4)	64.7 (9.0)	0.97	1.01 (0.97-1.05)
Non cohabitation with baby's father	19 (6 %)	15 (3 %)	0.01	2.6 (1.3-5.2)	17 (7 %)	11 (2 %)	0.005	3.2 (1.5-6.9)	2 (5 %)	4 (5 %)	1.00	1.0 (0.2-5.7)
Prepartal diagnosis of CNS anomaly	6 (2 %)	0 (0 %)	0.003	**	6 (2 %)	0 (0 %)	0.003	**	0 (0 %)	0 (0 %)		**
SGA	29 (9 %)	16 (3 %)	<0.0001	3.9 (2.1-7.3)	27 (10 %)	16 (3 %)	<0.0001	3.7 (1.9-6.9)	2 (5 %)	0 (0 %)	0.2222	**
Smoking during early pregnancy	99 (35 %)	156 (27 %)	0.03	1.4 (1.0-1.9)	83 (34 %)	138 (28 %)	0.11	1.3 (0.96-1.8)	16 (40 %)	18 (23 %)	0.0828	2.3 (0.99-5.1)
Suspected SGA	16 (5 %)	7 (1 %)	0.0007	4.2 (1.9-11.7)	14 (5 %)	7 (1 %)	0.003	4.2 (1.7-10.5)	2 (5 %)	0 (0 %)	0.2187	**

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Table 3. Statistically significant prepartal antecedents according to CP subtype.

Variable	Spastic diplegia and tetraplegia				Spastic hemiplegia			
	Case (n=121)	Control (n=242)	p-value	OR (95% CI)	Case (n=146)	Control (n=292)	p-value	OR (95% CI)
Birth length (cm)	49.5 (2.8)*	50.7 (2.2)	0.0007	0.8 (0.8-0.9)	50.2 (2.4)*	50.6 (2.0)	0.15	0.9 (0.8-1.0)
Birthweight (kg)	3.35 (0.63)*	3.60 (0.53)	0.0005	0.5 (0.3-0.7)	3.43 (0.56)*	3.60 (0.48)	0.001	0.5 (0.4-0.8)
Decreased fetal movements	8 (7 %)	4 (2 %)	0.03	4.2 (1.2-14.3)	3 (2 %)	6 (2 %)	1.00	1.0 (0.3-4.1)
Hypertension	4 (3 %)	15 (6 %)	0.36	0.5 (0.2-1.6)	10 (7 %)	7 (2 %)	0.049	3.0 (1.1-8.0)
Head circumference at birth (cm)	34.4 (2.2)*	35.3 (2.5)	0.004	0.8 (0.7-0.9)	34.7 (1.7)*	35.1 (1.8)	0.01	0.9 (0.8-1.0)
Maternal BMI (kg/cm2)	23.8 (3.3)*	23.1 (3.5)	0.03	1.1 (0.99-1.1)	24.1 (4.5)*	22.9 (3.7)	0.0067	1.1 (1.0-1.1)
Maternal weight week 34 (kg)	65.3 (10.6)*	64.2 (10.4)	0.29	1.01 (0.99-1.03)	66.1 (12.8)*	63.1 (11.2)	0.02	1.02 (1.0-1.04)
Non cohabitation with baby's father	11 (9 %)	5 (2 %)	0.008	4.6 (1.6-13.5)	6 (4 %)	6 (2 %)	0.35	2.0 (0.7-6.5)
Prepartal diagnosis of CNS anomaly	3 (3 %)	0 (0 %)	0.07	**	3 (2 %)	0 (0 %)	0.07	**
SGA	17 (14 %)	7 (3 %)	0.0002	5.5 (2.2-13.7)	10 (7 %)	9 (3.1%)	0.12	2.3 (0.9-5.8)
Smoking during early pregnancy	35 (31 %)	66 (30 %)	0.87	1.07 (0.7-1.8)	48 (36 %)	72 (26 %)	0.06	1.6 (1.0-2.5)
Suspected SGA	8 (7 %)	4 (2 %)	0.03	4.2 (1.2-14.3)	6 (4 %)	3 (1 %)	0.08	4.1 (1.0-16.8)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Intrapartal antecedents

As can be observed in Table 4 and 5 intrapartal antecedents such as low Apgar score and caesarean sectio were associated with all CP subtypes. The occurence of low Apgar score and caesarean section however differed substantially between subgroups of CP. As much as 70 % of the children with dyskinetic CP had an Apgar score at 5 min <7 compared to 6 % of the children with spastic hemiplegia. One third of the dyskinetic children were delivered by caesarean section compared to one fifth of the children with spastic hemiplegia. Delivery by emergency caesarean section was also much more common in the dyskinetic CP group, occuring in as much as 21 % of the cases.

Likewise, it was in the dyskinetic group that meconium staining of the amniotic fluid (44 %), obstetric catastrophe (5 %), umbilical cord compications (5 %) and vaccum extraction (24 %), were most commonly occuring. Meconium staining was also shown to be associated to spastic diplegia and tetraplegia, occuring in 36 %. Obstetric catastrophe and umbilical cord complications, even though most commonly occuring in dyskinetic CP, didn't reach significance in this group. Umbilical cord complications were associated with spastic hemiplegia, occuring in 3 % of its cases.

Postpartal antecedents

Demonstrated in Table 6 and 7 admittance to NICU and a diagnose of NE were associated with all CP subtypes. Similar to the intrapartal events, admittance to NICU and NE were most common in the dyskinetic CP group occuring in 85 % and 52 %, respectively. Likewise, meconium aspiration syndrome was most common in this group, occuring in 7 %, even though it didn't reach significance. Meconium aspiration syndrom was significantly associated with the total CP group, the total spastic CP group and the spastic diplegia and tetraplegia group, occuring in 3 %, 2 % and 4 % respectively.

Table 4. *Statistically significant intrapartal antecedents according to CP subtype.*

Variable	All CP				Spastic CP				Dyskinetic CP			
	Case (n=309)	Control (n=618)	p-value	OR (95% CI)	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)
Obstetric catastrophe	5 (2 %)	0 (0 %)	0.008	**	3 (1 %)	0 (0 %)	0.07	*	2 (5 %)	0 (0 %)	0.219	**
Umbilical cord complication	9 (3 %)	3 (0.5 %)	0.007	6.2 (1.7-22.9)	7 (3 %)	3 (1 %)	0.04	4.8 (1.2-18.6)	2 (5 %)	0 (0 %)	0.219	**
Meconium stained amniotic fluid	82 (31 %)	85 (15 %)	<0.0001	2.5 (1.7-3.5)	67 (29 %)	74 (15 %)	<0.0001	2.2 (1.5-3.2)	15 (44 %)	11 (15 %)	0.002	4.7 (1.8-11.8)
Vaccum extraction	33 (11 %)	30 (5 %)	0.002	2.3 (1.4-3.9)	23 (9 %)	26 (5 %)	0.06	1.8 (1.03-3.3)	10 (24 %)	4 (5%)	0.004	6.3 (1.8-21.4)
Caesaeran section	80 (26 %)	72 (12 %)	<0.0001	2.7 (1.9-3.8)	66 (25 %)	61 (11 %)	<0.0001	2.6 (1.7-3.7)	14 (33 %)	11 (13 %)	0.002	3.3 (1.4-8.2)
Acute caesarean section	29 (9 %)	28 (5 %)	0.007	2.2 (1.3-3.7)	24 (9 %)	22 (4 %)	0.01	2.3 (1.3-4.2)	5 (12 %)	6 (7 %)	0.564	1.8 (0.5-6.1)
Emergency caesarean section	38 (12 %)	3 (0.5 %)	<0.0001	28.8 (8.8-93.9)	29 (11 %)	3 (1 %)	<0.0001	21.5 (6.5-71.4)	9 (21 %)	0 (0 %)	<0.0001	**
Apgar score at 5 min <7	62 (21 %)	6 (1 %)	<0.0001	26.4 (11.3-61.9)	34 (13 %)	4 (1 %)	<0.0001	19.8 (7.0-56.6)	28 (70 %)	2 (2 %)	<0.0001	94.5 (19.9-448.5)

n (%) is presented for categorical variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0.

Table 5. Statistically significant intrapartal antecedents according to CP subtype.

Variable	Spastic diplegia and tetraplegia				Spastic hemiplegia			
	Case (n=121)	Control (n=242)	p-value	OR (95% CI)	Case (n=146)	Control (n=292)	p-value	OR (95% CI)
Obstetric catastrophe	0 (0 %)	0 (0 %)		**	3 (2 %)	0 (0 %)	0.073	**
Umbilical cord complication	2 (2 %)	2 (1 %)	0.808	2.0 (0.3-14.6)	5 (3 %)	1 (0.3 %)	0.035	10.3 (1.2-88.7)
Meconium stained amniotic fluid	39 (36 %)	32 (15 %)	<0.0001	3.3 (1.9-5.6)	28 (23 %)	42 (16 %)	0.164	1.5 (0.9-2.6)
Vaccum extraction	13 (11 %)	12 (5 %)	0.072	2.3 (1.02-5.2)	10 (7 %)	14 (5 %)	0.497	1.5 (0.6-3.4)
Caesaeran section	38 (31 %)	29 (12 %)	0.199	3.4 (2.0-5.8)	28 (19%)	32 (11 %)	0.030	1.9 (1.1-3.4)
Acute caesarean section	11 (9 %)	12 (5 %)	0.199	1.9 (0.8-4.5)	13 (9 %)	10 (3 %)	0.032	2.8 (1.2-6.4)
Emergency caesarean section	20 (17 %)	1 (0.4 %)	<0.0001	47.7 (6.3-360.1)	9 (6 %)	2 (0.2 %)	0.002	9.5 (2.0-44.7)
Apgar score at 5 min <7	25 (21 %)	3 (1 %)	<0.0001	21.4 (6.3-72.6)	9 (6 %)	1 (0.3 %)	0.0005	19.5 (2.5-155.7)

n (%) is presented for categorical variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0.

Table 6. Statistically significant postpartal antecedents according to CP subtype.

Variable	All CP				Spastic CP				Dyskinetic CP			
	Case (n=309)	Control (n=618)	p-value	OR (95% CI)	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)
Admitted to NICU	158 (53 %)	75 (12 %)	<0.0001	7.9 (5.7-11.0)	123 (47 %)	61 (12 %)	<0.0001	6.9 (4.8-9.9)	35 (85 %)	14 (17 %)	<0.0001	28.8 (10.2-81.3)
NE	71 (23 %)	1 (0.2 %)	<0.0001	184 (25.4-1327.0)	49 (18 %)	1 (0.2 %)	<0.0001	120 (16.5-873.0)	22 (52 %)	0 (0 %)	<0.0001	**
Meconium aspiration	8 (3 %)	1 (0.2 %)	0.002	16.4 (2.0-132)	5 (2 %)	1 (0.2 %)	0.035	10.2 (1.2-87.4)	3 (7 %)	0 (0 %)	0.071	**

n (%) is presented for categorical variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0.

Table 7. Statistically significant postpartal antecedents according to CP subtype.

Variable	Spastic diplegia and tetraplegia				Spastic hemiplegia			
	Case (n=121)	Control (n=242)	p-value	OR (95% CI)	Case (n=146)	Control (n=292)	p-value	OR (95% CI)
Admitted to NICU	63 (54 %)	34 (14 %)	<0.0001	7.1 (4.2-11.8)	60 (42 %)	27 (9 %)	<0.0001	7.0 (4.2-11.8)
NE	30 (25 %)	1 (0.4 %)	<0.0001	79.5 (10.7-591.1)	19 (13 %)	0 (0 %)	<0.0001	**
Meconium aspiration	5 (4.1 %)	1 (0.4 %)	<0.0001	10.4 (1.2-89.8)	0 (0 %)	0 (0 %)		**

n (%) is presented for categorical variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables. ** indicates that calculation of OR and 95% CI is impossible, since one group is 0.

Multivariable analysis

According to multivariable analysis, in were the combination of antecedents that together best predicted the onset of the different subtypes was derived, antecedents from prepartal, intrapartal as well as from the postpartal period were all featured, except in the dyskinetic group, were it was only intrapartal and postpartal antecedents that appeared (Table 8 and 9).

In conclusion, for all CP subtypes, but the dyskinetic subtype, antecedents from all time periods were identified as associated to poor outcome. In the dyskinetic subtype, only relations to antecedents from the intra- and postpartal period were identified. The findings indicate multifokal aetiology in spastic CP and diversity in timing of causal events.

Table 8. Multivariable antecedents according to CP subtype.

Variable	All CP		Spastic CP		Dyskinetic CP	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Not living with the baby's father	2.6 (1.1-6.0)	0.03	3.0 (1.1-7.9)	0.03		
Gestational diabetes						
Maternal weight at 34 weeks of gestation	1.02 (1.00-1.03)	0.02	1.02 (1.0-1.04)			
Birth length (cm)						
Birthweight (kg)	0.5 (0.4-0.7)	0.0002				
Head circumference at birth (cm)			0.8 (0.7-0.9)	0.0001		
Emergency caesarean section						
Apgar score at 5 min < 7					26.7 (5.0-143.7)	0.0001
Meconium stained amniotic fluid			1.7 (1.0-2.7)	0.04		
Admittance to NICU	4.4 (3.0-6.5)	<0.0001	6.4 (3.9-10.3)	<0.0001	7.6 (2.2-26.5)	0.002
NE	69.2 (9.4-511.9)		22.2 (2.8-174.1)	0.003		

All antecedents from univariable analyses attaining p<0.1 for CP were included in a stepwise multiple logistic regression analysis Variables with no events in the control group, even if they were significant in univariable analysis could not be included in the stepwise multiple logistic regression analysis

Table 9. Multivariable antecedents according to CP subtype.

Variable	Spastic diplegia and tetraplegia		Spastic hemiplegia	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Not living with the baby's father	5.7 (1.5-21.0)	0.009		
Gestational diabetes	13.1 (1.3-135.3)	0.03		
Maternal weight at 34 weeks of gestation				
Birth length (cm)	0.8 (0.7-0.9)	0.004		
Birthweight (kg)				
Head circumference at birth (cm)			0.8 (0.7-0.9)	0.002
Emergency caesarean section				
Apgar score at 5 min < 7				
Meconium stained amniotic fluid				
Admittance to NICU	3.2 (1.7-6.0)	0.0003	8.3 (4.7-14.9)	<0.0001
NE	19.7 (2.3-171.7)	0.007		

All antecedents from univariable analyses attaining p<0.1 for CP were included in a stepwise multiple logistic regression analysis Variables with no events in the control group, even if they were significant in univariable analysis could not be included in the stepwise multiple logistic regression analysis.

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4.2.2 Paper II: Cerebral palsy and perinatal infection in children born at term

The same study population analyzed in study I for relation between non-infectious antecedents and CP subtypes were now analysed to investigate the association between infection related antecedents and different CP subtypes.

Prepartal infection-related antecedents

As demonstrated in Table 10 and 11, few prepartal infection- related antecedents were related to the total spastic CP group, dyskinetic CP and the spastic diplegia and tetraplegia group. However, almost all analyzed prepartal infection-related antecedents were statistically significantly associated with the subtype spastic hemiplegia according to univariable analysis.

After adjustment for confounders (maternal age, maternal smoking, parity, non cohabitation with the baby's father, SGA and instrumental delivery) bacterial growth in urine, infectious disease, severe infection, antibiotic therapy and antibiotic therapy several times during pregnancy remained significanly associated with spastic hemiplegia.

Table 10. Prepartal infectious antecedents according to different CP subtypes.

	Spastic CP						Dyskinetic CP					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
Variable	**Case (n=267)**	**Control (n=534)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**Case (n=42)**	**Control (n=84)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Sexually transmitted disease	36 (14 %)	76 (15 %)	0.79	0.9 (0.6-1.5)	0.80	0.9 (0.6-1.6)	10 (25 %)	13 (16 %)	0.33	1.8 (0.7-4.5)	0.88	1.1 (0.3-3.9)
Sexually transmitted disease, several times	3 (1 %)	6 (1 %)	0.99	1.0 (0.3-4.1)	0.91	1.1 (0.3-4.5)	2 (5 %)	1 (1 %)	0.24	4.2 (0.0-2.7)	0.05	18.8 (1.0-370.2)
Hepatitis	3 (1 %)	2 (0.5 %)	0.23	3.0 (0.5-18.2	0.59	2.0 (0.2-24.6)	2 (5 %)	1 (1 %)	0.24	4.3 (0.4-48.4)	1.00	
During pregnancy:												
Bacterial growth in urine	18 (7 %)	18 (3 %)	0.03	2.1 (1.1-4.1)	0.006	3.4 (1.4-8.1)	2 (5 %)	3 (4 %)	0.75	1.4 (0.2-8.4)	0.87	1.2 (0.1-13.7)
Repeating bacterial growth in urine	6 (2 %)	10 (2 %)	0.72	1.2 (0.4-3.4)	0.28	2.2 (0.5-9.2)	1 (2 %)	2 (2 %)	1.00	1.0 (0.1-11.4)	0.34	3.5 (0.3-44.7)
Escherichia Coli bacteriuria	9 (3 %)	4 (1 %)	0.01	4.6 (1.4-15.2)	0.01	16.1 (1.9-137.2)	1 (2 %)	0 (0 %)	1.00	*	*	*
Group B Streptococcus bacteriuria	3 (1 %)	2 (0.5 %)	0.23	3.0 (0.5-18.2)	0.40	2.4 (0.3-17.6)	0 (0 %)	1 (1 %)	1.00	*	*	*
Bacterial growth in urine of unknown etiology	5 (2 %)	10 (2 %)	1.00	1.0 (0.2-3.0)	0.97	1.0 (0.2-5.7)	0 (0 %)	2 (2 %)	0.55	*	*	*
Any infectious disease	100 (37 %)	139 (26 %)	0.001	1.7 (1.2-2.3)	0.001	1.9 (1.3-2.8)	12 (29 %)	19 (23 %)	0.47	1.4 (0.6-3.2)	0.134	2.3 (0.8-6.7)
Severe infection	19 (7 %)	20 (4 %)	0.04	2.0 (1.0-3.8)	0.07	2.2 (1.0-5.1)	4 (10 %)	7 (8 %)	0.82	1.2 (0.3-4.2)	0.66	1.4 (0.3-6.8)
Chorioamnionitis	0 (0 %)	0 (0 %)		*	*	*	0 (0 %)	0 (0 %)	*	*	*	*
Antibiotic therapy	54 (20 %)	58 (11 %)	0.000	2.1 (1.4-3.1)	0.00	2.7 (1.6-4.4)	2 (5 %)	3 (4 %)	1.00	1.0 (0.4-2.9)	0.52	1.6 (0.4-6.1)
Antibiotic therapy several times	16 (6 %)	13 (2 %)	0.01	2.6 (1.2-5.4)	0.03	2.9 (1.1-7.5)	1 (2 %)	2 (2 %)	0.62	2.0 (0.1-33.2)	*	*

For categorical variables n (%) is presented. For comparison between groups and p-value, Fisher´s Exact test was used. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95 % CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Table 11. Prepartal infectious antecedents according to different CP subtypes.

	Spastic diplegia and tetraplegia						Spastic hemiplegia					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
	Case	Control	p-value	OR (95% CI)	p-value	OR (95% CI)	Case	Control	p-value	OR (95% CI)	p-value	OR (95% CI)
Variable	**(n=121)**	**(n=242)**					**(n=146)**	**(n=292)**				
Sexually transmitted disease	17 (15 %)	28 (12 %)	0.46	1.3 (0.7-2.4)	0.41	1.4 (0.6-3.0)	19 (13 %)	48 (17 %)	0.33	0.8 (0.42-1.3)	0.24	0.7 (0.3-1.3)
Sexually transmitted disease, several times	3 (3 %)	1 (0.5 %)	0.12	6.2 (0.64-60.7)	0.07	8.5 (0.8-87.8)	0 (0 %)	5 (2 %)	0.17	*	*	*
Hepatitis	2 (2 %)	2 (1 %)	0.49	2.0 (0.3-14.4)	0.70	1.7 (0.1-23.3)	1 (1 %)	0 (0 %)	1.00	*	*	*
During pregnancy:												
Bacterial growth in urine	7 (6 %)	7 (3 %)	0.19	2.06 (0.7-6.0)	0.24	2.2 (0.6-8.4)	11 (8 %)	11 (4 %)	0.09	2.1 (0.9-4.9)	0.009	4.7 (1.5-15.2)
Repeating bacterial growth in urine	2 (2 %)	4 (2 %)	1.00	1.0 (0.2-5.5)	0.66	1.6 (0.2-14.3)	4 (3 %)	6 (2 %)	0.65	1.3 (0.4-4.8)	0.36	2.6 (0.4-18.7)
Escherichia Coli bacteriuria	3 (3 %)	1 (0.5 %)	0.12	6.1 (0.6-59.5)	0.20	5.0 (0.4-56.5)	6 (4 %)	3 (1 %)	0.004	4.1 (1.0-16.8)	0.99	
Group B Streptococcus bacteriuria	1 (1 %)	1 (0.5 %)	0.62	2.0 (0.1-32.4)	1.00		2 (1 %)	1 (0.5 %)	0.26	4.0 (0.4-44.9)	0.18	5.4 (0.5-62.9)
Bacterial growth in urine of unknown etiology	3 (3 %)	6 (3 %)	1.00	1.0 (0.3-4.1)	0.86	1.2 (0.2-8.5)	2 (1 %)	4 (1 %)	1.00	1.0 (0.2-5.5)	1.00	
Any infectious disease	43 (36 %)	71 (29 %)	0.23	1.3 (0.8-2.1)	0.62	1.2 (0.7-2.1)	57 (39 %)	68 (23 %)	0.001	2.1 (1.4-3.2)	<.0001	2.9 (1.7-4.8)
Severe infection	7 (6 %)	14 (6 %)	1.00	1.0 (0.4-2.6)	0.28	0.5 (0.1-1.9)	12 (8 %)	6 (2 %)	0.004	4.3 (1.6-11.6)	0.001	15.4 (3.0-78.1)
Chorioamnionitis	0 (0 %)	1 (0.5 %)	*	*	*	*	0 (0 %)	0 (0 %)				*
Antibiotic therapy	21 (17 %)	35 (15 %)	0.47	1.2 (0.7-2.2)	0.93	1.0 (0.5-2.2)	33 (23 %)	23 (8 %)	<.0001	3.4 (1.9-6.1)	<.0001	6.3 (3.0-15.2)
Antibiotic therapy several times	7 (6 %)	8 (3 %)	0.27	1.8 (0.6-5.1)	0.92	1.1 (0.3-4.1)	9 (6 %)	5 (2 %)	0.02	3.8 (1.2-11.5)	0.012	15.6 (1.81-134.2)

For categorical variables n (%) is presented. For comparison between groups and p-value, Fisher´s Exact test was used. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95 % CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Intrapartal infection-related antecedents

In the spastic CP group, maternal antibiotic therapy several times before delivery, as well as during delivery, were significantly associated to poor outcome. Antibiotic treatment during delivery stayed related to spastic CP after adjustment for confounders.

In the group with spastic hemiplegia, antibiotic treatment during pregnancy was related to poor outcome, but didn't stay significantly associated in adjusted analysis.

No other CP subtype was related to infection related antecedents in the intrapartal period (Table 12-13).

Table 12. Intrapartal infectious antecedents according to different CP subtypes.

	Spastic CP						Dyskinetic CP					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
Variable	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)	p-value	OR (95% CI)
Before delivery:												
Antibiotic therapy	5 (2 %)	5 (1 %)	0.27	2.0 (0.6-7.0)	0.70	0.7 (0.1-3.9)	0 (0 %)	0 (0 %)		*	*	*
Antibiotic therapy several times	4 (2 %)	0 (0 %)	0.01	*	*	*	0 (0 %)	0 (0 %)		*	*	*
Temperature ≥38 degrees	8 (3 %)	7 (1 %)	0.11	2.3 (0.8-6.5)	0.51	1.5 (0.4-5.3)	1 (2 %)	1 (1 %)	0.61	2.1 (0.1-34.0)	1.00	
Temperature ≥38 degrees twice	5 (2 %)	6 (1 %)	0.40	1.7 (0.5-5.5)	0.97	1.0 (0.2-4.3)	1 (2 %)	1 (1 %)	0.61	2.1 (0.1-34.0)	1.00	
During delivery:												
Antibiotic therapy	8 (3 %)	2 (0.5 %)	0.008	8.2 (1.7-38.9)	0.05	8.7 (1.0-73.3)	3 (8 %)	1 (1 %)	0.11	6.5 (0.7-64.5)	0.36	4.4 (0.2-104.1)
Temperature ≥38 degrees	3 (1 %)	5 (1 %)	0.79	1.2 (0.3-5.1)	0.75	0.8 (0.2-3.6)	1 (2 %)	1 (1 %)	1.00	2.1 (0.1-33.6)	1.00	
Temperature ≥38 degrees twice	2 (1 %)	4 (1 %)	0.99	1.0 (0.2-5.5)	0.51	0.6 (0.1-3.3)	1 (2 %)	0 (0 %)	0.33	*	*	*

For categorical variables n (%) is presented. For comparison between groups and p-value, Fisher´s Exact test was used. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Table 13. Intrapartal infectious antecedents according to different CP subtypes.

	Spastic diplegia and tetraplegia						Spastic hemiplegia					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
Variable	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)	p-value	OR (95% CI)
Before delivery:												
Antibiotic therapy	3 (3 %)	1 (0.5 %)	0.12	6.1 (0.6-59.1)	0.94	0.9 (0.1-15.3)	2 (1 %)	4 (1 %)	0.99	1.0 (0.2-5.5)	0.71	0.7 (0.1-5.7)
Antibiotic therapy several times	2 (2 %)	0 (0 %)	0.11	*	*	*	2 (1 %)	0 (0 %)	0.11	*	*	*
Temperature ≥38 degrees	3 (3 %)	5 (2 %)	0.80	1.2 (0.3-5.1)	0.79	0.8 (0.1-4.4)	5 (3 %)	2 (1 %)	0.05	5.1 (1.0-26.8)	0.14	0.2 (0.0-1.8)
Temperature ≥38 degrees twice	1 (1 %)	4 (2 %)	0.53	0.5 (0.1-4.5)	0.99		4 (3 %)	2 (1 %)	0.11	4.0 (0.7-22.3)	0.14	5.8 (0.6-58.5)
During delivery:												
Antibiotic therapy	3 (3 %)	1 (0.5 %)	0.12	6.2 (0.6-60.4)	0.99		5 (4 %)	1 (0.5 %)	0.04	10.1 (1.2-87.5)	0.08	7.5 (0.8-69.9)
Temperature ≥38 degrees	2 (2 %)	2 (1 %)	0.48	2.0 (0.3-14.6)	0.85	1.2 (0.2-10.3)	1 (1 %)	3 (1 %)	0.74	0.7 (0.1-6.6)	0.50	0.5 (0.0-4.7)
Temperature ≥38 degrees twice	1 (1 %)	1 (0.5 %)	0.62	2.0 (0.1-32.5)	0.80	0.7 (0.0-11.9)	1 (1 %)	3 (1 %)	0.72	0.7 (0.1-6.4)	0.47	0.4 (0.0-4.4)

For categorical variables n (%) is presented. For comparison between groups and p-value, Fisher´s Exact test was used. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Postpartal infection-related antecedents

Maternal antibiotic treatment post partum was related to all CP subtypes in univariable analysis but didn't stay significantly associated after adjustment for confounders.

Neonatal infection was related to both dyskinetic CP and to spastic diplegia and tetraplegia ocuring in 10 % and 9 % respectively of the children that developed CP. It was not related to spastic hemiplegia, where the occurence was 3 %. Since there was no one in the control group, belonging to the dyskinetic group, that had neonatal infection, it was not possibel to perform adjusted analysis. Neonatal infection stayed significantly associated to spastic diplegia and tetraplegia in adjusted analysis (Table 14-15).

Table 14. Postpartal infectious antecedents according to different CP subtypes.

	Spastic CP						Dyskinetic CP					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
Variable	Case (n=267)	Control (n=534)	p-value	OR (95% CI)	p-value	OR (95% CI)	Case (n=42)	Control (n=84)	p-value	OR (95% CI)	p-value	OR (95% CI)
Post partum:												
Antibiotic therapy postpartum	23 (9 %)	16 (3 %)	0.001	3.1 (1.6-5.9)	0.27	1.6 (0.7-3.4)	7 (17 %)	3 (4 %)	0.02	5.5 (1.3-22.5)	0.07	4.5 (0.9-23.5)
Temperature ≥38 degrees	17 (6 %)	15 (3 %)	0.02	2.3 (1.1-4.7)	0.51	1.4 (0.6-3.4)	2 (5 %)	5 (6 %)	1.00	0.8 (0.2-4.4)	0.19	0.2 (0.0-2.3)
Temperature ≥38 degrees twice	12 (5 %)	5 (1 %)	0.003	5.0 (1.7-14.2)	0.11	2.8 (0.8-10.3)	1 (2 %)	4 (5 %)	0.81	0.5 (0.1-4.6)	0.99	*
Foul smelling amniotic fluid	2 (1 %)	2 (0.5 %)	0.47	2.1 (0.3-14.8)	0.46	2.2 (0.27-17.99)	0 (0 %)	0 (0 %)			*	*
Endometritis	3 (1 %)	4 (1 %)	0.59	1.5 (0.3-6.8)	0.35	0.4 (0.0-4.0)	1 (3 %)	1 (1 %)	0.60	2.1 (0.1-34.5)	0.99	1.0 (0.0-44.5)
Neonatal Infection	15 (6 %)	2 (0.5 %)	<.0001	15.8 (3.6-69.8)	0.004	10.2 (2.1-48.2)	4 (10 %)	0 (0 %)	0.01	*	*	*
Time from rupture of membranes until delivery (h)	14.8 (16.6)	12.5 (19.4)	0.07	1.0 (1.0-1.0)	0.80	1.0 (1.0-1.0)	14.3 (16.6)	17.7 (43.6)	0.43	1.0 (1.0-1.0)	0.03	0.9 (0.8-1.0)

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95 % CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Table 15. Postpartal infectious antecedents according to different CP subtypes.

	Spastic diplegia and tetraplegia						Spastic hemiplegia					
			Univariable analysis		Adjusted analysis				Univariable analysis		Adjusted analysis	
Variable	Case (n=121)	Control (n=242)	p-value	OR (95% CI)	p-value	OR (95% CI)	Case (n=146)	Control (n=292)	p-value	OR (95% CI)	p-value	OR (95% CI)
Post partum:												
Antibiotic therapy postpartum	14 (12 %)	11 (5 %)	0.02	2.8 (1.2-6.3)	0.41	1.5 (0.6-4.1)	9 (6 %)	5 (2 %)	0.02	3.8 (1.3-11.6)	0.40	1.9 (0.4-8.1)
Temperature ≥38 degrees	7 (6 %)	9 (4 %)	0.38	1.6 (0.6-4.3)	0.70	1.3 (0.4-4.6)	10 (7 %)	6 (2 %)	0.02	3.5 (1.2-9.7)	0.61	1.4 (0.4-5.5)
Temperature ≥38 degrees twice	4 (3 %)	4 (2 %)	0.34	2.0 (0.5-8.1)	0.54	1.8 (0.3-11.1)	8 (6 %)	5 (2 %)	0.008	17.1 (2.1-137.8)	0.09	7.2 (0.7-69.9)
Foul smelling amniotic fluid	1 (1 %)	2 (1 %)	0.99	1.0 (1.0-11.2)	0.85	0.8 (0.1-11.3)	1 (1 %)	0 (0 %)	1.00	*	*	*
Endometritis	0 (0 %)	3 (1 %)	0.11	*	*	*	3 (2 %)	1 (0.5 %)	0.12	6.2 (0.6-59.9)	0.70	1.7 (0.1-30.3)
Neonatal Infection	11 (9 %)	1 (0.5 %)	0.002	24.10 (3.1-189.0)	0.02	14.7 (1.7-126.5)	4 (3 %)	1 (0.5 %)	0.06	8.2 (0.9-74.0)	0.16	5.3 (0.5-55.0)
Time from rupture of membranes until delivery (h)	14.5 (16.7)	14.0 (24.4)	0.43	1.0 (1.0-1.0)	0.46	1.0 (1.0-1.0)	14.9 (16.6)	11.2 (13.9)	0.09	1.0 (1.0-1.0)	0.15	1.0 (1.0-1.1)

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95 % CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

To conclude, maternal infections during pregnancy only seem to be connected to spastic hemiplegia. However, neonatal infections are related to dyskinetic CP and to the group with spastic diplegia and tetraplegia.

4.2.3 Paper III: Antecedents of cerebral palsy according to severity of motor impairment

Out of the 309 children with CP, 197 children had a mild motor impairment, 17 a moderate motor impairment and 95 children had a severe motor impairment. Among the children with mild motor impairment, 46 children had spastic diplegia or tetraplegia, 141 had spastic hemiplegia and 10 had dyskinetic CP. In the moderate motor impairment group, 13 children had spastic diplegia or tetraplegia, one had spastic hemiplegia and three had dyskinetic CP. Of those with severe motor impairment, 62 children had spastic diplegia or tetraplegia, four had spastic hemiplegia and 29 had dyskinetic CP (Figure 2).

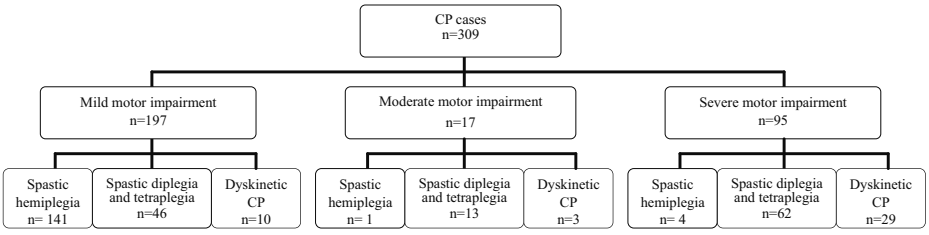


Figure 2. Distribution of subtypes among different severity of motor impairment in children with CP.

Univariable analysis

Prepartal antecedents

SGA, birth length, birthweight, head circumference at birth, infection related antecedents, gestational hypertension, maternal weight, placental weight and non cohabitation with the baby's father were all associated with mild motor impairment.

Similarly to those with mild motor impairment, measurements of poor intrauterine growth were associated with poor outcome in the group with severe motor impairment. However, there was no significant association between infection related antecedents and severe motor impairment, except for hepatitis. Maldevelopment, occuring in 8 % of the severlyimpaired

children and congenital infection, occurring in 4 %, were highly related to poor outcome. In addition, maternal smoking occured significantly more often in the severe motor impairment group (41 %) compared to in controls (27 %) (Appendix X).

Table 16. Significant prepartal antecedents of mild or severe motor impairment in cerebral palsy.

Variable	Mild motor impairment				Severe motor impairment				Cases only**
	Case (n=197)	Control (n=394)	OR (95 % CI)	p-value	Case (n=95)	Control (n=190)	OR (95 % CI)	p-value	p-value
Maternal characteristics									
Non cohabitation with baby's father	11 (6 %)	8 (2 %)	2.8 (1.1-7.2)	0.03	7 (7 %)	6 (3 %)	2.4 (0.8-7.3)	0.14	0.61
Maternal BMI (kg/m^2)	24.1 (4.2)	22.9 (3.6)	1.1 (1.03-1.1)	0.002	23.6 (3.1)	23.1 (3.6)	1.04 (0.96-1.1)	0.21	0.41
Hepatitis	1 (1 %)	2 (1 %)	1.0 (0.09-11.1)	1.00	4 (4 %)	1 (1 %)	8.4 (0.9-76.9)	0.04	0.04
Smoking during early pregnancy	56 (31 %)	95 (26 %)	1.3 (0.9-1.9)	0.19	38 (41 %)	48 (27 %)	1.9 (1.1-3.2)	0.02	0.11
Maternal weight week 34 (kg)	66.2 (12.3)	63.2 (10.7)	1.02 (1.008-1.04)	0.004	63.7 (9.6)	64.5 (10.5)	0.99 (0.97-1.02)	0.59	0.09
Pregnancy complications:									
Gestational hypertension	15 (8 %)	13 (3 %)	2.4 (1.1-5.2)	0.02	1 (1 %)	11 (6 %)	0.2 (0.02-1.4)	0.07	0.03
Maldevelopment diagnosed at birth	0 (0 %)	0 (0 %)	*	*	8 (8 %)	0 (0 %)	∞	<0.001	<0.001
Intrauterine growth:									
SGA	18 (9 %)	10 (3 %)	3.9 (1.7-8.5)	0.001	9 (10 %)	5 (3 %)	3.9 (1.3-11.9)	0.02	1.00
Birth length (cm)	50.1 (2.6)	50.6 (2.0)	0.9 (0.8-0.98)	0.04	50.1 (3.0)	50.6 (2.2)	0.9 (0.8-1.02)	0.16	0.87
Birthweight (kg)	3.4 (0.6)	3.6 (0.5)	0.6 (0.4-0.8)	0.001	3.4 (0.6)	3.6 (0.5)	0.5 (0.3-0.8)	0.005	0.68
Head circumference at birth (cm)	34.8 (1.7)	35.2 (1.9)	0.9 (0.8-0.98)	0.008	34.3 (2.2)	35.3 (2.5)	0.8 (0.7-0.9)	0.001	0.08
Placental weight (hg)	6.0 (1.5)	6.2 (1.5)	0.9 (0.8-1.0)	0.04	6.3 (1.6)	6.2 (1.4)	1.0 (0.9-1.2)	0.65	0.17
Factors related to prepartal infection:									
Congenital infection	0 (0 %)	0 (0 %)	*	*	4 (4 %)	0 (0 %)	∞	0.01	0.01
Infection during pregnancy	73 (37 %)	95 (24 %)	1.9 (1.3-2.7)	0.001	33 (35 %)	51 (27 %)	1.5 (0.9-2.5)	0.17	0.80
Antibiotic therapy during pregnancy	39 (20 %)	38 (10 %)	2.3 (1.4-3.8)	0.001	16 (17 %)	27 (14 %)	1.2 (0.6-2.4)	0.60	0.63

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. The estimates for birthweight and maternal weight are calculated to show the increased risk of CP per kg of body weight. ** Comparing mild motor impairment to severe motor impairment in cases only.

Intrapartal antecedents

Intrapartal antecedents significanty associated with mild motor impairment included antibiotic treatment, low Apgar score, caesarean section, meconium staining of the amniotic fluid, obstetric catastrophe, fever before onset of delivery, umbilical cord complication and vaccum extraction (Table 17). Notably, some antecedents were increasing in occurence with increasing severity of motor impairment. To exemplify, 12 % of those with mild motor impairment had Apgar score <7 at 5 min compared to 31 % in the moderate group and 37 % in the severe motor impairment group. In addition, vaccum extraction, significantly associated to severe motor impairment in univariable analysis followed the same pattern.

There was a strong correlation between low Apgar score, meconiumstained amniotic fluid, antibiotic treatment during delivery and emergency caesarean section and severe motor impairment.

Table 17. Significant intrapartal antecedents of mild or severe motor impairment in cerebral palsy.

Variable	Mild motor impairment				Severe motor impairment				Cases only**
	Case (n=197)	Control (n=394)	OR (95 % CI)	p-value	Case (n=95)	Control (n=190)	OR (95 % CI)	p-value	p-value
Intrapartal variables									
Temperature >38°C before onset of delivery	6 (3 %)	2 (1 %)	6.2 (1.2-30.8)	0.02	2 (2 %)	5 (3 %)	0.8 (0.2-4.2)	1.00	1.00
Umbilical cord complications	8 (4 %)	2 (1 %)	8.3 (1.7-39.4)	0.003	1 (1 %)	0 (0 %)	∞	0.33	0.28
Obstetric catastrophe	3 (2 %)	0 (0 %)	∞	0.04	2 (2 %)	0 (0 %)	∞	0.11	0.66
Meconium-stained amniotic fluid	47 (28 %)	52 (15 %)	2.2 (1.4-3.4)	0.001	30 (36 %)	26 (15 %)	3.3 (1.8-6.1)	<0.001	0.19
Antibiotic therapy during delivery	7 (4 %)	2 (1 %)	7.2 (1.5-34.8)	0.01	4 (4 %)	0 (0 %)	∞	0.01	0.75
Mode of delivery:									
Instrumental delivery	63 (32%)	71 (18 %)	2.2 (1.5-3.2)	<0.001	43 (45%)	27 (14 %)	5.0 (2.8-8.9)	<0.001	0.03
Vacuum extraction	19 (10 %)	20 (5 %)	2.0 (1.04-3.8)	0.052	13 (14 %)	10 (5 %)	2.9 (1.2-6.8)	0.02	0.32
Cesarean section	44 (22 %)	51 (13 %)	1.9 (1.2-3.0)	0.004	31 (33 %)	17 (9 %)	4.9 (2.6-9.5)	<0.001	0.06
Type of cesarean section:									
Acute	17 (9 %)	17 (4 %)	2.1 (1.05-4.2)	0.04	12 (13 %)	9 (5 %)	2.9 (1.2-7.2)	0.03	0.30
Emergency	20 (10 %)	3 (1 %)	14.7 (4.3-50.2)	0.000	15 (16 %)	0 (0 %)	∞	<0.001	0.18
Acute or emergency	37 (19 %)	19 (5 %)	4.6 (2.5-8.2)	<0.0001	27 (28 %)	9 (5 %)	8.0 (3.6-17.8)	<0.0001	0.07
Neonatal characteristics:									
Apgar score at 5 minutes < 7	23 (12 %)	3 (1 %)	17.6 (5.2-59.4)	<0.0001	34 (37 %)	3 (2 %)	36.5 (10.8-123.4)	<0.001	<0.001

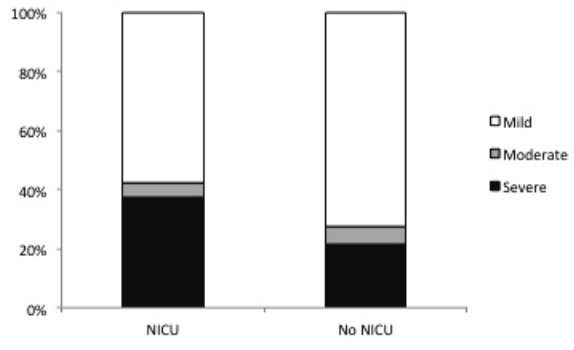
n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. Cesarean section (elective, acute, emergency), instrumental delivery (cesarean section, vaccum extraction). ** Comparing mild motor impairment to severe motor impairment in cases only.

Postpartal antecedents

Similarly to some of the intrapartal antecedents, admittance to NICU and neonatal encephalopathy, sigificantly associated to all severity groups were increasing in occurence with increasing severity of motor impairment. Infections in the postpartal period and meconium aspiration syndrome were shown to be highly related to severe motor impairment (Table 18).

There was a high percentage of children not admitted to a neonatal intensive care unit (i.e., 53 % with mild motor impairment and 35 % with severe motor impairment) (Figure 3).

Figure 3. Admittance to NICU according to severity of motor impairment



There was a difference in severity between those treated in the NICU and those who were not x^2 (2df)=8.85; p=0.01.

Table 18. Significant postpartal antecedents of mild or severe motor impairment in cerebral palsy.

Variable	Mild motor impairment				Severe motor impairment				Cases only**
	Case (n=197)	Control (n=394)	OR (95 % CI)	p-value	Case (n=95)	Control (n=190)	OR (95 % CI)	p-value	p-value
Postpartal variables:									
Maternal:									
Antibiotic therapy postpartum	12 (6 %)	11 (3 %)	2.3 (0.98-5.2)	0.07	17 (18 %)	5 (3 %)	8.2 (2.9-23.1)	<0.001	0.003
Neonatal:									
Admitted to NICU	91 (47 %)	43 (11 %)	7.2 (4.7-11.0)	<0.001	60 (65 %)	31 (16 %)	9.6 (5.4-17.0)	<0.001	0.005
Neonatal diagnoses from NICU:									
NE	31 (16 %)	1 (0.3 %)	73.4 (9.9-542.1)	<0.001	35 (37 %)	0 (0 %)	∞	<0.001	<0.001
Neonatal infection	6 (3 %)	1 (0.3 %)	12.3 (1.5-103.3)	0.01	7 (7 %)	1 (1 %)	15.0 (1.8-124.1)	0.0023	0.13
Meconium aspiration	2 (1 %)	0 (0 %)	∞	0.11	6 (6 %)	1 (1 %)	12.7 (1.5-107.4)	0.006	0.02

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. ** Comparing mild motor impairment to severe motor impairment in cases only.

Multivariable analysis

Mild motor impairment

In multivariable analysis model A, including all variables with $p < 0.1$ in the univariable analysis, maternal weight at gestational week 34 (kg) (OR 1.03 95 % CI: 1.01-1.1), antibiotic therapy during pregnancy (OR 3.8 95 % CI: 1.6-9.3), meconium-stained amniotic fluid (OR 2.6 95 % CI: 1.3-5.3), Apgar score at <7 at 5 min (OR ∞, p=0.01), admission to neonatal intensive care unit (OR 5.8 95 % CI: 2.8-12.1) and neonatal encephalopathy (OR 10.7 95 % CI: 1.1-103.4) were significantly associated with mild motor impairment in the final model (Appendix XI). According to model B, two additional antecedents - non cohabitation with baby's father (OR 3.1 95 % CI: 1.001-9.8) and placental weight (g) (OR 0.997 95 % CI: 0.995-0.999) - , not displayed in the first model, were significant, in addition to maternal weight at gestational week 34 (kg) (OR 1.04 95 % CI: 1.02-1.1) and antibiotic therapy during pregnancy (OR 4.4 95 % CI: 2.2-8.7), which were also significant in analysis model A (Appendix XI).

Severe motor impairment

According to multivariable analysis model A, smoking during early pregnancy (OR 2.4 95 % CI: 1.01-5.8), head circumference at birth (cm) (OR 0.6 95 % CI: 0.5-0.8), maldevelopment diagnosed at birth (p=0.004, OR ∞), emergency cesarean section (p=0.008, OR ∞), maternal antibiotic therapy postpartum (OR 7.1 95 % CI: 7.1-28.4) and neonatal encepalopathy (p<0.001, OR ∞) were included in the final model (Appendix XII). In multivariable analysis model B, excluding potential intermediate variables, two additional antecedents were significant: congenital infection (p=0.05, OR ∞) and maternal antibiotic therapy during delivery (p<0.02, OR ∞), in addition to head circumference at birth (cm) (OR 0.8 95 % CI: 0.6-0.95), maldevelopment diagnosed at birth (p<0.001, OR ∞) and maternal antibiotic therapy postpartum (OR 6.8 95 % CI: 2.1-21.8), which were also significant in analysis A (Appendix XII).

Comparisons between mild and severe motor impairment

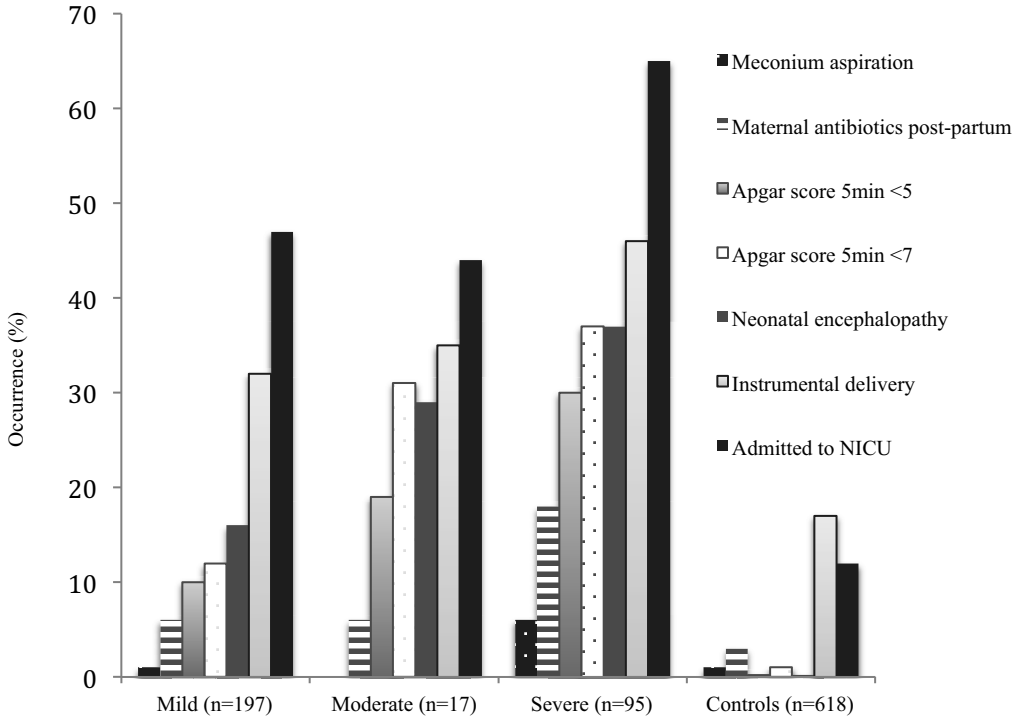
Maldevelopment diagnosed at birth, congenital infection, hepatitis, maternal addiction problems, instrumental delivery, Apgar score <7 at 5 min, maternal antibiotic therapy postpartum, admittance to neonatal intensive care unit and meconium aspiration were more common in the severe motor impairment group (Appendix X). Gestational hypertension was instead more common in the mild motor impairment group.

A multivariable analysis, only including cases was performed, using model B, in order to explore further what distinguishes the antecedent patterns in severe and mild motor impairment. Maldevelopment diagnosed at birth (p=0.001, OR ∞) was the only antecedent significantly associated with CP in the final model.

Trend analysis

There was a trend of increasing occurrence with increasing severity of motor impairment for the antecedents instrumental delivery, Apgar at 5 min <5, Apgar at 5 min <7, meconium aspiration, maternal postpartum antibiotic usage, NE and admittance to NICU (Appendix X and Figure 4).

Figure 4. Trend analysis.



Interaction analyses

To ascertain wheather antecedents have a synergistic effect, interaction analyses were performed. No such effect was found (Appendix XIII).

Neuroimaging patterns

The dominant pattern in mild motor impairment was white matter injury (OR 4.0 95 % CI: 2.1-7.7), while maldevelopment (OR 3.8 95 % CI: 1.9-7.7), cortical/subcortical lesions (OR 2.5 95 % CI1.2-4.9) and basal ganglia lesions (OR 3.9 95 % CI: 1.1-13.7) were the most common patterns in severe motor impairment (Table 19).

Table 19. Neuroimaging, according to severity of motor impairment.

Variable	Mild motor impairment			Severe motor impairment		
	Case (n=144)	OR (95 % CI)	p-value	Case (n=77)	OR (95 % CI)	p-value
Maldevelopment	12 (8 %)	0.2(0.1-0.5)	<0.001	23 (30 %)	3.8 (1.9-7.7)	<0.001
WMI	60 (42 %)	4.0 (2.1-7.7)	<0.001	10 (13 %)	0.2 (0.01-0.5)	<0.001
Cortical/subcortical lesions	20 (14 %)	0.5 (0.3-1.0)	0.06	21 (27 %)	2.5 (1.2-4.9)	0.01
Basal ganglia lesions	3 (2 %)	0.2 (0.06-0.9)	0.03	7 (9 %)	3.9 (1.1-13.7)	0.04
Miscellaneousfindings	12 (8 %)	1.1 (0.4-2.9)	1.00	6 (8 %)	0.9 (0.3-2.6)	1.00
Normal scans	37 (26 %)	1.9 (0.98-3.8)	0.07	10 (13 %)	0.4 (0.2-0.9)	0.03

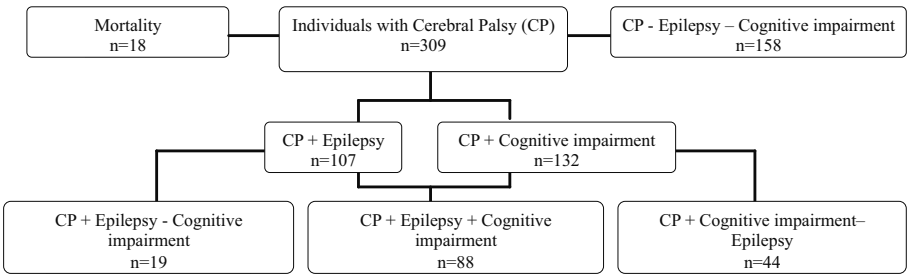
n (%) is presented for categorical variables. % is calculated on 144 cases of mild motor impairment and 77 cases of severe motor imapirment since 53 and 18 reports, respectively, were missing. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided).

To conclude, the antecedent pattern differed between different levels of motor impairment. Timing of antecedent action corresponded to neuroimaging patterns as well. Moreover, there was a trend of increasing occurrence with increasing severity of motor impairment for the antecedents instrumental delivery, Apgar at 5 min <5, Apgar at 5 min <7, meconium aspiration, maternal postpartum antibiotic usage, NE and admittance to NICU. Efforts to reduce CP with severe motor impairment will require an examination of pre-, intra- as well as postpartal antecedents.

4.2.4 Paper IV: Antecedents and neuroimaging patterns in cerebral palsy with accompanying impairments: a population-based study in children born at term

Among the 309 children with CP, 107 children had epilepsy, 132 had a cognitive impairment and 88 children had both epilepsy and cognitive impairment (Figure 5).

Figure 5. The recruited cohort. Distribution of accompanying impairments and mortality among children with CP born at term between 1983 and 1994.



Occurrence of accompanying impairments in CP varied by CP subtype and by severity of motor impairment (Table 14 and Figure 4-5). Accompanying impairments were most common in bilateral spastic CP, occuring in 64%. It was more common for children with epilepsy and cognitive impairment to have a severe motor impairment (GMFCS level IV- V), occuring in 73%.

CP and mortality

Early mortality had occurred in 17 % of the children with CP together with accompanying impairment compared to no death reported in the group with no accompanying impairements (App. XV). Mortality was recorded if death had occurred before December 31th 2009.

All individuals who died before the census date (n=18) had cognitive impairment, which was severe in 17. Fifteen had epilepsy, and the most common CP subtype was bilateral spastic CP. All individuals, but one, had a severe motor impairment (App. XV and Figure 5-7). Mean age at death was 10 years (range 2.5-24). Ten children died before reaching 10 years of age.

Figure 6. Prevalence of epilepsy, cognitive impaiment and mortality according to to different CP subtypes.

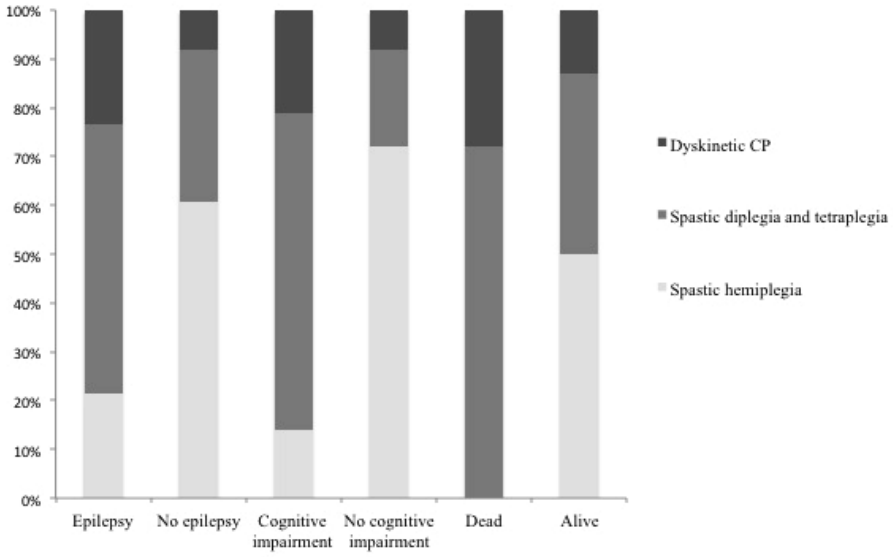
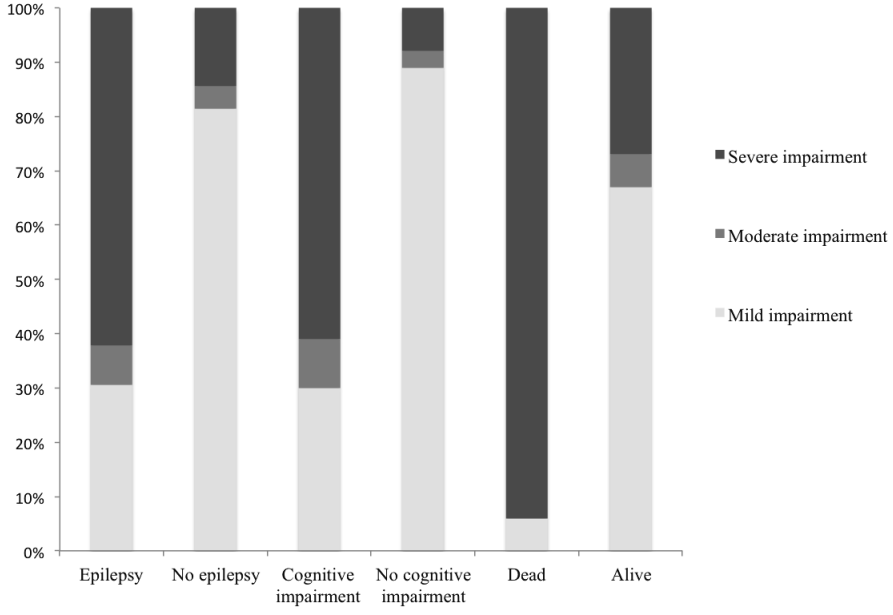


Figure 7. Prevalence of epilepsy, cognitive impaiment and mortality according to to secerity of motor impairment.



Variables significantly associated with epilepsy and the variables associated with cognitive impairment showed a substantial convergence when analysing epilepsy and cognitive impairment separately (Appendix XIV) due to the overlap between these two outcome (Figure 5). Below, the two outcome variables are presented together and are termed accompanying impairments. The analysis was performed in the 88 children with accompanying impairments using 158 children without these accompanying impairments as reference (Appendix XV).

Univariable analysis

Maternal characteristics

No statistical differences were found regarding maternal characteristics and diseases among children with CP together with accompanying impairments epilepsy and/or cognitive impairment compared to children with CP alone. Details of these factors are given in Appendix XV.

Prepartal antecedents

Poor intrauterine growth, represented by the following antecedents: birthweight, birth length, head circumference at birth, suspected SGA and SGA were significantly associated to accompanying impairments, epilepsy and cognitive impairment in CP. Early identified maldevelopment (7 %) and congenital infection (5%) were also significantly more common in these children according to univariable analyses.

Intrapartal antecedents

During the intrapartal period, the antecedents instrumental delivery, meconium stained amniotic fluid and Apgar score 5 min <7 were identifyed as related to accompanying impairments in CP. As much as 50 % of the children with accompanying impairments were delivered by instrumental delivery (caesarean section 35 %, vaccum extraction 15 %), 46 % had meconium staining in the amniotic fluid and 32 % had Apgar score <7 at 5 min.

Postpartal antecedents

It was more common among the children with epilepsy and cognitive impairment in addition to CP to have experienced neonatal infection (10 %), to develope NE (41 %) and meconium aspiration syndrome (7 %) as well as to be admitted to NICU (64 %) compared to the children with CP alone.

Multivariable analyses

Multivariable analyses were performed using two different sets of inclusion variables, to allow more exposure variables to appear. As many of the variables may be intermediates between exposure and outcome, and when significantly related to the exposure, they may prevent potentially causal variables to appear in the final model. Model A including all variables with p-values <0.1 from univariable analyses displayed the variables head circumference at birth (cm) (OR 0.8 (0.6-0.96), early identified brain maldevelopment ($p<0.001$, OR ∞) and NE (OR 6.6 95 % CI 2.8-15.3 in the final model. In multivariable analysis model B, excluding mode of delivery parameters, meconium stained amniotic fluid, Apgar score and NICU, birthweight (kg) (0.5 95 % CI 0.3-0.8) as well as neonatal infection (OR 5.4 95 % CI 1.04-28.4), not displayed in the first model, were significant, apart from early identified brain maldevelopment ($p<0.001$, OR ∞), which was also significant in analysis A (Table 20).

Table 20. Factors associated with epilepsy (EP) and cognitive impairment (CI) in CP.

	CP+ EP + CI	CP –EP – CI	Univariable analyses		Multivariable analyses[A]		Multivariable analyses[B]	
	(n=88)	(n= 157)	p-value	OR	p-value	OR	p-value	OR
Variable				(95% Conf. Int.)		(95% Conf. Int.)		(95% Conf. Int.)
Prepartum factors								
Suspected SGA	7 (8 %)	3 (2 %)	0.04	4.5 (1.1-17.7)				
Decreased SF-measurements	7 (8 %)	4 (3 %)	0.06	3.3 (0.9-11.7)				
Birth length (cm)	49.6 (3.1)	50.3 (2.5)	0.02	0.9 (0.8-0.97)				
Birthweight (kg)	3.3 (0.6)	3.5 (0.7)	0.002	0.5 (0.3-0.8)			0.003	0.5 (0.3-0.8)
Head circumference at birth (cm)	34.5 (2.2)	34.9 (1.8)	0.04	0.8 (0.7-0.97)	0.02	0.8 (0.6-0.96)		
SGA	12 (14 %)	8 (5 %)	0.03	3.0 (1.2-7.7)				
Early identified maldevelopment	6 (7 %)	1 (1 %)	0.009	11.5 (1.4-97.0)	0.02	∞	<0.001	∞
Congenital infection	4 (5 %)	0 (0 %)	0.02	(1.2-∞)				
Intrapartum factors								
Caesarean section	31 (35 %)	32 (20 %)	0.01	2.1 (1.2-3.8)				
Instrumental delivery	44 (50 %)	47 (30 %)	0.002	2.4 (1.4-4.1)				
Meconium-stained amniotic fluid	35 (46 %)	30 (23 %)	0.001	2.9 (1.6-5.4)				
Apgar score at 5 minutes < 7	26 (32 %)	24 (16 %)	0.004	2.6 (1.4-4.8)				
Postpartum factors								
Neonatal infection	9 (10 %)	3 (2 %)	0.01	5.9 (1.6-22.4)			0.03	5.4 (1.04-28.4)
Antibiotic therapy	14 (16 %)	12 (8 %)	0.06	2.2 (0.99-5.1)				
Meconium aspiration	6 (7 %)	0 (0 %)	0.002	(2.2-∞)				
NE	36 (41 %)	22 (14 %)	<0.001	4.3 (2.3-8.0)	<0.0001	6.6 (2.8-15.3)		
Admitted to NICU	53 (64 %)	73 (47 %)	0.02	2.0 (1.1-3.4)				

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U test was used for continuous variables. Caesarean section (elective, acute, emergency), instrumental delivery (caesarean section, vaccum extraction). The odds ratio (OR) and 95 % confidence interval (Conf. Int.) for a child of being diagnosed with CP and epilepsy and cognitive impairment were calculated for every study variable, using children without epilepsy and cognitive impairment as references. The estimates for birthweight are calculated to show the increased risk of CP per kg of body weight. Forward logistic regression was used for multivariable analyses. Multivariable analyses model A included all variables with p<0.1 from univariable analyses (SIII), model B included all the variables <0.1 from univariable analyses (SIII) except Apgar, NICU, mode of delivery parameters, meconium stained amniotic fluid and NE.

Neuroimaging

Given the time period studied, neuroimaging had been performed in 76 %, in 236 of 309 individuals (76 %), 75 of 88 with both accompanying impairments (53 CT, 22 MRI), and in 109 of 157 without accompanying impairments (95 CT, 14 MRI). Neuroimaging was performed with CT in 85 %.

Analysis of neuroimaging patterns in children with accompanying impairments in CP revealed that the most common pattern was maldevelopment (28 %) followed by cortical/subcortical lesions (28 %) and WMI (17 %) Basal ganglia lesions occurred in 7 % and miscellaneous lesions in 9 %. Normal findings occurred in 11 % of the reports (Table 21).

Table 21. Neuroimaging patterns in children with CP and epilepsy and cognitive impairment.

			Univariable analyses		Multivariable analyses	
Variable	**CP+EP+CI (n=75)**	**CP-EP-CI (n=108)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Maldevelopment	21 (28%)	9 (8%)	0.001	4.3 (1.8-10.0)	<0.001	7.2 (2.9-17.2)
WMI	13 (17%)	50 (46%)	<0.001	0.2 (0.1-0.5)		
Cortical/subcortical lesions	21 (28%)	12 (11%)	0.006	3.1 (1.4-6.8)	<0.001	5.4 (2.3-12.3)
Basal ganglia lesions	5 (7%)	2 (2%)	0.12	3.8 (0.7-20.1)	0.01	7.7 (1.4-41.8)
Miscellaneous findings	7 (9%)	7 (6%)	0.57	1.8 (0.6-5.4)		
Abnormal scans	67 (89%)	79 (73%)	0.008	3.1 (1.3-7.2)		

n (%) is presented for categorical variables. % was calculated on 75 CP+EP+CI cases and 108 CP-EP-CI cases since 13 and 49 reports were missing Fisher´s Exact test was used for comparison between groups or dichotomous variables and for p-value (2-sided). Logistic regression forward selection was used in multivariable analysis (miscellaneous findings and abnormal scans not included).

Analyses were also performed to ascertain whether identified antecedents were associated with certain neuroimaging patterns. As can be observed in table 22, children with maldevelopment more often had undergone a congenital infection, were significantly shorter, had a smaller head circumference and less co-habitation with the childrens father compared to children with other neuroimaging patterns. However, intrapartum and postpartum adverse events were less likely to have occurred in children with maldevelopment. Furthermore, none of these children had an Apgar score <7 at 5 minutes. They were less likely to have meconium-stained amniotic fluid, to have sustained NE and to have been admitted to the NICU compared to children with other neuroimaging patterns. A similar pattern was found in WMI where few children had Apgar score <7 at 5, NE and were admitted to NICU.

A different pattern was identified for the children with subcortical/cortical and basal ganglia lesions in where intrapartum and postpartum adverse events were more likely to have occurred. Meconium stained amniotic fluid, Apgar score <7 at 5 minutes, meconium aspiration, NE and admittance to NICU were much more common (Table 23) among those children. The temporal difference among the antecedents related to the different neuroimaging patterns is further highlighted in the multivariable analysis (Table 22-23).

Table 22. Associations between antecedents and neuroimaging findings among children with CP

	Maldevelopment (n=39)					WMI (n=74)				
		Univariable		Multivariable			Univariable		Multivariable	
Variable	**n (%)**	**p-value**	**OR (95 % CI)**	**p-value**	**OR (95 % CI)**	**n (%)**	**p-value**	**OR (95 % CI)**	**p-value**	**OR (95 % CI)**
Prepartum factors										
Birthweight (kg)	3.3 (0.5)	0.11	0.7 (0.4-1.2)			3.4 (0.7)	0.40	1.1 (0.7-1.7)		
Birth lengtht (cm)	48.7 (2.3)	<0.001	0.8 (0.7-0.9)	<0.001	0.6 (0.5-0.8)	50.2 (2.9)	0.62	1.0 (0.9-1.1)		
Head circumference at birth (cm)	34.0 (2.1)	0.01	0.8 (0.6-0.9)			35.2 (1.9)	0.15	1.1 (1.0-1.3)		
Suspected SGA	2 (5 %)	1.00	0.8 (0.2-3.9)			5 (7 %)	0.77	1.2 (0.4-3.8)		
SGA	3 (8%)	0.78	0.7 /0.2-2.6)	0.001	0.05 (0.006-0.4)	10 (14 %)	0.23	1.8 (0.8-4.4)		
Non cohabitation with baby's father	6 (16 %)	0.03	3.4 (1.2-10.1)			0 (0 %)	0.004	0	<0.001	0
Congenital infection	3 (8 %)	0.03	8.1 (1.3-50.4)			1 (1 %)	1.00	0.5 (0.06-4.9)		
Intrapartum factors										
Caesarean section	11 (28 %)	0.85	1.1 (0.5-2.3)			19 (26 %)	0.88	0.9 (0.5-1.7)		
Instrumental delivery	13 (33 %)	0.59	0.8 (0.4-1.6)			22 (30 %)	0.11	0.6 (0.3-1.1)		
Meconium-stained amniotic fluid	4 (13 %)	0.02	0.3 (0.09-0.8)			26 (39 %)	0.11	1.7 (0.9-3.1)	0.04	2.3 (1.04-5.2)
Apgar score at 5 minutes < 7	0 (0 %)	<0.001	0			7 (10 %)	0.005	0.3 (0.1-0.7)		
Postpartum factors										
Antibiotic therapy postpartum	7 (18 %)	0.06	2.8 (1.1-7.5)			2 (3 %)	0.03	0.2 (0.05-0.9)		
Neonatal infection	2 (5 %)	1.00	0.9 (0.2-4.3)			2 (3 %)	0.36	0.4 (0.08-1.8)		
Meconium aspiration	0 (0 %)	0.60	0			0 (0 %)	0.10	0		
NE	3 (8 %)	0.003	0.2 (0.06-0.7)			8 (11 %)	<0.001	0.2 (0.1-0.5)	<0.001	0.2 (0.07-0.5)
Admitted to NICU	15 (41 %)	0.048	0.5 (0.2-0.99)			27 (38 %)	0.001	0.4 (0.2-0.6)		

Table 23. Associations between antecedents and neuroimaging findings among children with CP

		Cortical/subcortical & basal ganglia lesions (n=53)			
		Univariable		Multivariable	
Variable	**n (%)**	**p-value**	**OR (95 % CI)**	**p-value**	**OR (95 % CI)**
Prepartum factors					
Birthweight (kg)	3.5 (0.7)	0.13	1.4 (0.9-2.1)		
Birth lengtht (cm)	50.9 (2.7)	0.02	1.2 (1.0-1.3)		
Head circumference at birth (cm)	35.1 (1.8)	0.21	1.1 (0.9-1.3)		
Suspected SGA	3 (6 %)	1.00	0.9 (0.3-3.5)		
Small for gestational age	4 (8 %)	0.79	0.7 (0.2-2.2)		
Non cohabitation with baby's father	4 (8 %)	0.76	1.2 (0.4-3.8)		
Congenital infection	0 (0 %)	0.59	0		
Intrapartum factors					
Caesarean section	18 (34 %)	0.22	1.5 (0.8-3.0)		
Instrumental delivery	25 (47 %)	0.11	1.7 (0.9-3.1)		
Meconium-stained amniotic fluid	22 (48 %)	0.01	2.5 (1.3-4.9)		
Apgar score at 5 minutes < 7	21 (40 %)	<0.001	3.5 (1.8-6.9)		
Postpartum factors					
Antibiotic therapy postpartum	7 (13 %)	0.27	1.8 (0.7-4.7)	0.03	4.0 (1.2-14.0)
Neonatal infection	5 (9 %)	0.17	2.3 (0.7-7.3)		
Meconium aspiration	5 (9 %)	0.007	9.4 (1.8-50.1)		
Neonatal encephalopathy	29 (55 %)	<0.001	5.5 (2.8-10.6)	<0.001	7.3 (3.1-17.5)
Admitted to NICU	43 (83 %)	<0.001	5.2 (2.4-11.4)		

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables and the Mann-Whitney U test was used for continuous variables. OR (95 % CI) =Odds Ratio and 95 % Confidence Interval. The estimates for birthweight are calculated to show the increased risk of brain lesion per kg of body weight. Caesarean section (elective, acute, emergency), instrumental delivery (caesarean section, vaccum extraction). and for p-value (2-sided) and the Mann-Whitney U test was used for continuous variables. Multivariable analysis, forward selection was used and all variables displayed in the table was included.

In conclusion, no additional factor other than those related to motor impairment was associated to accompanying impairments in CP. The timing of injury suggested by the antecedents found, was in agreement with neuroimaging patterns.

4.3 Neuroimaging

The role of neuroimaging in the different CP subtypes was also investigated. Neuroimaging was performed in 236 of 309 children with CP. Neuroimaging was performed with CT in 201 cases and with MRI in 35 cases.

As can be observed in Table 24-25, the dominating neuroimaging pattern for both spastic CP and the total CP group was WMI, representing patterns of prepartal origin (58), occuring in 36 % and 32 %, respectively. However, no child with dyskinetic CP had this neuroimaging pattern. Instead, patterns of subcortical/cortical injury (26 %) and basal ganglia lesions (26 %), of presumed late antepartum or intra- and postpartum origin (58) were most common in this CP subgroup. Maldevelopment was most common among children with spastic diplegia and tetraplegia, present in 25 % of the neuroimages in this group. Normal images were equally common in all subgroups, ranging from 20 % -24 %.

Table 24. Neuroimaging according to CP subtypes

	All CP	Spastic CP			Dyskinetic CP		
Variable	Case (n=236)	**Case (n=205)**	**p-value**	**OR (95% CI)**	**Case (n=31)**	**p-value**	**OR (95% CI)**
Maldevelopment	33 (14 %)	35 (17 %)	0.80	1.4 (0.5-4.2)	4 (13 %)	0.80	0.7 (0.2-2.1)
WMI	74 (31 %)	74 (36 %)	<0.001	*	0 (0 %)	<0.001	*
Cortical subcortical	42 (18 %)	34 (17 %)	0.21	0.6 (0.2-1.4)	8 (26 %)	0.21	1.7 (0.7-4.2)
Basal ganglie	11 (5 %)	3 (2 %)	<0.001	0.04 (0.01-0.2)	8 (26 %)	<0.001	23.4 (5.8-94.5)
Miscalleneous	19 (8 %)	15 (7 %)	0.29	0.5 (0.2-1.7)	4 (13 %)	0.29	1.9 (0.6-6.1)
Normal	51 (22 %)	44 (22 %)	0.82	0.9 (0.4-2.3)	7 (23 %)	0.82	1.1 (0.4-2.6)

Neuroimaging was performed with CT in 201 cases and with MRI in 35 cases. n (%) is presented for categorical variables. 62 reports were missing in the spastic CP group and 11 reports in the dyskinetic CP group. % is therefore counted on 205 cases of spastic CP and 31 cases of dyskinetic CP. Fisher´s Exact test was used for comparison between groups or dichotomous variabless. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. Logistic regression was performed were spastic CP and dyskinetic CP, respectively, were compared with the all other CP subtypes.

Table 25. Neuroimaging according to CP subtypes

	Spastic diplegia and tetraplegia			Spastic hemiplegia		
Variable	**Case (n=92)**	**p-value**	**OR (95% CI)**	**Case (n=113)**	**p-value**	**OR (95% CI)**
Maldevelopment	23 (25 %)	0.007	2.7 (1.3-5.4)	12 (11 %)	0.02	0.4 (0.2-0.9)
WMI	22 (24 %)	0.06	0.6 (0.3-1.0)	52 (46 %)	<0.0001	3.9 (2.2-7.1)
Cortical subcortical	16 (17 %)	1.00	0.96 (0.5-1.9)	18 (16 %)	0.50	0.8 (0.4-1.5)
Basal ganglie	2 (2 %)	0.21	0.3 (0.07-1.6)	1 (1 %)	0.01	0.1 (0.01-0.8)
Miscalleneous	7 (8 %)	1.00	0.9 (0.3-2.4)	8 (7 %)	0.64	0.8 (0.3-2.0)
Normal	22 (24 %)	0.52	1.2 (0.7-2.3)	22 (20 %)	0.53	0.8 (0.4-1.5)

n (%) is presented for categorical variables. Fisher´s Exact test was used for comparison between groups or dichotomous variables. % i calculated on 92 cases of spastic diplegia and tetraplegia and 113 cases of spastic hemiplegia since 29 and 33 reports were missing. Logistic regression was performed were spastic diplegia and tetraplegia and spastic hemiplegia respectively were compared with the all other CP subtypes.

4.4 Apgar score

Apgar <7 at 5 min is the most commonly used choice of measurement point regarding Apgar score in CP studies and is therefore the measurement point used in the studies described in this thesis. However, a thorough analysis of the different measurements points in the different CP subtypes was also performed.

Demonstrated in Table 26, low Apgar scores where most common in the group with dyskinetic CP, followed by spastic diplegia and tetraplegia and least common in the group with spastic hemiplegia. This was the overriding pattern at all three measurement points, 1 min, 5 min and 10 min. At 1 min, 75 % of the children with dyskinetic CP had an Apgar score <7 compared to 11 % of the children with spastic hemiplegia. At 10 min, still 60 % of the children with dyskinetic CP had an Apgar score <7 while only 4 % of the children with spastic hemiplegia had low Apgar scores. There were no statistical difference regarding cases and controls in the group with spastic hemiplegia when studying Apgar scores <3 at 5 min and <5 at 10 min.

Table 26. The occurence of low Apgar scores according to different CP subtypes.

	1 min			5 min			10 min		
Variable	**Case**	**Control**	**p-value**	**Case**	**Control**	**p-value**	**Case**	**Control**	**p-value**
Spastic and Dyskinetic CP		Case (n=309)	Control (n=618)						
Apgar <3	54 (18 %)	3 (1 %)	<0,0001	16 (5 %)	1 (0.5 %)	<0,0001	6 (2 %)	2 (0.5 %)	0,0423
Apgar <5	66 (22 %)	5 (1 %)	<0,0001	50 (17 %)	1 (0.5 %)	<0,0001	29 (10 %)	2 (0.5%)	<0,0001
Apgar <7	80 (27 %)	20 (3 %)	<0,0001	62 (21 %)	6 (1 %)	<0,0001	44 (15 %)	2 (0.5 %)	<0,0001
Spastic CP		Case (n=267)	Control (n=534)						
Apgar <3	31 (12 %)	2 (0.5 %)	<0,0001	8 (3 %)	0 (0 %)	0,0003	1 (0.5 %)	1 (0.5 %)	1
Apgar <5	37 (14 %)	4 (1 %)	<0,0001	25 (10 %)	0 (0 %)	<0,0001	15 (6 %)	1 (0.5 %)	<0,0001
Apgar <7	50 (19 %)	16 (3 %)	<0,0001	34(13 %)	4 (1 %)	<0,0001	20 (8 %)	1 (0.5 %)	<0,0001
Diplegic and Tetraplegic CP		Case (n=121)	Control (n=242)						
Apgar <3	23 (20 %)	1 (0.5 %)	<0,0001	7 (6 %)	0 (0 %)	0,0007	1 (1 %)	0 (0 %)	0,6923
Apgar <5	27 (23 %)	2 (1 %)	<0,0001	20 (17 %)	0 (0 %)	<0,0001	11 (9 %)	0 (0 %)	<0,0001
Apgar <7	35 (30 %)	9 (4 %)	<0,0001	25 (21 %)	3 (1 %)	<0,0001	15 (13 %)	0 (0 %)	<0,0001
Hemiplegic CP		Case (n=146)	Control (n=292)						
Apgar <3	8 (6 %)	1 (0.5 %)	0,015	1 (1 %)	0 (0 %)	0,6575	0 (0 %)	1 (0.5 %)	1.0000
Apgar <5	10 (7 %)	2 (1 %)	0,0008	5 (4 %)	0 (0 %)	0,0073	4 (3 %)	1 (0.5 %)	0,0876
Apgar <7	15 (11 %)	7 (2 %)	0,0011	9 (6 %)	1 (0.5 %)	0,0005	5 (4 %)	1 (0.5 %)	0,0338
Dyskinetic CP		Case (n=42)	Control (n=84)						
Apgar <3	23 (58 %)	1 (1 %)	<0,0001	8 (20 %)	1 (1 %)	0,001	5 (13 %)	1 (1 %)	0,0363
Apgar <5	29 (73 %)	1 (1 %)	<0,0001	25 (63 %)	1 (1 %)	<0,0001	14 (35 %)	1 (1 %)	<0,0001
Apgar <7	30 (75 %)	4 (5 %)	<0,0001	28 (70 %)	2 (2 %)	<0,0001	24 (60 %)	1 (1 %)	<0,0001

5 DISCUSSION

5.1 Methodological considerations

The main strength of this thesis is the population-based design. In a population-based case-control study all cases of the disease that you want to study within a given geographical area and occurring over a particular period of time are investigated. Controls are selected by taking a sample from the disease-free individuals in the same study population. Strengths of the case-control design are that it allows the analysis of several possible causes of the disease and it is very good at evaluating rare diseases. Case-control studies can provide important scientific knowledge with relatively little time, money and effort compared to other study designs. However, several limitations and challenges exist. Case control studies are particularly prone to bias, in particular selection and recall bias compared to other analytic design and there is also a risk of misclassification of exposure (150, 151).

Selection bias can occur whenever the inclusion of cases or controls into the study depends, in some way, on the exposure of interest. In the present thesis, the population-based design avoided the selection bias. Information (recall/observation) bias or errors in obtaining information from subjects once they have been entered in the study may also be a particular problem in a case-control design. In our studies the potential for errors in obtaining information must be considered. As with most retrospective studies, the quality of some data may be suboptimal. In particular, this may apply to the variables that are not standardized asked questions that is posed to all pregnant women (e.g. infection during pregnancy, antibiotic use during pregnancy), where the reporting may be incomplete. However, data in cases and controls were recorded in the same manner. Strength in our study is the standardized medical record templates used during pre- and intrapartal care. Misclassification refers to errors in the categorization of either exposure or disease status. Misclassification of the disease status or outcome was minimizes by detecting the cases through the very complete and accurate system of CP registration in western Sweden using multiple sources. The studies are based on data from the western CP register, which have provided a large study size and comprehensive population coverage. The possibility of random (non-differential) misclassification of the exposure cannot be excluded in the present studies.

Moreover, in case-control studies it is important that the controls come from the same population as the cases and selection of the controls should be independent of the exposures of interest. Researchers need also to collect data without knowledge of whether the data comes from case or control. Finally, the investigators should consider confounding in case-control studies, either at the design stage or by using analytical techniques. Taking into account these points increases the validity of the results and the confidence in the results is strengthened with the reader (152).

For the purpose of this thesis, the control participants were selected by identifying the child born immediately before and after the index case in each hospital. Only two persons carried out the data gathering, blinded to the outcome, and sat together while gathering the first data to ensure consistency in recording. A validation on data collection was also performed in where an independent researcher independently reviewed 20 of the obstetric records and compared the files to the recorded data in the database looking for any inconsistencies. No major inconsistencies were found.

Each case CP was matched with 2 control participants. Using a random sample would result in substantial confounding. To overcome confounding in the design and sampling stage the controls were matched for known confounding factors (sex, gestational age, place of birth, and multiple births). According to Schlesselmann, matching increases the efficiency of the study when the matching variable is a very strong determinant, but will actually reduce it when the matching is strongly related to the exposure. This is referred to as over-matching. The effect of the confounder itself on the risk of the outcome cannot be explored (153). When analyzing the data in a matched case-control study, each case and its controls perform one straum. In an individually matched case-control study, if either case or control has missing data, then the entire stratum is lost for analysis. Matching that is accompanied by an unmatched analysis can reduce the validity of case-control comparisons. An analysis that ignored the matching will result in an odds ratio biased toward conservatism (153, 154). Attempts were made to analyse taking advantage of the matching to controls, using survival analyses. Unfortunately, antecedents with strong associations to outcome and rarely occuring in the control group, failed to reach significance due to that the number in the control group got unfairly strong influence on the result unabeling us to use this method.

The large amount of risk factors and potential causes and timing of events in CP (2) make the choice of analytic method, inclusion of potential confounders and interpretation of results difficult (154). Philosophical and theoretical knowledge are necessary for including and taking into account the adequate possible confounding factors. Control of confounders was achieved in the study design, through matching, but also by adjusting simultaneously in the multivariable logistic regression model. The difficulty lies in evaluating and giving the associated factors discovered in the research the relevant significance. Associations between a a study variable/exposure and outcome can arise because of a cause and effect relationship, because the variable is part of a causal pathway (Figure 8.1), because the variable is confounded by the real cause (Figure 8.2), because some other factor(s) affect both the study variable and outcome (Figure 8.3) or because a mix of all is true (Figure 8.4). Different scenarios describing the different role antecedents can play and how complicated the interpretation of significant results can be are explainded elegantly by Hernandez-Diaz et al. (155).

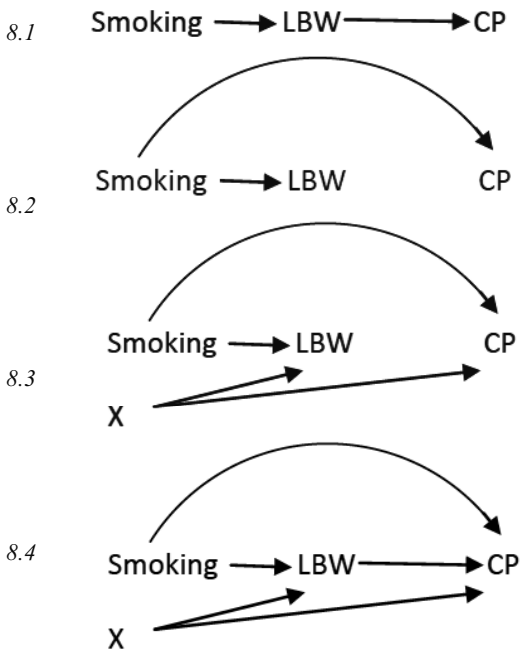


Figure 8. Causal structure demonstrating some of the different scenarios possible when having identified a significant antecedents, exemplified here by low birth weight (LBW) and the roles it can play in the association between a prepartal antecedents, smoking and CP. X, other unmeasured antecedent (e.g infection, maternal weight, maldevelopment).

Claiming that the studies described in this thesis helps to identify children early would be too bold. The associations found do not mean that the associations are causal. Even if a child does have an antecedent or a risk factor for CP; it does not mean that the child will develop CP. It just means that the risk of the child having CP is increased. However, studying antecedents associated with CP according to severity of motor impairment may generate hypotheses for the mechanisms of injury and ultimately help to prevent severe brain injury in that it give us clues on what we should focus our preventive strategies on and when those strategies might be effective. The knowledge provided by this thesis is, for example, that efforts to prevent CP with severe motor impairment seem to require examination of pre-, intra- as well as postpartal risk factors. Improved knowledge of when and how the injury has occured may also be important for prognosis and planning of the later treatment for the child.

The large amount of antecedents analysed lead to a risk of receiving false positive significanses. The question of whether adjustment is needed for multiple comparisons arises in explorative observational studies with large bodies of data. The argument is to reduce type I error and not reject the null hypothesis too easily. However, it can also be argued, that it is better not to adjust for multiple comparison, in order not to miss any important findings by increasing type II errors (156). In addition, we are analysing many variables; however, they are highly correlated. Many of these variables are describing the same phenomena, for example, poor intrauterine growth is elucidated by the variables; birth length, birth weight, head circumference, suspected SGA (through ultrasound), decreasing SF measurements and SGA. The same phenomena could be captured by several variables at different timepoints during gestation. Therefore, using simple Bonferroni correction would also be too conservative and would not give us the true picture. With a large number of partly correlated variables we calculated the effective number of tests using a permutation procedure. The effective number of tests was estimated to 29. Strengh in associations, plausability of association, consistency with previous studies and analogy among similar study variables provided guiding in determination of true associations. Moreover, a heatmap was constructed for overview of the correlation between important study variables (Figure 9). Relations between study variables are also presented in Appendix XIV and will be discussed throughout the Discussion of results.

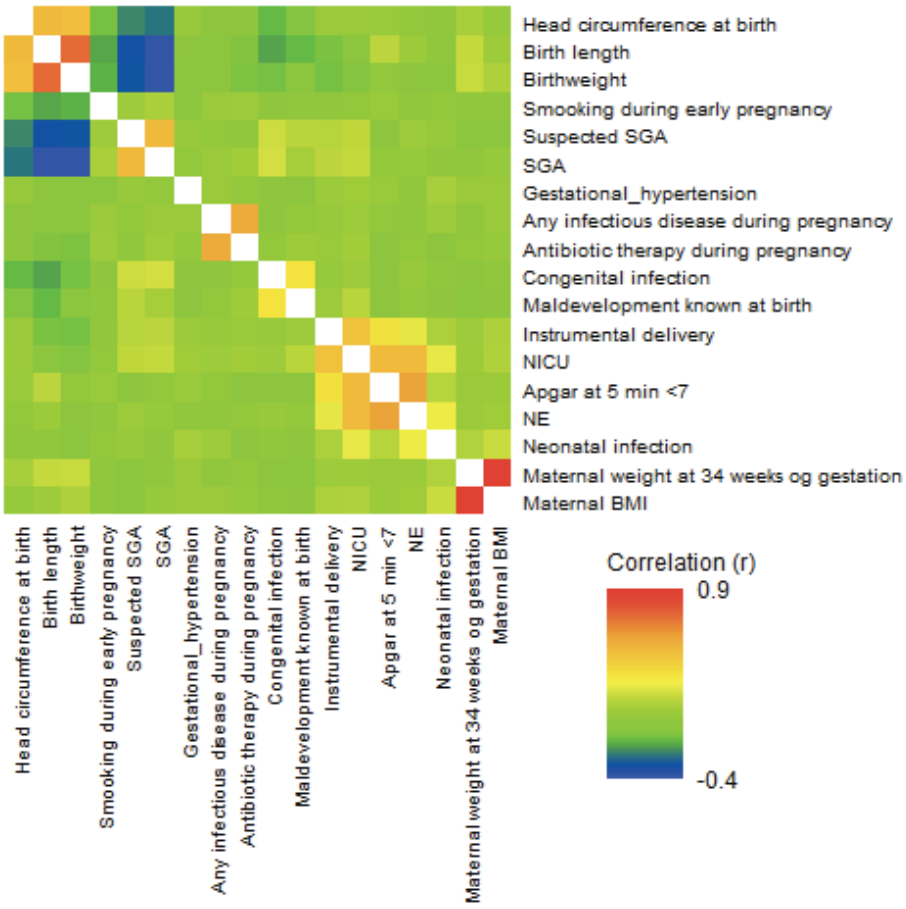


Figure 9. The figure illustrates correlations between important study variables.

We performed logistic regression using two different sets of inclusion variables, to allow more potential exposure variables to appear. As many of the variables may be intermediates between exposure and outcome, and when significantly related to the exposure, they may prevent exposure variables to appear in the final model. We have excluded variabels that are not etiological factors in themselves, but hightly correlated to outcome and therefore potentially blocking for other variables to appear in the model. Some of the excluded variables may have multiple causes and therefore become stronger correlated to outcome than the possible etiologic factor (ie admittance to NICU) and therefore, prevents the potentially causative factor from appearing in the final model.

The occurrence of interactions may be important for the interpretation of statistical models. If two relevant variables interact, the relationship between each of the interacting variables and the third "dependent variable" (in this thesis CP) depends on the value of the other interacting variable (Figure 10). In practice, this makes it difficult to predict the impact of changing the value of a variable, especially if the variables that it interacts with are difficult to measure or difficult to control (157, 158). Interaction analysis (Appendix XIII) were performed and are presented in Study III, to test the potential interplay between the identified antecedents.

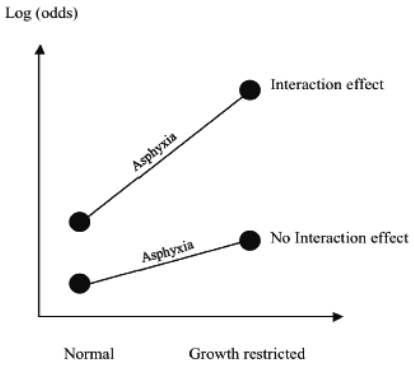


Figure 10. The figure illustrates that when there is an interaction effect between growth restriction and asphyxia, the log (odds) increase.

Neuroimaging was available in 80 % of cases. We did not have information on brainimaging in controls. In addition, most brainimaging examinations were performed with CT scans and not with MRI, since CT was custom at the time.

A limitation on generalizability was that data was analyzed on babies born >20 years ago. The age of the data enabled us to do a study of early mortality in these birth-year cohorts. The significance of the findings is not affected by age, most data is recorded in the same way today. However, the age of data was relevant for the neuroimaging reports that were not so frequently present in the past, and were most often done with CT scans.
The possibly several-year separation between the analysed antecedents and CP, epilepsy and cognitive impairment must be borne in mind, as much can occur during those years to obscure any correlation observed.

In summary, the validity of the results rest on the study design, on the data collection and analysis as well as in the consistency with previous result and with biological plausibility, confirmed by neuroimaging. The results from our study provide basis for future, confirmatory studies, with more recent data, more complete and higher quality neuroimaging reports.

5.2 Discussion on results

CP is a very diverse and complex condition and it does not have a clear-cut single cause. This condition encompasses a wide variety of causes, expressions of motor impairment, levels of severity and associated issues. Moreover, the injury to the developing brain causing CP occurs before, during, as well as after the child's birth.

The characteristics of antecedents and timing of events in the different CP subtypes and severities of motor impairment have not been fully explored. Infants born at term contribute to the majority of CP cases and their CP tends to be more disabling (6). Moreover, its prevalence is not declining (6, 26, 159).

Although CP is defined as a motor disorder, it is often accompanied by cognitive impairment, epilepsy, and sensory disabilities. No cure is available, so effective strategies for primary prevention is highly desirable, but the development of these requires an understanding of causal pathways.

Thus, the aim of this thesis was to identify antecedents that may be components of aetiological pathways to different CP subtypes and severities of motor impairment as well as to accompanying impairments in CP in children born at term, using data from a population based CP register.

The findings demonstrates the diversity in timing of events as well as the diversity in associated antecedents for different CP subtypes and severities of motor impairment.

5.2.1 Prepartal antecedents

Sociodemographic factors
Non cohabitation with the baby's father was associated with the total CP group and with the group with spastic diplegia and tetraplegia. It is unclear what this variable is indicating, but in previous studies, non cohabitation has shown to increase the odds of smoking, alcohol abuse as well as low birth weight (160, 161).

Recent studies in the US and Europe have found an increased risk of CP associated with socio-economic disadvantage (96, 162-167). According to Dolk et al, cases of CP classified as spastic bilateral had a stronger association with socio-economic disadvantage than did other CP types (165) which are in accordance with our findings. Further research is needed into the

causal mechanisms underlying the associations between socio-economic disadvantage and CP.

Our study was able to confirm associations of CP with smoking but not with alcohol use and illicit drug use, although maternal retrospective reporting bias may have influenced the data analyzed for these measures. Maternal smoking was related to the group with severe motor impairment, occuring in as much as 40 % in this group. Smoking during pregnancy has previously been reported associated with CP (168). Pregnant women who smoke are also at greater risk of delivering a growth-restricted infant than nonsmoking mothers (67, 68, 70). This is consistent with our findings. Cigarette smoke with reduction in blood flow has previously been shown to increase apoptosis, and it is possible that this could be one of the mechanisms playing a role in the growth restriction (71) as well as in the development of brain injury by the creation of a pathological hypoxic environment for the fetus (67) Moreover, smoking has also been associated with vaginal infections (72).

Hypertensive disorder

Hypertensive disorder in pregnancy has been shown to be an independent risk factor for CP (111, 112). However, there has been controversy regarding whether pre-eclampsia is associated with increased risk of CP (169, 170). Hypertension was not associated to CP, according to adjusted analysis. However, we found that pre-eclampsia and gestational hypertension were associated with poor intrauterine growth in our material. The relation between children born SGA and gestational hypertension is supported by previous findings (171).

SGA

Children born SGA are at increased risk of developing CP (2, 77, 101, 168, 172, 173). Low birthweight is also known to increase the risk for perinatal mortality and morbidity (74, 75, 168, 174). Birth weight was associated to the total group of CP, according to our findings. In a study by Freire et al. children with CP born SGA had a more severe motor impairment, communication difficulties and a higher frequency of cognitive impairment (171), which our data is also indicating.

It has been assumed that growth-restricted fetuses are especially susceptible to asphyxial injury at birth and that birth asphyxia is the link between growth restriction and CP. We found that birth length and head circumference at birth were related to low Apgar score which would be in line with this hypothesis. However, other large population-based studies have failed to confirm this hypothesis (114, 172, 175) and in yet another population-based study, brain imaging in growth-restricted children with CP did not suggest

global hypoxia–ischemia (126). A complex and dynamic interaction of maternal, placental and fetal environment is involved in ensuring normal fetal growth. An imbalance or lack of coordination in this complex system may lead to growth restriction (176-179).

A recent study examined the placental characteristics of infants eligible for hypothermic cooling and found 48 % had a placental weight <10th percentile (180). We found that low placental weight were associated with mild motor impairment. However, a recent study identified placental weight/birth weight as a predictor of short-term health risks for newborns and NE (181). Heavy placentae were also noted in a recent study by Chang *et al* reviewing placental reports of newborns with moderate to severe NE admitted for therapeutic hypothermia (182). However, one study by Wintermark showed that a growth-restricted placenta seemed to have a protective effect on risk of developing brain injury. It has been hypothesized that a growth-restricted placenta can act as an "ischemic preconditioning" in the brain and produce protection of the brain against other causes of fetal distress (180). The weight of the placenta and its imporance for adverse outcome seems unclear.

However, the placenta partially is a reflection of the environment of the fetus and can reveal underlying processes (eg, inflammations, hypoxia), which directly affect the development of brain injury. Prepartal processes in the placenta may contribute directly or indirectly to the brain injury by detracting nutrition, change fetal physiological state, and generate potentially neurotoxic substances. Chronic oxygen deficiency, malnutrition and altered endocrine status are seen in fetuses exposed to chronic placental insufficiency. Typically, this occurs as a result of a chronic deterioration of the exchange function of the placenta. Generally, placental insufficiency is due to factors that affect the uterine blood flow, umbilical cord blood flow or the placental exchange barrier (183).

Recent reports indicate that there are lesions in the placenta in three-quarters or more of infants with perinatal brain injury (180, 184-186). Placental histology was not studied for the purpose of this thesis since it was not routinealy described, investigated and documented. However, the placenta may be an important source of information about brain injury and the correlations between the placenta and clinical data is likely to play an important future role in perinatal medicine. The increased prevalence of abnormalities in the placenta of children who later receive a diagnosis CP underlines the importance of requesting placental histology in all cases where the child is in poor condition at birth (187). Interestingly, MRI has been studied as a noninvasive diagnostic method for early in-utero detection of placental inflammation and might lead to earlier intervention (188).

Both maternal and fetal etiologies are involved in IUGR. Maternal etiologies involve reduced blood volume, decreased uteroplacental blood flow, reduced oxygen-carrying capacity, teratogens, nutritional status as well as short interpregnancy intervals, race, low socioeconomic status and maternal age. Fetal etiologies consists of congenital malformations, genetic diseases, multiple pregnancies, infections, placental/umbilical cord abnormalities (2). According to our data, maternal infection, maternal antibiotic use during pregnancy, maternal weight, maternal BMI and smoking were associated to birth weight.

There are no studies suggesting that when IUGR is suspected during pregnancy, early delivery reduces the risk of CP. Detection or prediction on when the neuropathology of CP begins to be established, or when it becomes irreversible is not possible. A growth restricted fetus may show signs of distress during childbirth. It is not possible to distinguish wheather this reflects reduced capacity/reserves to cope with the normal stresses of birth or if it is an already established and ongoing neurological injury, or both. Distinguishing between these timings is not possible (189, 190).

Maternal weight may itself be a risk factor for CP, or a marker for a certain metabolic condition. Low weight of the mother has been connected to low birth weight. The highest risk has been observed among women with low BMI and inadequate weight gain (28). Wee found maternal BMI and maternal weight at week 34 to be associated with birth weight. The risk of a number of pregnancy-related complications, such as chronic hypertension, preeclampsia and eclampsia, abnormalities in angiogenesis and diabetes is increased among women with a high weight (191) . This is in line with our findings in where we found maternal BMI being associated with gestational hypertension. Moreover, women with a high BMI have an increased risk of having children with neural tube defects, and folate supplementation seems to work less well in preventing these defects (192). Thus, the relationship between risk factors related to maternal body habitus and various efforts to improve outcome should be further explored.

These findings suggest that enhanced monitoring and early intervention for infants with suspected low birthweight is warranted. Knowledge of the etiologies of fetal growth restriction is essential, so that future care can be targeted at prevention.

Neonates with poor growth are also more likely to have birth defects than those with normal growth (172, 193). This is in accordance with our findings where we found that a neuroimaging finding of maldevelopment was associated with short birth length and small head circumference. Moreover, among infants with fetal growth restriction, the presence of maldevelopment

have marked those at special risk for CP (172).

Maldevelopment

The prevalence of congenital anomalies in children with CP is much higher than in the general population and most are cerebral (2, 52, 54, 55, 70, 105, 106, 126, 194-199). Maldevelopment has been reported to occur in 11-13 % of individuals with CP (3, 6, 21, 65). However, because some children with severe congenital abnormalities, especially in the CNS, die before the age of 3 years, the proportion of CP attributable to congenital abnormalities is often underestimated (200). In our material, brain malformatin known at birth occured in 7 % of the children with CP with accompanying impairments and in 8 % of those with severe motor impairment. According to neuroimaging records 14 % of the total group of CP had neuroimaging patterns of maldevelopment. Most children with brain maldevelopment have severe motor impairment (3, 38) which are in accordance with our findings.

Furthermore, a previous study found that CNS abnormalities was more common among children with spastic quadriplegia than among children with diplegia or hemiplegia, a finding consistent with data from the NCPP (200, 201). In addition, Croen et al found that children with CP were 5 times as likely to have congenital malformations as were children without CP (200). Most common are abnormalities in the CNS. In a large case-control study of children with CP born > 35 gestation weeks, included in the Western Australian Register of developmental anomalies, and matched controls, congenital defects, that occured in as much as 40 % and fetal growth restriction, that occuried in 17 % were more strongly associated with CP than potentially asphyxial birth events which occured in 9 % and inflammation which occured in 5 % (202).

It has not been unusual that a child with CP was believed to have been exposed to oxygen deficiency at birth but later was discovered to have a brain malformation as the underlying cause of developmental delay (203). This is in contrast to our data where we found that no child with maldevelopment received low Apgar score at birth. Advances in neuro-imaging have also helped to change the perspective. MRI of children with CP, born at full term has commonly demonstrated brain malformations which have their origin during pregnancy (45, 204).

Environmental factors, such as teratogenic influences, congenital infections, nutrition and genetic predisposition is considered responsible for the genesis of cortical malformations (201, 205).

Most cortical organization is ended by approximately the twenty-fourth gestational week (204, 206). Therefore, abnormalities of cortical

development can easily be differentiated from brain injury caused by postnatal hypoxic-ischemic injury (207). To learn more about the timing of injury and the nature of the underlying etiological processes that lead to CP, it may be useful to characterize the co-occurrence of CP and congenital anomalies and delineate the specific types of abnormalities that occur with CP.

In a recent study by Blair et al. the combination of birth defects and fetal growth restriction was associated with a marked increase in the risk of CP (172) which is in contrast to our findings in where we found no interactive effect between these antecedents.

Many neurodevelopmental disorders can have common mechanisms (208-210). Nelson et al showed that more than a third of infants with neonatal seizures had a major malformation, and half of those with tonic or myoclonic epilepsies in infancy (45). Of the infants with NE, which precedes CP in as much as 20 % (202) according to a population-based study, almost a third had a birth defect, compared with only 4 % of controls (211).

With increased use of neuroimaging in sick newborns, early detection of fetal abnormalities has improved, however, asymptomatic newborns may not be evaluated completely. Imaging procedures can bring a lot to the identification and description of anomalies, but they were not available in the past and are not included systematically in many population-based studies. Moreover, image-processing tools differ in sensitivity; For example, MRI is more sensitive than ultrasound and CT in detecting cerebral malformations.

Routine ultrasound has increased our ability to detect abnormality of the fetal brain malformation early when termination of pregnancy is still an option, but there is no evidence to suggest a difference in the long-term outcomes (212).

Prepartal infection

Maternal reports of fever or infection during pregnancy have been shown to increase the risk of CP in a large Australian case-control study (168). Likewise, O'Callaghan reported in 2011 that maternal infection during pregnancy was associated with CP and occured in 41 % of CP cases (168). According to our results, infection during pregnancy occured in 36 % of all CP cases and was associated with spastic hemiplegia in where the occurence was 39 %. The lowest occurence of infection during pregnancy was reported in the dyskinetic CP group, in 29 % of cases. Antibiotic therapy during pregnancy, which could indicate exposure to infection, was likewise associated to spastic hemiplegia. Epidemiological studies have not found an association between upper respiratory infections during pregnancy and CP,

nor gastrointestinal infection, but some studies have shown an increased risk with bacterial urinary tract infections (168, 213, 214). Mann et al. reported an association between maternal urinary tract infections prior to the third trimester and an increased risk of CP (215). We did not analyse upper respiratory infection separately. However, we did find e-coli infection associated to the total group of CP and bacterial growth in urin during pregnancy associated to spastic hemiplegia, in accordance to previous studies.

Intrauterine infection either histological chorioamnionitis in the placenta and membranes or intrapartal pyrexia, was associated with a 4-fold increase in CP in term infants according to Wu et al. (97). Acute intrauterine infections may adversely affect placental function leading to fetal hypoxemia and even hypoxic fetal death (216, 217). The overall rate of clinical chorioamnionitis, only 0.1 % in out term born cohort, differ from prior studies in where an occurence of 1-4 % has been reported (218). Even though we had prior knowledge of that perinatal infections are less frequent in a Scandinavian population (219), this was even lower than we could anticipate.

Fetal viral infection has also been found associated with the CP (84, 98). Cytomegalovirus and Epstein-Barr virus infection during pregnancy have been shown to give an increased risk of CP according to studies using polymerase chain reaction techniques in neonatal blood spots (220).

We found that it was more common among those with severe motor impairment and those who had accompanying impairments in addition to CP to have had congenital infection compared to those with mild motor impairment and those that had no accompanying impairments. The association between infection and intellectual disability has been shown previously (221). Viral or bacterial infections may pass relatively unnoticed during pregnancy and the placenta is often not sent for histological examination for inflammatory pathology (74).

Different infectious agents have been shown to have different mechanism of injury. Viruses, for example, tend to produce a selective necrosis of specific cell types, while bacteria and fungi are less selective. In addition, STORCH (syphilis, toxoplasmosis, rubella, CMV, human immunodeficiency virus (HIV) and herpes simplex) infections also generate different patterns of calcifications seen on CT. Timing of injury during fetal life determine whether there are teratogenic or encephaloclastic effects (220). Thus, pathologic features and associated neuroimaging patterns depend on the stage of development of the CNS, the affinity of a specific infectious agent for a specific CNS cell type and the ability of the host to respond to that insult (222).

CNS infections, regardless of whether they were acquired in utero (congenital), during delivery or after childbirth are important causes of acute and long-term neurological morbidity. However, according to our results it seems like infection late in pregnancy and congenital infection is more likely to be associated with more severe motor impairment and more associated impairments than maternal infection early in pregnancy.

Cytokines are produced in response to infection and are able to mediate intravascular cell adhesion, coagulation and/or thrombosis, and vasoconstriction (223). The cytokines and/or other inflammatory mediators can gain access to the fetus via swallowed amniotic fluid or via the fetal lungs, eyes or nasal membranes. Cytokines can have a cytotoxic effect on brain oligodendrocytes and have the ability to increase permeability of the bloodbrain barrier which may also allow the passage of potentially toxic mediators into the incredibly sensitive developing brain (223).
It has been unclear whether the cytokines themselves mediate or cause white-matter damage or whether it is the bacteria or viruses per se that are responsible for the damage. A multicenter cohort of 1078 infants showed that fetal inflammatory responses contribute to cerebral white-matter damage and that maternal infection can damage the fetal brain without the presence of fetal brain infection (224). Another possible causal mechanism leading to CP is an abnormal inflammatory response in the fetus and the neonate. It has been suggested that regulatory polymorphisms of cytokines, that results in either an increased response to or susceptibility to infection may be able to influence the outcomes of severe infection (84, 225). The importance of inflammatory cytokines for various adverse outcome has also been studied by Furguson et al (226).

If the brain damage attributed to intrauterine infection and other risk factors involves cytokines as intermediates, then blockade of the proinflammatory cascade or promotion of endogenous inhibitors might prevent CP. Other potentially preventive strategies include corticosteroids given to mothers and thyroid hormone (227).

No relation was found between infection related antecedents and low Apgar score according to our data. This is consistent with findings reported in a study by Torfs et al. where it was only in the normal Apgar group that infection related variables were related to CP (69).

Antibiotic treatment

Between 19 %-44 % of pregnant women are prescribed antibiotics during pregnancy (228). In our material, 20 % of all cases and 11 % of all controls were prescribed antibiotics according to our records. It was most common among mothers to those with spastic hemiplegia, occuring in 23 % and least

common among mothers of children with dyskinetic CP to have used antibiotics during pregnancy.

Antibiotic therapy may be a marker of infection or prolonged intrauterine exposure to bacteria, bacterial products and cytokines. A single, large randomised-controlled-trial (ORACLE Childhood Study II) found an increased risk of childhood CP and possibly epilepsy following prophylactic antibiotic use in pregnant women with spontaneous preterm labor. Leviton et al have previously shown an association between maternal antibiotic use and WMI (229), a neuroimaging pattern often seen in children with CP. Meeraus et al. found no overall association between antibiotic prescribing in pregnancy and CP and/or epilepsy in childhood. However, they did find an increased risk of CP or epilepsy associated with macrolide prescribing in pregnancy (228). The association of macrolides and maldevelopment is supported by several studies (230-232). There is a growing body of evidence that macrolides are associated with adverse outcomes, including cardiovascular events in adults (233-235), cardiotoxicity (236), miscarriage (237) and even death (235).

However, the exact mechanism behind antibiotic use and injury is unclear. Several potential mechanisms underlying the adverse effects of prepartal antibiotics have been proposed. Prepartal antibiotics can shift the spectrum of neurological lesions in the fetus caused by infection towards less severe outcomes - the 'damaged-survivor' hypothesis. This mechanism could be manifested by increased survival and less severe neurological manifestations among survivors of treated, compared to among untreated women (228). Furthermore, a partially treated infection might prolong the exposure to inflammation and thereby increase the risk of brain injury. It may also involve treatment failures since macrolides are known to have gastrointestinal side effects (238, 239), which can result in the abandonment of the treatment, or due to resistant bacteria (240) or due to poor transplacental passage of macrolide antibiotics (compared with ampicillin (241, 242), a very commonly prescribed penicillin during pregnancy in primary care (243)).

Third, antibiotics may have direct adverse effect on the fetus (244). Maternal antibiotics have been shown to have a potentially feto-toxic effect, causing neonatal necrotizing enterocolitis, according to the ORACLE trial (244). It seems evident that antibiotics and choice of the type of antibiotics should be handled with caution (245). When deciding on administering any form of pharmacological therapy during pregnancy, you need to be sure that the overall benefits outweigh the risk of harm to the fetus. There is strong evidence of net benefits of prepartal antibiotics for mother and baby when infection is the predominant underlying mechanism of effect. For example, prepartal antibiotics have been shown to be effective for women with suspected bacterial infections, such as urinary tract infections (246) and as

prophylaxis for women with asymptomatic bacteriuria (247) and preterm prolonged rupture of membranes (248).

Not a single significant relation was found between dyskinetic CP and prepartal antecedents. Likewise, newborn growth measurements birthweight, length and circumference of the head were equal to that of control children indicating that subsequent events are probably more important for this CP subtype. This concurs with previous findings (114, 168, 173, 249, 250).

Clearly, our results together with previous epidemiological studies (68, 149, 202, 213, 214, 251-253) have provided evidence that prepartal antecedents are very important determinants of the risk of CP. Known prepartal factors may directly increase the risk of CP, or may interact with other exposures or intrapartal events to increase the risk, for example, by reducing the threshold at which stress or hypoxia/ischemia at parturition becomes neurotoxic (254). Brain injury could then continue to evolve after birth. However, we found no interaction effect between analysed pre- and intrapartal variables. This, however, has low power and we cannot rule out that we would have found interaction effects with a larger data material.

5.2.2 Intrapartal antecedents

Historically, suboptimal intrapartum care has been seen as the primary cause of CP (255). Still, this view is supported by some recents studies (169) and even after excluding well-known risk factors, such as placental abruption, uterine rupture, and cord prolapse (256-259). However, the predominating view is nowadays that most CP is not related to intrapartum asphyxia (198, 251, 260-263). Freud suggested in 1897 that a difficult birth, in certain cases, is merely a symptom of deeper effects that influence the development of the fetus (67). At birth, nonspecific signs of fetal compromise such as meconium-stained amniotic fluid, nonreassuring fetal heart rate patterns, low Apgar scores, and NE could all be associated with either acute intrapartal timing or chronic long-standing timing of the pathologies (ie, beginning before labor and during pregnancy). The same signs can be caused by not only hypoxia and/or ischemia, but also by other factors such as infection, placental and umbilical vessel thrombosis, an altered fetal inflammatory response (264) or genetic alterations (mutations) that may either directly cause CP or contribute to susceptibility to CP (252, 265). There is now increasing evidence that babies given a “birth asphyxia” label due to clinical signs such as low Apgar scores often do not have primary asphyxia (187, 266). Many such babies are in ill health due to longer-standing problems. In a study by McIntyre 2013, two thirds of infants with acute intrapartum hypoxia in addition had other plausible risk factors for CP (267).

There has been wide disparity in estimates of the proportion of CP attributed to birth asphyxia. In 1986, Nelson and Ellenberg (198) reported that the

proportion of CP that might reasonably be attributed to birth asphyxia was less than 10 %.

Commonly used markers of perinatal asphyxia is Apgar score (<6 at 5 min), umbilical cord pH (pH <7 or base deficit> 12 mmol / l) and the classic signs of fetal distress including meconium staining of the amniotic fluid and delay in spontaneous respiration. Other biochemical and electrophysiological assays have also been used to diagnose perinatal asphyxia, such as abnormal patterns of fetal heart rate (> 160 beats / min or <120 beats / min), dysfunction of non-CNS, electroencephalography and cerebral imaging patterns. International consensus criteria have been established to help guide towards when neuropathology may have originated only during delivery (264, 268, 269).

We did not analyse data on pH levels since the information on pH levels was too scarce in the records during the years studied. Nor did we collect data on CTG. Because of this, we could not analyse neuropathology that have become established only in labor and birth, based on criteria mentioned above as a potential antecedent of CP.

Potentially asphyxiating conditions
Acute fetal hypoxemia (umbilical cord occlusion) in late gestation results in neuronal death in the cerebral cortex and striatum according to Loeliger et al. 2003 (270). A large population-based study, noted that a tight umbilical cord around the fetal neck, requiring cutting before delivery of the shoulders, or a true umbilical knot increased the risk of spastic quadriplegia 18-fold (271). Tight cords may prevent or slow descent of the head into the pelvis in late pregnancy and may cause intermittent ischemia and hypoxia during delivery. It was in the dyskinetic group that umbilical cord compications (5 %) as well as obstetric catastrophe (5 %) were most commonly occurring, even though not a significant antecedent according to multivariable analyses. Several studies link epilepsy and cognitive impairment to hypoxic conditions during birth (36, 38, 145). Umbilical cord complications, placenta, abruption and obstetric catastrophe were rather rare events in children with CP with accompanhying impairments occurring in only 1 %.

Vaginal breech delivery, a well-known risk-factor for adverse perinatal outcome was not significantly associated with CP nor to its accompanying impairments according to our results, in contrast to other studies (124, 272).

Meconium stained amniotic fluid
Meconium causes vasoconstriction in isolated umbilical venous tissue (273, 274). Meconium-induced vascular necrosis has been associated with fetal distress, lower Apgar scores and arterial pH less than 7.19 (274). Meconium staining of the amniotic fluid was common among children with CP in our

material, occurring in 31 % of the total CP group and associated to spastic CP and mild motor impairment, according to multivariate analyses and is a well known antecedent to CP (77, 78). Meconium stained amniotic fluid was associated with low Apgar score, according to our findings.

Apgar score

It is common for clinicians to equate low Apgar scores with "birth asphyxia," but this is a mistake. In a Norwegian material Moster et al. (275) found that a 5 min Apgar score of 0-3 markedly increased the risk for both death and CP. Compared with infants with normal Apgar scores (7-10 at 1 minute), Norwegian babies with 5-minute Apgar scores of ≤3 experienced 81 times the risk of CP (37). The association between low Apgar scores and CP is supported by many previous studies (276, 277) (124). However, the findings like that of Moster et al. should not automatically be interpreted as providing support for the idea that CP has its origin in labor difficulties (278). The Apgar score is a shorthand measurement of the functioning of the cardiopulmonary system (pulse), the CNS (grimace, tone), and a combination of the two (respiration, color). Many factors other than forces of labor can affect one or both of these systems, including infection, pharmacologic agents, and preexisting neurologic abnormalities. Apgar score correlates poorly with cord blood acidosis (279). Low Apgar score may reflect both acute and chronic fetal compromise and is not in itself a cause of CP (168).

Low Apgar score was associated with all CP subtypes, according to our analyses. The occurence of low Apgar score however differed substantially between subgroups of CP. As much as 70 % of the children with dyskinetic CP had an Apgar score at 5 min <7 compared to 6 % of the children with spastic hemiplegia. Low Apgar score increased in occurrence with increasing severity of motor impairment.

Interestingly, poor intrauterine growth, represented by birth length and small head circumference were associated with low Apgar score. However, we also found that the children who were exposed to maternal infection or had maldevelopment were not represented in the group with low Apgar score.

Instrumental delivery

One third of the dyskinetic children were delivered by caesarean section compared to one fifth of the children with spastic hemiplegia. Delivery by emergency caesarean section was also much more common in the dyskinetic CP group, occuring in as much as 21 % of the cases. Instrumental delivery increased in occurrence with increasing severity of motor impairment. The

association of instrumental delivery and CP are supported by previous studies CP (280, 281).

CP rates have remained approximately the same for 50 years despite a 6-fold increase in cesarean birth (74). It is likely that the reported increased risks of elective caesarean section are related to the reason for the caesarean, rather than the procedure itself (282).

Even if most cases of CP in term infants have been attributed to prepartal events (20, 22, 42), this study revealed associations between various intrapartal antecedents and CP as well, in accordance with previous studies (124).

5.2.3 Postpartal antecedents

NICU

In relation to postpartum variabels, a large proportion of children that will develop CP present with symtoms in the postpartal period. However, many neonates that will later receive the CP diagnose present no obvious clinical features in the postpartal period (159). A high percentage of neonates are therefore not admitted to a NICU (i.e., 53 % with mild motor impairment and 35 % with severe motor impairment and 36 % of the children with CP accompanied by epilepsy and/or cognitive impairment) which is also demonstrated in a study by McIntyre in where 67 % of term-born children with CP, including 54 % of those with the most severe impairment, were not admitted to a NICU (283). This indicates that an analysis performed solely on admitted neonates may only reveal or explain a fraction of CP cases.

NE

NE is the clinical manifestation of disordered neonatal brain function. It is a relatively common clinical condition which results in serious consequences for many of the infants including death, CP, epilepsy and other significant cognitive, developmental and behavioural problems. The reported incidence of NE from different studies ranges from about 2.0 to 6.0 per 1000 live births (128, 284-286). The large majority of newborn infants showing signs of encephalopathy does not have objective proof of acute hypoxia or ischemia at birth, but have other causes of pre- or intrapartal compromise, such as infectious or genetic. It is estimated that 30 % of cases of NE in developed populations and 60 % in developing populations have some evidence of intrapartum hypoxic-ischaemia (287, 288). However, seizures in neonates are common and often suggest a serious underlying brain injury. There is a lack of evidence regarding optimal monitoring, evaluation, and treatment for newborns with seizures (289). Of note, only 13 % of term babies who exhibit

NE are later diagnosed with CP. Holden (290) reported that neonatal seizures result in a 55- to 70-fold increased risk of CP, a 5.3- fold increased risk of cognitive impairment, and an 18-fold increased risk of epilepsy, findings supported by others (291). One of the strongest predictors of outcome is underlying etiology, with poorer outcomes being seen in severe asphyxia, massive intraventricular hemorrhage, or underlying malformations of cortical development (292) Although there has been debate as to whether seizures, per se, cause further brain injury, there is now some compelling evidence, predominantly from animal studies, that they do (293).

The analyses of this thesis demonstrated that a diagnose of NE was associated with all CP subtypes. NE was most common in the dyskinetic CP group occuring in 52 %. NE, sigificantly associated to all severity groups were increasing in occurence with increasing severity of motor impairment. This is in accordance with previous findings (124). The presence of neonatal seizures has been shown to be a useful marker for the development of epilepsy in children with CP (38, 294), and our results are in accordance with these findings. It was more common among the children with epilepsy and cognitive impairment in addition to CP to develope NE (41 %). We found that NE increased the risk of epilepsy and/or cognitive impairment four-fold.

Neonatal infections

Neonatal infection was associated with a very high risk of both dyskinetic CP and with spastic diplegia and tetraplegia, occuring in 10 % and 9 % respectively of the children that developed CP. It was not related to spastic hemiplegia, where the occurence was only 3 %. Since there was no one in the control group, belonging to the dyskinetic group, that had neonatal infection, it was not possible to perform adjusted analysis in this subtype. Furthermore, neonatal infection was shown to be associated with epilepsy and cognitive impairment in children with CP. Maternal antibiotic treatment postpartum, which could indicate exposure to infection, was associated with severe motor impairment. In 2001, Wallace showed that children with CP caused by CNS infection more frequently had epilepsy than those with CP of other causes. Carlsson 2003 also showed that CNS infection is associated with epilepsy in CP (38).

In 2001, Wallace showed that children with CP caused by CNS infection more frequently had epilepsy than those with CP of other causes. Carlsson 2003 also showed that CNS infection is associated with epilepsy in CP (38). The link between infection and CP has also been described in a review by McIntyre (78). Clearly, infection early in life seems to be a potent risk factor

for permanent serious injury.

Meconium aspiration syndrome

Meconium aspiration syndrome was most common in the group with dyskinetic CP, occuring in 7 %. Meconium aspiration syndrom was significantly associated with the total CP group, the total spastic CP group and the spastic diplegia and tetraplegia group, occuring in 3 %, 2 % and 4 % respectively. Meconium aspiration syndrome was shown to be related to severe motor impairment. It was also more common among the children with epilepsy and cognitive impairment in addition to CP and meconium aspiration syndrome (7 %) compared to the children with CP alone.

5.2.4 Mortality

Research evidence from around the world demonstrates that the severity of disabilities is the primary determinant for survival of individuals with CP. Furthermore, epilepsy and cognitive impairment have been associated with poorer survival (294, 295). Our findings support these earlier data in that epilepsy in the individual with CP represented an 11-fold increased risk of early mortality and severe cognitive impairment a 55-fold increased risk.

5.2.5 Neuroimaging

Neuroradiology has become increasingly important in the diagnosis and management of children with CP (3, 57, 58, 60-65). Neuroimaging plays an important role in highlighting the timing of injury in CP and contributes to our understanding of the underlying etiology and pathogenesis (60). MRI, and diffusion tensor imaging, now are being used not only to improve diagnosis, but also to describe specific patterns of brain maldevelopment and injury and to choose suitable medical and rehabilitative interventions.

Given the time period studied, neuroimaging had been performed in 76 % of children and with CT in 85 %. However, the reports enabled us to study neuroimaging patterns in the different CP subtypes, severity of motor impairment and when accompanying impairment followed the CP diagnose and relating the neuroimaging patterns to the identified antecedents.

Different neuroimaging patterns are related to different timing of compromise, though not the cause. Specific regions and cells are susceptible to insults during various periods of brain development (60). The nature of the lesions depends on the stage of brain development when such a pathogenic event takes place (58).

The dominating neuroimaging pattern for both spastic CP and the total CP group was WMI, representing patterns of prepartal origin (58), occuring in 36 % and 32 %, respectively. However, no child with dyskinetic CP had this neuroimaging pattern. Instead, patterns of subcortical/cortical injury (26 %) and basal ganglia lesions (26 %), of presumed late antepartum or intra- and postpartum origin (58) were most common in this CP subgroup. Maldevelopment, caused by genetic or acquired impairments are considered to occur during the first and second trimester when cortical neurogenesis, characterized by proliferation, migration and organization takes place. Maldevelopment was most common among children with spastic diplegia and tetraplegia, present in 25 % of the neuroimages in this group. Normal images were equally common in all subgroups, ranging from 20 % -24 %.

WMI, was the dominant pattern in mild motor impairment. The origins of WMI have been described as inflammatory, perfusion failure or both (60). (296). Furthermore, Wu et al. reported in 2006 that intrauterine growth restriction was more strongly associated with WMI than with other neuroimaging findings (297). We could not confirm these findings since we found no association between infectious variables or growth restriction and WMI.

The occurrence of intra- and postpartum antecedents was highest in children with severe motor impairment. This corresponds well to the identified neuroimaging patterns in this group, i.e. subcortical/cortical injury and basal ganglia lesions, of presumed late antepartum or intra- and postpartum origin (58). Previous studies have found that children with basal ganglia lesions often have severe motor impairment (3).

Analysis of neuroimaging patterns in children with accompanying impairments in CP revealed that maldevelopment and cortical/subcortical lesions more often were found in children with accompanying impairments while WMI and normal scans instead were significantly less likely to be found. These findings are in accordance with Himmelmann and Carlsson (3, 38).

The analyses of neuroimaging patterns confirmed the timing of events suggested by the results of antecedents associated with different CP subtypes, severity of motor impairment and presence of accompanying impairments.

Although abnormal neuroimaging patterns can be identified in most children with CP, previous studies have shown that up to 32 %, but most commonly around 15 % of children with CP may exhibit normal or nonspecific findings, especially those with ataxic and dyskinetic forms. Moreover, those who

present normal neuroimaging images often have no obvious clinical features that distinguish them from those with abnormal imaging findings (159, 298).

5.3 Clinical implications

CP is a chronic condition with considerable impact on affected individuals. Preventive measures, overall, have not lowered CP prevalence. However, this is a complex issue since some causes of CP have decreased (e.g. brain injury from maternal rubella and from neonatal jaundice) but other causes have emerged (e.g. increased survival of very preterm born infants). Over the last 50 years, CP rates have remained the same despite major advances in obstetrics and neonatology including a 6-fold increase in cesarean delivery rates and liberal induction policies to reduce postmaturity (74). Interventions that have proven ineffectual include elective cesarean delivery, earlier emergency delivery in pregnancy, and electronic fetal heart rate monitoring (299). Observational studies show no protective effect of elective or emergency cesarean delivery for CP outcome (300).

There is a massive variance in clinical presentation and range of disability observed in individuals with CP. Similarly, the findings presented in this thesis demonstrate variance in antecedents and suggested timing of causal events in the different CP subtypes and levels of disability. Most of the factors associated with an increased risk of CP are themselves aetiologically diverse. This thesis demonstrates that there are a considerable number of antecedents associated with CP and that there is a need to acknowledge the differences in different subtypes and severities of motor impairment. The results presented in this thesis are not examples of causal factors, but merely antecedents associated with CP. The antecedents only indicate that the risk of the child having CP is increased. Therefore, based on our results it is not possible to state special interventions that will necessarily reduce the prevalence of CP. However, the results of this thesis can guide us towards potentially beneficial interventions. Preventive strategies need then to be evaluated statistically regarding their effectiveness in reducing the overall incidence of CP and in limiting the motor impairment and accompanying impairments.

Considering the number of antecedents identified and temporal difference among the antecedents and neuroimaging patterns, it seems like it is unlikey that any single preventive strategy will significantly reduce CP prevalence (195). It seems important that efforts to affect the pathways to CP are mulitfactorial and directed towards preventive strategies in the pre- intra- as well as the postpartal period.

Prepartal care

This thesis might indicate that it should be useful to reduce exposure of pregnant women to virus and other infections, recognizing and treating bacterial infection of the reproductive and urinary tracts, avoiding unnecessary exposure to cigarettes, controlling maternal health problems such as diabetes, hypertension and preclampsia as well as supporting optimal maternal nutrition and weight control and support mothers with difficult social situations. Moreover, thorough evaluation of a growth-restricted fetus and follow up is important.

It may be impossible to avoid maldevelopment of the brain occuring during the prepartal months in the case of a random mutation. Currently, there is conflicting evidence for folate and vitamin preventing birth defects, other than neural tube defects (78, 301, 302).

Intrapartal care

This thesis identifies instrumental births as associated with CP, especially in the subgroup of dyskinetic CP. Instrumental deliveries are not considered, in themselves, be the reason that the child developes a brain injury. Many instrumental deliveries are results of prolonged second stage labor. Thus, there are good reasons for early attempts to prevent prolonged labor such as through active management, mobilization, and continuous support provided by doulas (303). Another way to avoid prolonged labor is to increase the use of elective caesarean section, but it is clear that the large increase in elective caesarean section in developing countries over the past 30 years has not led to a decrease in CP. In addition, cesarean sections themselves are related to both maternal and fetal risks.

When there is a suspicion that a child has suffered for example oxygen deprivation during birth and might benefit from asphyxia treatment there should be a clear action plan for the care and treatment of these children.

Postpartal care

In order to provide timely therapeutic intervention for the fetus or infant at risk of brain damage we need to be able to detect when an insult has occurred. As indicated above there is ongoing debate as to when this is most likely to occur. Advanced neuroimaging is now providing the opportunity to identify and then monitor the evolution of brain injury in compromised fetuses and neonates. Another approach is to identify reliable markers of brain damage in the blood of newborns. The search for reliable, specific markers is on-going (296).

Total body cooling and selective head cooling have proven to be effective methods to minimize the extent of brain injury in treating newborns who have suffered from low oxygen supply to the brain during birth. It is estimated that one in every six to nine cases of CP due to birth asphyxia can be prevented if the infant receives hypothermia within six hours of the causal event. Cooling has proven to reduce mortality without increasing major disability in survivors (304-312). Thus, clinicians should consider offering therapeutic hypothermia as part of routine clinical care if detected before six hours of age in term and late preterm born infants with moderate-to-severe hypoxic ischaemic encephalopathy (313-315).

There seems to be hope for repair and protection of the brain after a profound neonatal insult. However, published clinical trials and animal studies tell us that hypothermia alone will not provide absolute protection or stimulate the necessary repairs to a sufficient extent for normal neurodevelopmental outcome (183, 316, 317). Although therapeutic hypothermia is an important progress and improve outcome, hypothermia offers only 11% reduction in risk of death or disability. Therefore, there is still a great need to find and evaluate other treatment options. Further, there are currently no clinically established interventions that can be provided prepartally to reduce brain injury after fetal distress (317).

Moreover, this thesis indicates that it should be of value to reduce exposure of newborns to virus and other infections since neonatal infections was shown to increase the risk of severe CP and CP together with accompanying impairments. It may also be beneficial for the newborns to be closely monitored for signs of infection (changes in temperature, pulse and breathing, presence of active hepatitis, skin vesicles or petechiae) insuring early recognition of infections that affect the nervous system (e.g. meningitis and encephalitis) as well as ophthalmologic examination, microbiological testing of the infant and mother, and serial follow-up serology of the infant to be performed (318) when infection is suspected.

6 CONCLUSION

The studies on CP described in this thesís has contributed to a greater understanding of the diversity of antecedents in regard to CP subtype, severities of motor impairment and occurence of epilepsy and cognitive impairment.

The antecedent pattern differed by CP subtype. All subtypes shared a mix of prepartal, intrapartal and postpartal antecedents, except for dyskinetic CP, for which intra- and postpartal events played a major role.

Maternal infections were associated only with the subgroup spastic hemiplegia whereas neonatal infection was associated with the subgroups with spastic diplegia or tetraplegia and dyskinetic CP.

The antecedent pattern differed by severity of motor impairment in CP. In both mild and severe motor impairment, significant pre- intra- and postpartal antecedents were identified.

The accompanying impairments epilepsy and cognitive impairment in CP were associated with poor intrauterine growth, maldevelopment, and intra- and postpartal adverse events.

The findings might illustrate some of the causal pathways to CP, namely hypoxia, malformations and infection.

No interaction was found and a multiplicative effect of the analyzed antecedents could thus not be supported.

Clearly, the nature of the fetal neuropathology and outcome depends on the nature and severity of the insult and the gestational age of the fetus at the time of the insult.

Since antecedents were identified from all timeperiods, during pregnancy, during delivery and after delivery, multifactorial preventive strategies, aiming at all time periods should be evaluated.

7 FUTURE PERSPECTIVES

CP has continued to affect 2-2.5 per 1,000 of the livebirth during a long time. However, the panorama of CP may over time be in a dynamic change when new interventions are introduced and some riskfactors decrease in occurrence (maternal smoking) at the same time as other known risk factors increase (increased number of multiples in the population related to assisted reproduction techniques, higher maternal delivery age, increasing maternal weight and diabetes).
A continuing study of infections, maternal health problems and body habitus is warranted. Hopefully, the newly introduced active interventions, such as rapid cooling of the asphyxiated newborn will lead to a decline of term born infants with CP, especially in the dyskinetic subgroup, or result in a milder motor impairment. It is estimated that one in six to nine cases of CP due to birth asphyxia can be prevented if the child gets hypothermia within 6 hours of causal event (313). Neuroimaging techniques such as MRI may also have a role in identifying infants who would benefit from neuroprotective strategies, such as head cooling and cell-based therapies that may someday be used to reduce injury in some children with CP. The idea is that the injury to the brain may be ongoing, rather than fixed (159, 315). It will be very interesting to know the outcome of future research investigating the effectivness of birth asphyxia treatment and outcome in different CP subtypes.

The CP registers worldwide, including the SCPE are excellent tools and will continue to provide the way forward when it comes to monitoring future trends, further explore causes and timing of the causal events as well as the effects of interventions and to address issues related to quality of life. A pilot study was recently conducted in Bangladesh to develop a national CP register (319). The more registers, the more different countries with different economic health care, the more knowledge will be provided.

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APPENDIX

Study I

Appendix I, Analysis, All spastic and dyskinetic CP

Variable	Case (n=309)	Control (n=618)	p-value	OR (95% CI)
Admitted to NICU	158 (52.5%)	75 (12.2%)	<.0001	7.93 (5.69-11.04)
Alcohol consumption during early pregnancy	151 (53.4%)	275 (47.5%)	0.1226	1.26 (0.95-1.68)
Apgar score at 5 minutes < 7	62 (20.6%)	6 (1.0%)	<.0001	26.42 (11.28-61.88)
Bad obstetric history	8 (2.6%)	11 (1.8%)	0.5528	1.47 (0.58-3.69)
Birth length (cm)	50.1 (2.7)	50.6 (2.1)	0.0029	0.90 (0.85-0.96)
Birthweight (kg)	3.43 (0.60)	3.61 (0.50)	<.0001	0.52 (0.40-0.68)
Bleeding during pregnancy	26 (8.4%)	53 (8.6%)	1.0000	0.98 (0.60-1.60)
Bleeding during first trimester	12 (3.9%)	29 (4.7%)	0.7040	0.82 (0.41-1.63)
Bleeding during second trimester	11 (3.6%)	14 (2.3%)	0.3497	1.59 (0.71-3.55)
Bleeding during third trimester	8 (2.6%)	13 (2.1%)	0.7971	1.24 (0.51-3.02)
Blood-stained amniotic fluid	5 (1.9%)	3 (0.5%)	0.1562	3.52 (0.83-14.83)
Breech presentation	13(4.3%)	14 (2.3%)	0.1453	1.92 (0.89-4.14)
Cephalic presentation	289 (95.7%)	593 (96.9%)	0.4558	0.71 (0.35-1.46)
Cesarean section	80 (25.9%)	72 (11.7%)	<.0001	2.65 (1.86-3.77)
Cesarean section, elective	13 (4.9%)	34 (5.5%)	0.4972	0.75 (0.39-1.45)
Cesarean section, acute (< 8 hours after decision)	29 (9.4%)	28 (4.5%)	0.0071	2.18 (1.27-3.74)
Cesarean section, emergency	38 (12.3%)	3 (0.6%)	<.0001	28.75 (8.80-93.93)
Decreased fetal movements	12 (3.9%)	13 (2.1%)	0.1777	1.88 (0.85-4.17)
Diabetes	5 (1.6%)	2 (0.3%)	0.0889	5.07 (0.98-26.31)
Epilepsy	1 (0.3%)	5 (0.8%)	0.7023	0.40 (0.05-3.43)
External cephalic version	4 (1.3%)	5 (0.8%)	0.6985	1.61 (0.43-6.03)
Gestational diabetes	6 (1.9%)	5 (0.8%)	0.2415	2.43 (0.73-8.02)
Gestational hypertension/chronic hypertension	16 (5.2%)	26 (4.2%)	0.6068	1.24 (0.66-2.35)
Head circumference at birth (cm)	34.6 (1.9)	35.2 (2.1)	<.0001	0.84 (0.77-0.92)
Infertility	24 (7.9%)	44 (7.2%)	0.8042	1.10 (0.66-1.85)
Intrauterine fetal death of one twin	1 (0.3%)	0 (0.0%)	0.6667	*
In vitro fertilization	1 (0.3%)	1 (0.2%)	1.0000	2.02 (0.13-32.46)
Large for gestational age	18 (5.8%)	27 (4.4%)	0.4146	1.35 (0.73-2.50)
Lung disease	5 (1.6%)	16 (2.6%)	0.4939	0.62 (0.23-1.71)
Maternal age	28.5 (5.4)	28.5 (5.1)	0.9380	1.00 (0.97-1.03)
Maternal allergy	66 (21.4%)	125 (20.3%)	0.7393	1.07 (0.77-1.50)
Maternal BMI (kg/cm^2)	23.9 (3.8)	23.0 (3.6)	0.0004	1.07 (1.03-1.12)
Maternal weight week 34 (kg)	65.7 (11.7)	63.7 (10.6)	0.0217	1.02 (1.00-1.03)
Meconium aspiration	8 (2.6%)	1 (0.2%)	0.0018	16.39 (2.04-131.65)
Meconium-stained amniotic fluid	82 (30.7%)	85 (15.3%)	<.0001	2.46 (1.73-3.48)
Miscariage	67 (21.8%)	127 (20.7%)	0.7588	1.07 (0.77-1.49)
Neonatal encephalopathy	71 (23.0%)	1 (0.2%)	<.0001	183.67 (25.43-1326.72)
Non cohabitation with baby's father	19 (6.3%)	15 (2.5%)	0.0109	2.60 (1.30-5.19)
Nulliparity, nominal	173 (56.2%)	374 (60.6%)	0.2206	0.83 (0.63-1.10)
Obstetric catastrophe	5 (1.6%)	0 (0.0%)	0.0081	*
Ovulation induction	3 (1.0%)	7 (1.2%)	1.0000	0.85 (0.22-3.31)
Placental abruption	1 (0.3%)	1 (0.2%)	1.0000	2.00 (0.12-32.13)
Placental weight (g)	603 (152)	621 (148)	0.0883	1.00 (1.00-1.00)
Polycystic ovarian syndrome	2 (0.6%)	2 (0.3%)	0.8135	2.01 (0.28-14.34)

Preeclampsia	25 (8.1%)	40 (6.5%)	0.4365	1.27 (0.76-2.14)
Prepartal diagnosis of CNS anomaly	6 (1.9%)	0 (0.0%)	0.0027	*
Previous deep vein thrombosis	2 (0.6%)	2 (0.3%)	0.8135	2.01 (0.28-14.34)
Previous preterm birth	4 (1.3%)	7 (1.2%)	1.0000	1.16 (0.34-3.99)
Previous cesarean section	27 (8.9%)	45 (7.4%)	0.5017	1.22 (0.74-2.01)
Psychiatric disorder, e.g. psychosis or depression	9 (2.9%)	6 (1.0%)	0.0591	3.06 (1.08-8.68)
Rheumatic disorder	5 (1.6%)	5 (0.8%)	0.4225	2.02 (0.58-7.03)
Small for gestational age	29 (9.4%)	16 (2.6%)	<.0001	3.90 (2.08-7.29)
Smoking during early pregnancy	99 (34.5%)	156 (26.9%)	0.0275	1.43 (1.05-1.94)
Spontaneous vaginal delivery	196 (63.4%)	516 (83.5%)	<.0001	0.34 (0.25-0.47)
Suspected small for gestational age	16 (5.2%)	7 (1.1%)	0.0007	4.77 (1.94-11.71)
Termination of pregnancy	61 (19.9%)	118 (19.2%)	0.8784	1.04 (0.74-1.47)
Thyroid disorder	6 (1.9%)	8 (1.3%)	0.6162	1.51 (0.52-4.40)
Trauma during pregnancy	5 (1.6%)	5 (0.8%)	0.4240	2.02 (0.58-7.02)
Umbilical cord complications	9 (2.9%)	3 (0.5%)	0.0072	6.16 (1.66-22.92)
Vacuum extraction	33 (10.7%)	30 (4.9%)	0.0019	2.34 (1.40-3.92)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Appendix II, Analysis, spastic CP

Variable	Case (n=267)	Control (n=534)	p-value	OR (95% CI)
Admitted to NICU	123 (47.3%)	61 (11.5%)	<.0001	6.90 (4.81-9.91)
Alcohol consumption during early pregnancy	134 (54.3%)	246 (49.4%)	0.2421	1.21 (0.89-1.65)
Apgar score at 5 minutes < 7	34 (13.0%)	4 (0.7%)	<.0001	19.84 (6.96-56.55)
Bad obstetric history	8 (3.0%)	10 (1.9%)	0.4442	1.62 (0.63-4.14)
Birth length (cm)	49.9 (2.6)	50.6 (2.1)	0.0009	0.88 (0.82-0.94)
Birthweight (kg)	3.40 (0.59)	3.60 (0.50)	<.0001	0.49 (0.37-0.65)
Bleeding during pregnancy	24 (9.0%)	51 (9.6%)	0.9069	0.94 (0.56-1.56)
Bleeding during first trimester	12 (4.5%)	27 (5.1%)	0.8756	0.88 (0.44-1.77)
Bleeding during second trimester	10 (3.7%)	14 (2.6%)	0.5019	1.45 (0.63-3.30)
Bleeding during third trimester	7 (2.6%)	12 (2.2%)	0.9138	1.17 (0.46-3.01)
Blood-stained amniotic fluid	2 (0.9%)	3 (0.6%)	1.0000	1.38 (0.23-8.30)
Breech presentation	11 (4.2%)	13 (2.5%)	0.2610	1.74 (0.77-3.95)
Cephalic presentation	250 (95.8%)	513 (97.2%)	0.4165	0.66 (0.30-1.47)
Cesarean section	66 (24.7%)	61 (11.4%)	<.0001	2.55 (1.73-3.74)
Cesarean section, elective	13 (4.9%)	30 (5.6%)	0.7940	0.86 (0.44-1.68)
Cesarean section, acute (< 8 hours after decision)	24 (9.0%)	22 (4.1%)	0.0103	2.30 (1.26-4.18)
Cesarean section, emergency	29 (10.9%)	3 (0.6%)	<.0001	21.54 (6.50-71.39)
Decreased fetal movements	11 (4.1%)	10 (1.9%)	0.1067	2.25 (0.94-5.37)
Diabetes	3 (1.1%)	1 (0.2%)	0.2218	6.03 (0.63-58.24)
Epilepsy	1 (0.4%)	4 (0.8%)	0.9193	0.50 (0.06-4.47)
External cephalic version	3 (1.1%)	4 (0.7%)	0.8587	1.51 (0.33-6.78)
Gestational diabetes	6 (2.2%)	4 (0.7%)	0.1506	3.04 (0.85-10.87)
Gestational hypertension/chronic hypertension	14 (5.2%)	22 (4.1%)	0.5790	1.29 (0.65-2.56)
Head circumference at birth (cm)	34.6 (1.9)	35.2 (2.2)	0.0002	0.84 (0.77-0.92)
Infertility	19 (7.2%)	37 (7.0%)	1.0000	1.04 (0.58-1.84)
Intrauterine fetal death of one twin	1 (0.4%)	0 (0.0%)	0.6667	*
In vitro fertilization	1 (0.4%)	1 (0.2%)	1.0000	2.03 (0.13-32.54)
Large for gestational age	15 (5.6%)	22 (4.1%)	0.4317	1.39 (0.71-2.72)

Lung disease	5 (1.9%)	12 (2.3%)	0.9509	0.83 (0.29-2.38)
Maternal age	28.4 (5.4)	28.4 (5.1)	0.8218	1.00 (0.97-1.03)
Maternal allergy	58 (21.7%)	107 (20.1%)	0.6490	1.10 (0.77-1.58)
Maternal BMI (kg/cm^2)	24.0 (4.0)	23.0 (3.6)	0.0004	1.07 (1.03-1.12)
Maternal weight week 34 (kg)	65.7 (11.9)	63.6 (10.8)	0.0147	1.02 (1.00-1.03)
Meconium aspiration	5 (1.9%)	1 (0.2%)	0.0349	10.16 (1.18-87.37)
Meconium-stained amniotic fluid	67 (28.8%)	74 (15.4%)	<.0001	2.21 (1.52-3.23)
Miscarriage	59 (22.1%)	113 (21.2%)	0.8476	1.05 (0.74-1.50)
Neonatal encephalopathy	49 (18.4%)	1 (0.2%)	<.0001	119.77 (16.44-872.57)
Non cohabitation with baby's father	17 (6.5%)	11 (2.1%)	0.0052	3.19 (1.47-6.90)
Nulliparity, nominal	155 (58.1%)	322 (60.3%)	0.5922	0.91 (0.68-1.23)
Obstetric catastrophe	3 (1.1%)	0 (0.0%)	0.0735	*
Ovulation induction	2 (0.8%)	5 (1.0%)	1.0000	0.79 (0.15-4.11)
Placental abruption	0 (0.0%)	1 (0.2%)	1.0000	*
Placental weight (g)	598 (154)	619 (150)	0.0685	1.00 (1.00-1.00)
Polycystic ovarian syndrome	2 (0.7%)	1 (0.2%)	0.5191	4.01 (0.36-44.33)
Preeclampsia	20 (7.5%)	34 (6.4%)	0.6459	1.19 (0.67-2.11)
Prepartal diagnosis of CNS anomaly	6 (2.2%)	0 (0.0%)	0.0026	*
Previous deep vein thrombosis	2 (0.7%)	2 (0.4%)	0.8163	2.00 (0.28-14.30)
Previous preterm birth	4 (1.5%)	6 (1.1%)	0.8698	1.35 (0.38-4.83)
Previous cesarean section	23 (8.7%)	35 (6.6%)	0.3621	1.34 (0.78-2.32)
Psychiatric disorder, e.g. psychosis or depression	7 (2.6%)	5 (0.9%)	0.1308	2.84 (0.89-9.04)
Rheumatic disorder	4 (1.5%)	4 (0.8%)	0.5173	2.01 (0.50-8.11)
Small for gestational age	27 (10.2%)	16 (3.0%)	<.0001	3.65 (1.93-6.90)
Smoking during early pregnancy	83 (33.6%)	138 (27.6%)	0.1095	1.33 (0.96-1.84)
Spontaneous vaginal delivery	178 (66.7%)	447 (83.7%)	<.0001	0.39 (0.28-0.55)
Suspected small for gestational age	14 (5.2%)	7 (1.3%)	0.0032	4.17 (1.66-10.45)
Thyroid disorder	6 (2.2%)	7 (1.3%)	0.4816	1.73 (0.57-5.19)
Trauma during pregnancy	3 (1.1%)	3 (0.6%)	0.6384	2.01 (0.40-10.03)
Umbilical cord complications	7 (2.6%)	3 (0.6%)	0.0378	4.78 (1.22-18.62)
Vacuum extraction	23 (8.6%)	26 (4.9%)	0.0578	1.84 (1.03-3.29)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Appendix III: Analysis, dyskinetic CP

Variable	Case (n=42)	Control (n=84)	p-value	OR (95% CI)
Admitted to NICU	35 (85.4%)	14 (16.9%)	<.0001	28.75 (10.17-81.28)
Alcohol consumption during early pregnancy	17 (47.2%)	29 (35.8%)	0.3358	1.60 (0.72-3.56)
Apgar score at 5 minutes < 7	28 (70.0%)	2 (2.4%)	<.0001	94.50 (19.91-448.53)
Bad obstetric history	0 (0.0%)	1 (1.2%)	1.0000	*
Birth length (cm)	51.6 (2.9)	50.7 (2.1)	0.3726	1.19 (0.97-1.45)
Birthweight (kg)	3.62 (0.61)	3.70 (0.47)	0.2839	0.73 (0.35-1.52)
Bleeding during pregnancy	2 (4.8%)	2 (2.4%)	0.8148	2.05 (0.28-15.09)
Bleeding during first trimester	0 (0.0%)	2 (2.4%)	0.8853	*
Bleeding during second trimester	1 (2.4%)	0 (0.0%)	0.6667	*
Bleeding during third trimester	1 (2.4%)	1 (1.2%)	1.0000	2.02 (0.12-33.19)
Blood-stained amniotic fluid	3 (8.8%)	0 (0.0%)	0.0555	*
Breech presentation	2 (4.9%)	1 (1.2%)	0.5006	4.26 (0.37-48.37)
Cephalic presentation	39 (95.1%)	80 (95.2%)	1.0000	0.97 (0.17-5.55)

Cesarean section	14 (33.3%)	11 (13.1%)	0.0164	3.32 (1.35-8.18)
Cesarean section, elective	0 (0.0%)	4 (4.8%)	0.3855	*
Cesarean section, acute (< 8 hours after decision)	5 (11.9%)	6 (7.1%)	0.5638	1.76 (0.50-6.13)
Cesarean section, emergency	9 (21.4%)	0 (0.0%)	<.0001	*
Decreased fetal movements	1 (2.4%)	3 (3.6%)	1.0000	0.66 (0.07-6.53)
Diabetes	2 (4.9%)	1 (1.2%)	0.5006	4.26 (0.37-48.37)
Epilepsy	0 (0.0%)	1 (1.2%)	1.0000	*
External cephalic version	1 (2.4%)	1 (1.2%)	1.0000	2.02 (0.12-33.19)
Gestational diabetes	0 (0.0%)	1 (1.2%)	1.0000	*
Gestational hypertension/chronic hypertension	2 (4.8%)	4 (4.8%)	1.0000	1.00 (0.18-5.69)
Head circumference at birth (cm)	35.2 (1.6)	35.4 (1.7)	0.3605	0.91 (0.69-1.19)
Infertility	5 (11.9%)	7 (8.4%)	0.7446	1.47 (0.44-4.94)
Intrauterine fetal death of one twin	0 (0.0%)	0 (0.0%)		*
In vitro fertilization	0 (0.0%)	0 (0.0%)		*
Large for gestational age	3 (7.1%)	5 (6.0%)	1.0000	1.20 (0.27-5.28)
Lung disease	0 (0.0%)	4 (4.8%)	0.3982	*
Maternal age	29.1 (5.1)	28.7 (4.5)	0.6424	1.02 (0.94-1.10)
Maternal allergy	8 (19.5%)	18 (21.4%)	1.0000	0.89 (0.35-2.26)
Maternal BMI (kg/cm^2)	23.6 (3.1)	23.1 (3.1)	0.5988	1.05 (0.92-1.19)
Maternal weight week 34 (kg)	65.4 (10.4)	64.7 (9.0)	0.9682	1.01 (0.97-1.05)
Meconium aspiration	3 (7.1%)	0 (0.0%)	0.0705	*
Meconium-stained amniotic fluid	15 (44.1%)	11 (14.5%)	0.0022	4.67 (1.84-11.83)
Miscarriage	8 (19.5%)	14 (16.9%)	0.8959	1.19 (0.46-3.13)
Neonatal encephalopathy	22 (52.4%)	0 (0.0%)	<.0001	*
Non cohabitation with baby's father	2 (4.9%)	4 (4.9%)	1.0000	1.00 (0.18-5.70)
Nulliparity, nominal	18 (43.9%)	52 (62.7%)	0.0741	0.47 (0.22-1.00)
Obstetric catastrophe	2 (4.8%)	0 (0.0%)	0.2187	*
Ovulation induction	1 (2.4%)	2 (2.4%)	1.0000	1.00 (0.09-11.35)
Placental abruption	1 (2.4%)	0 (0.0%)	0.6667	*
Placental weight (g)	634 (135)	635 (135)	0.8306	1.00 (1.00-1.00)
Polycystic ovarian syndrome	0 (0.0%)	1 (1.2%)	1.0000	*
Preeclampsia	5 (11.9%)	6 (7.1%)	0.5638	1.76 (0.50-6.13)
Prepartal diagnosis of CNS anomaly	0 (0.0%)	0 (0.0%)		*
Previous deep vein thrombosis	0 (0.0%)	0 (0.0%)		*
Previous preterm birth	0 (0.0%)	1 (1.2%)	1.0000	*
Previous cesarean section	4 (10.0%)	10 (12.0%)	0.9972	0.81 (0.24-2.76)
Psychiatric disorder, e.g. psychosis or depression	2 (4.9%)	1 (1.2%)	0.5006	4.26 (0.37-48.37)
Rheumatic disorder	1 (2.4%)	1 (1.2%)	1.0000	2.07 (0.13-34.03)
Small for gestational age	2 (4.8%)	0 (0.0%)	0.2222	*
Smoking during early pregnancy	16 (40.0%)	18 (22.8%)	0.0828	2.26 (0.99-5.14)
Spontaneous vaginal delivery	18 (42.9%)	69 (82.1%)	<.0001	0.16 (0.07-0.37)
Suspected small for gestational age	2 (4.8%)	0 (0.0%)	0.2187	*
Termination of pregnancy	11 (27.5%)	13 (15.7%)	0.1936	2.04 (0.82-5.09)
Thyroid disorder	0 (0.0%)	1 (1.2%)	1.0000	*
Trauma during pregnancy	2 (4.8%)	2 (2.4%)	0.8148	2.05 (0.28-15.09)
Umbilical cord complications	2 (4.8%)	0 (0.0%)	0.2187	*
Vacuum extraction	10 (23.8%)	4 (4.8%)	0.0048	6.25 (1.83-21.38)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Appendix IV, Analysis, spastic diplegia and tetraplegia

Variable	Case (n=121)	Control (n=242)	p-value	OR (95% CI)
Admitted to NICU	63 (53.8%)	34 (14.2%)	<.0001	7.07 (4.23-11.81)
Alcohol consumption during early pregnancy	56 (49.6%)	102 (45.9%)	0.6096	1.16 (0.73-1.82)
Apgar score at 5 minutes < 7	25 (21.2%)	3 (1.2%)	<.0001	21.41 (6.31-72.60)
Bad obstetric history	4 (3.3%)	3 (1.2%)	0.3451	2.71 (0.60-12.31)
Birth length (cm)	49.5 (2.8)	50.7 (2.2)	0.0007	0.82 (0.75-0.91)
Birthweight (kg)	3.35 (0.63)	3.60 (0.53)	0.0005	0.46 (0.31-0.69)
Bleeding during pregnancy	12 (9.9%)	24 (9.9%)	1.0000	1.00 (0.48-2.08)
Bleeding during first trimester	8 (6.6%)	11 (4.5%)	0.5495	1.49 (0.58-3.80)
Bleeding during second trimester	5 (4.1%)	9 (3.7%)	1.0000	1.12 (0.37-3.41)
Bleeding during third trimester	4 (3.3%)	5 (2.1%)	0.6971	1.62 (0.43-6.15)
Blood-stained amniotic fluid	1 (0.9%)	1 (0.5%)	1.0000	2.02 (0.13-32.58)
Breech presentation	7 (6.0%)	7 (2.9%)	0.2616	2.14 (0.73-6.24)
Cephalic presentation	109 (94.0%)	232 (96.7%)	0.3612	0.54 (0.19-1.52)
Cesarean section	38 (31.4%)	29 (12.0%)	<.0001	3.36 (1.95-5.80)
Cesarean section, elective	7 (5.8%)	13 (5.4%)	1.0000	1.08 (0.42-2.79)
Cesarean section, acute (< 8 hours after decision)	11 (9.1%)	12 (5.0%)	0.1991	1.92 (0.82-4.48)
Cesarean section, emergency	20 (16.5%)	1 (0.4%)	<.0001	47.70 (6.32-360.12)
Decreased fetal movements	8 (6.6%)	4 (1.7%)	0.0343	4.21 (1.24-14.28)
Diabetes	1 (0.8%)	1 (0.4%)	1.0000	2.00 (0.12-32.25)
Epilepsy	0 (0.0%)	1 (0.4%)	1.0000	*
External cephalic version	2 (1.7%)	0 (0.0%)	0.2210	*
Gestational diabetes	4 (3.3%)	1 (0.4%)	0.0883	8.24 (0.91-74.52)
Gestational hypertension/chronic hypertension	4 (3.3%)	15 (6.2%)	0.3620	0.52 (0.17-1.59)
Head circumference at birth (cm)	34.4 (2.2)	35.3 (2.5)	0.0038	0.80 (0.70-0.92)
Infertility	9 (7.6%)	14 (5.9%)	0.6824	1.31 (0.55-3.13)
Intrauterine fetal death of one twin	1 (0.8%)	0 (0.0%)	0.6667	*
In vitro fertilization	1 (0.9%)	1 (0.4%)	1.0000	2.03 (0.13-32.68)
Large for gestational age	8 (6.7%)	15 (6.2%)	1.0000	1.08 (0.44-2.61)
Lung disease	1 (0.8%)	2 (0.8%)	1.0000	1.00 (0.09-11.09)
Maternal age	28.1 (5.4)	28.5 (5.2)	0.5606	0.99 (0.95-1.03)
Maternal allergy	22 (18.2%)	44 (18.3%)	1.0000	0.99 (0.56-1.75)
Maternal BMI (kg/cm^2)	23.8 (3.3)	23.1 (3.5)	0.0276	1.07 (0.99-1.14)
Maternal weight week 34 (kg)	65.3 (10.6)	64.2 (10.4)	0.2852	1.01 (0.99-1.03)
Meconium aspiration	5 (4.1%)	1 (0.4%)	0.0341	10.38 (1.20-89.80)
Meconium-stained amniotic fluid	39 (35.8%)	32 (14.6%)	<.0001	3.26 (1.89-5.60)
Miscarriage	27 (22.3%)	53 (21.9%)	1.0000	1.02 (0.61-1.73)
Neonatal encephalopathy	30 (24.8%)	1 (0.4%)	<.0001	79.45 (10.68-591.12)
Non cohabitation with baby's father	11 (9.2%)	5 (2.2%)	0.0082	4.58 (1.55-13.51)
Nulliparity, nominal	65 (53.7%)	141 (58.3%)	0.4762	0.83 (0.54-1.29)
Obstetric catastrophe	0 (0.0%)	0 (0.0%)		*
Ovulation induction	2 (1.7%)	2 (0.8%)	0.8148	2.02 (0.28-14.50)
Placental abruption	0 (0.0%)	1 (0.4%)	1.0000	*
Placental weight (g)	601 (161)	619 (151)	0.3351	1.00 (1.00-1.00)
Polycystic ovarian syndrome	2 (1.7%)	0 (0.0%)	0.2222	*
Preeclampsia	9 (7.4%)	17 (7.0%)	1.0000	1.06 (0.46-2.46)
Prepartal diagnosis of CNS anomaly	3 (2.5%)	0 (0.0%)	0.0728	*
Previous deep vein thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	*
Previous preterm birth	1 (0.9%)	2 (0.8%)	1.0000	1.02 (0.09-11.33)
Previous cesarean section	9 (7.5%)	19 (7.9%)	1.0000	0.94 (0.41-2.14)
Psychiatric disorder, e.g. psychosis or depression	3 (2.5%)	3 (1.2%)	0.6411	2.02 (0.40-10.15)
Rheumatic disorder	1 (0.8%)	2 (0.8%)	1.0000	1.00 (0.09-11.09)

Small for gestational age	17 (14.2%)	7 (2.9%)	0.0002	5.52 (2.22-13.71)
Smoking during early pregnancy	35 (31.0%)	66 (29.5%)	0.8690	1.07 (0.66-1.76)
Spontaneous vaginal delivery	70 (57.9%)	201 (83.1%)	<.0001	0.28 (0.17-0.46)
Suspected small for gestational age	8 (6.6%)	4 (1.7%)	0.0343	4.21 (1.24-14.28)
Termination of pregnancy	21 (17.4%)	42 (17.4%)	1.0000	1.00 (0.56-1.77)
Thyroid disorder	2 (1.7%)	4 (1.7%)	1.0000	1.00 (0.18-5.51)
Trauma during pregnancy	3 (2.5%)	1 (0.4%)	0.2198	6.13 (0.63-59.54)
Umbilical cord complications	2 (1.7%)	2 (0.8%)	0.8082	2.03 (0.28-14.62)
Vacuum extraction	13 (10.7%)	12 (5.0%)	0.0722	2.31 (1.02-5.22)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Appendix V, Analysis, spastic hemiplegia

Variable	Case (n=146)	Control (n=292)	p-value	OR (95% CI)
Admitted to NICU	60 (42.0%)	27 (9.3%)	<.0001	7.04 (4.20-11.81)
Alcohol consumption during early pregnancy	78 (58.2%)	144 (52.2%)	0.2961	1.28 (0.84-1.94)
Apgar score at 5 minutes < 7	9 (6.3%)	1 (0.3%)	0.0005	19.53 (2.45-155.69)
Bad obstetric history	4 (2.7%)	7 (2.4%)	1.0000	1.15 (0.33-3.98)
Birth length (cm)	50.2 (2.4)	50.6 (2.0)	0.1499	0.92 (0.84-1.01)
Birthweight (kg)	3.43 (0.56)	3.60 (0.48)	0.0012	0.52 (0.35-0.78)
Bleeding during pregnancy	12 (8.2%)	27 (9.2%)	0.8716	0.88 (0.43-1.79)
Bleeding during first trimester	4 (2.7%)	16 (5.5%)	0.2912	0.49 (0.16-1.48)
Bleeding during second trimester	5 (3.4%)	5 (1.7%)	0.4215	2.04 (0.58-7.15)
Bleeding during third trimester	3 (2.1%)	7 (2.4%)	1.0000	0.85 (0.22-3.35)
Blood-stained amniotic fluid	1 (0.8%)	2 (0.8%)	1.0000	1.05 (0.09-11.73)
Breech presentation	4 (2.8%)	6 (2.1%)	0.8900	1.33 (0.37-4.80)
Cephalic presentation	141 (97.2%)	281 (97.6%)	1.0000	0.88 (0.25-3.05)
Cesarean section	28 (19.2%)	32 (11.0%)	0.0295	1.93 (1.11-3.35)
Cesarean section, elective	6 (4.1%)	17 (5.8%)	0.6088	0.69 (0.27-1.80)
Cesarean section, acute (< 8 hours after decision)	13 (8.9%)	10 (3.4%)	0.0322	2.75 (1.18-6.44)
Cesarean section, emergency	9 (6.2%)	2 (0.7%)	0.0024	9.52 (2.03-44.68)
Decreased fetal movements	3 (2.1%)	6 (2.1%)	1.0000	1.00 (0.25-4.06)
Diabetes	2 (1.4%)	0 (0.0%)	0.2212	*
Epilepsy	1 (0.7%)	3 (1.0%)	1.0000	0.66 (0.07-6.44)
External cephalic version	1 (0.7%)	4 (1.4%)	0.9203	0.50 (0.05-4.48)
Gestational diabetes	2 (1.4%)	3 (1.0%)	1.0000	1.34 (0.22-8.10)
Gestational hypertension/chronic hypertension	10 (6.8%)	7 (2.4%)	0.0498	2.99 (1.12-8.03)
Head circumference at birth (cm)	34.7 (1.7)	35.1 (1.8)	0.0120	0.88 (0.77-1.00)
Infertility	10 (6.9%)	23 (7.9%)	0.8774	0.87 (0.40-1.87)
Intrauterine fetal death of one twin	0 (0.0%)	0 (0.0%)		*
In vitro fertilization	0 (0.0%)	0 (0.0%)		*
Large for gestational age	7 (4.8%)	7 (2.4%)	0.2915	2.05 (0.71-5.96)
Lung disease	4 (2.7%)	10 (3.4%)	0.9485	0.79 (0.24-2.58)
Maternal age	28.6 (5.5)	28.3 (5.1)	0.8462	1.01 (0.97-1.05)
Maternal allergy	36 (24.7%)	63 (21.6%)	0.5416	1.19 (0.74-1.90)
Maternal BMI (kg/cm^2)	24.1 (4.5)	22.9 (3.7)	0.0067	1.08 (1.02-1.14)
Maternal weight week 34 (kg)	66.1 (12.8)	63.1 (11.2)	0.0231	1.02 (1.00-1.04)
Meconium aspiration	0 (0.0%)	0 (0.0%)		*
Meconium-stained amniotic fluid	28 (22.6%)	42 (16.1%)	0.1638	1.52 (0.89-2.60)

Miscarriage	32 (21.9%)	60 (20.7%)	0.8573	1.08 (0.66-1.75)
Neonatal encephalopathy	19 (13.0%)	0 (0.0%)	<.0001	*
Non cohabitation with baby's father	6 (4.2%)	6 (2.1%)	0.3491	2.04 (0.65-6.45)
Nulliparity, nominal	90 (61.6%)	181 (62.0%)	1.0000	0.99 (0.65-1.48)
Obstetric catastrophe	3 (2.1%)	0 (0.0%)	0.0731	*
Ovulation induction	0 (0.0%)	3 (1.0%)	0.5823	*
Placental abruption	0 (0.0%)	0 (0.0%)		*
Placental weight (g)	596 (149)	619 (149)	0.1207	1.00 (1.00-1.00)
Polycystic ovarian syndrome	0 (0.0%)	1 (0.3%)	1.0000	*
Preeclampsia	11 (7.5%)	17 (5.8%)	0.6185	1.32 (0.60-2.89)
Prepartal diagnosis of CNS anomaly	3 (2.1%)	0 (0.0%)	0.0731	*
Previous deep vein thrombosis	2 (1.4%)	2 (0.7%)	0.8148	2.01 (0.28-14.44)
Previous preterm birth	3 (2.1%)	4 (1.4%)	0.8551	1.52 (0.33-6.87)
Previous cesarean section	14 (9.7%)	16 (5.6%)	0.1642	1.83 (0.87-3.86)
Psychiatric disorder, e.g. psychosis or depression	4 (2.7%)	2 (0.7%)	0.1972	4.08 (0.74-22.57)
Rheumatic disorder	3 (2.1%)	2 (0.7%)	0.4175	3.04 (0.50-18.38)
Small for gestational age	10 (6.8%)	9 (3.1%)	0.1211	2.31 (0.92-5.82)
Smoking during early pregnancy	48 (35.8%)	72 (26.1%)	0.0569	1.58 (1.01-2.46)
Spontaneous vaginal delivery	108 (74.0%)	246 (84.2%)	0.0159	0.53 (0.33-0.86)
Suspected small for gestational age	6 (4.1%)	3 (1.0%)	0.0816	4.13 (1.02-16.75)
Termination of pregnancy	29 (19.9%)	63 (21.7%)	0.7506	0.89 (0.55-1.46)
Thyroid disorder	4 (2.7%)	3 (1.0%)	0.3431	2.71 (0.60-12.28)
Trauma during pregnancy	0 (0.0%)	2 (0.7%)	0.8879	*
Umbilical cord complications	5 (3.4%)	1 (0.3%)	0.0347	10.28 (1.19-88.73)
Vacuum extraction	10 (6.8%)	14 (4.8%)	0.4969	1.46 (0.63-3.37)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables and marked with *. Fisher´s Exact test was used for comparison between groups or dichotomous variables, The Mantel-Haenszel Chi-Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. * indicates that calculation of OR and 95% CI is impossible, since one group is 0. ORs for the continuous variables are presented per 1 unit increase in the continuous variable.

Study II

Appendix VI, Analysis Spastic CP

Variable	Case (n=267)	Control (n=534)	Univariable analysis		Adjusted analysis	
			p-value	OR (95% CI)	p-value	OR (95% CI)
Sexually transmitted disease	36 (13.8%)	76 (14.6%)	0.79	0.9 (0.6-1.5)	0.80	0.9 (0.6-1.6)
Sexually transmitted disease, several times	3 (1.2%)	6 (1.1%)	0.99	1.0 (0.3-4.1)	0.91	1.1 (0.3-4.5)
Hepatitis	3 (1.1%)	2 (0.4%)	0.23	3.0 (0.5-18.2	0.59	2.0 (0.2-24.6)
During pregnancy:						
Bacterial growth in urine	18 (6.7%)	18 (3.4%)	0.03	2.1 (1.1-4.1)	0.006	3.4 (1.4-8.1)
Repeating bacterial growth in urine	6 (2.2%)	10 (1.9%)	0.72	1.2 (0.4-3.4)	0.28	2.2 (0.5-9.2)
Escherichia Coli bacteriuria	9 (3.4%)	4 (0.7%)	0.01	4.6 (1.4-15.2)	0.01	16.1 (1.9-137.2)
Group B Streptococcus bacteriuria	3 (1.1%)	2 (0.4%)	0.23	3.0 (0.5-18.2)	0.40	2.4 (0.3-17.6)
Bacterial growth in urine of unknown etiology	5 (1.9%)	10 (1.9%)	1.00	1.0 (0.2-3.0)	0.97	1.0 (0.2-5.7)
Any infectious disease	100 (37.4%)	139 (26.0%)	0.001	1.7 (1.2-2.3)	0.001	1.9 (1.3-2.8)
Severe infection	19 (7.1%)	20 (3.7%)	0.04	2.0 (1.0-3.8)	0.07	2.2 (1.0-5.1)
Chorioamnionitis	0 (0.0%)	0 (0.0%)		*	*	*
Antibiotic therapy	54 (20.2%)	58 (10.9%)	0.000	2.1 (1.4-3.1)	0.00	2.7 (1.6-4.4)
Antibiotic therapy several times	16 (6.0%)	13 (2.4%)	0.01	2.6 (1.2-5.4)	0.03	2.9 (1.1-7.5)
Before delivery:						
Antibiotic therapy	5 (1.9%)	5 (0.9%)	0.27	2.0 (0.6-7.0)	0.70	0.7 (0.1-3.9)
Antibiotic therapy several times	4 (1.5%)	0 (0.0%)	0.01	*	*	*
Temperature ≥38 degrees	8 (3.0%)	7 (1.3%)	0.11	2.3 (0.8-6.5)	0.51	1.5 (0.4-5.3)
Temperature ≥38 degrees twice	5 (1.9%)	6 (1.1%)	0.40	1.7 (0.5-5.5)	0.97	1.0 (0.2-4.3)
During delivery:						
Antibiotic therapy	8 (3.1%)	2 (0.4%)	0.008	8.2 (1.7-38.9)	0.05	8.7 (1.0-73.3)
Temperature ≥38 degrees	3 (1.2%)	5 (1.0%)	0.79	1.2 (0.3-5.1)	0.75	0.8 (0.2-3.6)
Temperature ≥38 degrees twice	2 (0.8%)	4 (0.8%)	0.99	1.0 (0.2-5.5)	0.51	0.6 (0.1-3.3)
Post partum:						
Antibiotic therapy postpartum	23 (8.7%)	16 (3.0%)	0.001	3.1 (1.6-5.9)	0.27	1.6 (0.7-3.4)
Temperature ≥38 degrees	17 (6.4%)	15 (2.9%)	0.02	2.3 (1.1-4.7)	0.51	1.4 (0.6-3.4)
Temperature ≥38 degrees twice	12 (4.5%)	5 (1.0%)	0.003	5.0 (1.7-14.2)	0.11	2.8 (0.8-10.3)

Foul smelling amniotic fluid	2 (0.9%)	2 (0.4%)	0.47	2.1 (0.3-14.8)	0.46	2.21 (0.27-17.99)
Endometritis	3 (1.1%)	4 (0.8%)	0.59	1.5 (0.3-6.8)	0.35	0.4 (0.0-4.0)
Neonatal Infection	15 (5.6%)	2 (0.4%)	<.0001	15.8 (3.6-69.8)	0.004	10.2 (2.1-48.2)
Time from rupture of membranes until delivery (h)	14.8 (16.6)	12.5 (19.4)	0.07	1.0 (1.0-1.0)	0.80	1.0 (1.0-1.0)
Confounders:						
Maternal smoking	83 (33.6%)	138 (27.6%)	0.11	1.3 (1.0-1.8)		
Maternal age	28.4 (5.4)	28.4 (5.1)	0.82	1.0 (1.0-1.0)		
Maternal BMI	24.0 (4.0)*	23.0 (3.6)	0.0004	1.1 (1.0-1.1)		
Parity	155 (58.1%)	322 (60.3%)	0.59	0.9 (0.7-1.2)		
Non cohabitation with the father	17 (6.5%)	11 (2.1%)	0.005	3.2 (1.5-6.9)		
Instrumental delivery	89 (33.3%)	178 /66.7%)	0.000	2.6 (1.8-3.7)		

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Appendix VII, Analysis Dyskinetic CP

			Univariable analysis		Adjusted analysis,	
Variable	**Case (n=42)**	**Control (n=84)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Sexually transmitted disease	10 (25.0%)	13 (15.9%)	0.33	1.8 (0.7-4.5)	0.88	1.1 (0.3-3.9)
Sexually transmitted disease, several times	2 (5%)	1 (1.2%)	0.24	4.2 (0.0-2.7)	0.05	18.8 (1.0-370.2)
Hepatitis	2 (4.9%)	1 (1.2%)	0.24	4.3 (0.4-48.4)	1.00	
During pregnancy:						
Bacterial growth in urine	2 (4.8%)	3 (3.6%)	0.75	1.4 (0.2-8.4)	0.87	1.2 (0.1-13.7)
Repeating bacterial growth in urine	1 (2.4%)	2 (2.4%)	1.00	1.0 (0.1-11.4)	0.34	3.5 (0.3-44.7)
Escherichia Coli bacteriuria	1 (2.4%)	0 (0.0%)	1.00	*	*	*
Group B Streptococcus bacteriuria	0 (0.0%)	1 (1.2%)	1.00	*	*	*
Bacterial growth in urine of unknown etiology	0 (0.0%)	2 (2.4%)	0.55	*	*	*
Any infectious disease	12 (28.6%)	19 (22.6%)	0.47	1.4 (0.6-3.2)	0.134	2.3 (0.8-6.7)
Severe infection	4 (9.5%)	7 (8.3%)	0.82	1.2 (0.3-4.2)	0.66	1.4 (0.3-6.8)
Chorioamnionitis	0 (0.0%)	0 (0.0%)	*	*	*	*

Antibiotic therapy	2 (4.8%)	3 (3.6%)	1.00	1.0 (0.4-2.9)	0.52	1.6 (0.4-6.1)
Antibiotic therapy several times	1 (2.4%)	2 (2.4%)	0.62	2.0 (0.1-33.2)	*	*
Before delivery:						
Antibiotic therapy	0 (0.0%)	0 (0.0%)		*	*	*
Antibiotic therapy several times	0 (0.0%)	0 (0.0%)		*	*	*
Temperature ≥38 degrees	1 (2.4%)	1 (1.2%)	0.61	2.1 (0.1-34.0)	1.00	
Temperature ≥38 degrees twice	1 (2.4%)	1 (1.2%)	0.61	2.1 (0.1-34.0)	1.00	
During delivery:						
Antibiotic therapy	3 (7.5%)	1 (1.2%)	0.11	6.5 (0.7-64.5)	0.36	4.4 (0.2-104.1)
Temperature ≥38 degrees	1 (2.4%)	1 (1.2%)	1.00	2.1 (0.1-33.6)	1.00	
Temperature ≥38 degrees twice	1 (2.4%)	0 (0.0%)	0.33	*	*	*
Postpartum:						
Antibiotic therapy	7 (17.1%)	3 (3.6%)	0.02	5.5 (1.3-22.5)	0.07	4.5 (0.9-23.5)
Temperature ≥38 degrees	2 (4.9%)	5 (6.0%)	1.00	0.8 (0.2-4.4)	0.19	0.2 (0.0-2.3)
Temperature ≥38 degrees twice	1 (2.4%)	4 (4.8%)	0.81	0.5 (0.1-4.6)	0.99	*
Foul smelling amniotic fluid	0 (0.0%)	0 (0.0%)			*	*
Endometritis	1 (2.5%)	1 (1.2%)	0.60	2.1 (0.1-34.5)	0.99	1.0 (0.0-44.5)
Neonatal Infection	4 (9.5%)	0 (0.0%)	0.01	*	*	*
Time from rupture of membranes until delivery (h)	14.3 (16.6)	17.7 (43.6)	0.43	1.0 (1.0-1.0)	0.03	0.9 (0.8-1.0)
Confounders:						
Maternal smoking	16 (40.0%)	18 (22.8%)	0.08	2.3 (1.0-5.1)		
Maternal age	29.1 (5.1)*	28.7 (4.5)	0.64	1.0 (0.9-1.1)		
Maternal BMI	23.6 (3.1)*	23.1 (3.1)	0.60	1.1 (0.9-1.2)		
Parity	18 (43.9%)	52 (62.7%)	0.07	0.5 (0.2-1.0)		
Non cohabitation with the father	2 (4.9%)	4 (4.9%)	1.00	1.0 (0.9-5.7)		
Instrumental delivery	23 (54.8%)	19 (45.2%)	<0.0001	5.6 (2.4-12.7)		

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Appendix VIII, Analysis Spastic CP Diplegia and Tetraplegia

Variable	Case (n=121)	Control (n=242)	Univariable analysis		Adjusted analysis	
			p-value	OR (95% CI)	p-value	OR (95% CI)
Sexually transmitted disease	17 (14.7%)	28 (11.9%)	0.46	1.3 (0.7-2.4)	0.41	1.4 (0.6-3.0)
Sexually transmitted disease, several times	3 (2.6%)	1 (0.4%)	0.12	6.2 (0.64-60.7)	0.07	8.5 (0.8-87.8)
Hepatitis	2 (1.7%)	2 (0.8%)	0.49	2.0 (0.3-14.4)	0.70	1.7 (0.1-23.3)
During pregnancy:						
Bacterial growth in urine	7 (5.8%)	7 (2.9%)	0.19	2.06 (0.7-6.0)	0.24	2.2 (0.6-8.4)
Repeating bacterial growth in urine	2 (1.7%)	4 (1.7%)	1.00	1.0 (0.2-5.5)	0.66	1.6 (0.2-14.3)
Escherichia Coli bacteriuria	3 (2.5%)	1 (0.4%)	0.12	6.1 (0.6-59.5)	0.20	5.0 (0.4-56.5)
Group B Streptococcus bacteriuria	1 (0.8%)	1 (0.4%)	0.62	2.0 (0.1-32.4)	1.00	
Bacterial growth in urine of unknown etiology	3 (2.5%)	6 (2.5%)	1.00	1.0 (0.3-4.1)	0.86	1.2 (0.2-8.5)
Any infectious disease	43 (35.5%)	71 (29.3%)	0.231	1.3 (0.8-2.1)	0.62	1.2 (0.7-2.1)
Severe infection	7 (5.8%)	14 (5.8%)	1.00	1.0 (0.4-2.6)	0.28	0.5 (0.1-1.9)
Chorioamnionitis	0 (0.0%)	1 (0.4%)	*	*	*	*
Antibiotic therapy	21 (17.4%)	35 (14.5%)	0.47	1.2 (0.7-2.2)	0.93	1.0 (0.5-2.2)
Antibiotic therapy several times	7 (5.8%)	8 (3.3%)	0.27	1.8 (0.6-5.1)	0.92	1.1 (0.3-4.1)
Before delivery:						
Antibiotic therapy	3 (2.5%)	1 (0.4%)	0.12	6.1 (0.6-59.1)	0.94	0.9 (0.1-15.3)
Antibiotic therapy several times	2 (1.7%)	0 (0.0%)	0.11	*	*	*
Temperature ≥38 degrees	3 (2.5%)	5 (2.1%)	0.80	1.2 (0.3-5.1)	0.79	0.8 (0.1-4.4)
Temperature ≥38 degrees twice	1 (0.8%)	4 (1.7%)	0.53	0.5 (0.1-4.5)	0.99	
During delivery:						
Antibiotic therapy	3 (2.6%)	1 (0.4%)	0.12	6.2 (0.6-60.4)	0.99	
Temperature ≥38 degrees	2 (1.7%)	2 (0.8%)	0.48	2.0 (0.3-14.6)	0.85	1.2 (0.2-10.3)
Temperature ≥38 degrees twice	1 (0.8%)	1 (0.4%)	0.62	2.0 (0.1-32.5)	0.80	0.7 (0.0-11.9)
Postpartum:						
Antibiotic therapy	14 (11.7%)	11 (4.6%)	0.02	2.8 (1.2-6.3)	0.41	1.5 (0.6-4.1)
Temperature ≥38 degrees	7 (5.8%)	9 (3.8%)	0.38	1.6 (0.6-4.3)	0.70	1.3 (0.4-4.6)
Temperature ≥38 degrees twice	4 (3.3%)	4 (1.7%)	0.34	2.0 (0.5-8.1)	0.54	1.8 (0.3-11.1)
Foul smelling amniotic fluid	1 (0.9%)	2 (0.9%)	0.99	1.0 (1.0-11.2)	0.85	0.8 (0.1-11.3)

Endometritis	0 (0.0%)	3 (1.3%)	0.11	*	*	*
Neonatal Infection	11 (9.1%)	1 (0.4%)	0.002	24.10 (3.07-188.99)	0.02	14.7 (1.7-126.5)
Time from rupture of membranes until delivery (h)	14.5 (16.7)	14.0 (24.4)	0.43	1.0 (1.0-1.0)	0.46	1.0 (1.0-1.0)
Confounders:						
Maternal smoking	35 (31.0%)	66 (29.5%)	0.87	1.1 (0.7-1.8)		
Maternal age	28.1 (5.4)*	28.5 (5.2)	0.56	1.0 (1.0-1.0)		
Maternal BMI	23.8 (3.3)*	23.1 (3.5)	0.03	1.1 (1.0-1.1)		
Parity	65 (53.7%)	141 (58.3%)	0.48	0.8 (0.5-1.3)		
Non cohabitation with the father	11 (9.2%)	5 (2.2%)	0.008	4.6 (1.6-13.5)		
Instrumental delivery	51 (42.1%)	70 (57.9%)	0.000	3.6 (2.2-5.8)		

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Appendix IX, Analyis Spastic hemiplegia

			Univariable analysis		Adjusted analysis,	
Variable	**Case (n=146)**	**Control (n=292)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Sexually transmitted disease	19 (13.2%)	48 (16.8%)	0.33	0.8 (0.42-1.3)	0.24	0.7 (0.3-1.3)
Sexually transmitted disease, several times	0 (0.0%)	5 (1.7%)	0.17	*	*	*
Hepatitis	1 (0.7%)	0 (0.0%)	1.00	*	*	*
During pregnancy:						
Bacterial growth in urine	11 (7.5%)	11 (3.8%)	0.09	2.1 (0.9-4.9)	0.009	4.7 (1.5-15.2)
Repeating bacterial growth in urine	4 (2.7%)	6 (2.1%)	0.65	1.3 (0.4-4.8)	0.36	2.6 (0.4-18.7)
Escherichia Coli bacteriuria	6 (4.1%)	3 (1.0%)	0.004	4.1 (1.0-16.8)	0.99	
Group B Streptococcus bacteriuria	2 (1.4%)	1 (0.3%)	0.26	4.0 (0.4-44.9)	0.18	5.4 (0.5-62.9)
Bacterial growth in urine of unknown etiology	2 (1.4%)	4 (1.4%)	1.00	1.0 (0.2-5.5)	1.00	
Any infectious disease	57 (39.0%)	68 (23.3%)	0.001	2.1 (1.4-3.2)	0.000	2.9 (1.7-4.8)
Severe infection	12 (8.2%)	6 (2.1%)	0.004	4.3 (1.6-11.6)	0.001	15.4 (3.0-78.1)
Chorioamnionitis	0 (0.0%)	0 (0.0%)				*

Antibiotic therapy	33 (22.6%)	23 (7.9%)	<.0001	3.4 (1.9-6.1)	0.000	6.3 (3.0-15.2)
Antibiotic therapy several times	9 (6.2%)	5 (1.7%)	0.02	3.8 (1.2-11.5)	0.012	15.6 (1.81-134.2)
Before delivery:						
Antibiotic therapy	2 (1.4%)	4 (1.4%)	0.99	1.0 (0.2-5.5)	0.71	0.7 (0.1-5.7)
Antibiotic therapy several times before delivery	2 (1.4%)	0 (0.0%)	0.11	*	*	*
Temperature ≥38 degrees before delivery	5 (3.4%)	2 (0.7%)	0.05	5.1 (1.0-26.8)	0.14	0.2 (0.0-1.8)
Temperature ≥38 degrees twice before delivery	4 (2.8%)	2 (0.7%)	0.11	4.0 (0.7-22.3)	0.14	5.8 (0.6-58.5)
During delivery:						
Antibiotic therapy	5 (3.6%)	1 (0.4%)	0.04	10.1 (1.2-87.5)	0.08	7.5 (0.8-69.9)
Temperature ≥38 degrees	1 (0.7%)	3 (1.0%)	0.74	0.7 (0.1-6.6)	0.50	0.5 (0.0-4.7)
Temperature ≥38 degrees twice	1 (0.7%)	3 (1.0%)	0.72	0.7 (0.1-6.4)	0.47	0.4 (0.0-4.4)
Postpartum:						
Antibiotic therapy postpartum	9 (6.3%)	5 (1.7%)	0.02	3.8 (1.3-11.6)	0.40	1.9 (0.4-8.1)
Temperature ≥38 degrees	10 (6.9%)	6 (2.1%)	0.02	3.5 (1.2-9.7)	0.61	1.4 (0.4-5.5)
Temperature ≥38 degrees twice	8 (5.6%)	5 (1.7%)	0.008	17.1 (2.1-137.8)	0.09	7.2 (0.7-69.9)
Foul smelling amniotic fluid	1 (0.8%)	0 (0.0%)	1.00	*	*	*
Endometritis	3 (2.1%)	1 (0.3%)	0.12	6.2 (0.6-59.9)	0.70	1.7 (0.1-30.3)
Neonatal Infection	4 (2.7%)	1 (0.3%)	0.06	8.2 (0.9-74.0)	0.16	5.3 (0.5-55.0)
Time from rupture of membranes until delivery (h)	14.9 (16.6)	11.2 (13.9)	0.09	1.0 (1.0-1.0)	0.15	1.0 (1.0-1.1)
Confounders:						
Maternal smoking	48 (35.8%)	72 (26.1%)	0.0569	1.58 (1.01-2.46)		
Maternal age	28.6 (5.5)*	28.3 (5.1)	0.8462	1.01 (0.97-1.05)		
Maternal BMI	24.1 (4.5)*	22.9 (3.7)	0.0067	1.08 (1.02-1.14)		
Parity	90 (61.6%)	181 (62.0%)	1.0000	0.99 (0.65-1.48)		
Non cohabitation with the father	6 (4.2%)	6 (2.1%)	0.3491	2.04 (0.65-6.45)		
Instrumental delivery	38 (26.0%)	108 (74.0%)	0.01	1.9 (1.2-3.1)		

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. For comparison between groups and p-value, Fisher´s Exact test was used and Mann-Whitney U-test were used for p-value for continuous variables. *Are used when one group is 0, therefore it is not possible to calculate p-value, OR and 95% CI.Variables were adjusted for maternal smoking, maternal BMI, non cohabitation with the father of the child, parity, maternal age and instrumental delivery.

Study III

Appendix X, Antecedents of mild and severe motor impairment in cerebral palsy

Variable	Mild motor impairment				Severe motor impairment				Cases only**
	Case (n=197)	Control (n=394)	OR (95 % CI)	p-value	Case (n=95)	Control (n=190)	OR (95 % CI)	p-value	p-value
Maternal characteristics									
Maternal age	28.5 (5.2)	28.4 (5.0)	1.005 (0.97-1.04)	0.97	28.5 (5.8)	28.6 (5.3)	0.999 (0.96-1.05)	0.96	0.97
Non cohabitation with baby's father	11 (6 %)	8 (2 %)	2.8 (1.1-7.2)	0.03	7 (7 %)	6 (3 %)	2.4 (0.8-7.3)	0.14	0.61
Induced abortion	41 (21 %)	81 (21 %)	1.006 (0.7-1.5)	1.00	17 (18 %)	29 (15 %)	1.2 (0.6-2.4)	0.61	0.64
Spontaneous abortion	42 (21 %)	80 (20 %)	1.1 (0.7-1.6)	0.83	19 (20 %)	40 (21 %)	0.9 (0.5-1.7)	1.00	0.88
Bad obstetric history	4 (2 %)	9 (2 %)	0.9 (0.3-2.9)	1.00	4 (4 %)	2 (1 %)	4.2 (0.8-23.2)	0.10	0.28
Previous preterm birth	3 (2 %)	5 (1 %)	1.2 (0.3-5.1)	0.72	1 (1 %)	2 (1 %)	1.03 (0.09-11.5)	1.00	1.00
Previous cesarean section	18 (9 %)	27 (7 %)	1.4 (0.7-2.6)	0.33	8 (9 %)	14 (7 %)	1.2 (0.5-2.9)	0.81	1.00
Previous sexually transmitted disease	31 (16 %)	57 (15 %)	1.1 (0.7-1.8)	0.62	14 (15 %)	26 (14 %)	1.1 (0.5-2.2)	0.86	0.86
Nulliparity	111 (56 %)	237 (60 %)	0.9 (0.6-1.2)	0.38	52 (55 %)	115 (61 %)	0.8 (0.5-1.3)	0.44	0.90
Infertility	15 (8 %)	29 (7 %)	1.0 (0.5-2.0)	1.00	8 (89 %)	12 (6 %)	1.4 (0.5-3.5)	0.47	0.82
Maternal BMI (kg/m^2)**	24.1 (4.2)	22.9 (3.6)	1.1 (1.03-1.1)	0.002	23.6 (3.1)	23.1 (3.6)	1.04 (0.96-1.1)	0.21	0.41
Intercurrent disease:									
Maternal disease	49 (25 %)	72 (18 %)	1.5 (9.98-2.2)	0.07	17 (18%)	43 (23%)	0.8 (0.4-1.4)	0.44	0.23
Hepatitis	1 (1 %)	2 (1 %)	1.0 (0.09-11.1)	1.00	4 (4 %)	1 (1 %)	8.4 (0.9-76.9)	0.04	0.04
Maternal addiction problems	0 (0 %)	0 (0 %)	*	*	3 (3 %)	1 (1 %)	6.2 (0.6-60.7)	0.11	0.03
Smoking during early pregnancy	56 (31 %)	95 (26 %)	1.3 (0.9-1.9)	0.19	38 (41 %)	48 (27 %)	1.9 (1.1-3.2)	0.02	0.11
Alcohol consumption during early pregnancy	103 (57 %)	190 (51 %)	1.3 (0.9-1.8)	0.20	42 (47 %)	75 (42 %)	1.2 (0.7-2.0)	0.44	0.15
Maternal weight week 34 (kg)	66.2 (12.3)	63.2 (10.7)	1.02 (1.008-1.04)	0.004	63.7 (9.6)	64.5 (10.5)	0.99 (0.97-1.02)	0.59	0.09
Pregnancy complications:									
Preeclampsia	14 (7 %)	24 (6 %)	1.2 (0.6-2.3)	0.72	10 (11 %)	13 (7 %)	1.6 (0.7-3.8)	0.36	0.37
Gestational hypertension	15 (8 %)	13 (3 %)	2.4 (1.1-5.2)	0.02	1 (1 %)	11 (6 %)	0.2 (0.02-1.4)	0.07	0.03
Gestational diabetes	2 (2 %)	4 (1 %)	1.5 (0.3-6.8)	0.69	2 (2 %)	1 (1 %)	4.1 (0.4-45.4)	0.26	0.66
Bleeding during pregnancy	16 (8 %)	35 (9 %)	0.9 (0.5-1.7)	0.44	9 (10 %)	15 (8 %)	1.2 (0.5-2.9)	0,66	0.66
Trauma during pregnancy	3 (2 %)	4 (1 %)	1.5 (0.3-6.8)	0.69	2 (2 %)	1 (1 %)	4.1 (0.4-45.4)	0.26	0.66
Maldevelopment diagnosed at birth	0 (0 %)	0 (0 %)	*	*	8 (8 %)	0 (0 %)	∞	<0.001	<0.001
Decreased fetal movements	8 (2 %)	5 (3 %)	1.3 (0.4-3.9)	0.77	5 (5 %)	5 (3 %)	2.1 (0.6-7.3)	0.31	0.30
Intrauterine growth:									
Decreased SF height	6 (3 %)	16 (4 %)	0.7 (0.3-1.9)	0.65	5 (5 %)	6 (3 %)	1.7 (0.5-5.7)	0.52	0.35
Small for gestational age	18 (9 %)	10 (3 %)	3.9 (1.7-8.5)	0.001	9 (10 %)	5 (3 %)	3.9 (1.3-11.9)	0.02	1.00
Large for gestational age	13 (7 %)	15 (4 %)	1.8 (0.8-3.8)	0.15	5 (5 %)	11 (6 %)	0.9 (0.3-2.7)	1.00	0.80
Birth length (cm)**	50.1 (2.6)	50.6 (2.0)	0.9 (0.8-0.98)	0.04	50.1 (3.0)	50.6 (2.2)	0.9 (0.8-1.02)	0.16	0.87

Birthweight (kg)**	3.4 (0.6)	3.6 (0.5)	0.6 (0.4-0.8)	0.001	3.4 (0.6)	3.6 (0.5)	0.5 (0.3-0.8)	0.005	0.68
Head circumference at birth (cm)**	34.8 (1.7)	35.2 (1.9)	0.9 (0.8-0.98)	0.008	34.3 (2.2)	35.3 (2.5)	0.8 (0.7-0.9)	0.001	0.08
Placental weight (hg)	6.0 (1.5)	6.2 (1.5)	0.9 (0.8-1.0)	0.04	6.3 (1.6)	6.2 (1.4)	1.0 (0.9-1.2)	0.65	0.17
Factors related to prepartal infection:									
Severe infection during pregnancy	13 (7 %)	14 (4 %)	1.9 (0.9-4.2)	0.10	7 (7 %)	12 (6 %)	1.2 (0.4-3.1)	0.80	0.81
Escherichia coli bacteriuria during pregnancy	6 (3 %)	3 (1 %)	4.1 (1.0-16.5)	0.07	3 (3 %)	1 (1 %)	6.2 (0.6-60.1)	0.11	1.00
Group B *Streptococcus* bacteriuria during pregnancy	3 (2 %)	1 (0.3 %)	6.1 (58.8)	0.11	0 (0 %)	1 (1 %)	0	1.00	0.55
Bacterial growth in urine during pregnancy	13 (7 %)	13 (3 %)	0.5 (0.2-1.1)	0.09	6 (6 %)	6 (3 %)	2.1 (0.6-6.6)	0.22	1.00
Congenital infection	0 (0 %)	0 (0 %)	*	*	4 (4 %)	0 (0 %)	∞	0.01	0.01
Infection during pregnancy	73 (37 %)	95 (24 %)	1.9 (1.3-2.7)	0.001	33 (35 %)	51 (27 %)	1.5 (0.9-2.5)	0.17	0.80
Antibiotic therapy during pregnancy	39 (20 %)	38 (10 %)	2.3 (1.4-3.8)	0.001	16 (17 %)	27 (14 %)	1.2 (0.6-2.4)	0.60	0.63
Intrapartal variables									
Temperature >38°C before onset of delivery	6 (3 %)	2 (1 %)	6.2 (1.2-30.8)	0.02	2 (2 %)	5 (3 %)	0.8 (0.2-4.2)	1.00	1.00
Antibiotic therapy before onset of delivery	5 (3 %)	4 (1 %)	2.5 (0.7-9.6)	0.17	0 (0 %)	0 (0 %)	*	*	0.18
Breech presentation	6 (3 %)	11 (3 %)	1.1 (0.4-3.0)	0.80	6 (7 %)	3 (2 %)	4.3 (1.1-17.6)	0.06	0.21
Umbilical cord complications	8 (4 %)	2 (1 %)	8.3 (1.7-39.4)	0.003	1 (1 %)	0 (0 %)	∞	0.33	0.28
Obstetric catastrophe	3 (2 %)	0 (0 %)	∞	0.04	2 (2 %)	0 (0 %)	∞	0.11	0.66
Blood-stained amniotic fluid	2 (1 %)	2 (1 %)	2.1 (0.3-14.9)	0.60	2 (2 %)	1 (1 %)	4.3 (0.4-48.4)	0.24	0.60
Meconium-stained amniotic fluid	47 (28 %)	52 (15 %)	2.2 (1.4-3.4)	0.001	30 (36 %)	26 (15 %)	3.3 (1.8-6.1)	<0.001	0.19
Temperature >38°C during delivery	2 (1 %)	4 (1 %)	1.0 (0.2-5.6)	1.00	2 (2 %)	1 (1 %)	4.1 (0.4-45.9)	0.26	0.60
Antibiotic therapy during delivery	7 (4 %)	2 (1 %)	7.2 (1.5-34.8)	0.01	4 (4 %)	0 (0 %)	∞	0.01	0.75
Mode of delivery:									
Instrumental delivery	63 (32%)	71 (18 %)	2.2 (1.5-3.2)	<0.001	43 (45%)	27 (14 %)	5.0 (2.8-8.9)	<0.001	0.03
Vacuum extraction	19 (10 %)	20 (5 %)	2.0 (1.04-3.8)	0.052	13 (14 %)	10 (5 %)	2.9 (1.2-6.8)	0.02	0.32
Cesarean section	44 (22 %)	51 (13 %)	1.9 (1.2-3.0)	0.004	31 (33 %)	17 (9 %)	4.9 (2.6-9.5)	<0.001	0.06
Type of caesarean section:									
Elective	7 (4 %)	26 (7 %)	0.5 (0.2-1.2)	0.18	4 (4 %)	6 (3 %)	1.3 (0.4-4.9)	0.74	0.75
Acute	17 (9 %)	17 (4 %)	2.1 (1.05-4.2)	0.04	12 (13 %)	9 (5 %)	2.9 (1.2-7.2)	0.03	0.30
Emergency	20 (10 %)	3 (1 %)	14.7 (4.3-50.2)	0.000	15 (16 %)	0 (0 %)	∞	<0.001	0.18
Acute or emergency	37 (19 %)	19 (5 %)	4.6 (2.5-8.2)	<0.0001	27 (28 %)	9 (5 %)	8.0 (3.6-17.8)	<0.0001	0.07
Neonatal characteristics:									
Apgar score at 5 minutes < 7	23 (12 %)	3 (1 %)	17.6 (5.2-59.4)	<0.001	34 (37 %)	3 (2 %)	36.5 (10.8-123.4)	<0.001	<0.001
Postpartal variables:									
Maternal:									
Endometritis	3 (2 %)	4 (1 %)	1.5 (0.3-6.8)	0.69	1 (1 %)	1 (1 %)	2.1 (0.1-33.2)	0.55	1.00

Antibiotic therapy postpartum	12 (6 %)	11 (3 %)	2.3 (0.98-5.2)	0.07	17 (18 %)	5 (3 %)	8.2 (2.9-23.1)	<0.001	0.003
Temperature >38°C postpartum	11 (6 %)	10 (3 %)	2.2 (0.9-5.4)	0.10	8 (9 %)	8 (4 %)	2.1 (0.8-5.9)	0.17	0.45
Neonatal:									
Admitted to NICU	91 (47 %)	43 (11 %)	7.2 (4.7-11.0)	<0.001	60 (65 %)	31 (16 %)	9.6 (5.4-17.0)	<0.001	0.005
Neonatal diagnoses from NICU:									
Neonatal encephalopathy	31 (16 %)	1 (0.3 %)	73.4 (9.9-542.1)	<0.001	35 (37 %)	0 (0 %)	∞	<0.001	<0.001
Neonatal infection	6 (3 %)	1 (0.3 %)	12.3 (1.5-103.3)	0.01	7 (7 %)	1 (1 %)	15.0 (1.8-124.1)	0.0023	0.13
Meconium aspiration	2 (1 %)	0 (0 %)	∞	0.11	6 (6 %)	1 (1 %)	12.7 (1.5-107.4)	0.006	0.02

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. Cesarean section (elective 6 %, acute 13 %, emergency 17 %), instrumental delivery (cesarean section 35 %, vaccum extraction 15 %). ** Comparing mild motor impairment to severe motor impairment in cases only.

Appendix XI, Antecedents of mild motor impairment in cerebral palsy

Variable	Univariable analyses		Multivariable analyses[A]		Multivariable analyses[B]	
	OR (95 % CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Maternal characteristics						
Non cohabitation with baby's father	2.8 (1.1-7.2)	0.03				
Maternal BMI (kg/m^2)**	1.1 (1.03-1.1)	0.002				
Intercurrent disease:						
Maternal disease	1.5 (9.98-2.2)	0.07				
Maternal weight week 34 (kg)	1.02 (1.008-1.04)	0.004	1.03 (1.005-1.1)	0.01	1.04 (1.02-1.1)	<0.001
Pregnancy complications:						
Gestational hypertension	2.4 (1.1-5.2)	0.02				
Intrauterine growth:						
Small for gestational age	3.9 (1.7-8.5)	0.001				
Birth length (cm)**	0.9 (0.8-0.98)	0.04				
Birthweight (kg)**	0.6 (0.4-0.8)	0.001				
Head circumference at birth (cm)**	0.9 (0.8-0.98)	0.008				
Placental weight (g)	0.999 (0.997-1.000)	0.04			0.997 (0.995-0.999)	0.001
Factors related to prepartal infection:						
Escherichia coli bacteriuria during pregnancy	4.1 (1.0-16.5)	0.07				
Bacterial growth in urine during pregnancy	0.5 (0.2-1.1)	0.09				
Infection during pregnancy	1.9 (1.3-2.7)	0.001				
Antibiotic therapy during pregnancy	2.3 (1.4-3.8)	0.001	3.8 (1.6-9.3)	0.004	4.4 (2.2-8.7)	<0.001
Intrapartal variables						
Temperature >38°C before onset of delivery	6.2 (1.2-30.8)	0.02				
Umbilical cord complications	8.3 (1.7-39.4)	0.003				
Obstetric catastrophe	∞	0.04				
Meconium-stained amniotic fluid	2.2 (1.4-3.4)	0.001	2.6 (1.3-5.3)	0.01	n.i.	
Antibiotic therapy during delivery	7.2 (1.5-34.8)	0.01				
Mode of delivery:						
Vacuum extraction	2.0 (1.04-3.8)	0.052			n.i.	
Cesarean section	1.9 (1.2-3.0)	0.004			n.i.	
Type of caesarean section:						
Acute	2.1 (1.05-4.2)	0.04				
Emergency	14.7 (4.3-50.2)	0.000				
Neonatal characteristics:						
Apgar score at 5 minutes < 7	17.6 (5.2-59.4)	<0.001	∞	0.01	n.i.	
Postpartal variables:						

Maternal:					
Antibiotic therapy postpartum	2.3 (0.98-5.2)	0.07			
Neonatal:					
Admitted to NICU	7.2 (4.7-11.0)	<0.001	5.8 (2.8-12.1)	<0.001	n.i.
Neonatal diagnoses from NICU:					
Neonatal encephalopathy	73.4 (9.9-542.1)	<0.001	10.7 (1.1-103.4)	0.01	n.i.
Neonatal infection	12.3 (1.5-103.3)	0.01			

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. Estimates for maternal weight, birthweight and birth length are calculated to show the increased risk of CP per kg or cm, respectively. Forward logistic regression was used for multivariable analyses. Multivariable analyses model A included all variables with $p<0.1$ from univariable analyses (SII) and multivariable analysis model B included all variables with $p<0.1$ from univariable analyses (SII) except Apgar, NICU, mode of delivery parameters, meconium-stained amniotic fluid and NE. n.i.=not included in the model.

Appendix XII, Antecedents of severe motor impairment in cerebral palsy

	Univariable analyses		Multivariable analyses[A]		Multivariable analyses[B]	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Prepartal factors						
Smoking during early pregnancy	1.9 (1.1-3.2)	0.02	2.4 (1.01-5.8)	0.0496		
Gestational hypertension	0.2 (0.02-1.4)	0.07				
Suspected small for gestational age	10.5 (1.2-91.2)	0.02				
Birthweight (kg)	0.5 (0.3-0.8)	0.005				
Head circumference at birth (cm)	0.8 (0.7-0.9)	0.001	0.6 (0.5-0.8)	<0.001	0.8 (0.6-0.95)	0.008
Small for gestational age	3.9 (1.3-11.9)	0.02				
Maldevelopment diagnosed at birth	∞	<0.001	∞	0.003	∞	<0.001
Congenital infection	∞	0.01			∞	0.053
Intrapartal factors						
Breech presentation	4.3 (1.1-17.6)	0.06				
Antibiotic therapy	∞	0.01			∞	0.02
Cesarean section	4.9 (2.6-9.5)	<0.001				
Cesarean section, acute	2.9 (1.2-7.2)	0.03				n.i.
Cesarean section, emergency	∞	<0.001	∞	0.008		n.i.
Vaccum extraction	2.9 (1.2-6.8)	0.02				n.i.
Meconium-stained amniotic fluid	3.3 (1.8-6.1)	<0.001				n.i.
Apgar score at 5 minutes < 7	36.5 (10.8-123.4)	<0.001				n.i.
Postpartal factors						
Neonatal infection	15.0 (1.8-124.1)	0.002				
Antibiotic therapy	8.2 (2.9-23.1)	0.000	7.1 (1.8-28.4)	0.007	6.8 (2.1-21.8)	0.001
Meconium aspiration	12.7 (1.5-107.4)	0.006				
Neonatal encephalopathy	∞	<0.001	∞	<0.001		n.i.
Admitted to NICU	9.6 (5.4-17.0)	<0.001				n.i.

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact Test was used for comparison between groups and for p-value (2-sided) and the Mann-Whitney U Test was used for continuous variables. The estimates for maternal weight and birthweight are calculated to show the increased risk of CP per kg of body weight. Forward logistic regression was used for multivariable analyses. Multivariable analysis model A included all variables with p<0.1 from univariable analyses (SII) and multivariable analysis model B included all variables with p<0.1 from univariable analyses (SII) except Apgar, NICU, mode of delivery parameters, meconium- stained amniotic fluid and NE. n.i.=not included in the model.

Appendix XIII, Interaction analysis	Mild severity	Severe severity	All CP
Variables analysed	**p-value**	**p-value**	**p-value**
Maternal disease-birthweight	0.75	*	0.75
Maternal disease - SGA	1.00	*	1.00
Preeclampsia - birthweight	0.37	0.40	0.18
Preeclampsia - SGA	1.00	0.86	0.80
Antibiotics during pregnancy - SGA	1.00	1.00	1.00
Antibiotics during pregnancy - Birthweight	0.43	0.34	0.26
Severe infection during pregnancy - Birthweight	0.09	0.83	0.11
Severe infeciton during pregnancy - SGA	1.00	1.00	1.00
Gestational hypertension - birthweight	0.08	0.51	0.10
Gestational hypertension - SGA	0.57	*	0.95
Smoking during early pregnancy - birthweight	0.57	0.99	0.55
Smoking during early pregnancy - SGA	0.79	0.68	0.62
Maternal weight - birthweight	0.27	0.55	0.19
Maternal weight - SGA	0.09	0.10	0.009*
Maternal BMI - birthweight	0.66	0.77	0.53
Maternal BMI - SGA	0.26	0.04	0.13
Birthweight - NE	1.00	1.00	0.99
SGA - NE	1.00	1.00	1.00
Maternal diabetes - LGA	1.00	*	1.00
Gestational diabetes - LGA	1.00	0.26	1.00
Instrumental delivery - Apgar score	1.00	0.48	0.55
NE - Neonatal infection	1.00	1.00	0.999
Severe infection during pregnancy - Apgar	0.999	1.00	0.999
Severe infection during pregnancy -NE	1.00	1.00	1.00
Antibiotics during pregnancy - Apgar	0.999	0.999	0.999
Antibiotics during pregnancy - NE	0.999	1.00	0.999
Maternal disease - antibiotics during pregnancy	0.53	0.98	0.31
Acute or emergency cesarean - birthweight	0.53	0.48	0.89
Smoking during early pregnancy - antibiotics during pregnancy	0.97	0.95	0.84
Birthweight - meconium-stained amniotic fluid	0.19	0.07	0.85
SGA - meconium-stained amniotic fluid	0.43	0.99	0.93

*This was, however, an antagonistic interation

Appendix XIV, Interrelationship between the identified antecedents among children with CP (n=309)

		Birth length (cm)	Birthweight (kg)	Head circumference at birth (cm)	Small for gestational age (SGA)	Early identified maldevelopment	Congenital infection	Caesarean section	Instrumental delivery	Meconium stained amniotic fluid	Apgar score at 5 min <7	Neonatal infection	Meconium aspiration	Neonatal encephalopathy (NE)	Admitted to NICU
Suspected small for gestational age	p-value	<0.001	<0.001	<0.001	<0.001	0.01	<0.001	0.001	0.03	ns	ns	ns	ns	ns	0.02
	r	-0.31	-0.35	-0.29	0.53	0.15	0.20	0.20	0.13						0.14
Birth length (cm)	p-value		<0.001	<0.001	<0.001	ns	0.003	0.01	ns	ns	<0.001	0.003	ns	0.01	ns
	r		0.75	0.61	-0.45		-0.18	-0.15			0.25	-0.01		0.15	
Birthweight (kg)	p-value			<0.001	<0.001	ns	0.009	ns	ns	ns	ns	ns	ns	ns	ns
	r			0.57	-0.43		-0.15								
Head circumference at birth (cm)	p-value				<0.001	ns	<0.001	ns	ns	ns	0.03	ns		0.02	ns
	r				-0.37		-0.22				0.13			0.15	
Small for gestational age (SGA)	p-value					ns	<0.001	0.001	0.003	ns	ns	ns	ns	ns	0.005
	r						0.22	0.19	0.17						0.16
Early identified maldevelopment	p-value						<0.001	ns	ns	ns	ns	ns	ns	ns	ns
	r						0.30								
Congenital infection	p-value							ns	ns	ns	ns	ns	ns	ns	ns
	r														
Caesarean section	p-value								<0.001	0.002	<0.001	0.04	0.001	0.003	<0.001
	r								0.78	0.19	0.21	0.12	0.18	0.17	0.38
Instrumental delivery	p-value									0.003	<0.001	ns	0.002	<0.001	<0.001
	r									0.18	0.37		0.17	0.21	0.45

	p-value			0.003		<0.001	<0.001	0.001
Meconium stained amniotic fluid	r			0.19	ns	1.00	0.22	0.20
	p-value					<0.001	<0.001	<0.001
Apgar score at 5 min <7	r				ns	0.22	0.54	0.48
	p-value					0.005	<0.001	<0.001
Neonatal infection	r					0.16	0.21	0.21
	p-value						<0.001	0.006
Meconium aspiration	r						0.20	0.16
	p-value							<0.001
Neonatal encephalopathy (NE)	r							0.48
	p-value							
Admitted to NICU	r	r						

Appendix XV, Associations with epilepsy and cognitive impairment

Variable	CP+ epilepsy (n=107)	CP-epilepsy (n=202)	p-value	OR (95 % CI)	CP + cognitive impairment (n=132)	CP- cognitive impairment (n=177)	p-value	OR (95 % CI)
Admitted to NICU	64 (63 %)	94 (47 %)	0.02	1.9 (1.2-3.1)	73 (58 %)	85 (49 %)	0.13	1.5 (0.9-2.3)
Alcohol consumption during early pregnancy	50 (52 %)	101 (54 %)	0.71	0.9 (0.5-1.5)	61 (51 %)	90 (55 %)	0.47	0.8 (0.5-1.3)
Antibiotic therapy during pregnancy	18 (17 %)	42 (21 %)	0.45	0.8 (0.4-1.4)	24 (18 %)	36 (20 %)	0.67	0.9 (0.5-1.5)
Antibiotic therapy before onset of delivery	0 (0 %)	5 (3 %)	0.17	0 (0-2.1)	2 (2 %)	3 (2 %)	1.00	0.9 (0.1-5.4)
Antibiotic therapy during delivery	4 (4 %)	7 (4 %)	1.00	1.1 (0.3-4.0)	3 (2 %)	8 (5 %)	0.37	0.5 (0.1-2.0)
Antibiotic therapy postpartum	16 (15 %)	14 (7 %)	0.04	2.3 (1.1-4.9)	16 (12 %)	14 (8 %)	0.25	1.6 (0.7-3.4)
Apgar score at 5 minutes < 7	30 (30 %)	32 (16 %)	0.01	2.2 (1.3-3.9)	34 (27 %)	28 (16 %)	0.02	1.9 (1.1-3.4)
Bacterial growth in urine during pregnancy	8 (8 %)	12 (6 %)	0.63	1.3 (0.5-3.2)	8 (6 %)	12 (7 %)	1.00	0.9 (0.4-2.2)
Bad obstetric history	3 (3 %)	5 (3 %)	1.00	1.1 (0.3-4.8)	5 (4 %)	3 (2 %)	0.29	2.3 (0.5-9.8)
Birth length (cm)	49.6 (3.0)	50.4 (2.4)	0.02	0.9 (0.8-0.997)	49.7 (3.2)	50.44 (2.3)	0.05	0.9 (0.8-0.987)
Birthweight (kg)	3.3 (0.6)	3.5 (0.6)	0.002	0.6 (0.4-0.8)	3.3 (0.7)	3.5 (0.6)	0.02	0.6 (0.4-0.9)
Bleeding during pregnancy	11 (10 %)	15 (7 %)	0.40	1.4 (0.6-3.2)	12 (9 %)	14 (8 %)	0.84	1.2 (1.2 (0.5-2.6)
Blood-stained amniotic fluid	2 (2 %)	3 (2 %)	1.00	1.2 (0.2-7.5)	1 (1 %)	4 (3 %)	0.39	0.3 (0.04-2.9)
Breech presentation	3 (3 %)	10 (5 %)	0.55	0.6 (0.2-2.1)	5 (4 %)	8 (5 %)	1.00	0.8 (0.3-2.6)
Cephalic presentation	100 (97 %)	189 95 %)	0.55	1.8 (0.5-6.6)	123(96 %)	166 (95 %)	1.00	1.8 (0.5-6.6)
Caesarean section	37 (35 %)	43 (21 %)	0.01	2.0 (1.2-3.3)	42 (32 %)	38 (22 %)	0.05	1.7 (1.0-2.8)
Caesarean section, elective	6 (6 %)	7 (4 %)	0.38	1.7 (0.5-5.1)	8 (6 %)	5 (3 %)	0.25	2.2 (0.7-6.9)
Caesarean section, acute (< 8 hours after decision)	13 (12 %)	16 (8 %)	0.23	1.6 (0.7-3.5)	14 (11 %)	15 (9 %)	0.56	1.2 (0.6-2.8)
Caesarean section, emergency	18 (17 %)	20 (10 %)	0.10	1.8 (0.9-3.7)	20 (15 %)	18 (10 %)	0.22	1.6 (0.8-3.1)
Chronic hypertension	15 (14 %)	22 (22 %)	0.46	1.3 (0.7-2.7)	18 (14 %)	19 (11 %)	0.48	1.3 (0.7-2.6)
Cognitive impairment	88 (82 %)	44 (22 %)	<0.001	16.6 (9.1-30.2)				
Cognitive impairment, SMR	69 (65 %)	17 (8 %)	0.00	19.8 (10.5-37.3)				
Cognitive impairment, MMR	19 (18 %)	27 (13 %)	0.32	1.4 (0.7-2.7)				
Congenital infection	4 (4 %)	1 (0.5 %)	0.05	7.8 (0.9-70.7)	5 (4 %)	0 (0 %)	0.01	∞(1.2-∞)
Decreased fetal movements	4 (4 %)	8 (4 %)	1.00	0.9 (0.3-3.2)	9 (7 %)	3 (2 %)	0.03	4.2 (1.1-16.0)
Decreased SF measurements	8 (8 %)	6 (3 %)	0.09	2.6 (0.9-7.8)	9 (7 %)	5 (3 %)	0.11	2.5 (0.8-7.7)
Diabetes	1 (1 %)	4 (2 %)	0.66	0.5 (0.05-4.2)	1 (1 %)	4 (2 %)	0.40	0.3 (0.04-3.0)
Early identified maldevelopment	6 (6 %)	2 (1 %)	0.02	5.9 (1.2-30.0)	7 (5 %)	1 (1 %)	0.02	9.9 (1.2-81.1)
Epilepsy, child					88 (67 %)	19 (11 %)	0.00	16.6 (9.1-30.2)
Epilepsy, maternal	0 (0 %)	1 (0.5 %)	1.00	0 (0-73)	0 (0 %)	1 (1 %)	1.00	0 (0-53)
Endometritis	1 (1 %)	3 (2 %)	1.00	0.6 (0.06-6.1)	0 (0 %)	4 (2 %)	0.14	0 (0-
Escherichia coli bacteriuria during pregnancy	4 (4 %)	6 (3 %)	0.74	1.3 (0.4-4.6)	4 (3 %)	6 (3 %)	1.00	0.9 (0.2-3.2)
External cephalic version	2 (2 %)	2 (1 %)	0.61	1.9 (0.3-13.7)	2 (2 %)	2 (1 %)	1.00	1.3 (0.2-9.7)
Foul-smelling amniotic fluid	1 (1 %)	1 (0.6 %)	1.00	1.8 (0.1-29.9)	1 (1 %)	1 (1 %)	1.00	1.3 (0.08-21.1)

Gestational diabetes	2 (2 %)	4 (2 %)	1.00	0.9 (0.2-5.2)	2 (2 %)	4 (2 %)	1.00	0.7 (0.1-3.7)
Gestational hypertension	3 (3 %)	13 (6 %)	0.28	0.4 (0.1-1.5)	6 (5 %)	10 (6 %)	0.80	0.8 (0.3-2.2)
Group B Streptococcus bacteriuria during pregnancy	1 (1 %)	2 (1 %)	1.00	0.9 (0.09-10.5)	1 (1 %)	2 (1 %)	1.00	0.7 (0.06-7.4)
Head circumference at birth (cm)	34.5 (2.1)	34.9 (1.8)	0.10	0.9 (0.8-1.02)	34.4 (2.2)	35.1 (1.7)	0.01	0.8 (0.7-0.9)
Hepatitis	3 (3 %)	2 (1 %)	0.35	2.9 (0.5-17.5)	3 (2 %)	2 (1 %)	0.65	2.1 (0.3-12.5)
Induced abortion	17 (16 %)	44 (22 %)	0.23	0.7 (0.4-1.3)	24 (19 %)	37 (21 %)	0.67	0.9 (0.5-1.5)
Infection during pregnancy	35 (33 %)	77 (38 %)	0.39	0.8 (0.5-1.3)	45 (34 %)	67 (38 %)	0.55	0.8 (0.5-1.4)
Infertility	11 (11 %)	13 (7 %)	0.26	1.7 (0.7-3.9)	11 (9 %)	13 (7 %)	0.83	1.2 (0.5-2.7)
Intrauterine fetal death of one twin	0 (0 %)	1 (0.5 %)	1.00	0 (0-74)	1 (1 %)	0 (0 %)	0.43	∞(0.03-∞)
In vitro fertilization	1 (1 %)	0 (0 %)	0.35	∞ (0.05-∞)	1 (1 %)	0 (0 %)	0.43	∞(0.03-∞)
Instrumental delivery	52 (49 %)	61 (30 %)	0.002	2.2 (1.4-3.5)	58 (44 %)	55 (31 %)	0.02	1.7 (1.1-2.8)
Large for gestational age	3 (3 %)	15 (7 %)	0.13	0.4 (0.1-1.3)	5 (4 %)	13 (7 %)	0.23	0.5 (0.2-1.4)
Lung disease, e.g. asthma or chronic obstructive pulmonary disease	1 (1 %)	4 (2 %)	0.66	0.5 (0.05-4.2)	1 (1 %)	4 (2 %)	0.40	0.3 (0.04-3.0)
Maternal age	28.3 (5.5)	28.6 (5.3)	0.72	0.992 (0.95-1.04)	28.7 (5.7)	28.3 (5.2)	0.52	1.01 (0.97-1.05)
Maternal BMI (kg/cm^2)	23.7 (3.5)	24.0 (4.0)	0.50	0.978 (0.9-1.0)	23.7 (3.4)	24.1 (4.1)	0.52	0.974 (0.9-1.0)
Maternal dysplasia	4 (4 %)	10 (5 %)	0.78	0.7 (0.2-2.4)	6 (5 %)	8 (5 %)	1.00	1.01 (0.3-3.0)
Maternal weight week 34 (kg)	65.0 (11.9)	66.2 (11.5)	0.19	0.992 (0.97-1.01)	64.9 (10.8)	66.4 (12.2)	0.38	0.989 (0.97-1.009)
Meconium aspiration	6 (6 %)	2 (1 %)	0.02	5.9 (1.2-30.0)	8 (6 %)	0 (0 %)	0.001	∞(2.4-∞)
Meconium-stained amniotic fluid	38 (40 %)	44 (25 %)	0.01	2.0 (1.2-3.4)	49 (42 %)	33 (22 %)	<0.001	2.6 (1.5-4.5)
Mortality	15 (14 %)	3 (2 %)	<0.001	10.8 (3.1-38.3)	18 (14 %)	0 (0 %)	<0.001	∞(6.6-∞)
Neonatal encephalopathy	42 (39 %)	29 (14 %)	<0.001	3.9 (2.2-6.7)	43 (33 %)	28 (16 %)	0.001	2.6 (1.5-4.4)
Neonatal infection	9 (8 %)	5 (3 %)	0.02	3.6 (1.2-11.1)	11 (8 %)	3 (2 %)	0.01	5.3 (1.4-19.3)
Non cohabitation with baby's father	9 (9 %)	10 (5 %)	0.23	1.8 (0.7-4.5)	12 (9 %)	7 (4 %)	0.09	2.4 (0.9-6.3)
Nulliparity	56 (52 %)	117 (58 %)	0.34	0.8 (0.5-1.3)	77 (59 %)	96 (54 %)	0.49	1.2 (0.8-1.9)
Obstetric catastrophe	1 (1 %)	4 (2 %)	0.66	0.5 (0.05-4.2)	1 (1 %)	4 (2 %)	0.40	0.03 (0.04-3.0)
Ovulation induction	1 (1 %)	2 (1 %)	1.00	0.9 (0.08-10.4)	2 (2 %)	1 (1 %)	0.58	2.7 (0.2-29.7)
Placental abruption	1 (1 %)	0 (0 %)	0.35	∞ (0.05-∞)	1 (1 %)	0 (0 %)	0.43	∞(0.03-∞)
Placental weight (g)	582.9 (153.7))	613.9 (150.5)	0.19	0.999 (0.997-1.000)	612.2 (171.1)	596.13 (135.5)	0.68	1.001 (0.999-1.002)
Polycystic ovarian syndrome	1 (1 %)	1 (0.5 %)	1.00	1.9 (0.1-30.5)	2 (2 %)	0 (0 %)	0.18	∞(0.3-∞)
Preeclampsia	13 (12 %)	12 (6 %)	0.08	2.2 (0.96-5.0)	13 (10 %)	12 (7 %)	0.40	1.5 (0.7-3.4)
Prepartal diagnosis of CNS anomaly	2 (2 %)	4 (2 %)	1.00	0.9 (0.2-5.2)	4 (3 %)	2 (1 %)	0.41	2.7 (0.5-15.2)
Previous deep vein thrombosis	0 (0 %)	2 (1 %)	0.55	0 (0-10)	1 (1 %)	1 (1 %)	1.00	1.4 (0.08-21.9)
Previous preterm birth	1 (1 %)	3 (2 %)	1.00	0.6 (0.06-6.0)	1 (1 %)	3 (2 %)	0.64	0.4 (0.05-4.3)
Previous caesarean section	11 (10 %)	16 (8 %)	0.53	1.3 (0.6-3.0)	12 (9 %)	15 (9 %)	0.84	0.4 (0.05-4.3)
Psychiatric disorder, e.g. psychosis or depression	5 (5 %)	4 (2 %)	0.29	2.4 (0.6-9.2)	4 (3 %)	5 (3 %)	1.00	1.1 (0.3-4.1)
Rheumatic disorder	1 (1 %)	4 (2 %)	0.66	0.5 (0.05-4.2)	2 (2 %)	3 (2 %)	1.00	0.9 (0.1-5.5)
Sexually transmitted disease	18 (17 %)	28 (14 %)	0.50	1.3 (0.7-2.4)	19 (15 %)	27 (16 %)	0.87	0.9 (0.5-1.8)
Severe infection during pregnancy	7 (7 %)	17 (8 %)	0.82	0.8 (0.3-2.0)	9 (7 %)	14 (8 %)	0.83	0.9 (0.4-2.0)

Severity of CP:								
Mild CP	33 (31 % %)	164 (81 %)	<0.001	0.1 (0.1-0.2)	40 (30 %)	157 (89 %)	<0.001	0.06 (0.03-0.1)
Moderate CP	8 (8 %)	9 (5 %)	0.30	1.7 (0.6-4.6)	12 (9 %)	5 (3 %)	0.02	3.4 (1.2-10.0)
Severe CP	66 (62 %)	29 (14 %)	<0.001	9.6 (5.5-16.7)	80 (61 %)	15 (9 %)	<0.001	16.6 (8.8-31.3)
Small for gestational age	16 (15 %)	13 (6 %)	0.02	2.6 (1.2-5.6)	17 (13 %)	12 (7 %)	0.08	2.1 (0.9-4.5)
Smoking during early pregnancy	40 (40 %)	59 (32 %)	0.20	1.4 (0.9-2.3)	44 (35 %)	55 (34 %)	0.90	1.1 (0.6-1.7)
Spontaneous abortion	19 (18 %)	48 (24 %)	0.25	0.7 (0.4-1.3)	29 (22 %)	38 (22 %)	0.89	1.0 (0.6-1.8)
Spontaneous vaginal delivery	55 (51 %)	141 (70 %)	0.002	0.5 (0.3-0.7)	74 (56 %)	122 (69 %)	0.023	0.6 (0.4-0.9)
Subtype:								
Dyskinetic CP	25 (23 %)	17 (8 %)	<0.001	3.3 (1.7-6.5)	28 (21 %)	14 (8 %)	0.001	3.1 (1.6-6.3)
Spastic CP	82 (77 %)	185 (92 %)	<0.001	0.3 (0.2-0.6)	104 (79 %)	163 (92 %)	0.001	0.3 (0.2-0.6)
Spastic diplegia or tetraplegia	59 (55 %)	62 (31 %)	<0.001	2.8 (1.7-4.5)	86 (65)	35 (20 %)	<0.001	7.6 (4.5-12.7)
Spastic hemiplegia	23 (22 %)	123 (61 %)	<0.001	0.2(0.1-0.3)	18 (14 %)	128 (72 %)	<0.001	0.06 (0.03-0.1)
Suspected small for gestational age	10 (9 %)	6 (3 %)	0.03	3.4 (1.2-9.5)	10 (8 %)	6 (3 %)	0.12	2.3 (0.8-6.6)
Temperature >38°C before onset of delivery	3 (3 %)	6 (3 %)	1.00	0.9 (0.2-3.8)	4 (3 %)	5 (3 %)	1.00	1.1 (0.3-4.1)
Temperature >38°C during delivery	2 (2 %)	2 (1 %)	0.62	1.8 (0.3-13.1)	2 (2 %)	2 (1 %)	1.00	1.3 (0.2-9.3)
Temperature >38°C post partum	7 (7 %)	12 (6 %)	0.81	1.1 (0.4-2.9)	9 (7 %)	10 (6 %)	0.81	1.2 (0.5-3.1)
Thyroid disorder	0 (0 %)	6 (3 %)	0.10	0 (0-1.6)	1 (1 %)	5 (3 %)	0.25	0.3 (0.03-2.3)
Trauma during pregnancy	2 (2 %)	3 (2 %)	1.00	1.3 (0.2-7.7)	3 (2 %)	2 (1 %)	0.65	2.0 (0.3-12.4)
Umbilical cord complications	1 (1 %)	8 (4 %)	0.17	0.2 (0.03-1.9)	1 (1 %)	8 (5 %)	0.08	0.2 (0.02-1.3)
Unstained amniotic fluid	52 (55 %)	128 (74 %)	0.003	0.4 (0.3-0.7)	66 (57 %)	114 (76 %)	0.002	0.4 (0.3-0.7)
Vacuum extraction	15 (14 %)	18 (9 %)	0.18	1.7 (0.8-3.5)	16 (12 %)	17 (10 %)	0.58	1.3 (0.6-2.7)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact test was used for comparison between groups and for p-value (2-sided). The Mann-Whitney U-test was used for continuous variables. * indicates that calculation of Odds Ratio (OR) and 95 % Confidence Interval (CI is nonapplicable, since both groups are 0.

Appendix XVI, Associations with CP together with both epilepsy (EP) and cognitive impairment (CI)

Variable	CP+ EP + CI (n=88)	CP –EP – CI (n= 158)	(EP+CI) p-value	OR (95 % Conf. Int.)
Addiction problems	1 (1 %)	2 (1 %)	1.00	0.9 (0.08-10.0)
Admitted to NICU	53 (64 %)	74 (47 %)	0.02	2.0 (1.1-3.4)
Alcohol consumption during early pregnancy	42 (52 %)	82 (56 %)	0.58	0.9 (0.5-1.5)
Antibiotic therapy during pregnancy	14 (16 %)	32 (20 %)	0.50	0.7 (0.4-1.5)
Antibiotic therapy before onset of delivery	0 (0 %)	3 (2 %)	0.55	0 (0-4.4)
Antibiotic therapy during delivery	2 (3 %)	6 (4 %)	0.72	0.6 (0.1-3.1)
Antibiotic therapy postpartum	14 (16 %)	12 (8 %)	0.06	2.2 (0.99-5.1)
Apgar score at 5 minutes < 7	26 (32 %)	24 (15 %)	0.004	2.6 (1.4-4.8)
Bacterial growth in urine, unknown organism, during pregnancy	7 (8 %)	11 (7 %)	0.80	1.2 (0.4-3.1)
Bad obstetric history	3 (3 %)	3 (2 %)	0.67	1.8 (0.4-9.2)
Birth length (cm)	49.6 (3.1)	50.3 (2.5)	0.02	0.9 (0.8-0.97)
Birthweight (kg)	3.3 (0.6)	3.5 (0.7)	0.002	0.5 (0.3-0.8)
Bleeding during pregnancy	10 (11 %)	13 (8 %)	0.49	1.4 (0.6-3.4)
Bloodstained amniotic fluid	1 (1 %)	3 (2 %)	1.00	0.6 (0.06-5.7)
Breech presentation	3 (4 %)	8 (5 %)	0.75	0.7 (0.2-2.6)
Caesarean section	31 (35 %)	32 (20 %)	0.01	2.1 (1.2-3.8)
Caesarean section, elective	5 (6 %)	4 (3 %)	0.29	2.3 (0.6-8.9)
Caesarean section, acute (< 8 hours after decision)	11 (13 %)	13 (8 %)	0.37	1.6 (0.7-3.7)
Caesarean section, emergency	15 (17 %)	15 (10 %)	0.10	2.0 (0.9-4.2)
Chronic hypertension	13 (15 %)	17 (11 %)	0.42	1.4 (0.7-3.1)
Congenital infection	4 (5 %)	0 (0 %)	0.02	∞ (1.2-∞)
Decreased fetal movements	4 (5 %)	3 (2 %)	0.25	2.5 (0.5-11.3)
Decreased SF measurements	7 (8 %)	4 (3 %)	0.06	3.3 (0.9-11.7)
Diabetes	1 (1 %)	4 (3 %)	0.66	0.4 (0.05-4.0)
Early identified maldevelopment	6 (7 %)	1 (1 %)	0.009	11.5 (1.4-97.0)
Endometritis	0 (0 %)	3 (2 %)	0.56	0 (0-4.3)
Escherichia coli bacteriuria during pregnancy	4 (5 %)	6 (4 %)	0.75	1.2 (0.3-4.4)
External cephalic version	1 (1 %)	1 (1 %)	1.00	1.8 (0.1-29.2)
Foul smelling amniotic fluid	0 (0 %)	0 (0 %)	1.00	*
Gestation diabetes	2 (2 %)	4 (3 %)	1.00	0.9 (0.2-5.0)
Gestation hypertension	3 (3 %)	10 (6 %)	0.39	0.5 (0.1-2.0)
Group B *Streptococcus* bacteriuria during pregnancy	0 (0 %)	1 (1 %)	1.00	*
Head circumference at birth (cm)	34.5 (2.2)	34.9 (1.8)	0.04	0.8 (0.7-0.97)
Hepatitis	3 (3 %)	2 (1 %)	0.35	2.8 (0.5-16.8)
Induced abortion	14 (16 %)	34 (22 %)	0.40	0.7 (0.4-1.4)
Infection during pregancy	28 (32 %)	60 (38 %)	0.41	0.8 (0.4-1.3)
Infertility	11 (13 %)	13 (8 %)	0.27	1.6 (0.7-3.8)
Instrumental delivery	44 (50 %)	47 (30 %)	0.002	2.4 (1.4-4.1)
Intrauterine fetal death of one twin	0 (0 %)	0 (0 %)	1.00	*
In vitro fertilization	1 (1 %)	0 (0 %)	0.36	∞(0.04-∞)
Large for gestational age	3 (3 %)	13 (8 %)	0.18	0.4 (0.1-1.4)

Lung disease, e.g. asthma or chronic obstructive pulmonary disease	0 (0 %)	3 (2 %)	0.56	0 (0-4.3)
Maternal age	28.6 (5.8)	28.4 (5.2)	0.85	1.003 (0.96-1.05)
Maternal BMI (kg/cm^2)	23.3 (3.4)	24.2 (4.0)	0.27	0.96 (0.88-1.04)
Maternal dysplasia	2 (2 %)	6 (4 %)	0.72	0.6 (0.1-3.0)
Maternal epilepsy	0 (0 %)	1 (1 %)	1.00	0 (0-70)
Maternal weight week 34 (kg)	63.7 (11.0)	66.6 (11.8)	0.12	0.98 (0.96-1.008)
Meconium aspiration	6 (7 %)	0 (0 %)	0.002	∞ (2.2-∞)
Meconium-stained amniotic fluid	35 (46 %)	30 (23 %)	0.001	2.9 (1.6-5.4)
Mortality	15 (17 %)	0 (0 %)	<0.001	∞ (7.4-∞)
Neonatal encephalopathy	36 (41 %)	22 (14 %)	<0.001	4.3 (2.3-8.0)
Neonatal infection	9 (10 %)	3 (2 %)	0.01	5.9 (1.6-22.4)
Non cohabitation with baby's father	8 (9 %)	6 (4 %)	0.15	2.5 (0.8-7.6)
Nulliparity	48 (55 %)	88 (56 %)	0.89	1.0 (0.6-1.6)
Obstetric catastrophe	1 (1 %)	4 (3 %)	0.66	0.4 (0.05-4.0)
Ovulation induction	1 (1 %)	1 (1 %)	1.00	1.8 (0.1-28.7)
Placenta abruption	1 (1 %)	0 (0 %)	0.36	∞ (0.05-∞)
Placental weight	587.8 (155.5)	609.5 (150.6)	0.36	0.999 (0.997-1.001)
Polycystic ovarian syndrome	1 (1 %)	0 (0 %)	0.36	∞(0.05-∞)
Preclampsia	11 (13 %)	10 (6 %)	0.10	2.1 (0.9-5.2)
Prepartal diagnosis of CNS anomaly	2 (2 %)	2 (1 %)	0.62	1.8 (0.3-13.1)
Previous deep vein thrombosis	0 (0 %)	1 (1 %)	1.00	0 (0-70)
Previous preterm birth	1 (1 %)	3 (2 %)	1.00	0.6 (0.06-5.8)
Psychiatric disorder, e.g. psychosis or depression	4 (5 %)	4 (3 %)	0.46	1.8 (0.4-7.5)
Rheumatic disease	1 (1 %)	3 (2 %))	1.00	0.6 (0.06-5.8)
Severe infection during pregancy	5 (6 %)	12 (8 %)	0.79	0.7 (0.3-2.2)
Severity of CP:				
Mild CP	18 (21 % %)	142 (90 %)	<0.001	0.03 (0.01-0.06))
Moderate CP	6 (7 %)	3 (2 %)	0.07	3.8 (0.9-15.5)
Severe CP	64 (73 %)	13 (8 %)	<0.001	29.7 (14.2-62.1)
Sexually transmitted disease	14 (16 %)	23 (15 %)	0.85	1.1 (0.5-2.3)
Small for gestational age	12 (14 %)	8 (5 %)	0.03	3.0 (1.2-7.7)
Smoking during early pegnancy	30 (36 %)	45 (31 %)	0.47	1.2 (0.7-2.2)
Subtype:				
Dyskinetic CP	22 (25 %)	11 (7 %)	<0.001	4.5 (2.0-9.7)
Spastic CP	66 (75 %)	147 (93 %)	<0.001	0.2 (0.1-0.5)
Spastic diplegia or tetraplegia	56 (64 %)	32 (20 %)	<0.001	6.9 (3.8-12.3)
Spastic hemiplegia	10 (11 %)	115 (73 %)	<0.001	0.05 (0.02-0.1)
Spontaneous abortion	19 (22 %)	38 (24 %)	0.75	0.9 (0.5-1.7)
Spontaneous vaginal delivery	44 (50 %)	111 (70 %)	0.002	0.4 (0.2-0.7)
Suspected small for gestational age	7 (8 %)	3 (2 %)	0.04	4.5 (1.1-17.7)
Temperature >38°C before onset of delivery	3 (3 %)	5 (3 %)	1.00	1.1 (0.3-4.6)
Temperature >38°C during delivery	2 (2 %)	2 (1 %)	0.63	1.7 (0.2-12.4)
Temperature >38°C post partum	6 (7 %)	9 (6 %)	0.78	1.2 (0.4-3.5)
Thyroid disease	0 (0 %)	5 (3 %)	0.16	0 (0-1.9)
Trauma during pregnancy	2 (2 %)	2 (1 %)	0.62	1.8 (0.3-13.1)
Umbilical cord complications	1 (1 %)	8 (5 %)	0.16	0.2 (0.03-1.8)
Unstained amniotic fluid	40 (53 %)	101 (77 %)	0.001	0.2 (0.03-1.7)
Vacuum extraction	13 (15 %)	15 (10 %)	0.22	1.7 (0.7-3.7)

n (%) is presented for categorical variables. Mean (SD) is presented for continuous variables. Fisher´s Exact test was used for comparison between groups and for p-value (2-sided). The Mann-Whitney U-test was used for continuous variables. * indicates that calculation of Odds Ratio (OR) and 95 % Confidence Interval (Conf. Int.) is nonapplicable, since both groups are 0.