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Cerebral palsy in Norway – subtypes, severity and risk factors

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
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Children's and Women's Health

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Cerebral parese i Norge - forekomst, undertyper og alvorlighetsgrad

Cerebral parese (CP) er fortsatt den vanligste årsak til varig motorisk funksjonsnedsettelse hos barn. Det finnes ingen tidligere nasjonale studier som beskriver panoramaet av undertyper, alvorlighetsgrad eller risikofaktorer hos barn med CP i Norge. Dette er en populasjonsbasert studie av én fødselskohort, barn født 1996-1998, i Norge. Disse barna er registrert i Cerebral pareseregisteret i Norge. Definisjonen av CP og klassifikasjonen av de enkelte undertyper er den samme som er anbefalt og benyttes av Surveillance of Cerebral Palsy in Europe (SCPE).

Studien viste at forekomsten av CP i Norge var 2.1 per 1000 levende fødte, likt det som er funnet i andre sammenlignbare populasjoner. De fleste var klassifisert i undertypen spastisk bilateral (49 %), ca. en tredel (33%) i spastisk unilateral og mindre enn 10% i undertypene dyskinesi eller ataksi. Både denne fordelingen av de ulike CP undertyper og fordelingen av grader av grovmotoriske vansker var i samsvar med det som er funnet i andre vestlige land. Flere barn i denne studien hadde fin motoriske vansker og tilleggsvansker. Som tilleggsvansker regnet vi både talevansker og spisevansker samt syn- og hørselshemming, kognitive vansker og behandlingstrengende epilepsi.

Vi fant at både seteleie og igangsetting av fødsel var uavhengige risikofaktorer for CP. Det var en signifikant økning av risiko for å få CP hvis barnet ved forløsningstidspunktet lå i seteleie sammenlignet med hodeleie (bakhodefødsel). Risikoen var høyest blant enkeltfødte forløst vaginalt til termin. Seteleie var imidlertid ikke forbundet med spesielle undertyper CP eller grader av grov- eller fin- motoriske vansker. Det var også økt risiko for CP hos de barna der fødselen ble igangsatt. Etter igangsetting av fødsel var det en større andel av barna som fikk spastisk bilateral CP og, hos de født til termin, som hadde spastisitet i både armer og ben (alle fire ekstremiteter).

Da vi undersøkte ulike risikofaktorer (sykdom hos mor, kunstig befruktning, unormale forhold ved morkake, blødning i svangerskapet, veksthemming, avvikende leie (ikke bakhodeleie), lav Apgar (<7 ved 5 min) og prematur fødsel) fant vi at en økning av antall risikofaktorer var forbundet en eksponentiell økning av risiko for CP. Kombinasjoner av risikofaktorer var vanligere hos de premature enn hos barn født til termin. I begge grupper (barn født prematurt og barn født til termin) var det få barn med CP som hadde de samme risikofaktorene.

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List of papers

Paper I:

Cerebral palsy in Norway: Prevalence, subtypes and severity.

Guro L. Andersen, Lorentz M. Irgens, Ivar Haagaas, Jon S. Skranes, Alf E. Meberg, Torstein Vik.

Eur J Paediatr Neurol. 2008 Jan;12(1):4-13. Epub 2007 Jun 15.

Paper II:

Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study.

Guro L. Andersen, Lorentz M. Irgens, Jon Skranes, Kjell Å. Salvesen,

Alf Meberg, Torstein Vik.

Dev Med Child Neurol. 2009 Nov;51(11):860-5. Epub 2009 May 11

Paper III:

Induction of labor and cerebral palsy: a population-based study in Norway

Areej I. Elkamil, Guro L. Andersen, Kjell Å. Salvesen, Jon Skranes, Lorentz M. Irgens, Torstein Vik.

Accepted for publication

Paper IV:

The effects of multiple risk factors on cerebral palsy. A register based study.

Magne Stoknes* , Guro L. Andersen *, Areej I. Elkamil MD, Lorentz M. Irgens , Jon Skranes, Kjell Å. Salvesen, Torstein Vik. Submitted

*Shared first authorship

Abbreviations and Definitions

APO	= Apolipoprotein E
BW	= Birth weight
BFMF	= Bimanual Fine Motor Function
CP	= Cerebral palsy
DWMG	= Diffuse white matter gliosis
Early neonatal period	= First 7 days after birth
GA	= Gestational age
GMFSC	= Gross Motor Function Classification System
ICF	= International Classification of Functioning, Disability and Health
MACS	= Manual Ability Classification System
MRI	= Magnetic resonance imaging
Postneonatal	= More than 28 days after birth
PVL	= Periventricular leucomalacia
SCPE	= Surveillance of Cerebral palsy in Europe
SGA	= Small for gestational age
VLBW	= Very low birth weight (Birth weight <1500g)

Summary

Cerebral palsy (CP) is still the most common cause of chronic motor disability in childhood. Until now, there has not been any previous national study of the panorama of subtypes, severity or risk factors among children with CP in Norway. This is a population based study of a cohort of children with CP born 1996 to 1998 in Norway. These children are recorded in the Cerebral Palsy Register of Norway. The CP definition and classification system agreed on by the Surveillance of Cerebral Palsy in Europe (SCPE) are applied. The study showed that the prevalence of CP in Norway was 2.1 per 1000 live births, comparable with other similar populations.

Most children were classified in the spastic bilateral subtype (49%), about one third (33%) in the spastic unilateral subtype and less than 10% in the dyskinetic or in the ataxic subtype. Both the distribution of subtypes and gross motor function impairments were comparable with other populations in developed countries. More children in our study had fine motor function impairments, as well as associated impairments. The associated impairments included both impairment of speech and feeding, in addition to impairments of vision, hearing, cognition and presence of active epilepsy.

We identified both breech presentation and induction of labour as independent risk factors for CP. There was a significant increased risk of CP in children born in breech presentation compared to vertex presentation, in particular for singletons born at term by vaginal delivery. Breech presentation was however not associated with specific subtypes of CP or with the extent of gross or fine motor impairments. There was also an increased risk for CP in children after induction of labour. Induction of labour was associated with a higher proportion of children with the bilateral spastic subtype as well as in those born at term with four-limb involvement.

When we studied multiple risk factors (maternal disease, assisted fertilization, plurality, abnormal placental structure, bleeding in pregnancy, small for gestational age, abnormal presentation, Apgar score at 5 minutes <7 and preterm birth) we found that increasing number of risk factors were associated with an exponentially increased risk for CP. Combinations of these risk factors were more

common in children born preterm, while both among term and preterm born children, few shared the same combinations of risk factors.

Introduction and background

1.1 Historical perspective

"*But I, that am not shaped for sportive tricks,*
Nor made to court an amorous looking-glass;
I, that am rudely stamp'd, and want love's majesty
To strut before a wanton ambling nymph;
I, that am curtail'd of this fair proportion,
Cheated of feature by dissembling nature,
Deformed, unfinish'd, sent before my time"

This quote is taken from William Shakespeare (1564-1616), and is said by Gloucester, later King Richard, Act 1, *The tragedy of Richard III*. It is suggested to be the oldest association of prematurity (*"sent before his time*") and deformities (*"deformed and unfinished*"). About 250 years later a British orthopaedic surgeon by the name of William John Little (1810-94), also argued that prematurity and adverse events leading to perinatal asphyxia could cause poor outcomes later on in life.(1) Little originally reported this in 1843 as he described in his course of lectures at the Royal Orthopaedic Hospital in London a condition of "*spastic rigidity of the limbs of newborn children*".(2) In speaking to the obstetricians he stressed the importance of birth injuries and of neonatal abnormalities. His description of the syndrome was very complete and accurate, and by the end of the 19th century it was widely known as Little's disease.(3) Little also stressed the frequency of mental impairment, speech defects, difficulties in feeding and swallowing, functional disabilities of the upper limbs, constipation and the typical deformities in the lower limbs.(4)

Sir William Osler (1849-1919) introduces the concept "cerebral palsy" in his book *The Cerebral palsies of Children*.(5) He described this nonprogressive neuromuscular disease in children in his clinical study of children at the Infirmary for Nervous Diseases in Philadelphia, Pennsylvania. At the same time Sigmund Freud (1856-1939) expanded the clinical description of cerebral palsy and concluded that the condition was not a single disease but a collection of motor disorders related to lesions of the brain, originating during either infancy or birth.(6) He could however not find any neuropathological lesion that correlated with his clinical findings.

In a case report from 1912 by Sutherland in "Proceeding of the Royal Society of Medicine" a "Case of cerebral palsy" is described as follows:

> "*E.C: MALE, aged 1 year. Born at full term; first child; normal labor without instruments. Child weighed 9 lb. breast-fed for six weeks, then cows' milk and barley water. Became a fat child. At the age of 7 months began to have screaming attacks, drawing up his legs and twitching of head and eyes. At the age of 10 months had a series of general convulsions, lasting for 2 days, about nine each day. Since then has had an occasional general convulsion. Child is very fat and flabby. Face and head look large viewed from the front, but there is much flattening in the pantero-postero diameter, producing a brachy-cephalic condition. Constant jerking movements of the head, trunk and extremities take place, spasmodic and purposeless. He takes no notice of what is going on, seldom cries, and never smiles. He is unable to sit up, or to support himself sitting up, or to balance his head. The pupils react to light, and there is ocular paralysis or nystagmus. The fundi are normal. Vision is apparently present, but hearing seems absent*."(7)

From this thorough description it is obvious that the doctors even at that time were very aware of the many aspects and consequences of a diagnosis of CP. They were however often pessimistic as to the prognosis. Little's answer to the question *"Are these children worth all the effort and money spent on them*?" was *"I have had many cases under observation from one to twenty years and may mention as an encouragement to other practitioners that treatment based upon physiology and rational therapeutics affects an amelioration surprising to those who have not watched such cases. Many of the most helpless have been restored to considerable activity and enjoyment of life"*.(4)

From the 1940s it is known that the founders of the American Academy for Cerebral Palsy and Developmental Medicine in the USA as well as the members of The Little Club in the UK moved the concepts and descriptions of CP forward. The problem that they and others ran into was how to define and classify CP further.

In 1959 MacKeith and Polani defined CP as *"... a persisting but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development.*(8)

Bax in 1964 suggested a new definition based upon the work of an international group.(9) This definition has become classic and is still often used: *"CP is a disorder of movement and posture due to a defect or lesion of the immature brain."* Bax also added some "exclusion criteria":1) disturbances of short duration 2) disturbances due to progressive disease and 3) disturbances solely due to mental deficiency."(9) Still the definition was broad and allowed for many different disorders to be covered by the definition. This led Mutch, Hagberg and colleagues to modify the definition even further as they emphasized in their definition from 1992 to include motor impairment and its variability, as well as the exclusion of progressive disease.(10)

In 1998 a collaborative network for cerebral palsy registers and surveys in 14 centres in 8 countries across Europe was formed, "The Surveillance of Cerebral palsy in Europe"(SCPE). The aim of the network was *"to develop a central database of children with cerebral palsy in order to monitor trends in birth weight specific rates, to provide information for service planning and to provide a frame work for collaborative research."*(11) One of the main issues of the network was "*to agree on a definition for CP, to define inclusion and exclusion criteria, agree on a classification system, and define ways of describing levels of disability."*

The SCPE definition/description of cerebral palsy from 2000:

CP is a group of disorders i.e. it is an umbrella term; It is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non-progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain.

Surveillance of Cerebral Palsy in Europe, 2000 (11)

The SCPE definition includes five key elements: "CP is a group of disorders i.e. it is an umbrella term; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non- progressive

interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain." This SCPE definition agreed on in 2000 is the definition of CP applied further in this thesis.

This definition or rather description also emphasizes the motor impairment as a key element but does not exclude other difficulties ("*it involves a disorder of movement and/or posture and of motor function")*. In 2004 an international group started work on updating the definition and classification of cerebral palsy "*in light of emerging understanding of developmental neurobiology and changing concepts about impairments, functional status and participation."*(12)

The definition of cerebral palsy from 2005:

Cerebral palsy (CP) describes a group of disorders of the development of movement and posture, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and /or by a seizure disorder.

Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, Jacobsson B, Damiano D; Executive Committee for the Definition of Cerebral Palsy, 2005(12)

This "new" definition/description is very similar to the original SCPE definition, but has two additional important issues. First, "*activity limitation*" was added to exclude the disorders of movement and posture not associated with activity limitation. "Activity limitation" is used in the terminology of the ICF (The World Health Organization's International Classification of Functioning, Disability and Health (ICF)) in the understanding" …*difficulties an individual may have in executing activities" amplifies the previous concept of "disability"*.(13) Secondly, this new definition has taken into account what Little also stressed 150 years earlier: *"The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and /or by a seizure disorder."*(12)

From the aforementioned text it is clear that the diagnosis of CP has been and still is a clinical diagnosis. It is also clear that CP is a heterogeneous condition with

regards to both etiology and impairment types and severities. The etiological aspect of the CP definition is represented in the terms *"…due to a non-progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain"* and "*…attributed to non-progressive disturbances that occurred in the developing foetal or infant brain*."(11;12)

Interference/lesion/abnormality or disturbance refers to specific processes or events that interrupt, damage or influence the expected patterns of human brain maturation resulting in permanent (but non-progressive) impairment of the brain.(12) The terms "*developing*" or "*immature*" reflect the idea that disturbances that occur very early in human biological development have different impacts on motor function than disturbances that occur later. The maximum time limit or age for this to take place in order to diagnose it as CP is not precisely defined, but there is a general agreement that the "*disturbance*" must take place before function has developed for each considered function (walking, hand function etc). Therefore, the age range of 2-3 years is generally accepted.(14;15) Lesions/disturbances occurring after the age of 2-3 years are generally not designated as CP. In this thesis children with brain damage occurring after 2 years of age are not included as CP.

1.2 Definition

The definition/description of CP developed by the SCPE is applied in all of the papers included in this thesis: "CP is a group of disorders i.e. it is an umbrella term; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non- progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain".(11)

Because neurological signs can be transitory or change, a progressive disease that starts early and slowly progresses takes time to be revealed as clearly progressive. This means that early diagnosis of CP can be difficult. The diagnosis therefore has to be confirmed by the age of at least four years.(12)

There is no test (genetic, metabolic or immunologic) or a specific result from imaging (MRI, ultrasound) needed to make the diagnosis, the diagnosis is based on a clinical examination of the child. A decision tree, developed by the SCPE and translated into Norwegian, is applied for inclusion of CP cases in this study.(11) (Appendix 1 Decision tree)

Inclusion criteria

Children are diagnosed as having CP if they fulfilled the criteria in the SCPE definition, at the age of at least 4 years.

Exclusion criteria

1. Children in whom a progressive condition is identified
2. Children with hypotonia as the sole clinical feature
3. Children with isolated spinal neural tube defects

1.3 Classification

1.3.1 Subtypes

From the description of the CP case in 1912, it is clear that there were no standardized classification schemes or scales used to describe each case.(6) In recent years there has been much effort in the development of good scales for classifying the motor function of children with CP, while the classification of associated impairments has received much less attention. There still is a lot of work to be done, if at all possible, to agree on how to record or describe it in a standardized way.

As CP describes "*a group of disorders*" it also covers a range of clinical presentations and impairments. There have been many attempts made to classify CP to: 1) describe an individual with CP better with respect to the nature and severity of his or her problem, 2) compare series of cases of CP assembled in different places and 3) evaluate changes within the same individual with CP at different time points.(16) To be reliable, a classification has to be repeatable in relation to the same

subject, both by the same and different observers. To be valid it has to label which cases may or may not fall into a class according to established references.

Even Little back in the 19th century provided accurate descriptions of the various types of cerebral palsy, in particular what was later called spastic diplegia.(1)

A classification of CP may theoretically be based on aetiology, on radiological distribution, on anatomical distribution or on motor abnormalities. As will be further explored later in this thesis, CP may result both from the interaction of multiple risk factors or, as in many cases, have no apparent identified cause.(17) Classification by cause therefore seems unrealistic at present time. A classification based on cerebral imaging would expand our understanding of the nature of the brain lesions associated with CP, due to the advances in imaging techniques.(18) The correlation between cerebral imaging findings and clinical presentation is becoming stronger.(19) Still, however 12%- 30% of children with CP have no specific finding on an MRI scan.(19-22) The availability of scanning equipment and access to these examinations greatly varies between and within countries, making this an unrealistic option.

The previous classification systems have been based on the nature and typology of the motor disorder, as well as on the anatomical distribution. The focus has been on both the distributional pattern of the affected limb (hemiplegia, diplegia) and on the type of tone and movement abnormality (spastic, dyskinetic).

As mentioned earlier, the SCPE agreed on a classification of CP, which is now widely accepted and in use.(11) This also includes a hierarchical tree of the CP subtypes. Appendix 2 In this classification system the individuals are classified according to the dominating clinical phenomenon. This is to avoid mixed types. The SCPE has developed a *Reference and Training Manual* to ascertain agreement on classification of individual cases.(23) The SCPE classification divides CP into three groups based on the neuromotor abnormality; spastic, dyskinetic and ataxic. The SCPE has also emphasized that it is important to identify the "dominant" motor abnormality, the one contributing most to the activity limitation. This view is supported by others.(24) The validity and reliability of the SCPE guidelines has been tested and it was concluded in a study from 2008 that there was moderate agreement

(κ=0.59) about inclusion as a CP case.(25) However, the agreement on the classification by subtype was poorer and differed in assigning dyskinetic from spastic bilateral and judgment of distribution of spastic involvement.(25) Anyway, the development of the SCPE has had positive influence in standardizing and recording the examination of children with CP and in classifying the subtypes compared to previous systems.(26;27)

To be classified as spastic CP, spasticity has to predominate the clinical picture. Spasticity is defined as hypertonia in which resistance to passive movement increases with increasing velocity of movement or exhibits a spastic catch.(28;29) The spastic CP's are further divided into either bilateral or unilateral types depending on if one (unilateral) or two sides (bilateral) of the body are involved. Thus, the difficulties in differentiating between the quadriplegias, tetraplegias and diplegias is eliminated, as was the main problems with the previous classification systems of Ingram and Hagberg.(30;31) Some used the term diplegia to describe children with spastic CP whose only motor deficit was in the legs, while others included children who had arm involvement of lesser severity than leg involvement.(12) The WHO's International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD 10) also includes the terms quadriplegia and diplegia with no further explanation or definition on how to differentiate between them.(32) The problem has been whether presence or absence of prematurity, seizures and/or mental retardation is relevant in regards to the definitions of diplegia and/or quadriplegia or just an association. In a paper from 2003 Colver and Sethumadhavan discussed this problem and are in support of the SCPE classification system.(33)

Dyskinesia is further divided into dystonia and choreathetosis depending on the type and nature of the involuntary movements.(11)

The most common subtype is the spastic subtype accounting for 80-90% of all children with CP.(34-40) This high proportion of spastic subtype CP cases has been stable through the years. The spastic bilateral subtype accounts for about 45-58% of all CP cases, while the unilateral subtype accounts for 27%-38%.(34-40) The distribution of bilateral spastic and unilateral spastic CP varies with the gestational age. A higher proportion of preterm born children have the spastic bilateral subtype

and a higher proportion of term born children have the spastic unilateral subtype.(41) This is mainly explained by the different pathology leading to CP in the different gestational age groups.(42) Some authors have experienced an increasing number and rate of children with unilateral spastic CP with a simultaneous fall in the number and rate of bilateral spastic CP in both preterm and term born babies.(43)

The dyskinetic subtype accounts for 2-17% of cases.(34-40;44) This subtype is associated with lesions at different locations in the immature brain than the spastic subtype.(45) In a recent study performed by the SCPE there was an increase in prevalence of dyskinetic CP among children born at term. In children born preterm they were not able to show any significant increase.(46)

The least frequent subtype is ataxia which accounts for 2-7% of children with CP.(36-40;47)

In investigating the interrelationship between gestational age and nosologic characteristics (type, distribution and severity) it is found that spastic CP is significantly more present in preterm born children than in children born at term, and that dyskinetic CP is present remarkably less in preterm born children.(48) Furthermore, bilateral spastic CP gradually decreases from 100% in the extreme premature group to 50% in the term born infants. Inversely, unilateral spastic CP increased with increasing gestational age.(48)

1.3.2 Gross and fine motor function

The Gross Motor Function Classification System (GMFCS) in cerebral palsy was developed by Palisano and co-workers in 1997.(49;50) This system is based on self-initiated movements with emphasis on sitting (truncal control) and walking. The focus is to determine which level best represents the child's present abilities and limitations in motor function. Emphasis is on the child's usual performance at home, in school and in community settings. This system has shown to be both reliable and valid and of prognostic importance.(28;49;50) In addition specific patterns of neuroimaging findings in children with CP are also found to be associated with specific GMFCS levels.(51) The GMFCS is now widely used and together with the SCPE classification of subtypes contributes in the harmonization of subtypes and

function of children with CP. The GMFCS system was revised in 2007 to include youths 12 to 18 years of age.(52)

Attempts have also been made to create a valid classification system for fine motor function. The most common way to classify hand function in CP has been to use terms like “mild”, “moderate” and “severe” impairment.(53) In addition, House, Zancolli and Krägeloh Mann and Beckung have made classification scales for hand function in cerebral palsy.(54-57) The Bimanual Fine Motor Function (BFMF) was developed with the aim to correspond with the levels of the GMFCS.(57) This system takes into account asymmetry and also allows data to be extracted from medical records and is still in use by the SCPE.(58) However, it is claimed that along with the other scales mentioned above the BFMF does not classify function but rather aspects of grasping.(42) None of these scales for assessment of hand function have been tested for reliability yet.(42)

In 2006 a new classification, The Manual Ability Classification System (MACS), was designed to classify how children with CP use their hands when handling an object in daily activities.(59) The focus of MACS is on manual ability as defined in the International Classification of Functioning, Disability and Health (ICF).(13)

As the child’s motivation and cognitive capacity influence their ability to handle objects, that will also influence the MACS level. This means that a child may be classified at a lower level based on their actual performance.(59)

A recent study showed that there was high but not perfect correlation between the GMFCS and the MACS ($r=0.735$) and that there was only fair overall agreement ($\kappa=0.28$) between them.(60) This indicates both a different basic construction of the scales as well as that gross and fine motor function in children with CP do not necessarily run in parallel and should be independently classified. Both classification systems are meant to discriminate and categorize rather than “assess”. Studies have indicated that they complement each other for a total and complete classification of a child with CP.(59;61;62) (63) A recent study by Mutlu et al states that the usage of the two classification systems, GMFCS and MACS, to describe the capacity and

performance as defined by the ICF provides a quick and easy classification tool for indicating “activity limitation” in children with CP. (64)

1.3.3 Associated problems

As pointed out early by Little and confirmed by the latest definition of CP the motor disorder though it is the hallmark for the diagnosis seldom appears alone in cases of CP.(1)(65) It is also claimed that for many children with CP, it is the co-occurring conditions that often have the greatest impact on the child and family.(66) For intellectual impairment one study showed that there was no definite or absolute correlation between the degree of intellectual impairment and the subtype of CP.(67) Another study found that the severity of spastic motor impairment correlated with the degree and cognitive deficit. Those with spastic quadriplegia (bilateral) had the highest risk of cognitive impairment and those with spastic hemiplegia (unilateral) the lowest. In the dyskinetic subtype this relationship was not shown.(68) A recent study of a national cohort of children with CP from Iceland showed that those with spastic hemiplegia and diplegia had a better outcome on standard intelligence tests or developmental assessments than children with spastic quadriplegia and dyskinesia.(69) It was also shown that some children performed different in IQ subscales (children with spastic diplegia and quadriplegia performed significantly poorer on the performance task than on the verbal tasks) and that these differences seemed more strongly related to gestational age at birth than to motor impairment. It was also pointed out that limitation of movement and motor control may mask cognitive skills.(69)

The prevalence of epilepsy in children and adults with CP is shown to vary between 15% and 42%.(38;67;70;71). If cognitive impairment/mental retardation co-exist the prevalence rises to above 70%. (72) The prevalence also varies between subtype and level of gross motor function.(27;66) Epilepsy is most common in children with spastic cerebral palsy (28-35% of children with hemiplegia, 29%-36% in children with tetraplegia) and is less frequent in children with dyskinetic CP (8-13%).(18;67)

For most of the associated impairments the definition of each of them are often not standardized. The SCPE has defined both visual and hearing impairments as impaired or severely impaired.(11)

Fewer have examined the presence of impairments of speech and language. It is shown however that children with CP frequently have difficulties in communication because of both impaired language skills and impaired motor function.(73;74) The prevalence of non-verbal children varies from 16% to 43%.(66;70;73;75;76)

Feeding problems are also common in cerebral palsy ranging from sucking problems to swallowing problems with aspiration.(77) Growth and nutritional problems are also common and are shown to be more prominent with increasing severity of motor impairment.(78-80) The presence of gastrostomy as an indication of treatment for feeding and/or nutritional problems also varies with subtype and age of the child.(66;81)

1.4 Pathophysiology

CP is "*an umbrella term*" and "*involves a disorder of movement and/or posture and of motor function; and it is due to a non- progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing/immature brain*."(11) This description is vague when it comes to timing ("developing/immature brain") but it is a general view that the brain damage causing CP should take place within about 2-3 years of age.(15) Origin before the end of the neonatal period (28 days postpartum) is distinguished from a postneonatal origin.(11) In the following text the focus will be on the lesions/abnormalities occurring during pregnancy or in the neonatal period.

In general the normal functioning of the brain is dependent on adequate oxygen and glucose supply. Acute reduction in cerebral oxygen delivery will lead to breakdown of the neuronal energy metabolism within a few minutes.(82) The resulting stop in the Na^{+}/ K^{+}-pump leads to neuronal depolarization which induces glutamate release. Glutamate regulates calcium channels and thereby activates

enzymes initiating processes leading to cell death. Breakdown of energy metabolism also causes reduced protein synthesis. A second wave of neuronal cell damage occurs during the reperfusion phase induced by post ischemic release of oxygen radicals, synthesis of nitrogenoxid, inflammatory reactions and imbalance between different neurotransmitter systems. The nature of the lesions depends on the stage of brain development when such a pathogenic event takes place.(83)

During the 1st and 2nd trimester a cortical neurogenesis takes place and is characterized by proliferation, migration and organization of neuronal precursor cells.(83) Brain pathology at this stage is characterized by maldevelopments caused by genetic or acquired impairments and is described in 9-12% of children with CP.(20;22;83-85)

From the late second trimester (from about 20 weeks of gestational) and onwards it is now known that the neuropathology underlying CP includes a) white matter injury, known as periventricular leukomalacia, b) germinal matrix haemorrhage with intraventrivular extensions and/or c) gray matter injury i.e. injury to the cortex, basal ganglia and thalamus.(86) I will now describe each of these neuropathological pathways in more detail;

a. **White matter injury** or periventricular leucomalacia (PLV), has two components: focal necrosis, a cystic form (less common) and a non-cystic form (most common) and diffuse white matter gliosis (DWMG). The highest frequency occurs between 24 and 34 postconceptional weeks, but may also be found in term infants.

   Three main factors are considered to underlie PVL risk: 1) the existence of "watershed" (end –vascular) zones in the developing periventricular white matter (rather than in the cortex as in a more mature brain). This results in injury mainly to the long motor neurons descending to the lower legs leading to the dominating spastic bilateral l(diplegic) subtype seen in the preterm born child. 2) the immaturity of the autoregulatory systems of the cerebral circulation, so that drops in cerebral perfusion pressure are poorly compensated; and 3) the intrinsic

susceptibility of developing oligodendrocyte precursors to free radical, glutamate and cytokine injury. Studies have shown that inflammatory cytokines released through the course of an intrauterine infection play a central role in the genesis of PVL.(82;87-89) PVL is often accompanied by neuronal/axonal disease in cerebral white matter, thalamus, basal ganglia, cerebral cortex, brain stem and cerebellum and is regarded as a combination between destructive and impaired maturation mechanisms termed "encephalopathy of prematurity".(90)

Imaging studies indicate that PVL is present in about 50% of all children with very low birth weight ($\leq$ 1500g) and in 19.2% to 56% of all children with CP.(20;83;84;90). PVL is more frequently found in preterm than term born children.(22;83;90) Studies reporting the highest presence of PVL were not population based, and therefore preterm born children may have been overrepresented.(83).

One study showed that of 76 children (born GA 22-32) with cystic PVL 58 (44%) developed cerebral palsy. As expected, the risk of cerebral palsy was higher when cystic PVL was bilateral and localized in the parietal and occipital lobe.(91)

b. **Germinal matrix haemorrhage** Several sites in the brain are prone to haemorrhage in the setting of hypoxia-ischemia. In particular, the vessels of the germinal matrix are remodelling actively during the third trimester. The haemorrhages are commonly graded according to their extension; grade 1 is limited to germinal matrix, grade II means rupture of blood into the ventricles, grade III is accompanied by ventricular enlargement and grade IV involves the hemispheric parenchyma.(90) Morbidity and mortality increase with increasing grade of intracranial haemorrhage.(90)

c. **Gray matter injuries** These injuries involve injuries affecting the cortex as well as other gray matter sites (basal ganglia, thalamus, cerebellum and brainstem). (86) Vulnerabilities of neurons in different neuroanatomic locations at different postconceptional ages appear to

relate to developmentally regulated biochemical processes occurring at different rates in each gray matter site. This explains the unique pattern of injury at the different locations of the brain. The cortical disruptions are of two main types; disruption leading to abnormal neuronal organization (polymicrogyria, schizencephaly) and disruption of formed structures (hydranencephaly, porenchephaly). The former most often occurs between about 20 and 24 weeks of gestation and can result in gyral and cytoarchitectural disorganization. In contrast, the latter, occurring after approximately 26 weeks, results in infarction and cavitation of otherwise normally developed structures.

Damage occurring as a result of profound hypoxic ischemia at or near term causes injury to parts of the brain with a high metabolic rate.(92) The posterior putamina of the lentiform nucelei, the ventro-lateral nuclei of the thalami, the Hippocampus and the peri-Rolandic cortex are commonly affected. Again the precise topography of neuronal injury depends on the severity and temporal characteristics of the insult and the gestational age of the fetus. The dyskinetic subtype is by far the most likely subtype to be caused by this type of injury seen by acute perinatal hypoxic ischemia at term.(92)

A prolonged period of mild to moderate hypotension can cause damage to the brain in the parasagittal zones (”watershed areas”) that lies between the territories of the circulation of the anterior, middle and posterior cerebral arteries.(92) At or near term the pattern of this injury is characterized by necrosis of the cortex and immediately adjacent white matter. As was described under a) in the more immature preterm babies injuries in the watershed zones, then located more adjacent to the ventricles, affect mainly the long motor neurons to the lower leg while in term born children parasagittal injury usually affects larger areas resulting in tetraplegia, often with learning difficulties. However, in term babies there is a considerable overlap between the patterns of watershed damage and damage to the deep gray matter.(93)

Infarcts of the middle cerebral artery are reported mainly in children born at or near term although they may also occur in the very preterm infants.

Gray matter lesions are described in 18%-22% of all children with CP.(83;84)

The clinical manifestations of the lesions depend on the extent and type of injury.(94) These manifestations may change as they result from an insult to a growing, developing brain and thus is dynamic although derived from static pathology.(95) Injuries to the upper motor neurons decrease cortical input to the reticulospinal and corticospinal tracts. This affects motor control, decreases the number of effective motor units and produces abnormal motor control and weakness.(94) Loss of descending inhibitory input increases the excitability of neurons (gamma and alfa) producing spasticity.(96) If the lesion affects the extra pyramidal system, this results in movement disorders such as athetosis, chorea and dystonia.(94)

1.5 Etiology

The etiology of CP is still poorly understood. In general, observational studies like the present study can measure degree of association between exposures (risk factors) and disease (CP) but not necessarily causation. Further, it is not surprising that there are considerable problems associated with studies of CP etiology; the long time lag between recognition of CP and the presumed brain damage, disagreements among examiners about clinical findings in patients, and changes in clinical findings over time.(95) A challenge is that children with one or more perinatal risk factor may have had a non identified antenatal injury making them more vulnerable and it is thus difficult to decide what is an exposure and what is a cause.

In studies on the etiology focus has been put on possible antenatal causes and on multiple causes using the model of causal pathways.(97-101) One known and now successfully prevented causal pathway for the development of CP is that of kernicterus and choreathetoid CP.(Figure 1)

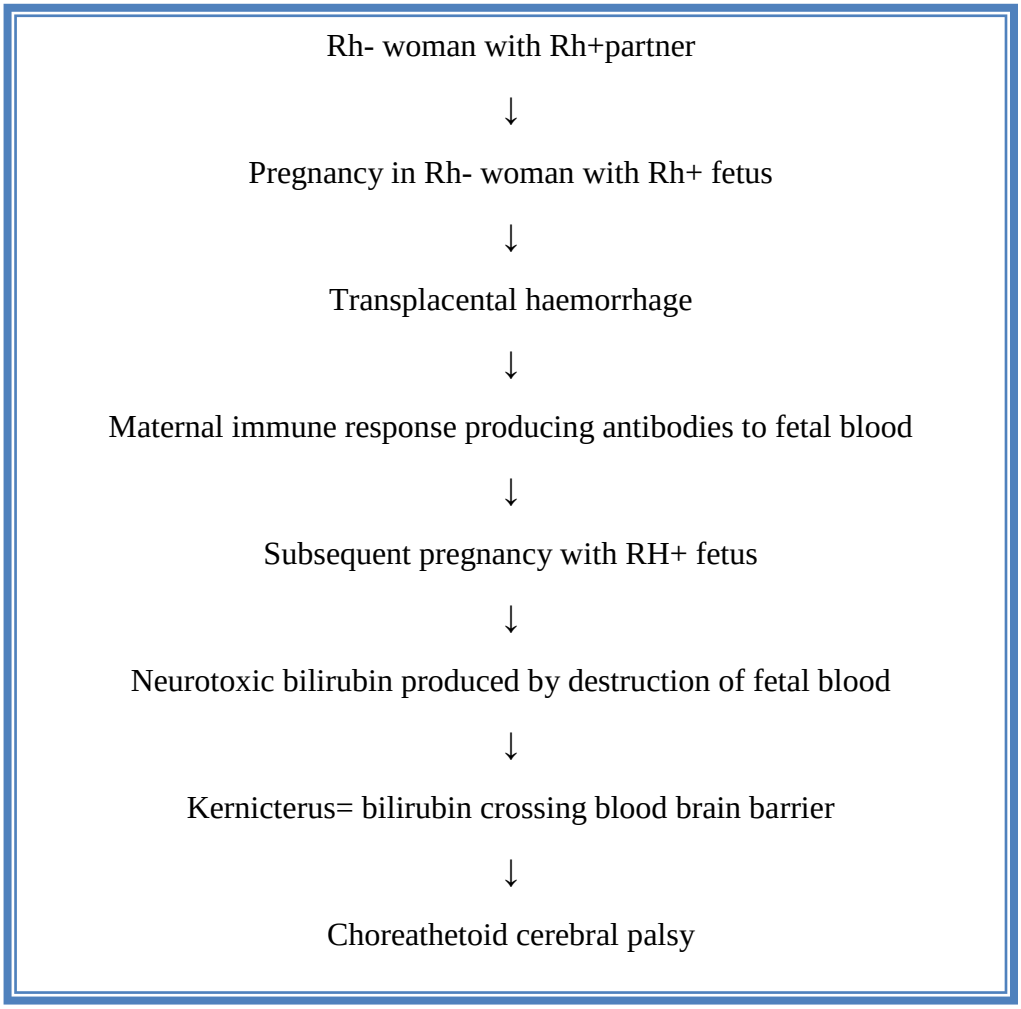


Figure 1: One known causal pathway. After Stanley, Blair and Alberman, 2000.(102)

In the following I will discuss the concepts of causality and risk factors in the etiology of CP.

1.5.1 Causality

There is a general concept that some events or conditions can be considered causes of other events or conditions. A cause is a reason for an effect, the producer of an action or the one event or condition responsible for an effect. Causes of diseases are typically the result of multiple mechanisms. A given causal mechanism requires the joint action of many component factors, or component causes. Furthermore, each component cause is an event or condition that plays a necessary role in the occurrence of some cases of a given disease.(103) Due to the lack of definite tests for CP, multiple, and different possible causes also constitutes a challenge in this

context. Therefore, a concept of "causal pathways" has been developed, meaning concepts of sequences of interdependent events that result in brain damage.(100) See Figure 1. Birth asphyxia previously regarded the most important cause of CP is an example of a fundamental pathogenic sequence (impaired gas exchange→1˚ energy failure→ Cytotoxic neuronal death→2˚ energy failure→ Apoptotoc neuronal death).(102) K B Nelson in 1999 claimed that as multiple causes may interact via exitotoxic, oxidative or other pathophysiologic pathways, a single factor, unless present to an overwhelming degree, may often be insufficient to produce cerebral damage, whereas two or three interacting pathogenic assaults may overwhelm natural defences and produce irreversible brain injury.(104)

1.5.2 Risk factors

A risk factor or exposure variable is a correlation and not necessarily causal, because correlation does not imply causation. Attempts to produce checklists that can determine whether an observed relation or exposure is causal have been made. The most widely cited is attributed to Hill who regarded temporality the most important criterion.(105) This implies that the cause comes before the effect.

The definition of CP states that the damage should occur in the developing foetal or infant brain.(11) It is known that the brain is vulnerable to different types of damage at different stages of development and also that a different range of causative factors is apparent for different CP subtypes.(83;86;106) Some risk factors have repeatedly been observed to be related to CP. Some of them are associated with CP at all gestational ages while others primarily affect either children born at term or preterm. However, in about 10-20% of children no apparent risk factor is identified.(107;108)*)* In addition, even though some of the prenatal and perinatal risk factors evaluated for CP are found to be fairly risky they are not necessarily associated with high absolute rates of CP, and most children with a given risk factor do not have CP. (109)

Controlled population studies are necessary to identify causes of cerebral palsy, and in recent years, neuroimaging information has also added to our knowledge of underlying pathophysiology.(22;83;84;107;110)

Risk factors associated with CP in previous studies will now be discussed. A systematic search in Medline and Embase has been performed. (Appendix 3a and b) In this thesis I have emphasized the risk factors that were possibly available for studies from the data accessible. In addition I have discussed briefly genetic causes. Because many references have addressed the same topic, more recent publications, systematic reviews and original observations have been prioritized. In addition, those studies covering birth years closest to those included in the present study were preferred.

Population based studies from both Sweden and Norway covering the birth years 1970-2002 suggested that the origin of CP is prenatal in 22-36% cases, perinatal/neonatal in 40-47% of cases while 19-38% of cases were unclassifiable.(34;44;111-113) Others have suggested that 70-80% of CP cases are due to prenatal factors and that birth asphyxia plays a minor role.(95) (114) Some prenatal risk factors are repeatedly observed to be related to CP; low gestational age, low birth weight, male gender, multiple gestation, intrauterine viral infection, maternal thyroid abnormalities and birth defects.(11;95;109;114-116)

It is well known that the risk of CP among surviving very premature infants is very high.(11) It is noteworthy that term or near-term infants, although individually at a relative low risk, constitute a large majority of all births and contribute to at least half of CP cases.(104)

In order to get an overview it seems reasonable to categorize the risk factors into four groups;1) pre-pregnancy factors, 2) factors early or late in pregnancy, 3) factors at term and 4) postneonatal factors. The last group, the postneonatal factors, referring to risk factors for lesions or episodes occurring more than 28 days after birth, will not be further explored in this thesis.(11) They account for 5-10% of all cases of CP.(34;117;118)

To get an impression of the prevalence of the different risk factors in the general population, data, when available, from the European Perinatal Health Report (from birth year 2004) and/or the Medical Birth Registry of Norway (MBRN) (from the birth years 1967-2008) are referred in the discussion of each risk factor.(119)

Prepregnancy risk factors

This group comprises factors occurring before the onset of pregnancy and includes: maternal age, parity, previous foetal death, in vitro fertilization, maternal disease, short pregnancy interval and genetic causes.

Maternal age

In Europe less than 3% of all children are born to mothers younger than 20 years of age and 7.5% - 24.3% to mothers older than 35 years.(119) In Norway about 6% of children are born to mothers younger than 20 years and about 11% to those older than 35 years. (Data from the MBRN for the birth years 1967-2008)

Both maternal age below 19 years and above 35 years and 40 years are associated with an increased risk of CP (maternal age > 40 years: OR= 1.4, maternal age >35 years : OR 1.9).(120;121) In a recent study from North England only those with a maternal age $\leq$ 20 years were associated with an increased risk of CP while those aged $\geq$35 years associated with a 20% increased rate of CP were not statistically significant.(122)

Parity

In Europe the percentages of first births (primiparity) ranged from 39.4%-55.6% and the percentages of firth and later births ranged from 2.3% to 13.8%.(119) High parity (parity >3) is associated with an increased risk for CP (OR = 1.6) among preterm born children while primiparity is associated with an increased risk (OR 1.2-1.8) for CP in all gestational age groups.(120;121;123)

Previous foetal death

Children of mothers who have previously experienced intrauterine foetal deaths have been associated with a 2-3 times increased risk for CP (OR = 2.23)(101;109)

In vitro fertilization

In Europe births after in vitro fertilization (IVF),which may include intracytoplasmic sperm injection, in vitro maturation, and frozen embryo transfer, represent up to 2% of all births.(119) In a study from Sweden of children born 1982-1995, they found that children born after in vitro fertilization (IVF) were at increased risk (OR = 3.7) of cerebral palsy.(124) It was concluded that this could largely, but not solely, be

explained by the high frequency of twins, by low birth weight and low gestational age, and that an effect of the IVF procedure per se or another factor not adjusted for could not be excluded.(124) In two recent studies, another Swedish and a Danish, it was found that the increased risk of CP in children born after IVF disappeared when corrected for multiplicity and gestational age.(125;126)

Maternal disease

In Norway maternal thyroid disease occurs in 0.6% of all pregnancies, maternal epilepsy in 0.6% and maternal diabetes mellitus (insulin dependent) in 0.1% of all pregnancies. (Data from the MBRN for the birth years 1967-2008) Maternal hyperthyroidism (RR = 4.9) and seizures (any active) (RR= 3.5) were associated with an increased risk of CP in the study by Nelson and Ellenberg of children born 1959-66.(109;127) They did not however find any association between maternal diabetes and CP. In a more recent Swedish study maternal insulin-dependent diabetes mellitus was associated with a twofold increased risk of CP (OR = 2.1) in children born 1984-1998.(120)

Short interpregnancy interval

In the study by Pinto Martin et al in 1998 it was found that significantly higher proportions of mothers to children with disabling CP had short interpregnancy interval compared to children with no-disabling CP: *"Although extensive literature exist on the association of short IPI and increased mortality and morbidity, the underlying mechanism has not been well studied. Nutritional hypothesis have been put forth by numerous authors but have never been carefully studied. Maternal depletion syndrome is a term that has been used to describe poor maternal and infant health in developing countries and might be applicable here. If, in fact, the adverse outcome experienced by infants born after a short IPI is a function of depleted maternal reserves, then this is amenable to interventions."*(128)

Genes

Mathematical analysis of prenatal and perinatal risk factors on children with CP born 1959-1970 indicated that an estimated 40% of etiologically undiagnosed cases of CP in the community (48% of those born at term and 24% of those born preterm) are

genetically caused.(129) The author found that the frequent genetic pathology was not accompanied by equally frequent dysmorfic signs, hinting that a genetic cause is unlikely to be expressed in abnormal karyotypes. Another exploratory population based study invested candidate single nucleotide polymorphism (SNP) in infants of all gestational ages. Two of the 28 SNPs examined, iNOS and LTA, were associated with CP in the total population, iNOS and EPCR variants were related to CP risk in term infants while ADRB and IL-8 were associated with CP in children who were born preterm.(130) Moreover, intrauterine infection increases perinatal mortality and morbidity, such as cerebral palsy. The mechanism may be through a gene-environment interaction. Polymorphisms of certain critical genes may be responsible for a harmful inflammatory response in those who possess them. Accordingly, polymorphisms that increase the magnitude or the duration of an inflammatory response were associated with an increased risk of preterm birth and thereby of cerebral palsy. (131).

Risk factors early in pregnancy

This group comprises factors occurring after conception and in the first part of pregnancy and includes: congenital malformations, gender, abnormal placenta structure or function, antenatal hemorrhages, preterm birth, deviation of foetal growth, multiple birth, preeclampsia and maternal infection.

Congenital malformations

In Europe congenital anomalies (any) occurs in about 2% of all life births, while malformations in the nervous system occurs in about 0.1%.(119) The coexistence of CP and congenital malformations in general and specific brain malformations in particular, has been reported in many studies to vary between 11% and 32%.(132-136)

In the study by Croen et al from the US singletons born 1983-1985 with congenital malformations had a five-fold increased risk of CP (OR= 5.2).(134) More recent studies from Western Australia and Europe have confirmed the magnitude of this increased risk.(133;135;137)

The European study of children with CP born in three regions in Europe (Denmark, France and England) during 1991-1999 showed that the prevalence of

cerebral anomalies was higher among children born at term (13%) than among those born preterm (3.8%).(136) The most common brain malformations in CP are shown to be lissencephali, schizencephali, cortical heterotopias, polymicrogyria and porencephaly. The causes of these malformations can be migration defects, coagulopathies with ischemia or bleeding, infections or unknown factors.*(*138) Blair et al in 2007 found that there was also an association between CP and non-cerebral congenital defects (OR= 4.8).(135)

Gene and chromosomal defects and environmental teratogenes are undoubtedly responsible for many congenital anomalies. Nevertheless, the majority of anomalies are of unknown etiology. The coexistence of CP with a wide variety of other congenital anomalies suggests a common pathogenic mechanism that may be distinct from genetic or teratogenic influences.(137)

Gender

In Norway 51.4% of all live born children are boys and 48.6% are girls. (Data from the MBRN for the birth years 1967-2008)

In the study by Jarvis et al of European children with CP born 1976-1990 the incidence of CP was 30% higher in males than in females.(139) Both lighter and heavier babies were found to be more likely to develop CP if they were males. This increased vulnerability of male babies was not reflected in higher rates of intrauterine growth retardation when this was judged by low growth velocity or disproportionate anatomy. There was however evidence that male babies were less mature for their gestational age both in skeletal ossification and also in cerebral maturity.(139) Estrogen and other sex hormones can protect the adult brain from stroke and other injuries and gender differences in the human immature brain appear to be strongly influenced by intrinsic differences between male and female cells. It therefore claimed that it is plausible that the skewed male/female ratio in the incidence of CP and related disorders, as well as the differential vulnerability-specific structures in the preterm brain is influenced directly by gender related chromosomes.(140)

Abnormal placental structure and or function

Pathological lesions of the placenta associated with maternal under-perfusion have been shown to be increased in children with CP in all BW and GA groups.(141-143) Among the lesions found in placentas of infants with CP, thrombotic lesions are the most common.(144) Vasculopathy of the placenta is also linked with encephalopatic manifestations in the newborn and can be recognized in children with perinatal stroke and later CP.(144)

Antenatal haemorrhages

In Norway vaginal bleeding between 13 and 28 weeks of gestation occurs in 0.8% of all pregnancies and in 0.7% after 28 weeks of gestation. (Data from the MBRN for the birth years 1967-2008)

Antenatal haemorrhages were shown to be associated with an increased risk for CP (RR=1.8) in a study from the US of children born 1959-1966.(97) An increased risk of CP (OR= 2.9) when compared to birth year matched controls was also shown by Palmer et al for children born 1980-1986 in Western Australia.(145) However, there was no increased risk when compared to gestational age and birth weight controls.

Preterm birth

Preterm birth is defined as birth before 37 weeks of gestation. In Europe the proportion of preterm births varies between 5% and 11%, and in Norway they account for about 6% of all births.(119) (Data from the MBRN for the birth years 1967-2008) Very preterm birth (<32 weeks of gestation) accounts for about 1% of all births in Europe.

Preterm birth is thought to be the strongest predictor for CP. The inverse relationship between increased risk of CP and being born at either lower birth weights or earlier gestational ages, or both, has been consistently well supported over time. (27) While overall prevalence of CP in three recent studies was about 2 per 1000 live births (2.0-2.4 per 1000 neonatal survivor), the prevalence in children born at term was about 1 per 1000 live births (1.2-1.7 per 1000 neonatal survivor), in children born 32-36 weeks of gestation about 6 per 1000 live births (4.9-8.0 per 1000 neonatal survivor) and in children born 28-31 weeks of gestation 50.1 per 1000 live

births (35.0-79.5 per 1000 neonatal survivor)(11;146-148) However, the risk of CP does not seem to decrease for each additional week of gestation; at 24, 25 and 26 weeks of gestation the event rate of CP varies little, but from 27 weeks and on, the event rate of CP starts to decrease significantly.(149) The increased risk of CP in preterm born babies is strongly connected to the vulnerability of the preterm brain to damage. One explanation for the link between extremely low gestational age and cerebral white matter damage is that the same disorders that lead to preterm birth can also damage the developing brain.(150) However, even late preterm born children (GA 34-36 weeks) are found to have a 3-fold increased risk of CP compared to term born children. (151) The mechanism may either be that of an altered or damaged brain growth by preterm delivery per se or by complications of preterm delivery. Another alternative is that the events that led to preterm delivery may also have contributed to the brain damage causing CP.(151)

Post term birth (GA>41 weeks) is also found to have an increased risk of CP (RR=1.4-3. 0) (152;153) In Norway 12.5% of all births are post term. (Data from the MBRN for the birth years 1967-2008)

Deviation of foetal growth

Babies with a low birth weight are at higher risk of poor perinatal outcome and of long-term cognitive and motor impairments. Babies have a low birth weight because of preterm birth or intrauterine growth restriction (IUGR) or for both these reasons.(119) Macrosomia or high birth weight (≥4500 g) is also associated with pregnancy complications. (154) Ideally, growth restriction should be measured with respect to the third or tenth percentile of birth weight at each gestational age (small-for-gestational age or SGA). However, agreed-upon norms for birth weight do not exist.(119)

In Europe the percentage of live births with a birth weight below 2500 g ranged from 4.2% to 8.5% of all births while the proportion of babies with very low birth weight (VLBW: < 1500g) was about 1%. (119) In Norway about 5% have a birth weight below 2500g. (Data from the MBRN for the birth years 1967-2008)

Deviation from optimum foetal growth at any gestational age is strongly associated with risk of cerebral palsy, in particular in more severe forms.(139*)* Jarvis

showed that among single births in England during 1976-1980 the risk for severe cerebral palsy in male babies was 16 times higher for those with a birth weight below the 3rd centile and four times higher when birth weight was above the 97th centile. In contrast, for mild cerebral palsy in female babies the excess risk at these growth extremes were about half of these magnitudes.

This relation between deviant growth and cerebral palsy might exist in either direction i.e. abnormal growth causes cerebral palsy or vice versa.(155) Several mechanisms could result in a concentration of CP at the extremes of growth. CP could be either the consequence or the cause of growth deviation. In the former situation, underlying causes of growth abnormality may be pursued or early delivery considered before foetal brain damage occurs. In the latter situation, brain damage associated with cerebral palsy precedes growth changes and recognition of growth restriction then may occur to late for prevention.(156)

It appears that foetal, placental and maternal hormones particularly insulin (IGF-I and II), epidermal growth factor, cytokines, and leptins are implicated in how growth velocity is normally controlled in utero.(139) In 1988 Khoury showed that although there seemed to be little evidence that brain lesions actually influence endocrine growth regulation, anencephalic foetuses did show poor growth even when allowing for the weight of the missing tissue. (157) Jarvis claims that at all gestations infants who are either smaller or larger than optimum size have a progressively increased risk of cerebral palsy.(155) Others have shown that poor intrauterine growth increases the risk of cerebral palsy particularly in moderately preterm born children.(158;159) Two further studies have shown that poor intrauterine growth is not shown to be a major risk factor in very preterm infants.(160;161) In a study from England of singletons born 1984-1990 small for gestational age (SGA) was associated with a reduced odds ratio for CP among both electively and spontaneously delivered preterm infants. In contrast, the risk for CP was doubled in term born children.(162) Gestational age and birth weight seems to remain the predominant factors for poor neurodevelopment in growth restricted infants.(163)

Multiple births

Compared with singletons, babies from multiple births have higher rates of stillbirth, infant mortality, preterm birth, low birth weight, and subsequent developmental problems.(119) In Europe the multiple rate varies between 1-2 %, in Norway the rate is about 1.3%.(119) (Data from the MBRN for the birth years 1967-2008)

The higher risk of CP in multiple births is well known.(104;164-167) Multiple pregnancies are related to preterm delivery, intrauterine growth restriction, birth defects and intrapartal complications. (95)It seems that the increased risk of cerebral palsy to twins is not entirely explained by their increased risk of prematurity and low birth weight."*Overall the CP rates for twins vary less with BW and GA than the rates for singletons. Being a twin itself increases the risk for CP*."(164) Topp in 2004 found a fourfold increased risk for CP in multiples (RR = 4.4).(168) She claims that as the rates are the same for multiples and singletons in gestational age and birth weight groups below 37 weeks and 2500g, the increased CP risk in multiple born infants is mainly associated with the risk of being born preterm. Furthermore, that the borderline higher CP rate in multiples born at term and with a birth weight above 2500g might be related to the higher risk of growth retardation in multiples.(168) In 2006 Pharoah also partly explains the increased risk in multiples with the increased risk of being born preterm.(166) For children of birth weight $\geq$ 2500g he reported a highly statistically significant three to fourfold increased risk of CP in twins compared with singletons. He reported that this increased risk was probably associated with monochorionic placentation with vascular anastomosis and possible hemodynamic instability with to-and fro shunting of blood between fetuses.(166) Pharoah also reported a greatly increased risk of CP in triplets. (RR = 12.7)

Preeclampsia

Preeclampsia is characterized by hypertension and proteinuria with or without oedema. (169) In Norway about 3% of all pregnancies are complicated by preeclampsia. (Data from the MBRN for the birth years 1967-2008) In the study from Sweden in 2006 it was found that an increased risk for CP was associated with preeclampsia (OR = 1.5).(120) Others have reported a decreased risk for CP associated with preeclampsia in preterm born children (OR for CP=0.7).(170)

Preeclampsia is also a known maternal risk factor for stroke in the infant. In addition, an arterial ischemic stroke in the perinatal period has been recognized as a major cause of CP especially in unilateral CP born term or near term.(171) (See Perinatal stroke) In a recent US study of singletons born 1996-2002 it was concluded that preeclampsia before the onset of 37 weeks of gestation was a significant risk factor for CP; "*that some of the association is probably attributable to high risk of preterm birth because of early preeclampsia, while a direct effect of preeclampsia on foetal brain development also seems likely*".(172)

Maternal infection

A clinical diagnosis of chorioamnionitis is usually based on criteria such as maternal fever, uterine tenderness, malodorous amniotic fluid, maternal or foetal tachycardia and maternal leukocytosis.(173) In a US study of term born children with disabling CP born 1983-1985 with both a maternal fever exceeding 38˚ C in labour and a clinical diagnosis of chorioamnionitis was associated with increased risk of unexplained CP (OR=9.3).(174) This was supported in two studies of term or near-term born children, one of children born 1991-1998 where chorioamnionitis was found an independent risk factor for CP (OR =3.8) and in another of term singletons born 1984-1993 where the presence of either chorioamnionitis, intrapartum pyrexia or neonatal sepsis were associated with a ten-fold increased risk of CP (OR=10.3).(162;175) Most studies investigating the association between intrauterine infection and CP among preterm born children have reported an increased risk.(162;173;175-178) One study of preterm born children reported no association; however in that study only singletons with GA< 32 weeks were included.(179) In the recent study by Neufeld et al of children born 1982-1998, infants born of woman who had any infection during their hospitalization before delivery had an increased risk for CP (OR = 3.1).(180)This increased risk was observed both in term (OR= 1.8) and preterm born children (OR = 2.3). The authors also concluded that the effect of maternal infection on CP was greater in preterm than in term infants.(180)

Risk factors late in pregnancy or at birth

This group comprises factors apparently occurring late in pregnancy or at birth. It includes: perinatal stroke, induction of labour, placental abruption and birth asphyxia.

Perinatal stroke

Stroke is 17 times more common in the perinatal period than later in childhood or beyond. In a population based study that included children whose perinatal stroke was diagnosed after the first month of life the rate was reported to be 1 of 5000 live births.(181)

Cerebral palsy is a common outcome for perinatal stroke. Thirty seven percent of infants with a recognized stroke in the newborn period and 82% of those with a later identified stroke had CP.(182) (171)

Artherial ischemic stroke is diagnosed primarily in neonates born at term and is reported to be responsible for 50% to 70% of congenital unilateral cerebral palsy in this population.(175;183;184) Risk factors for stroke must therefore also be considered risk factors for CP; they include maternal thromboembolic disease (thrombophilia, including history of thrombosis and the antiphospholipid syndrome) (OR for perinatal stroke= 16), preeclampsia (OR for perinatal stroke= 5.3), prolonged rupture of membranes (OR for perinatal stroke=3.8), chorioamnionitis (OR for perinatal stroke= 3.4), gestational hypertension (OR for perinatal stroke=4.4) and maternal diabetes (OR for perinatal stroke= 2.5).(184;185)

Induction of labour

The definition of induction of labour may vary between countries or even between maternity units within the same country, according to the use and timing of the procedures.(119) In some places, induction includes the use of drugs for cervical ripening and oxytocin for induction. In other places (including Norway) artificial rupture of membranes is also included. Thus, the prevalence also varies from less than 9% to well above 35% between different countries.(119) In Norway about 12% of all labours are induced. (Data from the MBRN for the birth years 1967-2008)

Induction of labour is found to increase the risk for CP in a Danish study of all singletons born 1982-1990 (OR for spastic CP=2.5) and in a study from England of singletons born at term during 1984-1993 (OR = 2.1).(162;186) In a number of developed countries the proportion of births following induction of labour have increased because even if labour is usually induced for maternal or foetal medical indications there has been a trend towards elective labour induction on maternal request with no medical indications.(187-189) One possible mechanism for early brain injury and later CP after induction could be that induction of labour is more often required in children with an antenatal brain insult. This assumption could be supported by animal studies showing that labour starts late in pregnancies in which the offspring had an antenatal brain insult.(190;191) Alternatively, induction of labour may directly or indirectly compromise the child during birth and may lead to, or exaggerate, a global brain insult. All drugs used for labour induction (prostaglandin E_1(misoprostol), prostaglandin E_2 and oxytocin) may lead to deceleration of the foetal heart rate, tachycardia or decreased short term variability; most likely through hyperstimulation of the uterus.(192-194). Hyperstimulation of the uterus, or excessive uterine activity, leads to less oxygen supply to the foetal brain and the development of metabolic acidosis which thereby may lead to or exaggerate a brain insult.(195;196)

Breech presentation

Breech deliveries account for a relatively small proportion, around 4%, of all births.(119)

In a study of children born in the 1960s, Nelson and Ellenberg found that breech presentation was a risk factor for cerebral palsy, while breech delivery was not.(109) A case- control study from Turkey found no association.(197) In that study a significant proportion of deliveries were home births. In contrast, two population based studies, one Danish and one Swedish, both found that breech presentation was associated with an increased risk for cerebral palsy (OR (term children vaginal birth)=3), although in the Danish study the increased risk was borderline (OR for CP=1.5).(198;199) The Danish study reported the increased risk to be independent of delivery mode, whereas the results of the Swedish study suggested that cerebral palsy might be prevented in some cases by caesarean section. Since breech delivery has

been associated with adverse perinatal outcome it may be reasonable to speculate that birth asphyxia could be in the causal pathway leading to cerebral palsy.(109) If this were the case one would expect lower Apgar scores, and more severe subtypes of cerebral palsy, such as dyskinetic-athetoid CP and spastic tetraplegia, to be more common in children with CP born in breech.(200-202) In the Danish study of singletons born at term, children with CP delivered by breech were not associated with these subtypes or with low Apgar scores.(198) Another possible mechanism could be that children with a prenatal brain injury are more likely to be born in breech presentation. Previous studies have reported conflicting results; both increased frequency of foetal malformations and no such association in children born in breech.(97;203). A third possible mechanism between breech presentation and CP is through the association of foetal growth restriction.(95;159) CP has been shown to correlate with SGA and studies have reported that neonates in breech weigh less than vertex controls. (204;205;205))

Placental abruption

The incidence of placental abruption is reported to be about 1% and it has been associated with a 20%-40% increased risk for preterm delivery. (206)

Placental abruption was highly associated with CP (OR= 8.58) in the Swedish study of children born 1984-1998.(120) Others have also shown that placental abruption has profound impact on both maternal and perinatal complications including severe birth asphyxia and perinatal death.(206-209)

Birth asphyxia

Intrapartum conditions leading to birth asphyxia was long believed to be the primary cause of CP.(115)This may be partly due to the use of nonspecific markers (low Apgar score, abnormal foetal heart rate, meconium in the amniotic fluid) that can be markers of foetal and newborn difficulties and not necessarily asphyxia.(175) What is asphyxia? One description is that of *"a condition of impaired gas exchange which leads, if persistent, to hypoxemia and hypercapnia". The process occurs during the first and second stages of labour secondary to interruption of placental blood flow and is identified by foetal acidosis which reflects the degree of anaerobic metabolism that is required during periods of hypoxia or increased oxygen demand".(210)* The

challenge for diagnosing perinatal asphyxia is that there is no single gold standard for accurate diagnosis of the condition due to the low specificity and sensitivity of the markers used.(211)

Since 1996 three consensus statements have addressed the diagnosis.(212-214) In all of them umbilical cord blood assessment (pH <7.00) is included. Umbilical cord blood assessment is regarded the most objective determinant of this foetal metabolic condition at the moment of birth.(215) Evidence suggests that an umbilical pH less than 7.00 is associated with an increased risk of adverse neurological sequelae.(216) All statements also included a low Apgar score as a criterion, but the two most recent only includes Apgar score as a criterion suggestive of intrapartum timing. Numerous factors can affect an Apgar score, they include intrapartum maternal sedation or anesthesia, congenital malformations, the individual assigning the score, resuscitate efforts and the presence of an infection. Although it can be subjective and by many regarded a poor predictor of long term neurological outcome, others have shown that there is a strong association between CP and Apgar score of 3 or less at both 1 and 5 minutes. (OR = 145)(217) On the other hand, most children with CP have normal Apgar scores.(218) In the European Perinatal Health Report with data from 2004 less than 2% of all children had Apgar score at 5 minutes of 3 or less.(119)

In a review article by Graham et al from 2008 five studies were identified that measured the proportion of cerebral palsy associated with intrapartum hypoxi-ishemia.(34;147;200;219-221) The studies covered the birth years 1975 to 2001 and the proportion of cerebral palsy caused by intrapartum hypoxia-ischemia varied between 8% and 28%. However, all studies had different definitions of hypoxia-ischemia as well as different levels of what was defined as low Apgar score. The relationship of the type of CP to acute perinatal events and asphyxia has been examined and it is shown that spastic CP is often associated with either severe partial, prolonged asphyxia with resulting subcortical white matter and cortical damage or acute total asphyxia resulting in extensive necrosis of the brain.(92) Furthermore, there seems to be strongest evidence for a causal link between acute prolonged hypoxic-ischemic and dyskinetic CP.(92)

1.6 Prevalence

The prevalence of CP in several recent population based studies varies between 1.6 and 3.6 per 1000 live births.(147;222-225) This variation is most likely due to the different definitions used; how the cases were ascertained and what denominator was used. Although most studies use live births as the denominator, many may argue that in the lower birth weight and gestational age groups neonatal survivors are the correct denominator to not underestimate the magnitude of cerebral palsy risk when neonatal survival is lowest. Some even suggest that because cerebral palsy has predominantly prenatal etiology fetuses at any gestation (rather than live births at that gestation) constitute the epidemiology appropriate denominator for calculating gestational age specific cerebral palsy rates.(226)

There has not been any consistent change in overall prevalence during the last 50 years.(227) The longest observations of CP prevalence have been performed in Western Sweden, Western Australia and North East England. (31;111;112;147;148;223;228) A decreasing trend has been reported from end of the 1950's to the beginning of the 1970's, thereafter increasing towards the beginning of the 1990's and from then on a decreasing trend.(31;111;112;147;148;223;228)

The prevalence varies with different gestational age and birth weight groups. The prevalence in different studies among children born at term is about 1 per 1000 live births (1.2-1.7 per 1000 neonatal survivor) , in children born 32-36 weeks of gestation about 6 per 1000 live births (4.9-8.0 per 1000 neonatal survivor) and in children born 28-31 weeks of gestation 50.1 per 1000 live births (35.0-79.5 per 1000 neonatal survivor).(44;146;153;225;229) The trend in prevalence among the different birth weight and gestational age groups also varies. The study by Platt et al from the SCPE showed that the prevalence of children with CP born with very low birth weight (VLBW)(BW< 1500g) decreased from 1980 to 1998.(230) Another recent study from the SCPE of children with normal birth weight showed that the prevalence remained stable for the same birth years.(231) In children born with moderate low birth weight (1500-2499g) the trend in prevalence is also stable, while among those born moderately preterm the trend decreased during the same period(200;232-234)

2. Aims

The general aim of this thesis is to describe the population of children with CP in Norway born 1996-1998. Until now there has not been a national registration of children with CP in Norway. My goal was to describe the children according to both subtypes and severity. In addition, because many risk factors have been identified by others to be associated with CP, I chose to concentrate on breech and induction of labor because there are few previous studies, and none in Norway. Because CP obviously has many possible etiologies I also wanted to look at how multiple risk factors could act together.

More specifically, the aims of the separate papers were to:

I: describe the prevalence, subtypes and severity of cerebral palsy (CP) in Norway.

II: study whether breech presentation is a risk factor for cerebral palsy (CP).

III: investigate the association between labor induction and later development of cerebral palsy (CP).

IV: examine the effects of multiple risk factors on cerebral palsy (CP).

3. Material and Methods

3.1 Study design

This is a population based study based on information recorded in a national cerebral palsy registry. Data from this registry is linked with data from The Medical Birth Registry of Norway (MBRN). A cohort of three birth years is included in the study.

3.2 Study population

All children with CP in Norway born between January 1st 1996 and December 31st 1998 were eligible for registration in the registry and thereby in this study. Data were collected between January 1st 2003 and March 31st 2006 and all children were at least four years old when their CP diagnosis was confirmed. This is in accordance with the recommendations of the SCPE.(11)

We received summary information on 374 children. Detailed information was obtained from 294 children (79%) (Paper I and II). After the two first papers were completed, we were informed that one child was excluded from the register which reduced the number of CP children to 373, and detailed information on 293 children. (Paper III and IV)

To describe the perinatal data (Paper I) and to examine the different risk factors (Paper II, III and IV) in children with CP the detailed clinical information (Appendix 4) was linked to the Medical Birth Registry of Norway (MBRN). Appendix 5 The perinatal data that were missing in children born abroad (N=15) (Paper II, III and IV) and children with a verified postneonatal cause were excluded (N=15). In Paper I and II we were able to link data on 245 children with CP with data from the MBRN.

On December 1st 1998 the MBRN changed their notification form for perinatal data and for information on the different risk factors. In Papers III and IV we decided to exclude children recorded according to the new notification form in order to avoid different definitions on some of the perinatal variables and risk

factors. In these two papers we were able to link data on 241 children with CP with data from the MBRN.

Background population

In Norway registration in the MBRN has been mandatory (since 1967) and ensures that obstetric and perinatal data are recorded prospectively at birth. (Appendix 5) The data are recorded by birth attendants (midwifes and pediatrians) within one week of delivery for all deliveries after 16 weeks of gestation. During 1996-98 177 272 children in Norway survived the first 7 days of life. In Paper I and II children with postneonatal CP (N=15) were also excluded from the background population leaving 177 257 children. In Paper III and IV we decided to exclude children recorded according to the new birth notification form (see Study population) leaving a background population of 176 591 children.

3.3 Data collection and ascertainment

In Norway all children with severe neurological disorders are treated in public hospitals and each of the 19 counties has 1-2 neurohabilitation centers. All these neurohabilitation centers accepted the invitation to participate in the registration of children with CP with 1-2 contact persons (mainly paediatricians) per centre responsible for collecting the data.

Summary data, based upon the neurohabilitation centres' own data recording systems, were mainly the number of children with CP, including those who had died. These data were used to calculate the overall prevalence, and to validate case ascertainment. The data were ascertained by the individual paediatricians. The age at diagnosis and classification of subtypes varied (age at registration), but all children were at least four years old when diagnosis and subtype were confirmed for this register.

3.4 Study variables

Outcome variables

Cerebral palsy was based upon the definition and classification agreed upon by the Surveillance of Cerebral Palsy in Europe in 1999.(11) A decision tree for inclusion and exclusion of cases and a hierarchical classification tree of CP subtypes developed by SCPE, translated into Norwegian, were distributed to each participating paediatrician in order to ensure consistency. In addition, a CD comprising of a Reference and Training Manual, developed by the SCPE was given to all participating professionals.(23) The manual includes detailed descriptions and definitions of CP and subtypes as well as videos of findings in typical cases. The ICD 10 codes for CP subtypes were applied, subdividing spastic unilateral CP further into a right and left type depending on whether the right or left side limbs were affected (i.e. right or left hemiplegia) and spastic bilateral type into quadriplegia and diplegia.

Gross motor function was reported as walking and sitting ability. Walking ability was classified on a four level scale ranging from normal walking without restrictions (level 0), walking with restrictions but without assistive devices (level 1), walking with assistive devices (level 2) to children completely unable to walk (level 3). Sitting ability was classified on a scale from zero to three, where zero indicated stable sitting, one indicated children sitting unstable but not in need of support, two indicated children in need of support, and three indicated children who were unable to sit even with support. We used the recorded walking and sitting ability data to assess gross motor function according to Gross Motor Function Classification System (GMFCS)**.**(49;50;235) Walking ability zero or one corresponded to GMFCS level I-II. Walking ability two corresponded to GMFCS level III. Walking ability three and sitting ability one or two corresponded to GMFCS level IV. Walking ability three and sitting ability three corresponded to GMFCS level V. Gross motor function was further dichotomized by defining GMFCS level I-III as being "good" and GMFCS level IV-V as being "poor" function.

Fine motor function was described as hand function in each hand separately on a scale from zero to three. Zero indicated normal hand function, one mild

impairment, two obviously reduced function and three indicated severely reduced hand function. We used the recorded information on hand function on each side to estimate Bimanual Fine Motor Function (BFMF)(Table 1)(57) Consistent with the dichotomization of gross motor function, BFMF level I-III was defined as "good" and BFMF level IV-V was defined as "poor" function.

	Normal function left hand	Impaired, but almost normal function in left hand	Obviously impaired function in left hand	Severely impaired function in left hand
Normal function right hand		BFMF I	BFMF II	BFMF III
Impaired, but almost normal function in right hand	BFMF I	BFMF II	BFMF III	BFMF III
Obviously impaired function in right hand	BFMF II	BFMF III	BFMF IV	BFMF IV
Severely impaired function in right hand	BFMF III	BFMF III	BFMF IV	BFMF V

Table 1 Estimated Bimanual Fine Motor Function

Associated impairments recorded in the study included cognitive development, feeding ability, communication, vision, hearing and epilepsy. Cognitive development was assessed by a cognitive test or by clinical judgement. The results were described as normal (i.e. IQ level ≥ 85), general learning difficulties (i.e. IQ level 70-84), mildly retarded (i.e. IQ level 50-69), moderately to severely retarded (i.e. IQ level < 50) or unknown. Mental retardation was defined as IQ below 70.

Feeding ability was classified on a scale from being independent (0), in need of some assistance (1), totally dependent on assistance (2), partly tube fed (3) to mainly tube fed (4). The presence of gastrostomy was also recorded.

Communication was recorded as verbal communication (i.e. speech), sign language and language understanding. Speech was classified on a scale from zero to four where zero indicated normal speech, one indicated indistinct speech, two indicated obviously indistinct speech, three indicated severely indistinct speech difficult to understand and four indicated children without speech. For children using graphic communication the type was recorded (writing, pictogram, pictures).

Vision was described as normal, impaired or severely impaired (i.e. no useful vision on the better eye, with correction, or when functional blindness occurred). Hearing was described as normal, impaired or severely impaired (i.e. the child considered functional deaf).

Epilepsy was defined as two unprovoked seizures, excluding febrile or neonatal seizures. Use of antiepileptic drugs was recorded and epilepsy was considered active when the child at the time of registration was taking an antiepileptic drug.

Exposure variables

Obstetric and perinatal data were obtained from the Medical Birth Registry of Norway (MBRN).

In all papers Apgar scores at 1 and 5 minutes were categorized into 3 groups; (group 1: scores 0 – 3, group 2: scores 4 – 6 and group 3: scores 7 – 10). Birth weight (BW) was recorded in grams and categorized (Paper I) into four groups (BW<1000g, BW 1000-1499g, BW 15000-2499g and BW $\geq$ 2500g). Gestational age (GA) was recorded in completed weeks based on the last menstrual period (LMP) and categorized (Paper I) into four groups (GA < 28 weeks, GA 28-32 weeks, GA 32-36 weeks and GA $\leq$ 37 weeks)

In Paper II the following additional exposure variables were studied as dichotomized (yes/no) variables: breech presentation, vertex presentation, assisted fertilization (included in-vitro fertilization (IVF) and intracytoplasmic sperm

injection (ICSI) methods), plurality, and prelabour rupture of membranes (PROM; any rupture of membranes persisting for more than 24 hours and prior to the onset of labour). Delivery mode was recorded as vaginal birth or caesarean section and caesarean section was specified as planned or emergency caesarean section. Small for gestational age (SGA) was defined as a newborn with a birth weight below the 10^{th} gestational age specific percentile. Gestational age (GA) was included in the multivariable analyses as a continuous variable (GA weeks) as well as dichotomized in preterm birth (i.e. born before 37 completed weeks) and term (i.e. equal to or above 37 weeks of gestation)

In Paper III and IV the following additional exposure variables were included: Induction of labor is recorded as amniotomy, oxytocin (Syntocinon®) infusion and prostaglandin analogues. Data on dosages or sequence of procedures were not detailed enough to study each induction method separately and we therefore decided in the main analyses and presentation of the results (Paper III) to exclude cases where caesarean section was listed as the method of induction. Data were also analyzed including cases where caesarean section was listed under labor induction.

In the MBRN, other available variables included maternal diseases such as diabetes, anemia, hypertension, preeclampsia, eclampsia, epilepsy, thyroid dysfunction, chronic renal disease, urinary tract infection, venereal diseases and rubella. In paper III we studied each maternal disease separately as well as maternal disease as a group, while in paper IV only as a group. The presence of congenital malformations detected in the first week of life was recorded (yes/no). Standard deviation scores for birth weight (*z-score = (actual birth weight – mean)/ standard deviation (SD)*) were calculated, corrected for gestational age and sex, using Norwegian reference curves.(236) The z-score as a continuous variable was used as a proxy for fetal growth. Large for gestational age was defined as a birth weight z-score higher than +2 SD.

Prolonged prelabour rupture of membranes (PROM) was defined as rupture of membranes 24 hours or longer prior to delivery. Preterm prelabour rupture of membranes (PPROM) was defined as rupture of membranes earlier than 37 weeks of gestation.

In paper IV the risk associated with abnormal placenta structure was also studied (defined as presence of fibrin or calcium depositions, placental oedema, bleeding in placenta, infarction in placenta, necrotic placenta or other pathological conditions in placenta), bleeding in pregnancy (yes/no) as well as placental abruption (yes/no).

3.5 Ethics

The study was approved by the Norwegian Data Inspectorate and the Regional Ethical committee (REC) for medical research in Mid-Norway. Written informed consent was obtained from the parents to record detailed data in the register and to link data from the Cerebral Palsy Register in Norway with data from the MBRN.

3.6 Statistical analyses

The statistical package for social sciences (SPSS) for Windows (SPSS Inc, Chicago, IL) was used for data analysis (version 12.0.1 for Paper I, version 16.0 for Paper II and version 17.0 for Paper III and IV). A significance level of 0.05 was chosen. The χ^2 test or Fisher's exact test were used to analyse differences in proportions between groups. Correlations between severity of gross and fine motor impairment with perinatal data were analysed using Spearman's rank correlation coefficient.(Paper I) We used Kappa statistics to compare different classification of subtypes (Paper I). By convention a kappa value higher than 0.80 suggests excellent agreement, 0.60-0.80 good, 0.40-0.60 moderate, 0.20-0.40 fair, and a kappa value below 0.20 suggests poor agreement.(237)

In Paper II and III logistic regression analyses were used to calculate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk for CP among children born after breech presentation (Paper II) or labour induction (Paper III) compared with children born after vertex presentation (Paper II) and non-induced labour (Paper III). Covariates evaluated as possible confounders were selected based upon theoretical considerations as well as upon bivariate statistical analyses. In Paper IV odds ratios (OR) with 95% confidence

intervals (CI) were calculated as estimates of the relative risk for CP. Odds ratios were also calculated for the combinations of two to seven risk factors, using children without any of the recorded risk factors as a reference. The number of cases with each specific combination of risk factors was counted in order to identify if some combinations were more common than others. For the most common combinations we estimated their combined OR and their interaction using the interaction contrast ratio ICR = OR(AB) – OR($A\overline{B}$) – OR($\overline{A}B$) + 1 where OR($A\ B$) denotes the OR for the combination of risk factor A and B, OR($A\overline{B}$) denotes the OR for the presence of A, but not B, and OR($\overline{A}B$) denotes the OR for the presence of B, but not A. An ICR-value above 0 indicates that the odds for CP for a given combination of risk factors is higher than the additive effect of each of the factors, and suggests biological interaction. For combinations with a positive ICR we calculated the proportion attributable (AP) to interaction as AP = ICR/ OR *(* AB *)*(238;239*)* For both ICR and AP the confidence intervals were calculated according to the methodology described by Hosmer and Lemeshow (1992).(240) All analyses were done for the total study population as well as for children born at term (≥ 37 weeks) and preterm (< 37 weeks) separately.

4. Summary of results

4.1 Results of papers included in this thesis

Paper I: Cerebral palsy in Norway: Prevalence, subtypes and severity.

In this paper we used the summary data to estimate the overall prevalence of CP in Norway for children born 1996-1998. The prevalence was 2.1 per 1000 live births. Detailed clinical data were used to describe the distribution of the different CP subtypes according to the classification system developed by the SCPE. Among all, 96 (33%) had the spastic unilateral CP type, 143 (49%) the spastic bilateral, 19 (6%) the dyskinetic and 15 (5%) the ataxic type. In 21 (7%) the subtype could not be classified by the referring centre. Altogether 161 (55%) children were able to walk, while 83 (29%) were unable to walk and in need of wheelchair. According to the GMFCS the gross motor function in this study was similar to other populations. Fine motor impairments according to BFMF were however more common in our study.

Only 81(28%) children solely had a motor impairment. Among the associated impairments feeding difficulties (dependent feeding) were present in 101 (35%), active epilepsy in 80 (28%), severely impaired or no speech in 82 (28%), mental retardation in 75 (28%), severely impaired vision in 15 (5%) and severely impaired hearing in 12 (4%) children. There were no differences in the distribution of associated impairments by gestational age except for epilepsy being present in a higher proportion of children born at term ($p < 0.01$ vs. children born < 32 weeks). Among children with bilateral spastic CP, more severe impairments in gross motor function were associated with increasing birth weight (Spearman's rho = 0.20; $p < 0.05$) and decreasing Apgar score at five minutes (Spearman's rho = - 0.20; $p < 0.05$), however not with gestational age (Spearman's rho = 0.16; $p = 0.09$) or with Apgar score at one minute (Spearman's rho = - 0.10; $p = 0.25$).

More severe impairments in fine motor function were associated with increasing birth weight (Spearman's rho = 0.32; $p < 0.01$) and gestational age (; Spearman's rho = 0.34; $p < 0.01$), with decreasing Apgar score at five minutes

(Spearman's rho = - 0.20; $p < 0.05$), but not with Apgar score at one minute (Spearman's rho = - 0.07; $p = 0.44$).

Paper II: Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study.

In this study we found that breech presentation was associated with an almost 4-fold risk of CP compared to children born in vertex presentation (OR 3.6; 95% CI 2.4-5.3). The increased risk was unaffected when adjusted separately for assisted fertilization and sex, but was reduced when adjusted for preterm birth, plurality, and smallness for gestational age. Multivariate adjustment only marginally affected the OR further. The increased risk persisted among singletons born at term (OR 3.0; 95% CI 1.5–5.9) and preterm (OR 2.6; 95% CI 1.4–5.0). Analyses stratified by mode of delivery showed that for vaginal breech delivery the increased risk for CP was confined to children born at term (OR 3.9 ;95% CI 1.6-9.7) whereas for those delivered in breech by Caesarean section the increased risk was only statistically significantly increased among children born preterm (OR 3.3; 95% CI 1.6-6.7). When we restricted the analyses to breech deliveries only, the relative risk for CP was 1.7 (95% CI 0.5–6.4) among singletons born at term vaginally compared with Caesarean section. No statistically significant differences were observed in subtype or severity of CP between children born after breech or vertex presentation. We concluded that breech presentation is a significant risk factor for CP especially among singletons born vaginally at term.

Paper III: Induction of labor and cerebral palsy: a population-based study in Norway

In this study we found that induction of labor had been performed in 24.1% of children with CP compared with 13.4% among children without CP (*p*-value < 0.001). Induction of labor was associated with an increased risk of CP compared to non-induced labor (OR 2.1, 95% CI 1.5-2.8) and in particular bilateral spastic CP was more frequent after labor induction compared with non- induced labor (OR 3.08; CI 2.09 – 4.54). Adjustment for maternal disease, gestational age, z-score for birth weight and PROM/ PPROM in the same model reduced the OR, but the association between induction of labor and CP (all and bilateral spastic) remained statistically

significant. In contrast, unilateral spastic CP was not associated with labor induction. The risk for bilateral CP when labor induction was performed was further increased among children born at term (OR 4.4; 95% CI 2.3 – 8.6). This risk was marginally reduced after adjustment for confounding effect of maternal disease, gestational age, z-score for birth weight and PROM/ PPROM in the same model (OR: 3.65; CI: 1.78 – 7.49). Further, four-limb involvement (i.e. quadriplegia) was significantly more frequent after labor induction (45.5 %) compared with non-induced deliveries (8.0%)($p< 0.001$). For preterm children there was no association between CP and induction.

Among children born after labor induction with CP seven (12%) had Apgar scores at 5 minutes equal to or below 3, and eight (12%) had Apgar scores at 5 minutes between 4 and 7. In contrast, among children born after labor induction that did not develop CP 410 (1.8%) had Apgar score at 5 minutes equal to or below 3 and 330 (1.5%) had scores between 4 and 7 ($p < 0.001$ versus CP-group).

In conclusion labor induction at term was associated with excess risk of CP bilateral spastic CP and in particular CP with four-limb involvement.

Paper IV: The effects of multiple risk factors on cerebral palsy. A register based study.

In this paper we examined the combined effects of multiple risk factors (maternal disease, assisted fertilization, plurality, pathological placental structure, bleeding in pregnancy, preterm birth, SGA, breech delivery, rupture of membranes 24 hours prelabour and placental abruption) for CP. Among all children 43 (18 %) had no risk factors, 22 % had one, 51 % had two to four, and 10 % had five or more risk factors . The odds ratio for CP increased exponentially ($p < 0.001$) from 2.4 (95% CI: 1.6; 3.6) if one risk factor was present to 2240 (95% CI: 138; 36395) if eight of the selected risk factors were present. Among patients born at term 33 (30 %) had no risk factors, 37 % had one, 33 % had two or more, and none had five or more risk factors. Among patients born preterm 9 % had no additional risk factor ($p < 0.001$ vs. term), 21 % had one, and 70 % had two or more ($p <0.001$ vs. term) risk factors. In both groups very few children shared the same combinations of risk factors. However,

among all children with CP the four most common combinations of risk factors were maternal disease and preterm delivery (in 27.4%), preterm delivery and induction (in 17.8%), maternal disease and induction (in 17.0%), and maternal disease and 5-minute Apgar score < 7(in 11.2%). Maternal disease and 5-minute Apgar score < 7 was the combination with the highest OR among both term and preterm born children.

In conclusion, we found that the risk for CP increased with increasing number of risk factors. Among children born preterm 70% had more than one risk factor in addition to being premature possibly consistent with the theory of a cascade of events resulting in CP.

5. Discussion

5.1 Main Findings

This is the first national population based study on CP in Norway. The prevalence was 2.1 per 1000 live births for children born 1996-1998. The panorama of CP was described according to subtypes using a new classification system (SCPE) and according to gross and fine motor function as well as associated impairments. We found that 33% had the spastic unilateral subtype, 49% the spastic bilateral, 6 % the dyskinetic and 5% the ataxic subtype. The distribution of the different subtypes and the degree of gross motor impairment were similar to other populations.(11;39;241-243) Associated impairments (severely impaired vision or hearing, active epilepsy, mental retardation or impaired speech) were present in 72% of the children and that was more common than in other populations. (70;225;242)

Two independent risk factors for CP, breech presentation and induction of labor were studied. In total 11.8% of children with CP were born in breech compared with 3.6 % of children without CP. Among those born in breech presentation 4.5 per 1000 children were diagnosed with CP compared to 1.3 per 1000 of those born in vertex. Thus, breech presentation was associated with an almost four-fold increased risk for CP (OR=3.6). When adjusted for preterm birth, plurality and smallness for gestational age the increased risk was reduced. The increased risk was highest among singletons born at term delivered vaginally. Severity or subtype did not differ between children with CP born in breech and vertex presentation.

Induction of labor had been performed in 24.1% of children with CP compared with 13.8% of children without CP. We found a twofold increased risk for spastic CP in children born after induced labor compared to non-induced labor (OR=2). Adjustments for gestational age, z-score for birth-weight and PPROM/PROM reduced the risk. The increased risk after induced labor were highest (OR =3.1) among children with bilateral spastic CP while there was no increased risk for unilateral spastic CP. Multiple pregnancy, placental abruption and birth presentation were also significantly associated with spastic CP.

We also found that multiple risk factors interact and increase the risk for CP. The risk increased exponentially with increasing number of risk factors. Among all children with CP only 18% had none of the identified risk factors. However, among children born preterm 70% had more than one risk factor. The most common combinations of risk factors among all children with CP were maternal disease and preterm delivery, preterm delivery and induction, maternal disease and induction, and maternal disease and 5-minute Apgar score < 7. Maternal disease and 5-minute Apgar score < 7 was the combination with the highest OR among both term and preterm born children. However, both among children born at term and preterm very few shared the same combinations of risk factors.

5.2 Validity

The internal validity of scientific research is to what degree the conclusions drawn are correct based on the available data. In the following I will discuss this by considering whether my results may be explained by chance, bias or confounding.

5.2.1 Chance

Estimates small in magnitude and with wide confidence intervals (CI) approaching the null value are more likely to be caused by chance than estimates with great magnitude and narrow CI's. For the prevalence estimates on subtypes in Paper I the CI's are small making them being due to chance unlikely. However, even though the results are consistent with other studies the magnitude of the estimates for the dyskinetic and ataxic subtypes are small and we have to be more cautious about the results.

In both Paper II and Paper III the CI's were small and the p values very low making the finding of an increased risk for CP in children born in breech presentation (Paper II) and after induction of labor (Paper III) due to chance unlikely. However, when we compared the association between CP and the mode of delivery in children born in breech the numbers in the different subgroups (singletons born at term and singletons born preterm) were small and we cannot rule out that these results are due to chance.

In Paper IV the findings of an increased risk for CP with increasing number of risk factors and with specific combinations of risk factors also had very low p-values making the results unlikely due to chance.

5.2.2 Bias

Bias can be defined as any systematic error that results in an incorrect estimate of the association between exposure and outcome.

Information bias

Systematic error in a study can arise because the information collected about or from study subjects is erroneous.(103) It can be in the form of differential misclassification, such as recall bias, or of nondifferential misclassification in which either exposure or disease is misclassified.

In this study the data from the Medical Birth Registry are collected before the neurological outcome of the infant is known, eliminating the risk of recall bias.

All children with CP had their diagnosis confirmed by the clinicians who themselves examined them. These clinicians received thorough information on the SCPE definition, inclusion and exclusion criteria as well as the classification tree for classification of subtypes to standardize the recordings as much as possible. The distribution of subtypes is also in accordance with other recent studies on CP.(38;43;244-246) In addition, ICD10 codes, familiar to the clinicians, were reported making information bias less likely. A recent publication has estimated misclassification to be about 5.2% in a population based CP register and we cannot rule out that this may be a possibility also in our register.(247) However, we find it unlikely that a systematic misclassification should have taken place.

When we assessed severity of cerebral palsy we decided to look at both gross and fine motor function as well as those associated impairments frequently reported by others (cognitive impairment, vision and hearing impairment, epilepsy) and those scarcely reported but experienced from our clinical work with children. To record gross motor function we decided to use walking and sitting ability. This was because by the time we first started to include children in the CP register for this study the GMFCS was not in general use neither in the SCPE nor by clinicians in Norway even

though it was well validated. However, when we were analyzing our data we decided to use the data on walking and sitting ability to assess the gross motor function according to the GMFCS. This was because more recent studies had assessed gross motor function according to the GMFCS and this gave us the ability to compare our results with others. To do so we were not able to differentiate between GMFCS level I and II and had to report them has one group (GMFCS I-II). For fine motor function we recorded hand function on each side separately to estimate the BMFM level. Even though validated instruments such as GMFCS and MACS were not applied in this study I consider information bias in gross and fine motor function less likely.

Some of the associated impairments (cognitive abilities, presence of active epilepsy, vision and hearing impairments) were reported according to the SCPE registration form. (Appendix 6)As far as we were aware, no other validated instruments were available for registration of these items at the start of the study (or at present time). Few studies had reported on speech abilities, language understanding and feeding abilities and impairments of which were not as generally accepted as possible accompanied impairments of children with CP, when this study started. On the basis of our clinical experience we decided to include these items in our register. We made five level scales to record each of these impairments. According to the new definition of CP, cognition, vision, hearing and communication is now well accepted as possible impairments in children with CP.(12) More recently two scales for classification of communication in individuals with CP, Communication Function Classification System (CSFS) and Functional Communication Classification System (FCCS) have been developed. (248;249) Both of them will be validated in many European languages next year.(Personal comment Daniel Vireilla, SCPE)

Selection bias

Selection bias is a systematic error that stems from the procedure used to select the subject of the study. A potential selection bias of this study could be that we received individual data on only 79% of children with CP. This includes only six (2%) parents that refused to let details of their child be recorded. The lack of data was mainly due to the poor response from four of the 19 counties due to work overload. Thus, selection bias is less likely.

We also find it most unlikely that perinatal data in children from neurohabilitaion centres able and unable to provide clinical data differ systematically making selection bias for the studies on risk for CP unlikely.

5.2.3 Confounding

A variable is considered to be a confounder if it can theoretically be associated with both exposure and outcome. In order to control for possible confounding factors in this study we used 1) multivariate analyses and 2) stratification.

1) Multivariable analyses: The variables were entered into the model according to the conceptual hierarchal framework approach proposed by Victora et al.(250) According to this framework variables are included by first adjusting for the variable being most apart and ”ahead” of the relevant exposure in a time-line leading to the outcome. Assisted fertilization, sex of the child, plurality, gestational age and smallness for gestational age were assessed as possible confounders in Paper II. Possible effects on the association between breech presentation and CP were explored for each possible confounder separately and by multivariate adjustments. In Paper III the variables included as possible confounders were maternal disease, assisted fertilization, multiple pregnancy, child’s sex, congenital malformations, preeclampsia, fetal lie, prolonged rupture of membranes, SGA or LGA and preterm birth. Finally, risk factors that changed the OR by at least 10% were included in our multivariable model. Apgar scores at one and five minutes were not included as potential confounders as it is likely to be an intermediate variable.

2) Stratification: In Paper II, III and IV confounding was assessed by stratified analyses among children born term and preterm. Prematurity is by many authors identified as the strongest predictors of CP.(27) Preterm birth may possibly be directly associated with both the different identified risk factors (exposures) and with CP (outcome). In Paper II we also performed stratified analyses among singletons because multiples (exposure) may be independently associated with CP (outcome).

5.3 Causality

The scientific method of investigating causality is to observe the effects of the exposure under a systematic planned series of experimental conditions.(102) In

epidemiological research natural occurring events must be observed and non causal associations may arise. These associations have been dealt with in the discussion of chance, bias and confounding. Thus, if the association between the exposure and outcome are unlikely to be due to chance, bias or confounding, the possibility of a causal relationship may be discussed.

Hill in 1964 proposed some criteria or characteristics widely applied as suggestive of a causal association. (103) These characteristics are: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence and analogy. I will now discuss causality in light of some of these criteria.

5.3.1 Strength of association

We found strong associations between breech delivery and risk of CP, and in particular among singletons born at term delivered vaginally. This is reflected in high odd ratios (OR > 3). Induction of labor showed an even stronger association with CP in children with the spastic bilateral subtype (OR >4). Both these findings may be consistent with a causal relationship.

In the study of multiple risk factors (Paper IV) we found very high OR‘s (OR: 2-48) as well as exponentially increasing ORs with increasing number of risk factors. Again we interpret this as genuine effects of the different risk factors on the development of brain injuries resulting in CP.

5.3.2 Consistency with other studies

Prevalence and subtypes

The overall prevalence of CP was found to be consistent with previous and recent studies in similar populations and of children born in the same time period.(43;43;44;67;148;241;241;251-254)

The distribution of subtypes and severity is also consistent with most other studies.(39;70;242;255) Compared to the results from a recent study from Denmark the distribution of subtypes was similar for the birth years 1991-1994, but differed in that they found a higher proportion of the spastic unilateral subtype in both the

preterm and term born children born during the birth years 1995-1998.(43) In that study the proportion of unilateral CP had increased significantly from the previous birth year period (1991-1994) and they speculated in both better neonatal care and better ascertainment of the less severe unilateral cases as an explanation for this increase.

Gross and fine motor function

In general our result on gross motor function assessed as GMFCS were similar to other studies, except for the proportion of children with the most severe gross motor function (GMFCS V) which was reported less in our study.(39;147;243) The fact that we estimated the GMFSC from walking and sitting ability may be an explanation. The previous studies recorded GMFCS directly. However, the proportion of children able to walk is quite similar to a recent study from Denmark. (43)

Few other studies have described fine motor function using BFMF, although a study from Sweden reported lower proportions of BFMF level IV and V than in our study.(38) This may be due to our study making estimations of BFMF while in the study by Himmelmann et al the reporting physicians recorded in the BFMF directly.(38) The differences between the two studies can also be due to the different birth years covered in the two studies. More severe impairments in both fine and gross motor function were associated with low Apgar scores, consistent with another previous Norwegian study.(217)

Associated impairments

The results from other population based studies have shown that the proportion of children with co-occurring impairments range from 31% to 65% for intellectual disability (IQ< 70), 20% to 46% for epilepsy, 2%-6% for hearing loss and 2% to 19% for visual impairment. (38;40;58;75;253;256;257) Our results are consistent with these findings. The proportion of children without any associated impairments was smaller in our study than in the study by Himmelmann et al, but they did not include speech impairment in their study. (38) We did not find any differences in the distribution of associated impairments by gestational age except for epilepsy being present in a higher proportion of children born at term consistent with others.(38)

In the present study the proportion of children with mental retardation was higher in children with bilateral spastic CP compared to those with the unilateral subtype consistent with previous and recent studies. (67;69;258)

Few previous studies had described the prevalence of speech and communication disorders among children with cerebral palsy but those available reported that the prevalence of children unable to speak (non-verbal)was about 20%.(70;73;225) In our study 28% had severely impaired or no speech. If we consider both those with severely impaired and no speech as non-verbal the proportion is higher than in the other studies. However, in a recent publication from the Cerebral Palsy Register in Norway including 564 children born 1996-2003 19% had no speech consistent with those previous reports.(259) In a recent study from Iceland they reported 16% of children with CP as non-verbal.(74)

Feeding difficulties reported as dependent feeding were found in 35% of all children and in the majority of children with most severe motor impairments, consistent with others.(260) We found that gastrostomy was present in 15 % of all children and in 40% of children with dyskinetic CP. In a study from the Netherlands they reported gastrostomy present in 19% of children. In that study only children with mental retardation and severe motor impairment were included. Thus, both findings are consistent with others reporting presence of gastrostomy to vary with CP subtype.(81)

Breech presentation

Breech delivery has been associated with adverse perinatal outcome in general and with CP in particular in previous studies.(109;120;198) The magnitude of the association was similar in the study from Sweden but less and not significant in the Danish study. A case- control study from Turkey found no association, but in that study a significant proportion of deliveries were home births.(197) In our study the increased risk was seen in all children with CP and also in both term and preterm born children separately. In the Danish study only singletons at term were studied but in the Swedish all children with CP were included.(120;198) We did not find that breech presentation was associated with specific subtypes of CP. In the Danish study breech presentation was associated with the diplegic subtype.(198)

We also found that singeltons in breech delivered vaginally at term had an increased risk compared to those born by Caesarean section consistent with the Swedish study.(120) In Europe, in 9 of the 19 countries or regions for which data were available, in 2004 80% or more of breech babies were delivered by caesarean section. In contrast, only 35% of those in Lithuania, 55% of those in Italy, 65% of those in Slovenia, and 66% of those in Norway were delivered by caesarean section.(119)

When we restricted the analyses to breech deliveries only the risk for CP was only marginally increased for singletons born at term delivered vaginally compared to Caeserean section. In a review by Krebs in 2005 she concludes that results from larger population based studies in Sweden, the Netherlands and UK are consistent in showing an increased foetal risk associated with vaginal delivery of term breech.(204). In a recent publication Kotaska also claims that vaginal breech birth can be associated with a higher risk of perinatal mortality and short term neonatal morbidity than elective Caesarean section.(261). Further that careful case selection and labour management may achieve a level of safety similar to elective caesarean section. These statements were based upon knowledge of the physiology of breech birth, and the result of the term Breech Trial and cohort studies.(261;262) However, few have studied long term morbidities such as CP.

Labour induction

In this study labour induction was associated with an increased risk for total CP but in particular for bilateral spastic CP. Few studies have addressed induction of labour as a possible independent risk factor. Another more recent population based study also found an increased risk of CP among children after induction of labour.(186)

A theory is that induction of labour may compromise the child and thereby induce a brain injury. In support of this, studies addressing short term outcome of labour induction have found associations with neonatal seizures and encephalopathy and others have suggested that newborn encephalopathy may be a precursor of CP at term.(263-267).

In contrast two previous studies, one from 1985 and one from 1994, did not find any association between induction of labour and CP.(109;268) The former was a

case control study of singletons at term born 1987-90 while the latter was a prospective study of children born between 1959 and 1966. Thus, differences in study design and time period may explain the diverging results.

Multiple risk factors

We found that 12 selected single risk factors (maternal disease, assisted fertilization, plurality, pathological placental structure, bleeding in pregnancy, preterm birth, SGA, breech delivery, rupture of membranes 24 hours prelabour and placental abruption) were associated with an increased risk for CP. The magnitude of the increased risk was similar to findings by others for each single risk factor. (Figure 2)

Few previous studies have looked at the combination of risk factors. Consistent with our study, Blair and Stanley found that the risk for spastic CP increased exponentially with increasing number of risk factors, that risk factors were more common in preterm birth than in term born children, that some combinations increased the risk for spastic CP when occurring together and that each route leading to CP contributed only a small portion of cases.(100;101) We found that in 18% of the children none of the identified risk factors were present. In the study by Blair and Stanley the proportion without identified risk factors was 35%.(100;101) This difference may be explained by differences in design and in the quality and availability of the recorded risk factors.

Palmer in 1995 stated that as there is probably an interrelationship between many antenatal antecedents of CP these factors can interact in many different ways.(145) Nelson in 2008 proposed that a causal web of risk factors is a realistic model on how these factors interact.(185) Our finding of a large number of different combinations may be consistent with this. In term born children we found that only 1/3 had more than one risk factor, hence individual susceptibility as part of a causal web may play a larger role, However we also found that the OR's increased exponentially with increasing number of risk factors and that the consecutive combination of some risk factors (maternal disease and low Apgar score and maternal disease and preterm delivery) were more detrimental. In addition multiple risk factors were present in 70% of children born preterm and in 90% if prematurity

are included. Both these findings may be consistent with the theory of a causal pathway or a cascade of events also proposed by others.(102)

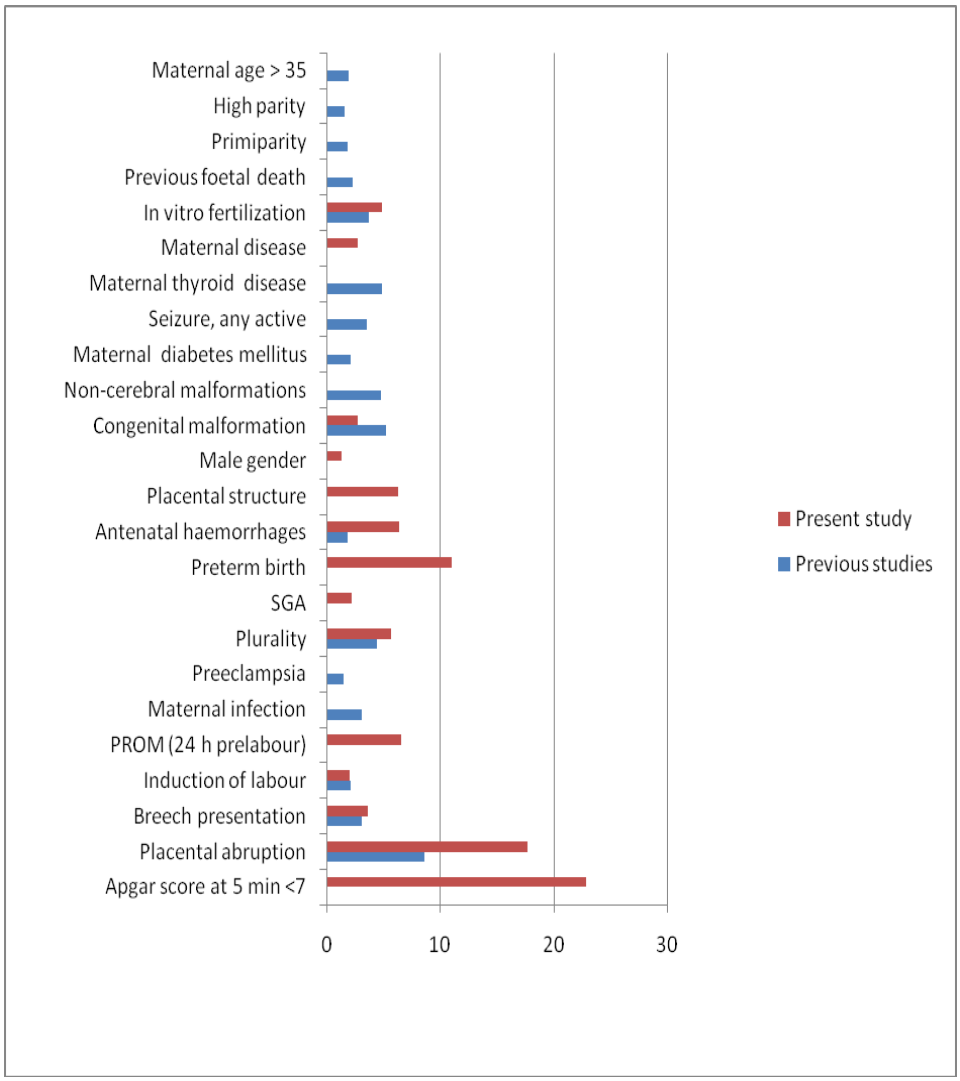


Figure 2: OR or RR for CP in the presence of single specific risk factors.For the present study the reference is the children without the specific risk factor. For references of previous studies see section **1.5.2 Risk factors**

5.3.2 Biological plausibility

Breech presentation

A possible mechanism for the association of breech presentation and CP is birth asphyxia as it has been speculated that birth asphyxia could be in the causal pathway leading to cerebral palsy.(109) If this were the case, one could expect lower Apgar scores and more severe subtypes of cerebral palsy, such as dyskinetic-athetoid CP and spastic tetraplegia, to be more common in children with CP born in breech.(200-

202) The spastic bilateral subtype and the dyskinetic subtype are more often associated with extensive brain injuries or gray matter injuries originating late in pregnancies.(92) The two most recent consensus statements on diagnosing asphyxia include CP to be either quadriplegic or dyskinetic as an essential criterion.(212;214) We did not find any association between breech delivery and specific subtypes of CP. On the other hand we did find that children with CP born in breech presentation had a lower Apgar score after 1 minute, but not at 5 minutes compared to those born in vertex. Others have found a depressed Apgar score at 1 minute after all vaginal breech deliveries compared to vertex.(202;269) A low Apgar score is associated with increased risk for CP in other studies.(217;270) In the Danish study of singletons born at term, children with CP delivered by breech were not associated with either of these subtypes or with low Apgar scores.(198)

Another possible mechanism could be that children with a prenatal brain injury are more likely to be born in breech presentation. We found that 7% of children born in breech had a congenital malformation compared with 3% born in vertex in support of this interpretation. Previous studies have reported conflicting results; both increased frequency of foetal malformations and no such association in children born in breech.(97;203)

A third possible mechanism between breech presentation and CP is through the association of foetal growth restriction.(95;159) CP has been shown to be associated with SGA and studies have reported that neonates in breech weigh less than vertex controls.(204;205;205)) In this study after adjusting for SGA, the increased risk for CP persisted.

Another finding in our study was the less increased risk among children born in breech delivered by Caesarean section. This is consistent with the findings of Thorngren-Jerneck et al.(120) If a vaginal delivered child in breech presentation is injured during the delivery this may explain the findings. This was also the theory behind the recommendation after The Term Breech Trial and the later Cochrane review, Caesarean section being a more indulgent way of delivering children in breech.(262) (271) The Danish study by Kreps et all found that the increased risk was independent of delivery mode and that breech presentation possibly itself is an independent risk factor.(198) Breech presentation may thus be associated with CP

through more than one mechanism and perhaps be part of a network or web of causal factors.

Labor induction

Labor induction at term was associated with an increased risk of spastic bilateral CP, and in particular the quadriplegic subtype in favor of a causal relationship. The lower Apgar score at five minutes in the CP group also supports this view. (217;270) This is also supported by studies finding that induction of labor may directly or indirectly compromise the child during birth.(192;272)

Another possible mechanism is that in pregnancies with children with antenatal brain injuries, labour starts late and consequently is more often induced. This is supported by animal studies.(190;191) This is also in support of the theory that CP results from the interaction of multiple risk factors.(273)

Multiple risk factors

We found that among both children born at term and preterm increasing numbers of risk factors were associated with increasing risk for CP. This may support the view that more than one risk factor interact either consecutively or in a web resulting in brain injury.(100;182;273) For the more vulnerable preterm born children a "chain reaction "or cascade of events may be more likely. For children born at term if one risk factor is not sufficient, a web of risk factors my interact and possibly result in brain damage in a vulnerable child.(102;273) In addition, very few children shared the same combinations of risk factors. This supports both possible mechanisms in that the child's own resistance, depending on their genotype, leads to different vulnerability for environmental damage.(101;182;227) Because there are genetic contributions to a number of obstetric risk factors for CP, including preterm birth, abruption of the placenta, breech presentation, preeclampsia, foetal growth restriction, chorioamnionitis and others it has been claimed that genes can influence vulnerability to CP at a number of points along the causal pathway. (130)

In the study of multiple risk factors we even found evidence for biological interaction between the combination of two specific risk factors; preterm birth and maternal disease and CP using statistical methods.(237-239)

6. Generalizability

To assess the external validity referring to the extent to which the results may be applicable to other similar populations we have to evaluate if our population is representative. Our population represents a cohort of three birth years in a whole country. The overall prevalence of CP was found to be consistent with previous studies in similar populations. (43;67;241;251-253) It also seems representative to similar populations born in the same time period.(44;148;241;254) (43) For children born earlier (before 1996) or later (after 1998) neonatal care may possibly have been somewhat different but the great advances in neonatal care were achieved more than a decade before our oldest children were born. The long time lag between possible causes and diagnosis of CP is common for all populations having accepted 4-5 years of age as the optimal age for classification of a CP subtype, as was recommended by the SCPE in 2000.(11) Different countries may have different recommendations or guidelines for both delivery of breech presentation and induction of labor which also can make the results of these studies possibly less generalizable. However, the results of our study have relevance for most populations of children with CP in the industrialized world born until present time.

Thus, the study on prevalence, subtypes and severity are more consistent than the studies on breech and induction of labour, in which more research with more detailed information are needed to support or not support our findings. I also consider the study on multiple causes representative for those birth years.

7. Clinical implications

Our description of subtypes and impairments in a three year birth cohort of children with CP in Norway is important in the identification of needs and treatment options for these children. Because of the relative large proportion of children with associated impairments such as feeding problems and speech problems more

emphazise can be put on these problematic areas. Traditionally motor impairments have been the target for treatment and habilitation of children with CP. Studies have shown that quality of life and participation are domains in which we have less focus on and know less about.(274) Feeding difficulties in a child with CP have been identified by parents to significantly impair their families' participation and quality of life. (275;276)A recent publication identified that about 35% of children with CP had impaired or no speech, while no more than 60% of them used alternative or augmentative communication aids.(259) Non verbal children are more often to have multiple disabilities. Both non verbal status and severe dysarthria are shown to be associated with intellectual status, gross motor function (GMFCS), and the quadriplegic and dyskinetic subtypes.(74)

Feeding problems are associated with poor growth and nutritional status in children with CP.(277) Longitudinal investigations have found that early nutritional supplementation by gastrostomy results in improved linear growth in children with severe CP if commenced early in life.(278;279) Being non-verbal and dependent on tube feeding are factors that have even been associated with early death.(280) By identifying both feeding problems and speech problems we have the opportunity to intervene on these important areas.

The identification of two independent as well as combinations of risk factors and how they possibly act and interact may give a rise in hope of prevention. The finding of an increased risk for CP among singletons born in breech delivered vaginally compared to caesarean section, though not statistically significant, may mean that a few cases could theoretically be prevented had caesarean section been performed in all cases of breech delivery. In addition, the finding of an association of labour induction and bilateral spastic CP with four limb involvement may indicate perinatal injury, also possibly preventable if the increased risk is associated with certain drugs or procedures. Still, of course there are probably risk factors which are not yet identified and in particular not identified in this study. Further, if the different risk factors act together in a web or a chain it might be difficult to identify exactly how they interact. Nevertheless, if we are able to remove one or two factors in such a web or chain this might prevent the risk. If the antenatal brain injury occurs very

early in pregnancy this will make prevention difficult. One also has to be aware of that genetic causes cannot be expected to respond to attempts to prevent CP even early in pregnancy. On the other hand prevention in a wider context could imply prevention of the extent of the injury and thereby the severity of CP. In a study by Blackman et al from 2009 they found that the presence of a specific variant (ε 4) of a certain gene (APOE) on chromosome 19 is associated with a lowered severity of CP.(281) The protein encoded by this gene (Apolipoprotein E) has an important function in the maintenance of neurons and repair after injury and the authors therefore claim that it could have a protective effect in brain development.

8. Future studies

This was the first national study of subtypes and severity of children with CP in Norway. The children in the study were born more than 12-15 years ago. The Cerebral Palsy Registry in Norway allows us to study the panorama of children born more recently. The use of validated scales for classification on gross and fine motor function and associated impairments (i.e. speech) may give us an even better picture of the panorama of CP in Norway and thereby possibilities to plan services better for these children.

By including more recent birth cohorts our sample sizes will be larger and results from studies on risk factors may be more robust. Multicenter studies on breech presentation and induction of labour are needed to explore the possible associations further. The linkage of the CPRN to the MBRN is very important and the recordings in their new notification form allow for more details in the studies of risk factors. Moreover, future studies should include more details on antenatal, obstetric and perinatal factors. Finally, the influence on genes in the etiology as well as studies on trends in CP will be needed to clarify the etiology further.

9. Conclusion

In this study of the panorama of CP in Norway we found that the prevalence, the distribution of subtypes and the gross motor impairments were similar to other Western populations. In contrast, a higher proportion in our population had fine

motor impairments and associated impairments. We also found that both breech presentation and induction of labour were associated with an increased risk for CP. More studies are needed to clarify if brain injury associated with these risk factors may be preventable. Combinations of risk factors were more common in children born preterm than at term, but few children shared the same risk factors. With increasing number of risk factors the risk for CP increased exponentially.

Reference List

(1) Little WJ. On the Influence of Abnormal Parturition, Difficult Labours, Premature births and Asphyxia Neonatorum, on the Mental and Physical Condition of the Child especially in relation to Deformities. 3[Trans Obstet Soc London], 293. 1861.

(2) Little WJ. Deformities of the Human Frame. [Lancet], 1:5-7;38-44;70-74;209-12;230-33;257-60;290-93;318-20;346-9;350-54. 1843.

(3) Little WJ. On the nature and course treatment of deformities of human frame.Beeing a course of lectures delivered at the Royal Orthopedic Hospital in 1843 and 1844. 1853. London, Longman,Brown, Green, and Longmans.

(4) Evans ES. Cerebral palsy. Proc R Soc Med 1946 Apr;39:317-20.

(5) Osler W. The cerebral palsies of children: a clinical study from the infirmary for nervous diseases. 1[Classics in Developmental medicine]. 1889. Oxford, England, Blackwell Scientific.

(6) Freud S. Infantile Cerebral Paralysis. Trans.by Russin L.A, editor. 158. 1968. University of Miami, University of Miami press.

(7) Sutherland MD. Case of Cerebral Palsy. 5[Proc R Soc Med], 166. 1912. Sect Study Dis Child.

(8) Mac Keith RC. The Little Club.Memorandum on terminology and classification of 'cerebral palsy'. Mac kenzie ICK PP, editor. 1[Cereb Palsy Bull], 27-35. 1959.
Ref Type: Generic

(9) Bax MC. Terminology and classification of cerebral palsy. Dev Med Child Neurol 1964 Jun;6:295-7.

(10) Mutch L, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol 1992 Jun;34(6):547-51.

(11) Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol 2000 Dec;42(12):816-24.

(12) Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 2005 Aug;47(8):571-6.

(13) World Health Organization. International Classification of Functioning, Disability and Health. [World Health Organization]. 2001. Geneva.

(14) Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 2005 Aug;47(8):571-6.

(15) Rethlefsen SA, Ryan DD, Kay RM. Classification systems in cerebral palsy 1. Orthop Clin North Am 2010 Oct;41(4):457-67.

(16) Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007 Feb;109:8-14.

(17) Blair E, Stanley F. When can cerebral palsy be prevented? The generation of causal hypotheses by multivariate analysis of a case-control study. Paediatr Perinat Epidemiol 1993 Jul;7(3):272-301.

(18) Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2004 Mar 23;62(6):851-63.

(19) Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. Dev Med Child Neurol 2007 Feb;49(2):144-51.

(20) Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. JAMA 2006 Oct 4;296(13):1602-8.

(21) Korzeniewski SJ, Birbeck G, DeLano MC, Potchen MJ, Paneth N. A systematic review of neuroimaging for cerebral palsy. J Child Neurol 2008 Feb;23(2):216-27.

(22) Robinson MN, Peake LJ, Ditchfield MR, Reid SM, Lanigan A, Reddihough DS. Magnetic resonance imaging findings in a population-based cohort of children with cerebral palsy. Dev Med Child Neurol 2009 Jan;51(1):39-45.

(23) Platt MJ, Krageloh-Mann I, Cans C. Surveillance of cerebral palsy in europe: reference and training manual. Med Educ 2009 May;43(5):495-6.

(24) Paneth N. Establishing the diagnosis of cerebral palsy. Clin Obstet Gynecol 2008 Dec;51(4):742-8.

(25) Gainsborough M, Surman G, Maestri G, Colver A, Cans C. Validity and reliability of the guidelines of the surveillance of cerebral palsy in Europe for the classification of cerebral palsy. Dev Med Child Neurol 2008 Nov;50(11):828-31.

(26) Pharoah PO. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity, on behalf of the SCPE Collaboration

Arch Dis Child 2009 Dec;94(12):917-8.

(27) Pakula AT, Van Naarden BK, Yeargin-Allsopp M. Cerebral palsy: classification and epidemiology
12. Phys Med Rehabil Clin N Am 2009 Aug;20(3):425-52.

(28) Rethlefsen SA, Ryan DD, Kay RM. Classification systems in cerebral palsy
1. Orthop Clin North Am 2010 Oct;41(4):457-67.

(29) Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics 2003 Jan;111(1):e89-e97.

(30) Ingram TT. A study of cerebral palsy in the childhood population of Edinburgh. Arch Dis Child 1955 Apr;30(150):85-98.

(31) Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. I. Analysis of the general changes. Acta Paediatr Scand 1975 Mar;64(2):187-92.

(32) ICD-10: International statistical classification of diseases and related health problems. Geneva: World Health Organization; 2009.

(33) Colver AF, Sethumadhavan T. The term diplegia should be abandoned. [Review] [46 refs]. Arch Dis Child 2003 Apr;88(4):286-90.

(34) Hagberg B, Hagberg G, Olow I, von WL. The changing panorama of cerebral palsy in Sweden. VII. Prevalence and origin in the birth year period 1987-90. Acta Paediatr 1996 Aug;85(8):954-60.

(35) Bottos M, Granato T, Allibrio G, Gioachin C, Puato ML. Prevalence of cerebral palsy in north-east Italy from 1965 to 1989. Dev Med Child Neurol 1999 Jan;41(1):26-39.

(36) Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. Acta Paediatr 2001 Mar;90(3):271-7.

(37) Mongan D, Dunne K, O'Nuallain S, Gaffney G. Prevalence of cerebral palsy in the West of Ireland 1990-1999. Dev Med Child Neurol 2006 Nov;48(11):892-5.

(38) Himmelmann K, Beckung E, Hagberg G, Uvebrant P. Gross and fine motor function and accompanying impairments in cerebral palsy. Dev Med Child Neurol 2006 Jun;48(6):417-23.

(39) Howard J, Soo B, Graham HK, Boyd RN, Reid S, Lanigan A, et al. Cerebral palsy in Victoria: motor types, topography and gross motor function. J Paediatr Child Health 2005 Sep;41(9-10):479-83.

(40) Sigurdardottir S, Thorkelsson T, Halldorsdottir M, Thorarensen O, Vik T. Trends in prevalence and characteristics of cerebral palsy among Icelandic children born 1990 to 2003

Dev Med Child Neurol 2009 Mar 20.

(41) Krageloh-Mann I, Hagberg G, Meisner C, Schelp B, Haas G, Eeg-Olofsson KE, et al. Bilateral spastic cerebral palsy--a comparative study between southwest Germany and western Sweden. II: Epidemiology. Dev Med Child Neurol 1994 Jun;36(6):473-83.

(42) Krageloh-Mann I, Cans C. Cerebral palsy update
Brain Dev 2009 Aug;31(7):537-44.

(43) Ravn SH, Flachs EM, Uldall P. Cerebral palsy in eastern Denmark: declining birth prevalence but increasing numbers of unilateral cerebral palsy in birth year period 1986-1998. European Journal of Paediatric Neurology 2010 May;14(3):214-8.

(44) Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. Acta Paediatr 2005 Mar;94(3):287-94.

(45) Yokochi K, Aiba K, Kodama M, Fujimoto S. Magnetic resonance imaging in athetotic cerebral palsied children
Acta Paediatr Scand 1991 Aug;80(8-9):818-23.

(46) Himmelmann K, Hagberg G, Wiklund LM, Eek MN, Uvebrant P. Dyskinetic cerebral palsy: a population-based study of children born between 1991 and 1998. Dev Med Child Neurol 2007 Apr;49(4):246-51.

(47) Hagberg B, Hagberg G. The changing panorama of cerebral palsy--bilateral spastic forms in particular. Acta Paediatr Suppl 1996 Oct;416:48-52.

(48) Himpens E, Oostra A, Franki I, Calders P, Vanhaesebrouck P, Van den BC. Influence of gestational age on nosologic CP characteristics in a high-risk population. Eur J Pediatr 2009 Jul 16.

(49) Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997 Apr;39(4):214-23.

(50) Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000 Oct;80(10):974-85.

(51) Towsley K, Shevell MI, Dagenais L. Population-based study of neuroimaging findings in children with cerebral palsy
Eur J Paediatr Neurol 2010 Sep 22.

(52) Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System
Dev Med Child Neurol 2008 Oct;50(10):744-50.

(53) Claeys V, Deonna T, Chrzanowski R. Congenital hemiparesis: the spectrum of lesions. A clinical and computerized tomographic study of 37 cases

Helv Paediatr Acta 1983 Dec;38(5-6):439-55.

(54) House JH, Gwathmey FW, Fidler MO. A dynamic approach to the thumb-in palm deformity in cerebral palsy. J Bone Joint Surg Am 1981 Feb;63(2):216-25.

(55) Zancolli EA, Zancolli ER, Jr. Surgical management of the hemiplegic spastic hand in cerebral palsy. Surg Clin North Am 1981 Apr;61(2):395-406.

(56) Krageloh-Mann I, Hagberg G, Meisner C, Schelp B, Haas G, Eeg-Olofsson KE, et al. Bilateral spastic cerebral palsy--a comparative study between south-west Germany and western Sweden. I: Clinical patterns and disabilities. Dev Med Child Neurol 1993 Dec;35(12):1037-47.

(57) Beckung E, Hagberg G. Neuroimpairments, activity limitations, and participation restrictions in children with cerebral palsy. Dev Med Child Neurol 2002 May;44(5):309-16.

(58) Pakula AT, Van Naarden BK, Yeargin-Allsopp M. Cerebral palsy: classification and epidemiology
Phys Med Rehabil Clin N Am 2009 Aug;20(3):425-52.

(59) Eliasson AC, Krumlinde-Sundholm L, Rosblad B, Beckung E, Arner M, Ohrvall AM, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. Dev Med Child Neurol 2006 Jul;48(7):549-54.

(60) Gunel MK, Mutlu A, Tarsuslu T, Livanelioglu A. Relationship among the Manual Ability Classification System (MACS), the Gross Motor Function Classification System (GMFCS), and the functional status (WeeFIM) in children with spastic cerebral palsy. Eur J Pediatr 2009 Apr;168(4):477-85.

(61) Damiano D, Abel M, Romness M, Oeffinger D, Tylkowski C, Gorton G, et al. Comparing functional profiles of children with hemiplegic and diplegic cerebral palsy in GMFCS Levels I and II: Are separate classifications needed? Dev Med Child Neurol 2006 Oct;48(10):797-803.

(62) Morris C, Galuppi BE, Rosenbaum PL. Reliability of family report for the Gross Motor Function Classification System
Dev Med Child Neurol 2004 Jul;46(7):455-60.

(63) Gunel MK, Mutlu A, Tarsuslu T, Livanelioglu A. Relationship among the Manual Ability Classification System (MACS), the Gross Motor Function Classification System (GMFCS), and the functional status (WeeFIM) in children with spastic cerebral palsy. Eur J Pediatr 2009 Apr;168(4):477-85.

(64) Mutlu A, Akmese PP, Gunel MK, Karahan S, Livanelioglu A. The importance of motor functional levels from the activity limitation perspective of ICF in children with cerebral palsy Int J Rehabil Res 2010 May 27.

(65) Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007 Feb;109:8-14.

(66) Shevell MI. Current understandings and challenges in the management of cerebral palsy
Minerva Pediatr 2009 Aug;61(4):399-413.

(67) Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil 2006 Feb 28;28(4):183-91.

(68) Fennell EB, Dikel TN. Cognitive and neuropsychological functioning in children with cerebral palsy. J Child Neurol 2001 Jan;16(1):58-63.

(69) Sigurdardottir S, Eiriksdottir A, Gunnarsdottir E, Meintema M, Arnadottir U, Vik T. Cognitive profile in young Icelandic children with cerebral palsy. Dev Med Child Neurol 2008 May;50(5):357-62.

(70) Chan HS, Lau PH, Fong KH, Poon D, Lam CC. Neuroimpairment, activity limitation, and participation restriction among children with cerebral palsy in Hong Kong. Hong Kong Med J 2005 Oct;11(5):342-50.

(71) Wallace SJ. Epilepsy in cerebral palsy. Dev Med Child Neurol 2001 Oct;43(10):713-7.

(72) Hadjipanayis A, Hadjichristodoulou C, Youroukos S. Epilepsy in patients with cerebral palsy. Dev Med Child Neurol 1997 Oct;39(10):659-63.

(73) Pennington L, Goldbart J, Marshall J. Direct speech and language therapy for children with cerebral palsy: findings from a systematic review. Dev Med Child Neurol 2005 Jan;47(1):57-63.

(74) Sigurdardottir S, Vik T. Speech, expressive language, and verbal cognition of preschool children with cerebral palsy in Iceland
Dev Med Child Neurol 2010 Oct 11.

(75) Beckung E, White-Koning M, Marcelli M, McManus V, Michelsen S, Parkes J, et al. Health status of children with cerebral palsy living in Europe: a multi-centre study. Child Care Health Dev 2008 Nov;34(6):806-14.

(76) Sigurdardottir S, Vik T. Speech, expressive language, and verbal cognition of preschool children with cerebral palsy in Iceland
Dev Med Child Neurol 2010 Oct 11.

(77) Rogers B, Arvedson J, Buck G, Smart P, Msall M. Characteristics of dysphagia in children with cerebral palsy. Dysphagia 1994;9(1):69-73.

(78) Fung EB, Samson-Fang L, Stallings VA, Conaway M, Liptak G, Henderson RC, et al. Feeding dysfunction is associated with poor growth and health status in children with cerebral palsy. J Am Diet Assoc 2002 Mar;102(3):361-73.

(79) Stevenson RD, Conaway M, Chumlea WC, Rosenbaum P, Fung EB, Henderson RC, et al. Growth and health in children with moderate-to-severe cerebral palsy. Pediatrics 2006 Sep;118(3):1010-8.

(80) Day SM, Strauss DJ, Vachon PJ, Rosenbloom L, Shavelle RM, Wu YW. Growth patterns in a population of children and adolescents with cerebral palsy. Dev Med Child Neurol 2007 Mar;49(3):167-71.

(81) Reilly S, Skuse D, Poblete X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. J Pediatr 1996 Dec;129(6):877-82.

(82) Jensen A, Garnier Y, Middelanis J, Berger R. Perinatal brain damage--from pathophysiology to prevention. Eur J Obstet Gynecol Reprod Biol 2003 Sep 22;110 Suppl 1:S70-S79.

(83) Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. Dev Med Child Neurol 2007 Feb;49(2):144-51.

(84) Towsley K, Shevell MI, Dagenais L. Population-based study of neuroimaging findings in children with cerebral palsy
Eur J Paediatr Neurol 2010 Sep 22.

(85) Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development: update 2001
Neurology 2001 Dec 26;57(12):2168-78.

(86) Folkerth RD. Neuropathologic substrate of cerebral palsy. Journal of Child Neurology 20 (12) ()(pp 940-949), 2005 Date of Publication: Dec 2005 2005;(12):940-9.

(87) Yoon BH, Park CW, Chaiworapongsa T. Intrauterine infection and the development of cerebral palsy. [Review] [40 refs]. BJOG: An International Journal of Obstetrics & Gynaecology 2003 Apr;110:Suppl-7.

(88) Dammann O, Leviton A. Role of the fetus in perinatal infection and neonatal brain damage. [Review] [44 refs]. Curr Opin Pediatr 2000 Apr;12(2):99-104.

(89) Hansen-Pupp I, Hallin AL, Westas L, Cilio C, Berg AC, Stjernqvist K, et al. Inflammation at birth is associated with subnormal development in very preterm infants. Pediatr Res 2008 Aug;64(2):183-8.

(90) Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. [Review] [211 refs]. Lancet Neurology 2009 Jan;8(1):110-24.

(91) Ancel PY, Livinec F, Larroque B, Marret S, Arnaud C, Pierrat V, et al. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. Pediatrics 2006 Mar;117(3):828-35.

(92) Rennie JM, Hagmann CF, Robertson NJ. Outcome after intrapartum hypoxic ischaemia at term. [Review] [62 refs]. Seminars In Fetal & Neonatal Medicine 2007 Oct;12(5):398-407.

(93) Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy J Pediatr 2005 Apr;146(4):453-60.

(94) Koman LA, Smith BP, Shilt JS. Cerebral palsy. Lancet 2004 May 15;363(9421):1619-31.

(95) Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. [Review] [95 refs]. Best Practice & Research in Clinical Obstetrics & Gynaecology 2004 Jun;18(3):425-36.

(96) Goldstein EM. Spasticity management: an overview J Child Neurol 2001 Jan;16(1):16-23.

(97) Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. N Engl J Med 1986 Jul 10;315(2):81-6.

(98) Nelson KB. Prenatal origin of hemiparetic cerebral palsy: how often and why? Pediatrics 1991 Nov;88(5):1059-62.

(99) Stanley FJ. The aetiology of cerebral palsy. [Review] [39 refs]. Early Hum Dev 1994 Feb;36(2):81-8.

(100) Blair E, Stanley F. Aetiological pathways to spastic cerebral palsy. Paediatr Perinat Epidemiol 1993 Jul;7(3):302-17.

(101) Blair E, Stanley F. When can cerebral palsy be prevented? The generation of causal hypotheses by multivariate analysis of a case-control study. Paediatr Perinat Epidemiol 1993 Jul;7(3):272-301.

(102) Stanley F, Blair E, Alberman E. Cerebral palsies:epidemilogy and causal pathways. 2000. London, Mac Keith.

(103) Rothman KJ. Epidemiology.An Introduction. 2002. New York, Oxford Univeristy Press, Inc.

(104) Nelson KB, Grether JK. Causes of cerebral palsy. [Review] [53 refs]. Curr Opin Pediatr 1999 Dec;11(6):487-91.

(105) Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med 1965 May;58:295-300.

(106) Van den Broeck C, Himpens E, Vanhaesebrouck P, Calders P, Oostra A. Influence of gestational age on the type of brain injury and neuromotor outcome in high-risk neonates. Eur J Pediatr 2008 Sep;167(9):1005-9.

(107) Krageloh-Mann I, Cans C. Cerebral palsy update
Brain Dev 2009 Aug;31(7):537-44.

(108) Rosen MG, Hobel CJ. Prenatal and perinatal factors associated with brain disorders. Obstetrics & Gynecology 1986 Sep;68(3):416-21.

(109) Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. Am J Dis Child 1985 Oct;139(10):1031-8.

(110) Hoon J. Neuroimaging in cerebral palsy: Patterns of brain dysgenesis and injury. Journal of Child Neurology 20 (12) ()(pp 936-939), 2005 Date of Publication: Dec 2005 2005;(12):936-9.

(111) Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden. IV. Epidemiological trends 1959-78. Acta Paediatr Scand 1984 Jul;73(4):433-40.

(112) Himmelmann K, Hagberg G, Uvebrant P. The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999-2002
Acta Paediatr 2010 Sep;99(9):1337-43.

(113) Meberg A, Broch H. Etiology of cerebral palsy. J Perinat Med 2004;32(5):434-9.

(114) Clark SM, Ghulmiyyah LM, Hankins GD. Antenatal antecedents and the impact of obstetric care in the etiology of cerebral palsy. [Review] [25 refs]. Clinical Obstetrics & Gynecology 2008 Dec;51(4):775-86.

(115) Nelson KB. Cerebral palsy: what is known regarding cause?. [Review] [21 refs]. Ann N Y Acad Sci 1986;477:22-6.

(116) Torfs CP, van den BB, Oechsli FW, Cummins S. Prenatal and perinatal factors in the etiology of cerebral palsy. J Pediatr 1990 Apr;116(4):615-9.

(117) Blair E, Stanley FJ. An epidemiological study of cerebral palsy in Western Australia, 1956-1975. III: Postnatal aetiology. Developmental Medicine & Child Neurology 1982 Oct;24(5):575-85.

(118) Cans C, McManus V, Crowley M, Guillem P, Platt MJ, Johnson A, et al. Cerebral palsy of post-neonatal origin: characteristics and risk factors. Paediatr Perinat Epidemiol 2004 May;18(3):214-20.

(119) Euro-Peristat Project. European Perinatal Health Report. 1-280. 2008.

(120) Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. Obstetrics and Gynecology 108 (6) ()(pp 1499-1505), 2006 Date of Publication: Dec 2006 2006;(6):1499-505.

(121) Wu YW, Croen LA, Shah SJ, Newman TB, Najjar DV. Cerebral palsy in a term population: Risk factors and neuroimaging findings. Pediatrics 118 (2) ()(pp 690-697), 2006 Date of Publication: Aug 2006 2006;(2):690-7.

(122) Glinianaia SV, Rankin J, Colver A. Cerebral palsy rates by birth weight, gestation and severity in North of England, 1991-2000 singleton births

Arch Dis Child 2010 Nov 10.

(123) Topp M, Langhoff-Roos J, Uldall P. Preterm birth and cerebral palsy. Predictive value of pregnancy complications, mode of delivery, and Apgar scores. [Review] [38 refs]. Acta Obstet Gynecol Scand 1997 Oct;76(9):843-8.

(124) Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: A population-based study. Lancet 359 (9305) ()(pp 461-465), 2002 Date of Publication: 09 Feb 2002 2002;(9305):461-5.

(125) Hvidtjorn D, Grove J, Schendel D, Svaerke C, Schieve LA, Uldall P, et al. Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: A population-based cohort study. Human Reproduction 25 (8) ()(pp 2115-2123), 2010 Date of Publication: August 2010 2010;(8):2115-23.

(126) Kallen AJB, Finnstrom OO, Lindam AP, Nilsson EME, Nygren K-G, Otterblad Olausson PM. Cerebral palsy in children born after in vitro fertilization. Is the risk decreasing? European Journal of Paediatric Neurology 14 (6) ()(pp 526-530), 2010 Date of Publication: 2010 2010;(6):526-30.

(127) Hong T, Paneth N. Maternal and infant thyroid disorders and cerebral palsy. [Review] [49 refs]. Semin Perinatol 2008 Dec;32(6):438-45.

(128) Pinto-Martin JA, Cnaan A, Zhao H. Short interpregnancy interval and the risk of disabling cerebral palsy in a low birth weight population. Journal of Pediatrics 132 (5) ()(pp 818-821), 1998 Date of Publication: 1998 1998;(5):818-21.

(129) Costeff H. Estimated frequency of genetic and nongenetic causes of congenital idiopathic cerebral palsy in west Sweden. Ann Hum Genet 2004 Sep;68(Pt 5):515-20.

(130) Gibson CS, Maclennan AH, Dekker GA, Goldwater PN, Sullivan TR, Munroe DJ, et al. Candidate genes and cerebral palsy: a population-based study. Pediatrics 2008 Nov;122(5):1079-85.

(131) Holst D, Garnier Y. Preterm birth and inflammation-The role of genetic polymorphisms. [Review] [56 refs]. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2008 Nov;141(1):3-9.

(132) Pharoah PO. Prevalence and pathogenesis of congenital anomalies in cerebral palsy. Arch Dis Child Fetal Neonatal Ed 2007 Nov;92(6):F489-F493.

(133) Garne E, Dolk H, Krageloh-Mann I, Holst RS, Cans C. Cerebral palsy and congenital malformations. Eur J Paediatr Neurol 2008 Mar;12(2):82-8.

(134) Croen LA, Grether JK, Curry CJ, Nelson KB. Congenital abnormalities among children with cerebral palsy: More evidence for prenatal antecedents. J Pediatr 2001 Jun;138(6):804-10.

(135) Blair E, Al AF, Badawi N, Bower C. Is cerebral palsy associated with birth defects other than cerebral defects? Developmental Medicine & Child Neurology 2007 Apr;49(4):252-8.

(136) Rankin J, Cans C, Garne E, Colver A, Dolk H, Uldall P, et al. Congenital anomalies in children with cerebral palsy: a population-based record linkage study. Dev Med Child Neurol 2010 Apr;52(4):345-51.

(137) Pharoah PO. Prevalence and pathogenesis of congenital anomalies in cerebral palsy. Archives of Disease in Childhood Fetal & Neonatal Edition 2007 Nov;92(6):F489-F493.

(138) Rackauskaite G, Balslev T, Hertz JM. [Cerebral palsy--what is the influence of genetic factors?]. Ugeskr Laeger 2005 Apr 11;167(15):1625-9.

(139) Jarvis S, Glinianaia SV, Arnaud C, Fauconnier J, Johnson A, McManus V, et al. Case gender and severity in cerebral palsy varies with intrauterine growth. Arch Dis Child 2005 May;90(5):474-9.

(140) Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol 2007 Jan;49(1):74-8.

(141) Redline RW, Minich N, Taylor HG, Hack M. Placental lesions as predictors of cerebral palsy and abnormal neurocognitive function at school age in extremely low birth weight infants (<1 kg). Pediatr Dev Pathol 2007 Jul;10(4):282-92.

(142) Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. Arch Pathol Lab Med 2000 Dec;124(12):1785-91.

(143) Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M. Placental lesions associated with neurologic impairment and cerebral palsy in very low-birth-weight infants. Arch Pathol Lab Med 1998 Dec;122(12):1091-8.

(144) Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Hum Pathol 1999 Jul;30(7):759-69.

(145) Palmer L, Blair E, Petterson B, Burton P. Antenatal antecedents of moderate and severe cerebral palsy. Paediatr Perinat Epidemiol 1995 Apr;9(2):171-84.

(146) Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics 2002 Dec;110(6):1220-5.

(147) Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. Acta Paediatr 2005 Mar;94(3):287-94.

(148) Watson L BESF. Report of the Western Australia cerebral palsy register to birth year 1999. 2009. Perth, Australia, Telethon Institute for Child Health Research.

(149) Himpens E, Van den BC, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Child Neurol 2008 May;50(5):334-40.

(150) Leviton A. Preterm birth and cerebral palsy: is tumor necrosis factor the missing link?. [Review] [72 refs]. Developmental Medicine & Child Neurology 1993 Jun;35(6):553-8.

(151) Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr 2009 Feb;154(2):169-76.

(152) Blair E, Stanley F. The epidemiology of the cerebral palsies. [Fetal and neonatal neurology. 4 th edition], 867-868. 2009. Edinburgh, Churchill LIvingston Elsevier.

(153) Moster D, Wilcox AJ, Vollset SE, Markestad T, Lie RT. Cerebral palsy among term and postterm births. JAMA - Journal of the American Medical Association 304 (9) ()(pp 976-982), 2010 Date of Publication: 01 Sep 2010 2010;(9):976-82.

(154) Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia
Am J Obstet Gynecol 2008 May;198(5):517-6.

(155) Jarvis S, Glinianaia SV, Torrioli MG, Platt MJ, Miceli M, Jouk PS, et al. Cerebral palsy and intrauterine growth in single births: European collaborative study. Lancet 2003 Oct 4;362(9390):1106-11.

(156) Jarvis S, Glinianaia SV, Blair E. Cerebral palsy and intrauterine growth. [Review] [56 refs]. Clin Perinatol 2006 Jun;33(2):285-300.

(157) Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. Pediatrics 1988 Jul;82(1):83-90.

(158) Blair E, Stanley F. Intrauterine growth and spastic cerebral palsy. I. Association with birth weight for gestational age. American Journal of Obstetrics & Gynecology 1990 Jan;162(1):229-37.

(159) Uvebrant P, Hagberg G. Intrauterine growth in children with cerebral palsy. Acta Paediatr 1992 May;81(5):407-12.

(160) Murphy DJ, Sellers S, MacKenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. Lancet 1995 Dec 2;346(8988):1449-54.

(161) Topp M, Uldall P, Langhoff-Roos J. Trend in cerebral palsy birth prevalence in eastern Denmark: birth-year period 1979-86. Paediatr Perinat Epidemiol 1997 Oct;11(4):451-60.

(162) Greenwood C, Yudkin P, Sellers S, Impey L, Doyle P. Why is there a modifying effect of gestational age on risk factors for cerebral palsy? Arch Dis Child Fetal Neonatal Ed 2005 Mar;90(2):F141-F146.

(163) Baschat AA, Viscardi RM, Hussey-Gardner B, Hashmi N, Harman C. Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters. Ultrasound in Obstetrics & Gynecology 2009 Jan;33(1):44-50.

(164) Bonellie SR, Currie D, Chalmers J. Comparison of risk factors for cerebral palsy in twins and singletons. Dev Med Child Neurol 2005 Sep;47(9):587-91.

(165) Pharoah PO, Adi Y. Consequences of in-utero death in a twin pregnancy. Lancet 2000 May 6;355(9215):1597-602.

(166) Pharoah PO. Risk of cerebral palsy in multiple pregnancies. [Review] [77 refs]. Clin Perinatol 2006 Jun;33(2):301-13.

(167) Blickstein I. Do multiple gestations raise the risk of cerebral palsy?. [Review] [60 refs]. Clin Perinatol 2004 Sep;31(3):395-408.

(168) Topp M, Huusom LD, Langhoff-Roos J, Delhumeau C, Hutton JL, Dolk H, et al. Multiple birth and cerebral palsy in Europe: a multicenter study. Acta Obstet Gynecol Scand 2004 Jun;83(6):548-53.

(169) Haram K, Bjorge L, Guttu K, Bergsjo P. [Pre-eclampsia--a review]. Tidsskr Nor Laegeforen 2000 May 10;120(12):1437-42.

(170) Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. American Journal of Obstetrics & Gynecology 2009 Sep;201(3):269.

(171) Nelson KB. Perinatal ischemic stroke
Stroke 2007 Feb;38(2 Suppl):742-5.

(172) Mann JR, McDermott S, Hardin J, Gregg A. Uncovering the complex relationsship between pre-eclampsia, preterm birth and cerebral palsy. [Paediatric and Perinatal Epidemiology], 1-11. 2010. Blackwell Publishing LTD.

(173) Wu YW, Colford JM, Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. [Review] [83 refs]. JAMA 2000 Sep 20;284(11):1417-24.

(174) Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight.[Erratum appears in JAMA 1998 Jan 14;279(2):118]. JAMA 1997 Jul 16;278(3):207-11.

(175) Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA 2003 Nov 26;290(20):2677-84.

(176) Jacobsson B, Hagberg G, Hagberg B, Ladfors L, Niklasson A, Hagberg H. Cerebral palsy in preterm infants: A population-based case-control study of antenatal and intrapartal risk factors. Acta Paediatrica, International Journal of Paediatrics 91 (8) ()(pp 946-951), 2002 Date of Publication: 2002 2002;(8):946-51.

(177) O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. Paediatr Perinat Epidemiol 1998 Jan;12(1):72-83.

(178) Shatrov JG, Birch SC, Lam LT, Quinlivan JA, McIntyre S, Mendz GL. Chorioamnionitis and cerebral palsy: a meta-analysis. [Review] [37 refs]. Obstetrics & Gynecology 2010 Aug;116(2:Pt 1):t-92.

(179) Grether JK, Nelson KB, Walsh E, Willoughby RE, Redline RW. Intrauterine exposure to infection and risk of cerebral palsy in very preterm infants. Archives of Pediatrics and Adolescent Medicine 157 (1) ()(pp 26-32), 2003 Date of Publication: 01 Jan 2003 2003;(1):26-32.

(180) Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. J Perinatol 2005 Feb;25(2):108-13.

(181) Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 2005 Feb 9;293(6):723-9.

(182) Nelson KB, Chang T. Is cerebral palsy preventable?. [Review] [70 refs]. Curr Opin Neurol 2008 Apr;21(2):129-35.

(183) Uvebrant P. Hemiplegic cerebral palsy. Aetiology and outcome. Acta Paediatrica Scandinavica - Supplement 1988;345:1-100.

(184) Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. Journal of the American Medical Association 293 (6) ()(pp 723-729), 2005 Date of Publication: 09 Feb 2005 2005;(6):723-9.

(185) Nelson KB. Causative factors in cerebral palsy. Clin Obstet Gynecol 2008 Dec;51(4):749-62.

(186) Nielsen LF, Schendel D, Grove J, rn D, Jacobsson B, Josiassen T, et al. Asphyxia-related risk factors and their timing in spastic cerebral palsy. BJOG: An International Journal of Obstetrics & Gynaecology 2008 Nov;115(12):1518-28.

(187) Mealing NM, Roberts CL, Ford JB, Simpson JM, Morris JM. Trends in induction of labour, 1998-2007: a population-based study. Aust N Z J Obstet Gynaecol 2009 Dec;49(6):599-605.

(188) Simpson KR, Thorman KE. Obstetric "conveniences": elective induction of labor, cesarean birth on demand, and other potentially unnecessary interventions. J Perinat Neonatal Nurs 2005 Apr;19(2):134-44.

(189) Lerchl A, Reinhard SC. Where are the Sunday babies? II. Declining weekend birth rates in Switzerland
Naturwissenschaften 2008 Feb;95(2):161-4.

(190) Gersting J, Schaub CE, Keller-Wood M, Wood CE. Inhibition of brain prostaglandin endoperoxide synthase-2 prevents the preparturient increase in fetal adrenocorticotropin secretion in the sheep fetus
Endocrinology 2008 Aug;149(8):4128-36.

(191) Liggins GC, Kennedy PC, Holm LW. Failure of initiation of parturition after electrocoagulation of the pituitary of the fetal lamb
Am J Obstet Gynecol 1967 Aug 15;98(8):1080-6.

(192) RCOG Royal College of Ostetricians and Gynaecologists. Labour Induction. Clinical guidelines. 2.ed. 2008. London, RCOG Press.

(193) Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy. Cochrane Database Syst Rev 2000;(2):CD000941.

(194) Crane JM, Young DC, Butt KD, Bennett KA, Hutchens D. Excessive uterine activity accompanying induced labor
Obstet Gynecol 2001 Jun;97(6):926-31.

(195) Peebles DM, Spencer JA, Edwards AD, Wyatt JS, Reynolds EO, Cope M, et al. Relation between frequency of uterine contractions and human fetal cerebral oxygen saturation studied during labour by near infrared spectroscopy. Br J Obstet Gynaecol 1994 Jan;101(1):44-8.

(196) Bakker PC, Kurver PH, Kuik DJ, van Geijn HP. Elevated uterine activity increases the risk of fetal acidosis at birth. Am J Obstet Gynecol 2007 Apr;196(4):313-6.

(197) Ozturk A, Demirci F, Yavuz T, Yildiz S, Degirmenci Y, Dosoglu M, et al. Antenatal and delivery risk factors and prevalence of cerebral palsy in Duzce (Turkey). Brain and Development 29 (1) ()(pp 39-42), 2007 Date of Publication: Jan 2007 2007;(1):39-42.

(198) Krebs L, Topp M, Langhoff-Roos J. The relation of breech presentation at term to cerebral palsy. Br J Obstet Gynaecol 1999 Sep;106(9):943-7.

(199) Herbst A, Thorngren-Jerneck K. Mode of delivery in breech presentation at term: increased neonatal morbidity with vaginal delivery. Acta Obstet Gynecol Scand 2001 Aug;80(8):731-7.

(200) Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. Acta Paediatr 2001 Mar;90(3):271-7.

(201) Rosenbloom L. Dyskinetic cerebral palsy and birth asphyxia. Developmental Medicine & Child Neurology 1994 Apr;36(4):285-9.

(202) Luterkort M, Marsal K. Umbilical cord acid-base state and Apgar score in term breech neonates. Acta Obstet Gynecol Scand 1987;66(1):57-60.

(203) Luterkort M, Persson PH, Weldner BM. Maternal and fetal factors in breech presentation
Obstet Gynecol 1984 Jul;64(1):55-9.

(204) Krebs L. Breech at term. Early and late consequences of mode of delivery. [Review] [251 refs]. Dan Med Bull 2005 Dec;52(4):234-52.

(205) Luterkort M, Polberger S, Weldner BM, Persson PH, Bjerre I. Growth in breech presentation. Ultrasound and post-partal assessment of growth in 225 fetuses presenting by the breech in the 33rd gestational week
Acta Obstet Gynecol Scand 1986;65(2):157-60.

(206) Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes
JAMA 1999 Nov 3;282(17):1646-51.

(207) Kayani SI, Walkinshaw SA, Preston C. Pregnancy outcome in severe placental abruption. BJOG: An International Journal of Obstetrics & Gynaecology 2003 Jul;110(7):679-83.

(208) Sheiner E, Shoham-Vardi I, Hadar A, Hallak M, Hackmon R, Mazor M. Incidence, obstetric risk factors and pregnancy outcome of preterm placental abruption: a retrospective analysis
J Matern Fetal Neonatal Med 2002 Jan;11(1):34-9.

(209) Perlman JM. Intrapartum asphyxia and cerebral palsy: is there a link?. [Review] [94 refs]. Clin Perinatol 2006 Jun;33(2):335-53.

(210) Perlman JM. Intrapartum Asphyxia and Cerebral Palsy: Is There a Link? Clinics in Perinatology 33 (2) ()(pp 335-353), 2006 Date of Publication: Jun 2006
2006;(2):335-53.

(211) Pin TW, Eldridge B, Galea MP. A review of developmental outcomes of term infants with post-asphyxia neonatal encephalopathy
Eur J Paediatr Neurol 2009 May;13(3):224-34.

(212) MacLennan A. A template for defining a causal relationship between acute intrapartum events and cerebral palsy: international consensus statement. International Cerebral Palsy Task Force. [Review] [70 refs]. Australian & New Zealand Journal of Obstetrics & Gynaecology 2000 Feb;40(1):13-21.

(213) Committee on Fetus and Newborn, American Academy of Pediatrics, Committee on Obsteric Practice ACoOaG. Use and abuse of the Apgar score. 98 (1)[Pediatrics], 141-142. 1996.

(214) Task Force American College of Obstericians and Gynecologists and the American Academy of Pediatrics. Neonatal encephalopathy and cerebral palsy. Defining the pathogenesis and pathophysiology. 2003. Washington DC, American College of Obsterics and Gynecology.

(215) ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 348, November 2006: Umbilical cord blood gas and acid-base analysis. Obstetrics & Gynecology 2006 Nov;108(5):1319-22.

(216) Goldaber KG, Gilstrap LC, III. Correlations between obstetric clinical events and umbilical cord blood acid-base and blood gas values. [Review] [42 refs]. Clinical Obstetrics & Gynecology 1993 Mar;36(1):47-59.

(217) Moster D, Lie RT, Irgens LM, Bjerkedal T, Markestad T. The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants. J Pediatr 2001 Jun;138(6):798-803.

(218) Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics 1981 Jul;68(1):36-44.

(219) Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. American Journal of Obstetrics and Gynecology 199 (6) ()(pp 587-595), 2008 Date of Publication: December 2008 2008;(6):587-95.

(220) Badawi N, Watson L, Petterson B, Blair E, Slee J, Haan E, et al. What constitutes cerebral palsy? Dev Med Child Neurol 1998 Aug;40(8):520-7.

(221) Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy.[Erratum appears in J Pediatr 1988 Aug;113(2):420]. J Pediatr 1988 Apr;112(4):515-9.

(222) Smith L, Kelly KD, Prkachin G, Voaklander DC. The prevalence of cerebral palsy in British Columbia, 1991-1995. Can J Neurol Sci 2008 Jul;35(3):342-7.

(223) Surman G, Hemming K, Platt MJ, Parkes J, Green A, Hutton J, et al. Children with cerebral palsy: severity and trends over time
Paediatr Perinat Epidemiol 2009 Nov;23(6):513-21.

(224) Yeargin-Allsopp M, Van Naarden BK, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. Pediatrics 2008 Mar;121(3):547-54.

(225) Watson L, Blair, Stanley F. Report of the Western Australian cerebral palsy register. To birth year 1999. 2006. Perth, Institutet for Child health research. 2006.

(226) Joseph KS, Allen AC, Lutfi S, Murphy-Kaulbeck L, Vincer MJ, Wood E. Does the risk of cerebral palsy increase or decrease with increasing gestational age? BMC Pregnancy Childbirth 2003 Dec 23;3(1):8.

(227) Blair E. Epidemiology of the cerebral palsies
Orthop Clin North Am 2010 Oct;41(4):441-55.

(228) Hagberg B, Hagberg G, Olow I, von WL. The changing panorama of cerebral palsy in Sweden. V. The birth year period 1979-82. Acta Paediatr Scand 1989 Mar;78(2):283-90.

(229) Surveillance of Cerebral Palsy in Europe (SCPE) collaboration of European Cerebral Palsy Registers. Prevalence and characteristics of children with cerebral palsy in Europe. 44[Developmental Medicine and Child Neurology], 633-639. 2002.

(230) Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, et al. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. Lancet 369 (9555) ()(pp 43-50), 2007 Date of Publication: 06 Jan 2007 2007;(9555):43-50.

(231) Sellier E, Surman G, Himmelmann K, Andersen G, Colver A, Krageloh-Mann I, et al. Trends in prevalence of cerebral palsy in children born with a birthweight of 2,500 g or over in Europe from 1980 to 1998
Eur J Epidemiol 2010 Sep;25(9):635-42.

(232) Topp M, Uldall P, Greisen G. Cerebral palsy births in eastern Denmark, 1987--90: implications for neonatal care. Paediatr Perinat Epidemiol 2001 Jul;15(3):271-7.

(233) Surman G, Newdick H, Johnson A. Cerebral palsy rates among low-birthweight infants fell in the 1990s. Dev Med Child Neurol 2003 Jul;45(7):456-62.

(234) Andersen GL, Romundstad P, De La Cruz J, Himmelmann K, Sellier E, Cans C, et al. Cerebral palsy among children born 1980-1998 moderately preterm or with moderate low birth weight: A European register based study. 2010. Submitted.

(235) Russell DJ, Avery LM, Rosenbaum PL, Raina PS, Walter SD, Palisano RJ. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity. Phys Ther 2000 Sep;80(9):873-85.

(236) Skjaerven R, Gjessing HK, Bakketeig LS. New standards for birth weight by gestational age using family data. Am J Obstet Gynecol 2000 Sep;183(3):689-96.

(237) Altman DG. Practical statistics for medical research,1st ed. 1991. London, Chapman&Hal /CRC Press.

(238) Rothman KJ. Modern Epidemiology. 1998. Boston, Little.

(239) Ahlbom A, Alfredsson L. Interaction: A word with two meanings creates confusion Eur J Epidemiol 2005;20(7):563-4.

(240) Hosmer DW, Lemeshow S. Confidence interval estimation of interaction Epidemiology 1992 Sep;3(5):452-6.

(241) Blair E, Watson L. Epidemiology of cerebral palsy. [Review] [51 refs]. Seminars In Fetal & Neonatal Medicine 2006 Apr;11(2):117-25.

(242) Himmelmann K, Beckung E, Hagberg G, Uvebrant P. Gross and fine motor function and accompanying impairments in cerebral palsy. Dev Med Child Neurol 2006 Jun;48(6):417-23.

(243) Nordmark E, Hagglund G, Lagergren J. Cerebral palsy in southern Sweden I. Prevalence and clinical features. Acta Paediatr 2001 Nov;90(11):1271-6.

(244) Himmelmann K, Beckung E, Hagberg G, Uvebrant P. Bilateral spastic cerebral palsy--prevalence through four decades, motor function and growth. European Journal of Paediatric Neurology 2007 Jul;11(4):215-22.

(245) Sigurdardottir S, Thorkelsson T, Halldorsdottir M, Thorarensen O, Vik T. Trends in prevalence and characteristics of cerebral palsy among Icelandic children born 1990 to 2003
Dev Med Child Neurol 2009 Mar 20.

(246) Mongan D, Dunne K, O'Nuallain S, Gaffney G. Prevalence of cerebral palsy in the West of Ireland 1990-1999. Dev Med Child Neurol 2006 Nov;48(11):892-5.

(247) Zarrinkalam R, Russo RN, Gibson CS, VAN EP, Peek AK, Haan EA. CP or not CP? A review of diagnoses in a cerebral palsy register
Pediatr Neurol 2010 Mar;42(3):177-80.

(248) Hidecker MJ. Communication activity and participation research
Dev Med Child Neurol 2010 May;52(5):408-9.

(249) Barty E, Caynes K. Development of a Functional Communication Classification Scale. 2009. Sydney, Australia, International Cerebral Palsy Conference.

(250) Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach
Int J Epidemiol 1997 Feb;26(1):224-7.

(251) Nelson KB. Can we prevent cerebral palsy? N Engl J Med 2003 Oct 30;349(18):1765-9.

(252) Colver AF, Gibson M, Hey EN, Jarvis SN, Mackie PC, Richmond S. Increasing rates of cerebral palsy across the severity spectrum in north-east England 1964-1993. The North of England Collaborative Cerebral Palsy Survey. Arch Dis Child Fetal Neonatal Ed 2000 Jul;83(1):F7-F12.

(253) Parkes J, Dolk H, Hill N, Pattenden S. Cerebral palsy in Northern Ireland: 1981--93. Paediatr Perinat Epidemiol 2001 Jul;15(3):278-86.

(254) Sundrum R, Logan S, Wallace A, Spencer N. Cerebral palsy and socioeconomic status: a retrospective cohort study. Arch Dis Child 2005 Jan;90(1):15-8.

(255) Bottos M, Granato T, Allibrio G, Gioachin C, Puato ML. Prevalence of cerebral palsy in north-east Italy from 1965 to 1989. Developmental Medicine & Child Neurology 1999 Jan;41(1):26-39.

(256) Murphy CC, Yeargin-Allsopp M, Decoufle P, Drews CD. Prevalence of cerebral palsy among ten-year-old children in metropolitan Atlanta, 1985 through 1987. J Pediatr 1993 Nov;123(5):S13-S20.

(257) Watson L BESF. Report of the Western Australia cerebral palsy register to birth year 1999. 2009. Perth, Australia, Telethon Institute for Child Health Research.

(258) Edebol-Tysk K. Epidemiology of spastic tetraplegic cerebral palsy in Sweden. I. Impairments and disabilities. Neuropediatrics 1989 Feb;20(1):41-5.

(259) Andersen G, Mjøen T, Vik T. Prevalence of speech problems and the Use of Aumentative and Alternative Communication in children with Cerebral Palsy: A registry-based study in Norway. 19[Perspectives on Augmentative and Alternative Communication], 12-20. 2010. American speech-language- hearing association.

(260) Calis EA, Veugelers R, Sheppard JJ, Tibboel D, Evenhuis HM, Penning C. Dysphagia in children with severe generalized cerebral palsy and intellectual disability. Dev Med Child Neurol 2008 Aug;50(8):625-30.

(261) Kotaska A. Breech birth can be safe, but is it worth the effort?
J Obstet Gynaecol Can 2009 Jun;31(6):553-6.

(262) Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group
Lancet 2000 Oct 21;356(9239):1375-83.

(263) Minchom P, Niswander K, Chalmers I, Dauncey M, Newcombe R, Elbourne D, et al. Antecedents and outcome of very early neonatal seizures in infants born at or after term. British Journal of Obstetrics & Gynaecology 1987 May;94(5):431-9.

(264) Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full-term infants
BMJ 1995 Sep 2;311(7005):598-602.

(265) Gaffney G, Flavell V, Johnson A, Squier M, Sellers S. Cerebral palsy and neonatal encephalopathy. Archives of Disease in Childhood Fetal & Neonatal Edition 1994 May;70(3):F195-F200.

(266) Badawi N, Felix JF, Kurinczuk JJ, Dixon G, Watson L, Keogh JM, et al. Cerebral palsy following term newborn encephalopathy: a population-based study. Dev Med Child Neurol 2005 May;47(5):293-8.

(267) Dixon G, Badawi N, Kurinczuk JJ, Keogh JM, Silburn SR, Zubrick SR, et al. Early developmental outcomes after newborn encephalopathy
Pediatrics 2002 Jan;109(1):26-33.

(268) Gaffney G, Sellers S, Flavell V, Squier M, Johnson A. Case-control study of intrapartum care, cerebral palsy, and perinatal death. BMJ 1994 Mar 19;308(6931):743-50.

(269) Molkenboer JF, Vencken PM, Sonnemans LG, Roumen FJ, Smits F, Buitendijk SE, et al. Conservative management in breech deliveries leads to similar results compared with cephalic deliveries
J Matern Fetal Neonatal Med 2007 Aug;20(8):599-603.

(270) Lie KK, Groholt E-K, Eskild A. Association of cerebral palsy with Apgar score in low and normal birthweight infants: Population based cohort study. BMJ 341 (7777) ()(pp 817), 2010 Date of Publication: 16 Oct 2010 2010;(7777):817.

(271) Hofmeyr GJ, Hannah ME. Planned caesarean section for term breech delivery Cochrane Database Syst Rev 2000;(2):CD000166.

(272) Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2001;(3):CD000941.

(273) Nelson KB. Causative factors in cerebral palsy. [Review] [54 refs]. Clinical Obstetrics & Gynecology 2008 Dec;51(4):749-62.

(274) Colver AF, Dickinson HO. Study protocol: determinants of participation and quality of life of adolescents with cerebral palsy: a longitudinal study (SPARCLE2)
BMC Public Health 2010;10:280.

(275) Vik T, Skrove MS, Dollner H, Helland G. [Feeding problems and growth disorders among children with cerebral palsy in south and north Trondelag]. Tidsskr Nor Laegeforen 2001 May 20;121(13):1570-4.

(276) Vargus-Adams JN, Martin LK. Measuring what matters in cerebral palsy: a breadth of important domains and outcome measures
Arch Phys Med Rehabil 2009 Dec;90(12):2089-95.

(277) Troughton KE, Hill AE. Relation between objectively measured feeding competence and nutrition in children with cerebral palsy. Dev Med Child Neurol 2001 Mar;43(3):187-90.

(278) Sanders KD, Cox K, Cannon R, Blanchard D, Pitcher J, Papathakis P, et al. Growth response to enteral feeding by children with cerebral palsy. JPEN J Parenter Enteral Nutr 1990 Jan;14(1):23-6.

(279) Sullivan PB, Juszczak E, Bachlet AM, Lambert B, Vernon-Roberts A, Grant HW, et al. Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study. Dev Med Child Neurol 2005 Feb;47(2):77-85.

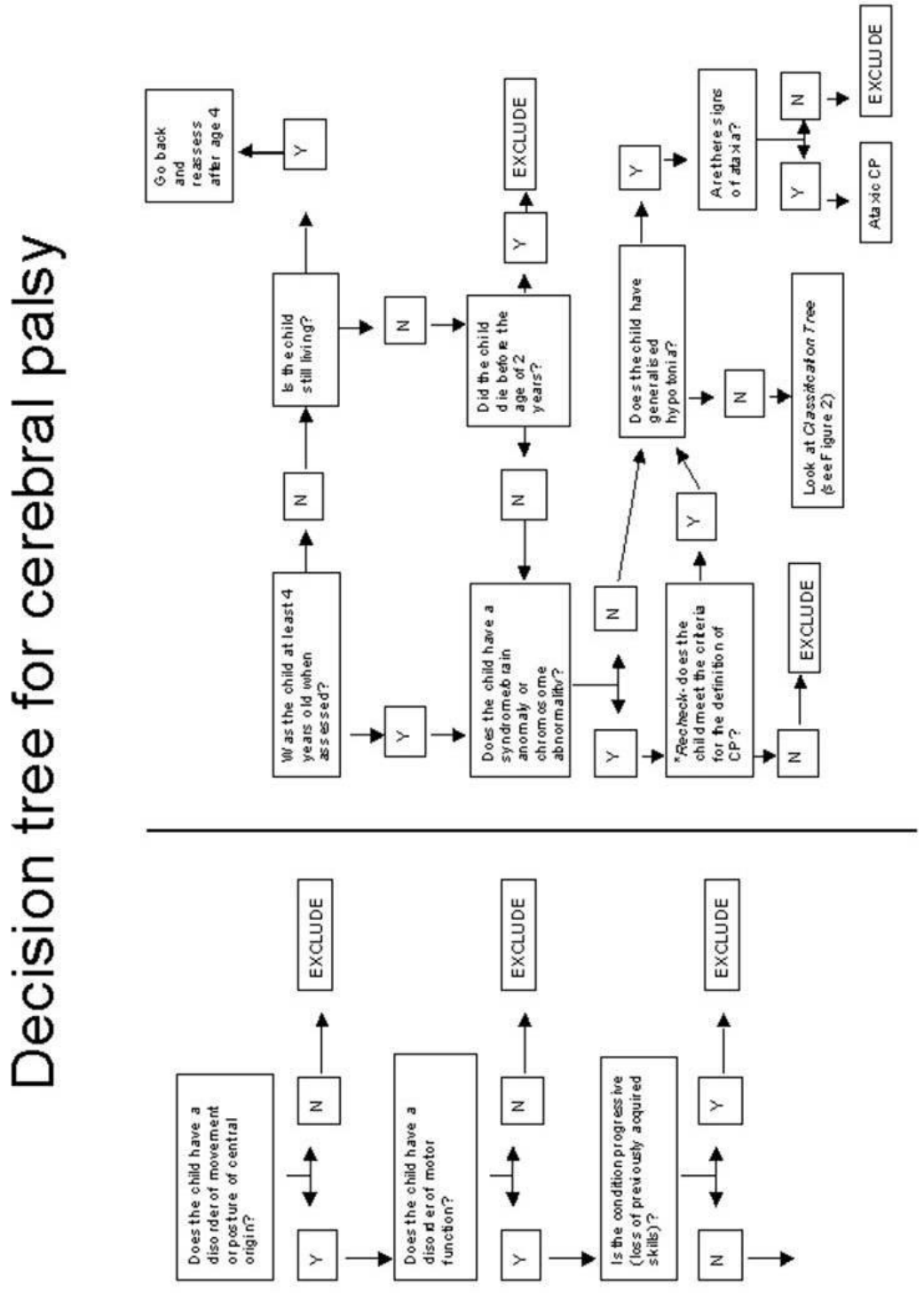
(280) Katz RT. Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. NeuroRehabilitation 2003;18(3):261-70.

(281) Blackman JA. Apolipoprotein E genotype and cerebral palsy
Dev Med Child Neurol 2010 Jul;52(7):600.

(282) Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. Acta Paediatr 2005 Mar;94(3):287-94.

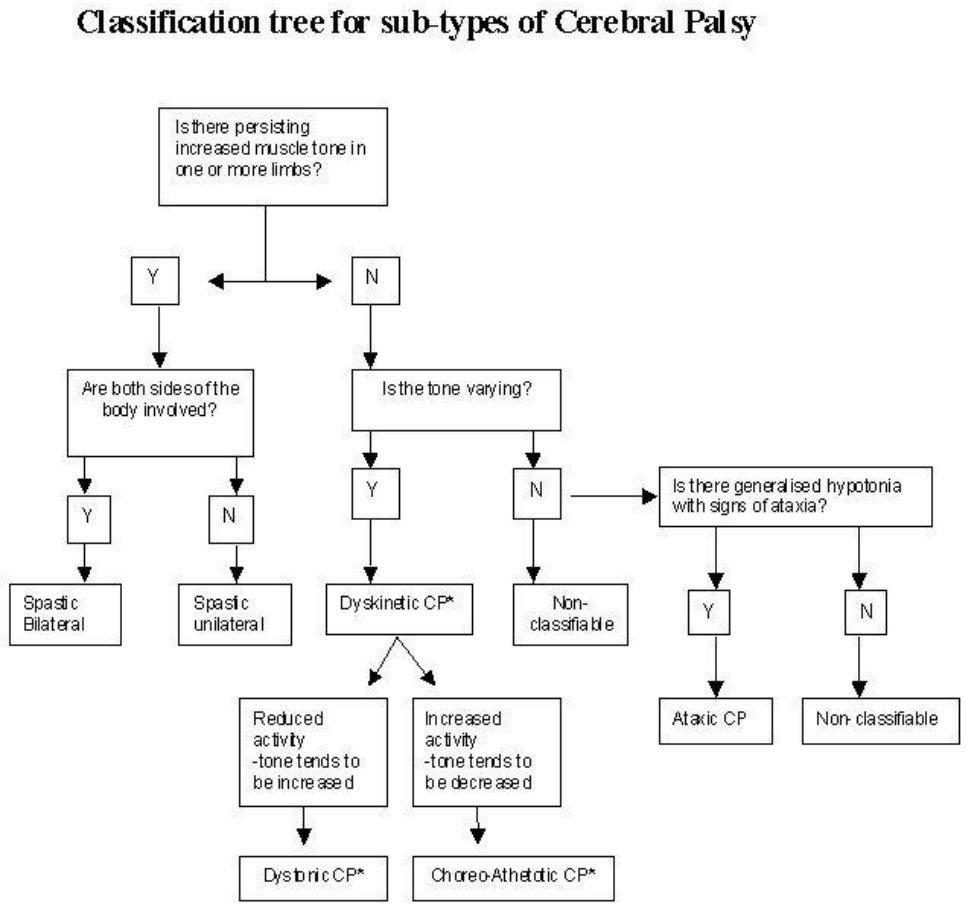
Appendix 1 Decision tree for cerebral palsy

with permission (C.Cans 2010)



Appendix 2 Classification tree for subtypes of Cerebral palsy.

with permission (C.Cans 2010)



Appendix 3 a)Search history, Embase 1980-2010 week 45

Search Strategy:

#	Searches	Results
1	cerebral palsy/	18036
2	cerebral pals*.tw.	14034
3	or/1-2	19697
4	fertilization in vitro/	30716
5	maternal age/	14969
6	parity/	16434
7	fetus death/	17690
8	pregnancy complication/	66027
9	multiple pregnancy/	9374
10	newborn hypoxia/	5353
11	Apgar score/	8664
12	cesarean section/	44029
13	labor induction/	9041
14	congenital disorder/	58459
15	prolonged pregnancy/	2151
16	(placenta disease* or ((premature or preterm) adj3 birth*) or bleeding in pregnancy or (intrauterine adj3 growth restriction) or fetal growth retardation).tw.	15929
17	(pre-eclampsi* or eclampsi*).tw.	9641
18	((maternal adj3 thyroid disease*) or (maternal adj3 diabetes) or (maternal adj3 epilepsy)).tw.	2021
19	((Fertili?ation adj3 in adj3 vitro) or maternal age or parity or (previous adj3 fetal death) or congenital abnormalit*).tw.	45543
20	((pregnancy adj3 complication*) or pregnancy multiple*).tw.	7433
21	(Asphyx* neonatorum or neonatal asphyx* or (labo?r adj3 induced) or (pregnancy adj3 prolonged) or (breech adj3 presentation) or c?esarean section or (pregnancy adj3 complication*)).tw.	39443
22	or/4-21	293112
23	3 and 22	1823

Search history, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950-2010 week 45

Search Strategy:

#	Searches	Results
1	Cerebral Palsy/	13125
2	cerebral pals*.tw.	12065
3	or/1-2	15961
4	exp Fertilization in Vitro/	23938
5	maternal age/	14533
6	Parity/	18793
7	Fetal Death/	21916
8	exp Pregnancy Complications/	298139
9	exp Epilepsy/	112165
10	exp Pregnancy/	649570
11	9 and 10	3675
12	exp Pregnancy, Multiple/	25434
13	Asphyxia Neonatorum/	6249
14	Apgar Score/	6013
15	Cesarean Section/	29979
16	Labor, Induced/	7225
17	Congenital Abnormalities/	27830
18	Pregnancy, Prolonged/	2156
19	((Fertili?ation adj3 in adj3 vitro) or maternal age or parity or (previous adj3 fetal death) or congenital abnormalit*).tw.	43296
20	((maternal adj3 thyroid disease*) or (maternal adj3 diabetes) or (maternal adj3 epilepsy)).tw.	1816
21	(pre-eclampsi* or eclampsi*).tw.	8805
22	(placenta disease* or ((premature or preterm) adj3 birth*) or bleeding in pregnancy or (intrauterine adj3 growth restriction) or fetal growth retardation).tw.	14328
23	or/4-8,11-22	425143
24	3 and 23	1855

Appendix 4 The Cerebral palsy Registry of Norway Registration form (2003-2006)

SKJEMA FOR KARTLEGGING AV BARN MED CEREBRAL PARESE

Returadresse: Dr. Guro L. Andersen, Habiliteringstjenesten, Barneseksjonen, SiV, Postboks 1209 Trudvang, 3105 TØNSBERG

1. **Barnets fødselsnummer** ☐☐☐☐☐☐ ☐☐☐☐☐ (dato / personnummer)
2. **Er samtykkeerklæring undertegnet?** 1 ☐ Ja
3. **Alder ved CP diagnose (i måneder)** ☐☐☐
4. **Postneonatal årsak?** 0 ☐ Nei 1 ☐ Ja

   Beskriv (Diagnose ICD-10): _____

   _____
5. **Alder ved postneonatal årsak (i måneder)** ☐☐☐
6. **Barnets status i dag** 0 ☐ Død 1 ☐ Levende
7. **Hvis død, evt. dødsdato** ☐☐ ☐☐ ☐☐ (dag / måned / år)
8. **Siste registreringsdato (dato for siste kliniske undersøkelse)** ☐☐ ☐☐ ☐☐ (dag / måned / år)
9. **CP klassifisering** (I parentes ICD-10 kode)

Spastisk unilateral	1 ☐	Hø hemiplegi (G 80.2)
	2 ☐	Ve hemiplegi (G 80.2)
Spastisk bilateral	3 ☐	Diplegi (G 80.1)
	4 ☐	Kvadriplegi (G 80.8)
Dyskinetisk	5 ☐	Dystoni (redusert aktivitet, tendens til økt tonus) (G 80.3)
	6 ☐	Choreo-atetose (økt aktivitet, tendens til nedsatt tonus) (G 80.3)
Ataxi	7 ☐	(G 80.4)
Ikke klassifiserbar/ blandingsformer	0 ☐	(G 80.9)

10. Håndfunksjon ho hånd

0 ☐ Normal funksjon
1 ☐ Lette motoriske tegn påvisbare, men tilnærmet normal funksjon.
2 ☐ Tydelig nedsatt funksjon
3 ☐ Alvorlig nedsatt funksjon, (lite funksjonelle bevegelser)
7 ☐ Vet ikke

11. Håndfunksjon ve hånd

0 ☐ Normal funksjon
1 ☐ Lette motoriske tegn påvisbare, men tilnærmet normal funksjon.
2 ☐ Tydelig nedsatt funksjon
3 ☐ Alvorlig nedsatt funksjon, (lite funksjonelle bevegelser)
7 ☐ Vet ikke

12. Gangfunksjon

0 ☐ Normale forhold
1 ☐ Motoriske tegn påvisbare ,men går uten hjelpemidler
2 ☐ Går med hjelpemidler
3 ☐ Kan ikke gå, selv med hjelpemidler; avhengig av rullestol
7 ☐ Vet ikke

13. Alder når barnet begynte å gå (i måneder)

☐☐☐

14. Sitte funksjon

0 ☐ Normal, sitter stabilt
1 ☐ Lett funksjonsnedsettelse, sitter litt ustabilt
2 ☐ Sitter kun med støtte
3 ☐ Kan ikke sitte, selv med støtte
7 ☐ Vet ikke

15. Scoliose

0 ☐ Ingen
1 ☐ Lett (fleksibel, korrigerbar)
2 ☐ Moderat (fleksibel, korrigerbar)
3 ☐ Alvorlig (fiksert, ikke korrigerbar)
7 ☐ Vet ikke

16. Intellektuell fungering

0 ☐ Normal (IQ ≥ 85)
1 ☐ Generelle lærevansker (IQ 70-84)
2 ☐ Lett utviklingshemming (IQ50-69)
4 ☐ Moderat-dyp utviklingshem. (IQ <50)
7 ☐ Ukjent

17. IQ testet?

0 ☐ Nei, klinisk vurdering
1 ☐ Ja
2 ☐ Nei, ikke testbar
7 ☐ Vet ikke

18. Alder ved IQ-test (i måneder) ☐☐☐

Spesifiser test og testresultat:

Kommunikasjonsform (barnets uttrykksmåte)

19. Talespråk (Talefunksjon)

0 ☐ Normal tale *(Gå til spørsmål 22)*
1 ☐ Talen lett utydelig
2 ☐ Talen utydelig, dog forståelig
3 ☐ Talen meget utydelig, vanskelig å forstå
4 ☐ Intet talespråk
7 ☐ Vet ikke

20. Tegnspråk (signaler, gester). Motorisk utførelse

0 ☐ Bra utført, lett å forstå
1 ☐ Lett utydelige tegn
2 ☐ Utydelige tegn, dog forståelig
3 ☐ Meget utydelige tegn, vanskelig å forstå
4 ☐ Intet tegnspråk
7 ☐ Vet ikke

21. Grafisk kommunikasjon. Type

0 ☐ Skriver
1 ☐ Pictogram (PCS/Rebus)
2 ☐ Bilder
4 ☐ Bruker ikke grafisk kommunikasjon
7 ☐ Vet ikke

22. Språkforståelse

0 ☐ Normal, forstår tale
1 ☐ Lett nedsatt, forstår enkel tale (dagligtale)
2 ☐ Moderat nedsatt, forstår signalord eller gester/tegn
4 ☐ Forstår ikke tale
7 ☐ Vet ikke

23. Synshemming

0 ☐ Normalt syn
1 ☐ Nedsatt syn
4 ☐ Alvorlig nedsatt syn (blind eller ikke brukbart syn)
7 ☐ Vet ikke

24. Hørselhemming

0 ☐ Normal hørsel
1 ☐ Lett hørselsnedsettelse
4 ☐ Alvorlig hørselsnedsettelse, fungerer som døv
7 ☐ Vet ikke

25. Epilepsi? (Definert som 2 uprovoserte anfall/ krampeanfall ekskl. febrile eller neonatale kramper) 0 ☐ Nei 1 ☐ Ja

26. Hvis ja, bruker barnet antiepileptika nå? 0 ☐ Nei 1 ☐ Ja

27. Ernæring (sett evt. flere kryss)

0 ☐ Spiser selv
1 ☐ Spiser med hjelp (delvis)
2 ☐ Må mates (oralt)
3 ☐ Sondeernæres delvis
4 ☐ Sondeernæres i hovedsak
7 ☐ Vet ikke

28. Gastrostomi PEG/MicKey? 0 ☐ Nei 1 ☐ Ja

Naturlige funksjoner

29. Urin

0 ☐ Kontinent
4 ☐ Inkontinent
7 ☐ Vet ikke

30. Avføring

0 ☐ Kontinent
4 ☐ Inkontinent
7 ☐ Vet ikke

31. Postneonatal cerebral MR-undersøkelse? 0 ☐ Nei 1 ☐ Ja 7 ☐ Vet ikke

32. Andre diagnoser (syndromer, kromosomfeil, medfødte misdannelser eller andre cerebrale diagnoser):

ICD-10 ☐ ☐☐.☐	
ICD-10 ☐ ☐☐.☐	
ICD-10 ☐ ☐☐.☐	
ICD-10 ☐ ☐☐.☐	
ICD-10 ☐ ☐☐.☐	
ICD-10 ☐ ☐☐.☐	

33. Evt kommentarer

_____

_____

_____

_____

Utfylt av:

DATO: _____

NAVN: _____

STILLING: _____

INSTANS: _____

SKJEMAET SENDES TIL:
Dr. Guro L. Andersen, Habiliteringstjenesten, Barneseksjonen, SiV,
Postboks 1209 Trudvang
3105 TONSBERG

Appendix 5 The birth notification form (1967-Dec 1998)

The Medical Birth Registry of Norway

Sosialdepartementet
Helsedirektoratet
Oslo – Dep.

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut skjema for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet	Barnet ver 1 ☐ Levende født 2 ☐ Dødfødt foster	Født dag, mnd., år	Klokkeslett	Personnr.	Skriv ikke her
	1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling		Kjønn 1 ☐ Gutt 2 ☐ Pike		
	Etternavn, alle fornavn (bare for levendefødte)				
	Fødested. Navn og adresse på sykehuset/fødehjemmet		Kommune		
Faren	Etternavn, alle fornavn		Født dag, mnd., år	Bostedskommune	
Moren	Etternavn, alle fornavn. Pikenavn			Født dag, mnd., år	
	Bosted. Adresse		Kommune		
	Ekteskapelig status 1 ☐ Ugift 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt			Ekteskapsår (gifte)	
	Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte	
	Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:				
Morens helse **før** svanger-skapet	1 ☐ Normal 2 ☐ Sykdom (spesifiser):				
			Siste menstruasjons første blødningsdag		
Morens helse **under** svanger-skapet	1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):				
Ble fød-selen provo-sert	1 ☐ Nei 2 ☐ Ja				
Inngrep under fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
	Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor				
Komplika-sjoner i for-bindelse med fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
Fostervann, placenta og navlesnor	1 ☐ Normalt 2 ☐ Patologisk (spesifiser):				
Barnets tilstand	Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja				
	For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:				
	Lengde (i cm)	Vekt (i g)	For døde innen 24 timer Livet varte i	Timer	Min.
	For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen Dødsårsak:				
	Seksjon? 1 ☐ Nei 2 ☐ Ja				
Alvorlige arvelige lidelser i slekten	Sykdommens art og hos hvilke slektninger				

W.J Seip Oul. 150000 11.66. PL 816.

Sted (sykehusets stempel) Dato Jordmor Lege

Appendix 6 SCPE Data Collection Form for Cerebral Palsy

DRAFT SCPE Data Collection Form for Cerebral Palsy — Short Form October 2006 v2

Space for logo **CONFIDENTIAL** **Space for logo**

Name of register/database

	First Name	Last/Family Name	Male/Female	Register ID Number
Name of child			Sex	No.
Date of birth	day / month / year			

CEREBRAL PALSY: DEFINITION

Cerebral palsy is an umbrella term for a group of disorders; is permanent but not unchanging; involves a disorder of movement and/or posture and of motor function; is due to a non progressive interference/lesion/abnormality of the developing immature brain. Children who acquire this condition up to the age of 5 years are also included on the database.

Please refer to the Decision Tree for identifying cerebral palsy in the Reference & Training Manual.

1. Is this child believed to have or suspected of having cerebral palsy? *Please tick ☑ one box*
   - Yes → Go to Question 2
   - No → Enter diagnosis in box below then go to Question 36

Current diagnosis:

2. In what year was the mother born? Year of birth ☐☐☐☐ Not known ☐

3. Number of previous pregnancies resulting in a live birth or stillbirth (excluding miscarriages and therapeutic abortions) None ☐ One ☐ Two ☐ >Two ☐ Not known ☐

4. Hospital of birth ☐ Not known ☐

5. Birthweight (g) ☐☐☐☐ Not known ☐

6. Gestational age (completed weeks) ☐☐ Not known ☐

7. Delivery mode Vaginal delivery ☐ CS elective/ before labour ☐ Emergency/ during labour ☐ Not known ☐

8. Birth number (number of infants born at the same delivery) One ☐ Two ☐ > Two ☐ Not known ☐

9. If from a multiple delivery, what was the birth order of this child? First ☐ Second ☐ Third/higher ☐ Not known ☐

10. What was the Apgar score at 5 minutes? (score 0-10) 5 mins ☐ Not known ☐

11. Was this child admitted to a neonatal care unit? Yes ☐ No ☐ Not known ☐

12. If **Yes**, did the child receive ventilation by respirator or CPAP for ≥ 24 hours? (Exclude mask insufflation or intubation for short duration e.g. in transport) Yes ☐ No ☐ Not known ☐

13. Convulsions withing the first 72 hours? Yes ☐ No ☐ Not known ☐

14. Has imaging been performed? Yes ☐ No ☐ Not known ☐

15. Is there a postneonatal MRI scan available? Yes ☐ No ☐ Not known ☐

Please go to Question 16

1

CEREBRAL PALSY

Register ID Number

TYPE of CEREBRAL PALSY *Please refer to the Classification Tree for sub-types of cerebral palsy in the Reference & Training Manual*

16.
Please tick ☑ the appropriate boxes from the following options.

Spastic bilateral (BSCP) ☐

unilateral (hemiplegia, USCP) ☐

→ *if unilateral spastic, which is the affected side ?* Right ☐ Left ☐

Dyskinetic ☐

→ *if dyskinetic, which type ?* Dystonic ☐ Choreo-athetotic ☐ Not known ☐

Ataxic ☐

Non-classifiable ☐

→ *If non-classifiable, what is the reason ?* SCPE criteria ☐ Not enough information ☐

POSTNEONATAL CEREBRAL PALSY

17.
Do you think it most likely that the cause of the impairment occurred ***AFTER*** the first 27 days of life?

Yes ☐ → *go to Question 18*
No ☐ → *go to Question 20*
Not known ☐ → *go to Question 20*

18. What do you think is the likely cause of this child's motor impairment?

19. If known, please give the **age** at which this occurred **Age in months** ☐☐ **Not known** ☐

Please go to Question 20

2

Register ID Number

GROSS MOTOR FUNCTION CLASSIFICATION (GMFCS) between the 4th and 6th birthdays*

20. Please read each of the following paragraphs and tick the box of the level that most closely describes this child.

Tick ☑ one box

I	Children walk indoors and outdoors, and climb stairs. Emerging ability to run and jump.	1
II	Children walk without the need for any assistive mobility device indoors and for short distances on level surfaces outdoors. Children climb stairs holding onto a railing but are unable to run or jump.	2
III	Children sit on a regular chair but may require pelvic or trunk support to maximize hand function. Children walk with an assistive mobility device on level surfaces and may climb stairs with assistance from an adult. Children frequently are transported when travelling for long distances or outdoors on uneven terrain.	3
IV	Children may at best walk short distances with a walker and adult supervision but have difficulty turning and maintaining balance on uneven surfaces. Children are transported in the community. Children may achieve self-mobility using a power wheelchair.	4
V	Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited.	5

Taken from: Palisano R., Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and validation of a gross motor function classification system for children with cerebral palsy. *Dev Med Child Neurol*, 39, 214-223, 1997.

*If required the Gross Motor Function Classification for **ALL YEARS UP TO AGE 12** can be downloaded from http://www-fhs.mcmaster.ca/canchild/

BIMANUAL FINE MOTOR FUNCTION CLASSIFICATION (BFMF) at minimum age of 4 years

21. Please read each of the following paragraphs and tick the box of the level that most closely describes this child.

Tick ☑ one box

1	One hand manipulates without restriction; other hand manipulates without limitation *OR* has limitations in more advanced fine motor skills.	1
2	One hand manipulates without restriction; other hand has ability only to grasp or hold *OR* both hands have limitations in more advanced fine motor skills.	2
3	One hand manipulates without restriction; other hand has no functional ability *OR* one hand has limitations in more advanced fine motor skills; other hand has ability only to grasp or worse. Child needs help with tasks.	3
4	Both hands have ability only to grasp; *OR* one hand has ability only to grasp; other hand has ability only to hold or worse. Child needs support and/or adapted equipment.	4
5	Both hands have ability only to hold or worse. Child requires total assistance, even with adaptations.	5

Taken from: Beckung E. Hagberg G. Neuroimpairments, activity limitations and participation restrictions in children with cerebral palsy. *Dev Med Child Neurol* 2002;44:309-316.

Please go to Question 22

VISION IMPAIRMENT

Register ID Number

22. Is a **vision impairment** of any type present?
Tick ☑ one box

Yes ☐ → *go to Question 23*
No ☐ → *go to Question 24*
Not known ☐ → *go to Question 24*

23. Does the child use spectacles or other aids to vision? Yes ☐ No ☐ Not known ☐

24. Severe vision impairment (blind or no useful vision, after correction, in the better eye)
If the level of vision loss is <6/60 (Snellen scale) or <0.1 (Decimal scale) in both eyes, this will conform to the SCPE criteria for 'Severe vision impairment', please tick '**Yes**' below.

Does this child have severe vision impairment? Yes ☐ No ☐ Not known ☐

HEARING IMPAIRMENT

25. Is **hearing impairment** present?
Tick ☑ one box

Yes ☐ → *go to Question 26*
No ☐ → *go to Question 27*
Not known ☐ → *go to Question 27*

26. Severe hearing impairment (Severe or profound hearing loss, before correction, in the better ear)
If the level of hearing loss is >70db in both ears, this will conform to the SCPE criteria for 'Severe hearing impairment', please tick '**Yes**' below.

Does this child have severe hearing impairment? Yes ☐ No ☐ Not known ☐

Please go to Question 27

COGNITIVE IMPAIRMENT

Register ID Number

27. Is cognitive impairment present?
Please tick ☑ one box

Yes → *go to Question 28*
No → *go to Question 32*
Not known → *go to Question 32*

28. If **Yes,** please provide an estimate of the level of impairment by ticking ☑ one of the boxes below. An assessment of the degree of cognitive impairment can be made on the behavioural responses of the child

	IQ, if available OR	*Clinical assessment*	
	70 – 84	Borderline/Probable impairment	1
Equivalent to ICD10 Codes F70 to F73	50 – 69	Mild impairment	2
	20 - 49	Moderate/Severe impairment	3
	less than 20	Severe/Profound impairment	4
	<50	Impairment unspecified	5

29. If available, please give results of the most recent developmental test:

30. date of test: day / month / year

31. age (**in months**) at test:

EPILEPSY/SEIZURES

SCPE definition: Two or more unprovoked seizures, ***excluding*** febrile or neonatal seizures.

32. Has this child ever suffered from epilepsy or multiple seizures? *Tick ☑ one box*

Ever → *go to Question 33*
Never → *go to Question 34*
Not known → *go to Question 34*

33. Is the child still on medication for epilepsy/seizures?

Yes ☐ No ☐ Not known ☐

Please go to Question 34

CONGENITAL ANOMALY

Register ID Number

SCPE definition: Associated congenital anomalies should be recorded if listed in Smith's Recognisable Patterns of Human Malformation (5th Edition), Kenneth Lyons MD.

34. Does this child have a congenital anomaly? *Tick ☑ one box*

Yes ☐ → *go to Question 35*

No ☐ → *go to Question 36*

Not known ☐ → *go to Question 36*

35. If **Yes**: please specify:

SYNDROMES

SCPE definition: Associated syndromes should be recorded if listed in Smith's Recognisable Patterns of Human Malformation (5th Edition), Kenneth Lyons MD.

36. Does this child have a syndrome/genetic disorder thought to be the cause of their CP? *Tick ☑ one box*

Yes ☐ *go to Question 37*

No ☐ *go to Question 38*

Not known ☐ *go to Question 38*

37. If **Yes**: please specify:

Comments

If you consider that there is anything unusual or of note in this child's prenatal or perinatal history which is not covered by the previous questions, please record it there

This data collection form is based on the SCPE classification and definition of cerebral palsy (SCPE Collaborative Group. Surveillance of cerebral palsy in Europe: A collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol.* 2000; 42:816-824) with some elements taken from the standard form for recording clinical findings in children with a motor deficit of central origin (Evans *et al*, *Dev Med Child Neurol.* 1989; 31:119-127).

38. **Name of person completing this form (*please use BLOCK capitals*):**

Signed: **Date:**

Centre: **Status:** e.g community paediatrician

Thank you for completing this data collection form, please return it to the address below

Contact details:

Name of register/database:
Address:

Tel:
Fax:
Email:

Paper I

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 12 (2008) 4–13

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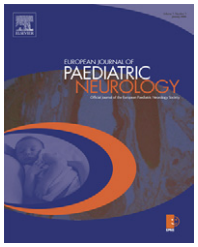

Original article

Cerebral palsy in Norway: Prevalence, subtypes and severity

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ABSTRACT

Background/aim: To describe prevalence, subtypes and severity of cerebral palsy (CP) in Norway using criteria proposed by the Surveillance of Cerebral Palsy in Europe (SCPE) network.

Material: All children in Norway with CP born in January 1996–December 1998 were registered in the Cerebral Palsy Registry of Norway. The Medical Birth Registry of Norway provided the perinatal data.

Results: A total of 374 children with CP were identified with a prevalence of 2.1 per 1000 live births. Detailed information was obtained from 294 (79%) children. Median age at clinical assessment was 6.9 years (range: 1.9–10.2 years). Thirty-three percent of the children had spastic unilateral CP, 49% spastic bilateral, 6% dyskinetic, 5% ataxic CP and 7% were not classified. Severely impaired vision and hearing were present in 5% and 4% of the children, respectively. Active epilepsy was present in 28%, mental retardation in 31% and severely impaired or no speech in 28% children. The most severe impairments in gross motor function were observed in children with low Apgar scores, and the most severe impairments in fine motor function in children born at term, with normal birth weight and low Apgar scores.

Conclusion: Compared with other populations, the prevalence of CP as well as the proportions of subtypes and gross motor impairments were similar, whereas fine motor impairments and associated impairments were more common. The classification of children with mixed forms of CP is still a challenge. Children were more severely affected if Apgar scores were low, and if they were born at term.

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1. Introduction

Cerebral palsy (CP) comprises a group of permanent and non-progressive disorders of movement and posture caused by a central nervous lesion, damage or dysfunction originating early in life (Surveillance of Cerebral Palsy in Europe (SCPE) 2000).[1]

Studies have reported that the prevalence of CP may vary between 1.5 and 3.0 per 1000 live births.[2–8] These differences in prevalence may reflect "true" differences but may also be the result of variations in ascertainment of CP cases or inconsistent definition and classification of CP. We are not aware of other studies comprising a complete national cohort.

Moreover, the subtypes and severity of CP as well as the proportion of patients with associated impairments vary between studies, and this variation is likely to be due to differences in diagnostic criteria and classification.[7,9–15] Recently, a European network, the Surveillance of Cerebral Palsy in Europe (SCPE), has agreed upon a definition of CP, and has suggested a revised classification in subtypes which may be less dependent on individual judgement.[1]

In 2002, the Cerebral Palsy Registry of Norway (CPRN), comprising data of all children with CP born in 1996 onwards, was established in Norway. As essentially all children with CP are diagnosed and treated at public hospitals or habilitation centres, Norway may be well suited for population-based studies. Moreover, the child neurologists who diagnose and are responsible for the medical follow-up are relatively few in number and have a well-established network enabling agreement on definitions and classification. Finally, the Medical Birth Registry of Norway (MBRN) established in 1967 provides essential perinatal data on risk factors for CP as well as perinatal survival.

In this article, we want to report the first results of CPRN. The aims are to describe (a) prevalence of CP in Norwegian children born in 1996–1998; (b) relative proportions of CP subtypes based on the SCPE classification system; (c) severity of CP; (d) occurrence of associated impairments and (e) associations between CP subtypes, severity and associated impairments on one hand and gestational age, birth weight and Apgar scores on the other.

2. Materials and methods

All Norwegian children with a diagnosis of CP born between January 1, 1996 and December 31, 1998 were eligible for registration. Data were collected between January 1, 2003 and March 31, 2006.

2.1. *Case ascertainment*

In Norway, all children with severe neurological disorders are treated in public hospitals, and each of the 20 counties has one habilitation centre caring for children with CP. All centres were invited to take part in the study providing summary and individual data. Summary data, based upon the habilitation centres' own data recording systems, were mainly the number of children with CP, including children who had died. These data were used to calculate the overall prevalence, and to validate case ascertainment. The diagnosis was confirmed when the children were at least 4 years.

The individual data were collected by a senior paediatrician in a standardised form. In principal, registration was based upon the definition and classification agreed upon by the Surveillance of Cerebral Palsy in Europe in 1999 (SCPE 2000).[1] A decision tree for inclusion and exclusion of cases and a hierarchical classification tree of CP subtypes developed by SCPE, translated into Norwegian, were distributed to each participating child neurologist in order to ensure consistency. In addition, a CD comprising a Reference and Training Manual, developed by SCPE (Krägeloh-Mann I 2003) was given to all participating professionals. The manual comprised detailed descriptions and definitions of CP and subtypes as well as videos of findings in typical cases. According to the guidelines, CP is divided into spastic, dyskinetic and ataxic subtypes. The spastic subtype is further divided into a unilateral (limbs on one side of the body are involved) and a bilateral (limbs on both sides of the body are involved) type. In this study, spastic unilateral CP was further subdivided into a right and left type depending on whether the right or left side limbs were affected (i.e. right or left hemiplegia). The spastic bilateral type was further subdivided into quadriplegia and diplegia.

2.2. *Gross and fine motor function*

Gross motor function was reported as walking and sitting ability. Walking ability was classified on a four-level scale ranging from normal walking without restrictions (level 0), walking with restrictions but without assistive devices (level 1), walking with assistive devices (level 2) and to children completely unable to walk (level 3).

Sitting ability was classified on a scale from zero to three, where zero indicated stable sitting, one indicated children sitting unstable but not in need of support, two indicated children in need of support, and three indicated children who where unable to sit even with support.

Fine motor function was described as hand function in each hand separately on a scale from zero to three. Zero indicated normal hand function, one minor motor signs, but nearly normal function, two obviously reduced function and three indicated severely reduced hand function (no useful function).

We used the recorded walking and sitting ability to assess gross motor function according to Gross Motor Function Classification System (GMFCS).[16–18] Walking ability zero or one corresponded to GMFCS levels I–II. Walking ability two corresponded to GMFCS level III. Walking ability three and sitting ability one or two corresponded to GMFCS level IV. Walking ability three and sitting ability three corresponded to GMFCS level V. Gross motor function was further dichotomised by defining GMFCS levels I–III as being "good" and GMFCS levels IV–V as being "poor" function.

We used the recorded information on hand function on each side to estimate Bimanual Fine Motor Function (BFMF) as indicated in Table 1.[13] Consistent with the dichotomisation of

Table 1 – Bimanual fine motor function estimated from recording of hand function in each hand separately

	Normal function left hand	Minor motor signs, but almost normal function in left hand	Obviously impaired function in left hand	Severely impaired function in left hand (no useful function)
Normal function right hand	BFMF I	BFMF I	BFMF II	BFMF III
Minor motor signs, but almost normal function in right hand	BFMF I	BFMF II	BFMF III	BFMF III
Obviously impaired function in right hand	BFMF II	BFMF III	BFMF IV	BFMF IV
Severely impaired function in right hand (no useful function)	BFMF III	BFMF III	BFMF IV	BFMF V

gross motor function, BFMF levels I–III was defined as "good" and BFMF levels IV–V was defined as "poor" function.

2.3. *Associated impairment*

Cognitive development was assessed by a cognitive test or by clinical judgement.

The results were described as normal (i.e. IQ level $\geqslant$85), general learning difficulties (i.e. IQ level 70–84), mildly retarded (i.e. IQ level 50–69), moderately to severely retarded (i.e. IQ level $<$50) or unknown. Mental retardation was defined as IQ below 70.

Feeding ability was classified on a scale from being independent (0), in need of some assistance (1), totally dependent on assistance (2), partly tube fed (3) to mainly tube fed (4). The presence of gastrostomy was also recorded.

Communication was recorded as verbal communication (i.e. speech), sign language and language understanding. Speech was classified on scale from zero to four where zero indicated normal speech, one indicated indistinct speech, two indicated obviously indistinct speech, three indicated severely indistinct speech difficult to understand and four indicated children without speech. For children using graphic communication, the type was recorded (writing, pictogram, pictures).

Vision was described as normal, impaired or severely impaired (i.e. no useful vision on the better eye, with correction, or when functional blindness occurred). Hearing was described as normal, impaired or severely impaired (i.e. the child considered functional deaf).

Epilepsy was defined as two unprovoked seizures, excluding febrile or neonatal seizures. Use of antiepileptic drugs was recorded and epilepsy was considered active when the child at the time of registration was taking an antiepileptic drug.

2.4. *Risk factors*

Obstetric and perinatal data were obtained from the MBRN.

2.5. *Ethics*

The study was approved by the Regional Ethical Committee (REC) for Medical Research in Mid-Norway, and by the Norwegian Data Inspectorate. The individual registration of data and the linkage of data to the MBRN required consent by the parents.

2.6. *Statistical methods*

The statistical package for social sciences (SPSS) for Windows version 12.0.1 (SPSS Inc., Chicago, IL) was used for data analysis, and a significance level of 0.05 was chosen. The χ^2-test or Fisher's exact test were used to analyse differences in proportions between groups. Correlations between severity of gross and fine motor impairment with perinatal data were analysed using Spearman's rank correlation coefficient. We used Kappa statistics to compare the classification of children with bilateral CP in being quadriplegic or diplegic with a classification of the same children based upon the severity of motor impairment in "poor" or "good". By convention, a kappa value of higher than 0.80 suggests excellent agreement, 0.60–0.80 good, 0.40–0.60 moderate, 0.20–0.40 fair and a kappa value below 0.20 suggests poor agreement.[19]

3. Results

In all, 374 children born in 1996–1998 were identified with CP corresponding to a prevalence of 2.1 per 1000 live births. Detailed data were recorded for 294 (79%) of these children, 149 (50.7%) boys and 145 (49.3%) girls. Fifteen (5%) children were born abroad and 19 (6%) had a postneonatal cause. Median age at diagnosis was 15 months (range: 0–100 months) and median age at clinical assessment was 6.9 years (range: 1.9–10.2 years).

3.1. *Subtypes of CP*

Of the 294 children, 96 (33%; 95% CI: 28–39) had the spastic unilateral CP type, 143 (49%; 95% CI: 41–53) the spastic bilateral, 19 (6%; 95% CI: 4–10) the dyskinetic and 15 (5%;

95% CI: 3–8) the ataxic type. In 21 (7%; 95% CI: 4–11), the subtype could not be classified by the referring centre. These were recorded as non-classified.

3.2. Gross and fine motor function

Table 2 shows gross and fine motor function. Altogether, 161 (55%) children were able to walk independently. Median age when these started to walk was 22 months (range: 10–77 months). Another 46 (16%) children were able to walk with assistive devices and the median age when they started to walk was 36 months (range: 18–80 months). Eighty-three (29%) children were unable to walk, 17 of 19 children with dyskinetic and 54 (38%) of 141 children with bilateral spastic CP.

Severely impaired gross motor function (GMFCS: IV–V) was present in 1 (1%) child with unilateral CP compared with 53 (38%) children with bilateral ($p<0.01$) and 16 (89%) of children with dyskinetic CP ($p<0.01$ vs. unilateral).

BFMF was estimated to level IV or V in 97 (35%) children. In children with spastic bilateral CP 61 (44%) had level IV or V and in children with dyskinetic CP all except one had level IV or V ($p<0.01$). Among 61 children with BFMF level I 26 (42%) had normal function in both hands. Twenty-one of these 26 children had spastic bilateral CP, all spastic diplegia.

3.3. Risk factors

Table 3 shows the occurrence of CP subtypes according to birth weight, gestational age and Apgar scores. Informed consent to link the child's clinical data to the MBRN was obtained for all 294 children. Gestational age (GA) was recorded in the MBRN in 236 (80%) children, birth weight (BW) in 264 (90%) and Apgar score at 1 min in 261 (89%) and at 5 min in 256 (87%) children.

3.3.1. Gestational age

Of all children, 124 (53%) were born at term and 28 (12%) children were born before 28 weeks of gestation. In the general Norwegian population, 93% of children were born at term, and 0.9% were born before week 28 of gestation in 1998.[20] A lower proportion, 43/116 (38%), of children with spastic bilateral CP was born at term compared with 81/120 (68%) of the other subtypes ($p<0.01$), and a higher proportion of children with dyskinetic and ataxic CP were born at term ($p<0.01$ vs. other subtypes).

Table 2 – Gross and fine motor function in 294 children with cerebral palsy

	CP subtype					
	Unilateral N (%)	Bilateral N (%)	Dyskinetic N (%)	Ataxic N (%)	Not classified N (%)	Total N (%)
Walking ability						
Walks without restrictions	3 (3)	0	0	0	1 (5)	4 (1)
Walks without assistive devices	87 (92)	52 (37)	0	12 (80)	6 (29)	157 (54)
Walks with assistive devices	4 (4)	35 (25)	2 (10)	3 (20)	3 (14)	46 (16)
Unable to walk, in need of wheelchair	1 (1)	54 (38)	17 (90)	0	11 (52)	83 (29)
Total	95 (100)	141 (100)	19 (100)	15 (100)	21 (100)	290 (100)
Sitting ability[a]						
Sits stable	88 (94)	47 (31)	0 (0)	8 (53)	7 (33)	150 (52)
Mild impairment, sits a little unstable	6 (6)	50 (33)	1 (5)	7 (47)	3 (14)	67 (23)
Sits only with support	0	39 (26)	12 (67)	0	8 (38)	49 (17)
Unable to sit, even with support	0	15 (10)	5 (28)	0	3 (14)	23 (8)
Total	94 (100)	151 (100)	18 (100)	15 (100)	21 (100)	289 (100)
GMFCS level[b]						
GMFCS 1 or 2	90 (95)	51 (36)	0	12 (80)	7 (33)	160 (55)
GMFCS 3	4 (4)	36 (26)	2 (11)	3 (20)	3 (15)	48 (17)
GMFSC 4	1 (1)	38 (27)	11 (61)	0	8 (38)	58 (20)
GMFCS 5	0	15 (11)	5 (28)	0	3 (14)	23 (8)
Total	95 (100)	140 (100)	18 (100)	15 (100)	21 (100)	289 (100)
BFMF level[c]						
BFMF level I	29 (32)	29 (21)	0	1 (8)	2 (10)	61 (21)
BFMF level II	44 (48)	39 (28)	0	7 (54)	4 (19)	94 (33)
BFMF level III	18 (20)	10 (7)	1 (5)	0	3 (14)	32 (11)
BFMF level IV	1 (1)	30 (22)	4 (21)	4 (31)	5 (24)	44 (16)
BFMF level V	0	31 (22)	14 (74)	1 (8)	7 (33)	53 (19)
Total	92 (100)	139 (100)	19 (100)	13 (100)	21 (100)	284 (100)

[a] One unilateral unknown.
[b] Gross Motor Function Classification System levels estimated from walking and sitting abilities.
[c] Bimanual Fine Motor Function levels estimated from hand function in each hand separately.

Tabel 3 – Children with CP born in Norway 1996–1998 according to CP subtype by gestational age (GA), birth weight (BW) and Apgar score

	Unilateral N (%)	Bilateral N (%)	Dyskinetic N (%)	Ataxic N (%)	Not classified N (%)	Total N (%)
GA						
GA <28 weeks	7 (10)	18 (16)	1 (6)	1 (7)	2 (5)	29 (12)
GA 28–32 weeks	6 (9)	29 (25)	1 (6)	0	3 (16)	39 (17)
GA 32–36 weeks	10 (15)	26 (22)	2 (11)	2 (15)	4 (21)	44 (19)
GA ⩾37 weeks	45 (66)	43 (38)	14 (81)	11 (79)	11 (58)	124 (53)
Total	68 (100)	116 (100)	18 (100)	14 (100)	20 (100)	236 (100)
Birthweight						
BW <1000 g	6 (7)	13 (11)	1 (6)	1 (7)	2 (10)	23 (9)
BW 1000–1499 g	10 (12)	28 (22)	1 (6)	0	2 (10)	41 (16)
BW 1500–2499 g	14 (17)	40 (32)	1 (6)	1 (7)	5 (24)	61 (23)
BW ⩾2500 g	53 (64)	45 (36)	16 (84)	13 (87)	12 (57)	139 (53)
Total	83 (100)	126 (100)	19 (100)	15 (100)	21 (100)	264 (100)
Apgar (1 min)						
Apgar 0–3	8 (10)	25 (20)	9 (50)	3 (21)	8 (40)	53 (20)
Apgar 4–6	10 (12)	34 (27)	5 (28)	1 (7)	4 (20)	54 (21)
Apgar 7–10	64 (78)	67 (53)	4 (22)	11 (73)	8 (40)	154 (59)
Total	82 (100)	126 (100)	17	15 (100)	20 (100)	261 (100)
Apgar (5 min)						
Apgar 0–3	3 (4)	11 (9)	5 (29)	1 (7)	4 (21)	24 (9)
Apgar 4–6	5 (6)	21 (17)	6 (35)	2 (13)	4 (21)	38 (15)
Apgar 7–10	74 (90)	91 (75)	6 (35)	12 (80)	11 (58)	194 (76)
Total	82 (100)	123 (100)	17 (100)	15 (100)	19 (19)	256 (100)

3.3.2. *Birth weight*

A birth weight ⩾2500 g was found in 139 (53%) children compared with 95% in the total population, and 23 (9%) had BW below 1000 g, against 0.9% in the total population.[20] A lower proportion of children with bilateral CP had birth weight ⩾2500 g compared with the other subtypes ($p<0.01$).

3.3.3. *Apgar scores*

A higher proportion of children with dyskinetic CP had low Apgar scores (0–3) at 1 and 5 min compared with all other subtypes ($p<0.05$). Among children with bilateral CP, low Apgar scores (0–3) at 1 min were more common than among children with the unilateral subtype ($p<0.05$).

Severity of impairments in gross motor function (Table 4) was not associated with gestational age or birth weight, but increased with decreasing Apgar score at 1 (Spearman's $\rho=-0.30$; $p<0.01$) and 5 min (Spearman's $\rho=-0.32$; $p<0.01$). The severity of impairments in fine motor function increased with increasing gestational age (Spearman's $\rho=0.34$; $p<0.01$) and birth weight (Spearman's $\rho=0.32$; $p<0.01$) and with decreasing Apgar score at 1 (Spearman's $\rho=-0.22$; $p<0.01$) and 5 min (Spearman's $\rho=-0.30$; $p<0.01$).

3.4. *Associated impairments (Table 5)*

Cognitive development was assessed by a cognitive test in 85 (29%) children or based upon clinical judgement in 161 (54%) children. In 28 (9%), cognitive development was unknown, in 12 (4%) children, it was not known if a test was performed and in 11 (4%) data on cognitive development were missing. Seventy-five (31%) of the children who had their cognitive development assessed were considered mentally retarded. The proportion of children with mental retardation was higher among children with spastic bilateral than among children with spastic unilateral CP ($p<0.01$).

A higher proportion of children with bilateral spastic CP had severely impaired vision compared with children with unilateral CP ($p<0.05$), whereas there were no differences between the CP subtypes in hearing impairment.

Active epilepsy was found in 18 (19%) children with unilateral CP compared with 8 (42%) with dyskinetic ($p=0.07$) and 42 (30%) children with spastic bilateral CP ($p=0.05$).

Among all children, 201 (72%) had normal or impaired, however, understandable speech. Thirty-one (11%) children communicated with the help of pictures or pictograms, but only 28 (34%) of 82 children with severely or no speech used these communication forms. In children with spastic unilateral CP, 85 (90%) had normal speech, whereas 17 of 19 with dyskinetic CP had severely impaired or no speech ($p<0.01$). However, in the latter group, language understanding was assessed as normal or only slightly impaired in 14 children.

Only one child had all of these associated impairments (i.e. mental retardation, severely impaired vision, severely impaired hearing, impaired speech and active epilepsy).

Table 4 – Severity of impairments in gross and fine motor function in children with CP by gestational age (GA), birth weight (BW) and Apgar score

	Estimated GMFCS[a]				Estimated BFMF[b]			
	I–II N (%)	III N (%)	IV–V N (%)	Total N (%)	I–II N (%)	III N (%)	IV–V N (%)	Total N (%)
GA								
GA <28 weeks	15 (54)	5 (18)	8 (29)	28 (100)	19 (70)	3 (11)	5 (19)	27 (100)
GA 28–31 weeks	17 (44)	10 (26)	12 (31)	39 (100)	24 (63)	4 (11)	10 (26)	28 (100)
GA 32–36 weeks	24 (57)	8 (19)	10 (24)	42 (100)	23 (54)	7 (16))	13 (30)	43 (100)
GA ⩾37 weeks	68 (55)	16 (13)	39 (32)	123 (100)	50 (42)	14 (12)	55 (46)	119 (100)
BW								
BW <1000 g	14 (64)	3 (14)	5 (23)	22 (100)	15 (71)	3 (14)	3 (12)	21 (100)
BW 1000–1499 g	20 (49)	11 (27)	10 (24)	41 (100)	26 (65)	4 (10)	10 (25)	40 (100)
BW 1500–2499	32 (53)	10 (17)	18 (30)	60 (100)	39 (64)	5 (8)	17 (28)	61 (100)
Vekt ⩾2500 g	79 (58)	19 (14)	39 (29)	137 (100)	58 (44)	18 (14)	57 (43)	133 (100)
Apgar (1 min)								
Apgar 0–3	16 (31)	10 (19)	26 (50)	52 (100)	17 (33)	3 (6)	31 (61)	51 (100)
Apgar 4–6	27 (51)	8 (15)	8 (34)	53 (100)	30 (57)	7 (13)	16 (30)	53 (100)
Apgar 7–10	100 (66)	25 (16)	27 (18)	152 (100)	89 (60)	20 (14)	39 (26)	148 (100)
Apgar (5 min)								
Apgar 0–3	4 (17)	5 (22)	14 (61)	23 (100)	3 (13)	1 (4)	19 (83)	23 (100)
Apgar 4–6	15 (40)	7 (18)	16 (42)	38 (100)	16 (44)	5 (11)	16 (44)	36 (100)
Apgar 7–10	123 (64)	30 (16)	38 (20)	191 (100)	114 (61)	25 (13)	49 (26)	188 (100)

[a] GA was available in 232 children, BW in 260, Apgar 1 in 257 and Apgar 5 in 252 children who had their GMFCS assessed.
[b] GA was available in 227 children, BW in 255, Apgar 1 in 252 and Apgar 5 in 247 children who had their BFMF assessed.

In contrast, 81 (28%) children had solely a motor impairment. A higher proportion of children with unilateral CP (43/96 (45%)) had motor impairment only compared with 35 (24%) of 143 children with bilateral CP ($p<0.01$), 2 (13%) of 15 children with ataxic ($p<0.05$) and 1 (5%) of 21 children with non-classified CP ($p<0.01$). No children with dyskinetic CP had motor impairment only. Sixty-six (82%) of these 81 children without associated impairment had GMFCS levels I–II, 8 (10%) had level III and 6 (7%) had level IV. An even stronger association was found for fine motor function with 71 (87%) children with BFMF levels I–II, 4 (5%) with level III and 3 (4%) with level IV.

A total of 101 (34%) children were unable to eat independently and needed help from a care taker, either for oral feeding ($N = 66$), or for tube feeding partly or mainly ($N = 35$). Among children with dyskinetic CP, 8 (40%) of 20 had gastrostomy, compared with 26 (19%) of 139 children with spastic bilateral CP ($p<0.05$).

There were no differences in the distribution of associated impairments by gestational age except for epilepsy being present in a higher proportion of children born at term ($p<0.01$ vs. children born <32 weeks) (data not shown).

3.5. *CP subtypes*

3.5.1. *Unilateral spastic CP*

Among the 96 children with unilateral spastic cerebral palsy, the extremities on the right side were affected (right-sided hemiplegia) in 52 (54%) and on the left side (left-sided hemiplegia) in 44 (46%) children. There were no major differences in right and left unilateral CP in cognitive development, speech abilities, vision, hearing, epilepsy or feeding. Fine motor function of the non-affected hand was normal in all children classified as right unilateral CP. However, in the children classified as left unilateral CP, the function in the non-affected hand was impaired in six (14%) ($p<0.05$ vs. right unilateral).

3.5.2. *Bilateral CP*

Among children with bilateral spastic CP, more severe impairments in gross motor function were associated with increasing birth weight (Fig. 1a; Spearman's $\rho = 0.20$; $p<0.05$) and decreasing Apgar score at 5 min (Spearman's $\rho = -0.20$; $p<0.05$), however not with gestational age (Fig. 2a; Spearman's $\rho = 0.16$; $p = 0.09$) or with Apgar score at 1 min (Spearman's $\rho = -0.10$; $p = 0.25$).

More severe impairments in fine motor function were associated with increasing birth weight (Fig. 1b; Spearman's $\rho = 0.32$; $p<0.01$) and gestational age (Fig. 2b; Spearman's $\rho = 0.34$; $p<0.01$), with decreasing Apgar score at 5 min (Spearman's $\rho = -0.20$; $p<0.05$), but not with Apgar score at 1 min (Spearman's $\rho = -0.07$; $p = 0.44$).

Among children with spastic bilateral CP 25 (71%) of 35 children born before 32 weeks of gestation had normal IQ compared with 12 (34%) of 35 children born at term ($p<0.01$). Thirty-seven (84%) of 44 children born before 32 weeks had normal or only slightly impaired speech compared with 17 (40%) of 43 children born at term ($p<0.01$).

Among the children with spastic bilateral CP, 99 were diplegic and 44 were quadriplegic. Instead of using these

Table 5 – Associated impairments in 294 children with CP

	CP subtypes					
	Unilateral N (%)	Bilateral N (%)	Dyskinetic N (%)	Ataxi N (%)	Not classified N (%)	Total N (%)
Mental retardation[a]						
No	75 (89)	72 (61)	7 (47)	5 (56)	6 (43)	165 (69)
Yes	9 (11)	46 (39)	8 (53)	4 (44)	8 (57)	75 (31)
Speech						
Normal	85 (90)	78 (56)	0	9 (60)	7 (35)	179 (62)
Impaired, understandable	7 (7)	13 (9)	2 (7)	4 (27)	2 (10)	28 (10)
Severely impaired/no	2 (2)	49 (35)	17 (90)	2 (13)	11 (55)	82 (28)
Vision[b]						
Normal/impaired	91 (98)	120 (92)	19 (100)	15 (100)	16 (89)	261 (95)
Severely impaired	2 (2)	11 (8)	0	0	2 (11)	15 (5)
Hearing[c]						
Normal/impaired	90 (98)	128 (95)	17 (94)	14 (93)	19 (95)	268 (96)
Severely impaired	2 (2)	7 (5)	1 (6)	1 (7)	1 (5)	12 (4)
Active epilepsy						
No	76 (81)	96 (70)	11 (58)	11 (73)	13 (62)	207 (72)
Yes	18 (19)	42 (30)	8 (42)	4 (27)	8 (38)	80 (28)
Feeding						
Independent	87 (92)	80 (57)	1 (6)	12 (80)	7 (33)	188 (65)
Dependent	8 (8)	59 (42)	17 (94)	3 (20)	14 (67)	101 (35)
Gastrostomi						
No	89 (98)	113 (81)	12 (60)	14 (93)	16 (76)	244 (85)
Yes	2 (2)	26 (19)	8 (40)	1 (7)	5 (24)	42 (15)

[a] Mental status was unknown in 42 children, 8 of these had unilateral, 19 bilateral, 3 dyskinetic, 6 ataxic and 6 unclassified CP.
[b] Vision was unknown in 13 children, 1 had unilateral, 10 bilateral and 2 unclassified CP.
[c] There were 1 unknown in the unilateral, 8 in the bilateral and 1 in the dyskinetic group.

terms, SCPE has proposed to further describe children with bilateral CP by their gross (GMFCS) and fine (BFMF) motor abilities. According to our definition, 87 of the children with spastic bilateral CP had "good" gross motor function, 76 had "good" fine motor function, 53 had "poor" gross motor and 63 had "poor" fine motor function. Kappa values suggested good agreement in the classification of children as diplegic or quadriplegic and "good" or "poor" gross ($\kappa = 0.69$) or fine ($\kappa = 0.72$) motor function.

4. Discussion

In this study, we found that the prevalence of CP as well as the proportions of subtypes and severity were essentially the same as in other populations.[1,2,7,9,12] However, fine motor function may be more severely impaired and associated impairments may be more common in Norway than in some other populations.[7,14,15] The different proportions of dyskinetic CP reported in other studies are probably due to differences in classification. The severity of gross motor function was not associated with gestational age or birth weight. In contrast, the severity of fine motor impairment increased with increasing gestational age and birth weight. The impairments of both fine and gross motor function increased with decreasing Apgar scores.

To standardise the recordings as much as possible, the reporting clinicians were thoroughly informed of the SCPE guidelines on definition and subclassification in a number of meetings and by receiving the R&T Manual. It may thus be considered a strength of the study that the assessments of the children were done by these clinicians who themselves examined the patients. The prospective recording of perinatal data is another strength of the study making information or recall bias unlikely. It may be considered a limitation of the study that we received individual data on only 79% of the children. However, only six (2%) parents refused to let details of their child be recorded. Lack of data was mainly (67%) due to poor response from 4 of the 20 counties. Thus, selection bias is less likely and we consider the data on distribution of subtypes and severity to be representative of the total CP population in Norway.

The prevalence of CP has been reported to vary between 1.5 and 3 per 1000 live borns, and our results are consistent with this.[1,2,7,9,12] Due to the public and homogenous organisation of the care for handicapped children in Norway, we consider the ascertainment of cases to be complete, however, we cannot rule out that we have missed a few cases.

The proportion of children with various subtypes of CP in this study was essentially similar to the proportions reported in other studies.[7,12,14,21]

In children with unilateral spastic CP it may be noteworthy that children with paresis of the left side more often than

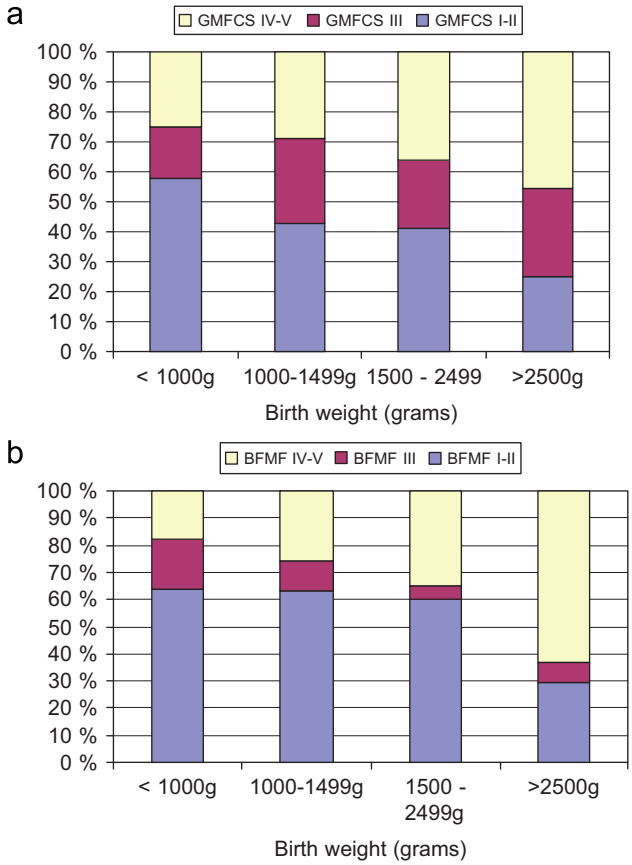

Fig. 1 – Severity of CP and birth weight. (a) Gross motor function classification (GMFCS) and birth weight (grams) in children with spastic bilateral CP. Birth weight is shown in four categories on the *x*-axis. The *y*-axis shows percent of children with estimated GMFCS levels I–II (less severe impairment), III (intermediate impairment) and IV–V (most severe impairment). (b) Bimanual fine motor function (BFMF) and birth weight (grams) in children with spastic bilateral CP. Birth weight is shown in four categories on the *x*-axis. The *y*-axis shows percent of children with estimated BFMF levels I–II (less severe impairment), III (intermediate impairment) and IV–V (most severe impairment).

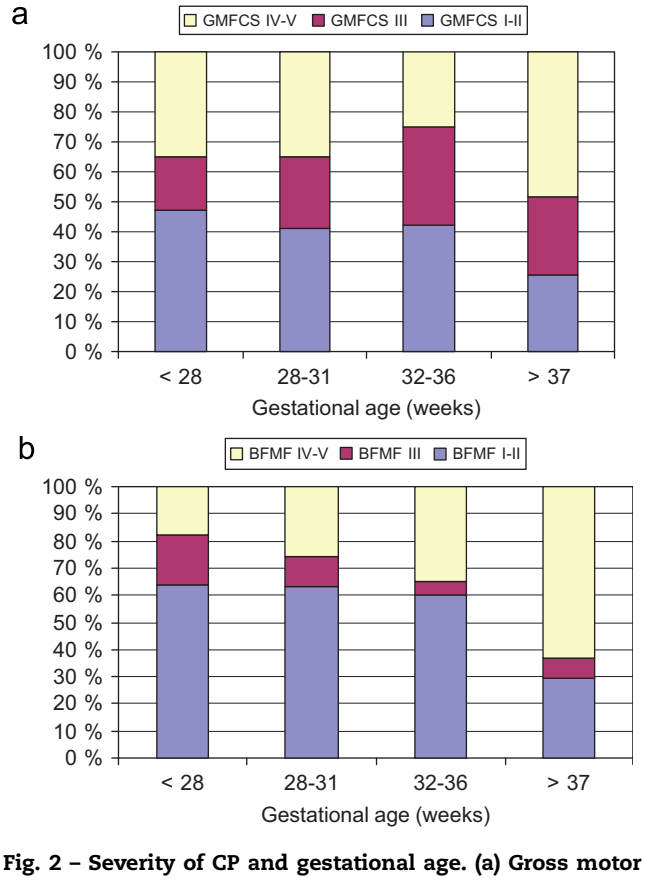

Fig. 2 – Severity of CP and gestational age. (a) Gross motor function classification (GMFCS) and gestational age (GA) in children with spastic bilateral CP. Gestational age is shown in four categories on the *x*-axis. The *y*-axis shows percent of children with estimated GMFCS levels I–II (less severe impairment), III (intermediate impairment) and IV–V (most severe impairment). (b) Bimanual fine motor function (BFMF) and gestational age (GA) in children with spastic bilateral CP. Gestational age is shown in four categories on the *x*-axis: $<$28, 28–31, 32–36 and $\geqslant$37 weeks. The *y*-axis shows percentage of children with estimated BFMF levels I–II (less severe impairment), III (intermediate impairment) and IV–V (most severe impairment).

children with paresis of the right side had impaired hand function on the non-affected side. Other authors have also reported that children with hemiplegia may have impairment in bimanual coordination beyond their unilateral impairments, although they did not report differences between paresis on the left- and the right side.[22] It may thus be questioned whether such children should indeed have been classified as bilateral CP; however, impairments of the non-affected side were mild in our study.

Children with bilateral spastic CP were further characterised by the severity of motor impairments and by using the traditional diagnoses of diplegia and quadriplegia. When we compared these two different ways of characterising children with bilateral CP, we found good agreement in the classification of children with less severe motor impairments (i.e. GMFCS or BFMF levels I–III) and diplegia, and between those with more severe motor impairments (i.e. GMFCS or BFMF levels IV–V) and quadriplegia. However, the proportion of children with quadriplegic CP in our study (15%) was lower than reported in one study from Australia (32%),[12] whereas it was higher than in two studies from western Sweden (6% and 10%, respectively).[7,9]

That different classifications explain the different proportions of quadriplegic and dyskinetic cases is also supported by the differences in proportions of unclassified cases, which was 7% in our compared with none in the Swedish studies.[6,9,11] Moreover, the children with non-classified CP in our study had gross and fine motor function and occurrence of associated impairments similar to children with spastic bilateral or dyskinetic CP. It is therefore likely that some of the children in the unclassified group are children with dyskinetic CP *and* spasticity, and that the reporting clinician had difficulties in deciding on the most dominating symptom in cases of mixed forms. Thus, our results suggest that the

discrimination between these two subtypes as proposed by SCPE is still a challenge to clinicians.

Only 8% of the children were not able to walk or to sit even with support, assessed as GMFCS V in our study. Other studies have reported higher proportions of children with GMFCS level V.[9,11,12]

Few studies have so far described fine motor function using BFMF. We found a somewhat higher proportion (35%) of children with BFMF levels IV and V than the 26% reported by Himmelmann et al.[7] This may mainly be due to differences in the recording of the data, since BFMF levels in our study were estimated from descriptions of fine motor function in each hand separately, whereas in the study of Himmelmann et al.,[7] the reporting physicians estimated BFMF levels directly. Moreover, our children were born in 1996–1998 while Himmelmann et al. covered the birth years 1991–1998.[7]

In the present study, the proportion of children without any associated impairment was 28%. Himmelmann et al.[7] reported 48% of children with CP to be without associated impairment; however, they did not include speech impairment. When we excluded speech impairments, we found that 34% of the children had no associated impairment, which is still lower than reported by Himmelmann et al.[7]

There are few reports on speech abilities and language understanding in children with CP. However, the proportion (28%) of children with severely impaired or no speech in our study was higher than the 20% reported in two previous studies.[14,15] Eleven percent of the children used graphic communication, a higher proportion than reported by Chan et al. (3%).[14] The age of the children and the distribution of subtypes is very similar to Chan, but in their study, parents were the informants, in contrast to health professionals in our study. Whereas health professionals may report children who have the necessary equipment, however using this equipment only in specific training sessions, parents are likely to report daily *use* of communication aids.[23] This may in part explain the differences. The severity of associated impairments increased with increasing gross and fine motor impairment, as observed by Himmelmann et al.[7]

Although children born before week 28 of gestation had a substantial increased risk of getting CP, they comprised only 12% of the total CP population. The major part of children with CP was born at term, consistent with most other studies.[11,21,24,27] However, a Swedish study reported that only 35% of children with CP born between 1991 and 1993 were born at term.[9]

More severe impairments in both fine and gross motor function were associated with low Apgar scores, consistent with Moster et al.[28] However, whether severe perinatal stress is the cause, or whether newborns with more severe brain damage tolerate the stress of birth less well, cannot be answered in this study. Moreover, the severity of gross motor impairment was not associated with gestational age or birth weight, whereas severity of fine motor impairment increased with increasing gestational age and birth weight. These findings could be due to variations in the timing and mechanisms of the insult leading to different subtypes of CP with different degrees of severity. However, similar results were observed when we restricted the analyses to children with bilateral CP. The findings may therefore, at least partly, be explained by the hypothesis of selective vulnerability of the periventricular regions of the brain in the 24–34 weeks of pregnancy (watershed areas), and by assuming that children with CP born prematurely have an injury to the brain limited to these areas and therefore have better gross and fine motor function and lesser degree of associative impairments.[25,26] The children with bilateral CP born at term with evidence of a peri- or neonatal hypoxic ischemic event, however, are at risk of more extensive brain injury including the grey matter, cortex and central nuclei and therefore more severe CP involving both upper and lower limbs.[25,26] Our results may thus be consistent with the current opinion that both perinatal stress as well as the timing of an insult play significant roles in determining the severity of impairments in motor function.[29]

We found no differences in the distribution of associated impairments by gestational age except for epilepsy being present in a higher proportion of children born at term. Also Himmelmann et al.[7] found that a higher proportion of children born at term had epilepsy, however, they found that children born <28 weeks of gestation had the highest proportion of all other accompanying impairments. However, when we restricted the analyses to children with the spastic bilateral subtype, we found that more children born at term had mental retardation and severely affected communicative abilities than children born <32 weeks of gestation, and that more severe gross and fine motor function impairment indicated increasing degree of severity of associative impairments. Again, this may be explained by different vulnerability of the immature and the mature brain.[25,26]

In conclusion, the prevalence of CP in Norway as well as the proportions of subtypes and severity were essentially the same as in other populations.[1,2,7,9,12] However, fine motor function may be more severely impaired and associated impairments more common in Norway than in some other populations.[7,14,15] The severity of gross motor function was associated with low Apgar score at 1 and 5 min but not with gestational age or birth weight. In contrast, the severity of fine motor impairment increased with increasing gestational age and birth weight, and with decreasing Apgar score at 1 and 5 min.

The classification of CP proposed by SCPE, supplemented by a description of gross and fine motor function, was a useful tool for recording and describing the panorama of CP in Norway, but the classification of children with mixed forms remains a challenge.

Acknowledgements

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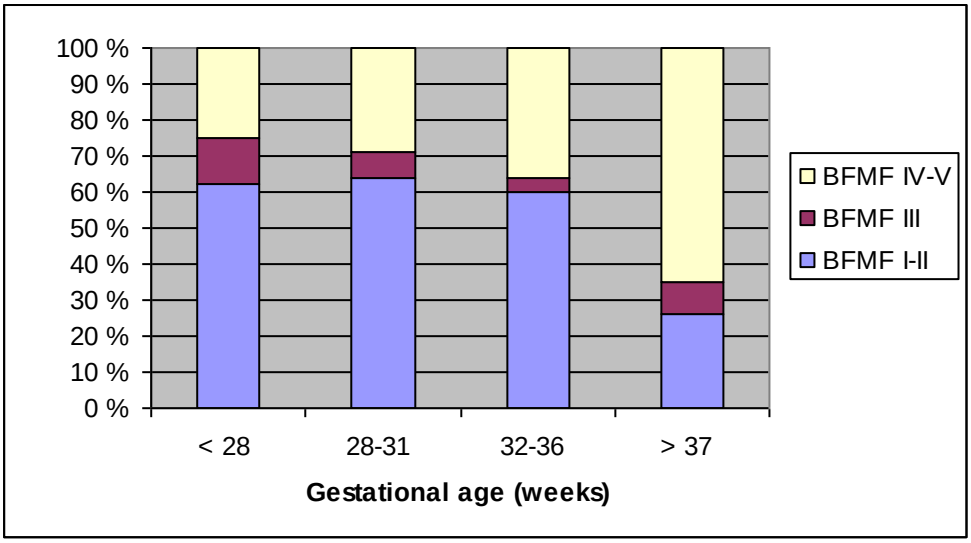
REFERENCES

1. Surveillance of Cerebral Palsy in Europe (SCPE) Collaborative Group. Surveillance of cerebral palsy in Europe: a

collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol* 2000;**42**:816–24.
2. Blair E, Watson L. Epidemiology of cerebral palsy. *Semin Fetal Neonatal Med* 2006;**1**:117–25.
3. Meberg A, Broch H. Etiology of cerebral palsy. *J Perinat Med* 2004;**32**:434–9.
4. Nelson KB. Can we prevent cerebral palsy? *N Engl J Med* 2003;**349**:1765–9.
5. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disab Rehab* 2006;**28**:183–91.
6. Hagberg B, Hagberg G, Beckung E, Uvebrandt P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94. *Acta Paediatr* 2001;**90**:271–7.
7. Himmelmann K, Bechung E, Hagberg G, Uvebrandt P. Gross and fine motor function and accompanying impairments in cerebral palsy. *Dev Med Child Neurol* 2006;**48**:417–23.
8. Mc Manus V, Guillem P, Surman G, Cans C. SCPE work, standardisation and definition—an overview of the activities of SCPE: a collaboration of European CP registers. *Chin J Contemp Pediatr* 2006;**8**:261–5.
9. Normark E, Hägglund G, Lagergren J. Cerebral palsy in Southern Sweden. I. Prevalence and clinical features. *Acta Paediatr* 2001;**90**:1271–6.
10. Schenker R, Coster WJ, Parush S. Neuroimpairments, activity performance, and participation in children with cerebral palsy mainstreamed in elementary schools. *Dev Med Child Neurol* 2005;**47**:808–14.
11. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrandt P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatr* 2005;**94**:287–94.
12. Howard J, Soo B, Graham HK, et al. Cerebral palsy in Victoria: motor types, topography and gross motor function. *J Paediatr Child Health* 2005;**41**:479–83.
13. Bechung E, Hagberg G. Neuroimpairments, activity limitations and participation restriction in children with cerebral palsy. *Dev Med Child Neurol* 2002;**44**:309–16.
14. Chan HSS, Lau PHB, Fong KH, Poon D, Lam CCC. Neuroimpairment, activity limitation, and participation restriction among children with cerebral palsy in Hong Kong. *Hong Kong Med J* 2005;**11**:342–50.
15. Watson L, Stanley F, Blair E. *Report of the Western Australian Cerebral Palsy Register*. Perth: Western Australian CP Register; 1999.
16. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;**39**:214–23.
17. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther* 2000;**80**:974–85.
18. Rosenbaum PL, Walter SD, Hanna SE. Prognosis for gross motor function in cerebral palsy: creation of motor development curves. *J Am Med Assoc* 2002;**288**:1357–63.
19. Altmann DG. *Practical statistics for medical research*, 1st ed. London: Chapman & Hall/CRC Press; 1991.
20. Medical Birth Registry of Norway. Annual report 1997, Bergen, 1998.
21. Bottos M, Granato T, Allibrio G, Gioachin C, Puato ML. Prevalence of cerebral palsy in north-east Italy from 1965 to 1989. *Dev Med Child Neurol* 1999;**41**:26–39.
22. Charles J, Gordon AM. Development of hand-arm bimanual intensive training (HABIT) for improving bimanual coordination in children with hemiplegic cerebral palsy. *Dev Med Child Neurol* 2006;**48**:931–6.
23. Østensjø S, Carlberg EB, Vollestad NK. Motor impairments in young children with cerebral palsy: relationship to gross motor function and everyday activities. *Dev Med Child Neurol* 2004;**46**:580–9.
24. SCPE-Surveillance of Cerebral Palsy in Europe 1976–1990. Scientific report, Imprimerie des Boulevard, 2002.
25. Krägeloh-Mann, I, Petersen D, Hagberg B, Michaelis R. Brain lesions in the newborn. In: Lou HC, Greisen G, Falck Larsen J, editors. *Alfred Benzon symposium*, vol. 37. Copenhagen: Munksgaard; 1994.
26. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy. The European cerebral palsy study. *JAMA* 2006;**296**:1602–8.
27. Stanley F, Blair E, Alberman E. *Cerebral palsies: epidemiology and causal pathways*. *Clinics in developmental medicine*. London: Mac Keith Press; 2000.
28. Moster D, Lie R, Irgens L, Bjerkedal T, Markestad T. The association of apgar score with subsequent death and cerebral palsy: a population-based study in term infants. *J Pediatr* 2001;**138**:798–803.
29. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet* 2003;**361**:736–42.

Correct Figure 2b



Paper II

Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study

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AIM To study whether breech presentation is a risk factor for cerebral palsy (CP).
METHODS Perinatal data from 177 272 children born in breech or vertex presentation in Norway during 1996 to 1998 were retrieved from the Medical Birth Registry of Norway. Data were collected between 1 January 2003 and 31 March 2006. Data on 245 children with CP were recorded in the Norwegian Cerebral Palsy Registry. Odds ratios (OR) with 95% confidence intervals (CI) for CP among children born in breech compared with vertex presentation were calculated. Confounding was addressed in logistic regression and stratified analyses.
RESULTS Among the 245 children with CP (46.5% females and 53.5% males), 31% had unilateral, 49% bilateral, 7% dyskinetic, and 5% the ataxic subtype, and 8% of cases were unclassified. Among children born in breech, the OR for CP was 3.6 (95% CI 2.4–5.3). The increased risk was reduced when adjusted for preterm birth, plurality, and smallness for gestational age. Among singletons born in breech by vaginal delivery at term, the OR for CP was 3.9 (95% CI 1.6–9.7). Severity or subtype of CP did not differ between breech and vertex presentation.
INTERPRETATION Breech delivery is a significant risk factor for CP, in particular among singletons born by vaginal delivery at term.

The term cerebral palsy (CP) covers a group of permanent, but not unchanging, disorders of movement, posture, and motor function, which are due to a non-progressive interference, lesion, or abnormality of the immature or developing brain.[1] In most cases, the cause is unknown.

Breech delivery is associated with increased perinatal morbidity and mortality,[2–10] and investigators in the Term Breech Trial[6] and the authors of a Cochrane review[7] concluded that planned Caesarean delivery should be preferred for the term fetus. However, this recommendation has been challenged.[11–16]

Few investigators have reported the long-term outcome of children born in breech presentation.[3,6–10,17] In a study of children born in the 1960s, Nelson and Ellenberg found that breech presentation was a risk factor for CP, whereas breech delivery was not.[18] In a review of studies published between 1969 and 1993, Scheller and Nelson did not find clear evidence that Caesarean section reduced the risk of CP associated with breech presentation.[19] However, they were not able to identify any randomized controlled studies, and observational studies had insufficient sample size to address this question appropriately.[19]

More recently, three studies of the association between CP and breech delivery had diverging results.[3,10,17] In a case–control study in Turkey, the investigators found no association;[17] in that study a significant proportion of deliveries were home births. In contrast, in two population-based studies, one Danish and one Swedish, breech presentation was found to be a risk factor for CP.[3,10] However, whereas the Danish investigators reported the increased risk to be independent of delivery mode,[3] the results of the Swedish study suggested that CP might be prevented in some cases by Caesarean section.[10]

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Differences in obstetric practice, study design, and sample size may partly explain the diverging results in those previous studies.

Because breech delivery has been associated with adverse perinatal outcome, and in light of the Term Breech Trial,[6] it may be reasonable to speculate that birth asphyxia could be part of the causal pathway leading to CP. If this were the case one would expect lower Apgar scores and more severe subtypes of CP, such as the dyskinetic–athetoid form and spastic tetraplegia to be more common in children with CP born in breech.[20,21] In the Danish study of singletons born at term, breech delivery was not associated with these subtypes.[3]

In the present study, we have used data from a national CP registry linked with data from the Medical Birth Registry of Norway (MBRN) to test the hypothesis that breech presentation is a risk factor for CP, independent of other risk factors, and to study whether a possible increased risk is associated with mode of delivery. We also aimed to assess whether breech presentation is associated with low Apgar scores and severity or subtype of CP.

METHOD

Study design

All children born in breech or vertex position in Norway between 1 January 1996 and 31 December 1998 who survived the early neonatal period (first 7d of life) were included. Data on maternal health, pregnancy, delivery, and the early neonatal period were obtained from the MBRN.

For this cohort, clinical information on CP was collected between 1 January 2003 and 31 March 2006, when the children were at least 4 years old. Neuropaediatric habilitation centres in Norway provided summary and detailed data, including national identification numbers.[22]

Study population

A total of 177 272 children were eligible, comprising 98% of all births in Norway during 1996 to 1998.

CP was diagnosed in 374 children, and detailed data were recorded in 294 (79%). Fifteen children were born abroad, and perinatal data were missing. Fifteen children had a postneonatal cause (i.e. more than 28d after birth)[22] and were excluded. We were successfully able to match 245 (93%) of the remaining 264 children with CP with data from the MBRN. The matching was done by the MBRN using each child's unique 11-digit personal identification number. Thus, the final study population comprised 177 257 children, of whom 245 had CP (46.5% females and 53.5% males).

Study variables

Exposure variables

Since 1967, the medical registration of births has been compulsory in Norway, ensuring that obstetric and perinatal data are recorded prospectively at birth. Covariates recorded in the MBRN include assisted fertilization, plurality, pre-labour rupture of membrane (any rupture persisting for more than 24 hours and occurring before the onset of labour), mode of delivery, gestational age, birthweight, sex, and smallness for gestational age. Delivery mode is recorded as vaginal birth or Caesarean section, and Caesarean section is specified as planned or emergency. Smallness for gestational age is calculated by the MBRN as a birthweight below the 10th centile for the gestational age.[23]

Gestational age was calculated from the first day of the last menstrual period and was classified into term (37wks or more) and preterm (before 37wks). Gestational age was also analysed as a continuous variable. Information on gestational age was missing in 9% of all newborns.

Outcome variables

CP was diagnosed according to the definition and classification agreed by the Surveillance of Cerebral Palsy in Europe in 1999.[1,22] Data for each child with CP were recorded by a senior paediatrician on a standardized form. Gross and fine motor functions were recorded according to the Gross Motor Function Classification System and the Bimanual Fine Motor Function scales.[22]

Ethics

The study was approved by the Regional Ethical Committee for Medical Research in Mid-Norway and by the Norwegian Data Inspectorate. The individual registration of data and linkage to the MBRN required parental consent.

Statistical methods

The Statistical Package for Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc, Chicago, IL, USA) was used for data analyses. Differences in proportions between groups were analysed using χ^2 statistics. The significance tests were two-tailed and a significance level of 0.05 was chosen.

We calculated odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk that a child born in breech presentation would be diagnosed with CP, using children born in vertex as reference. The OR is approximately equal to the relative risk if the outcome of interest is rare, as is the case in the present study.[24]

In the assessment of possible confounders we used both multivariate analyses and stratification. Logistic regression analyses were used to calculate OR adjusted for possible

confounders. We explored a number of possible confounders, applying the hierarchical model proposed by Victora et al. as a conceptual framework.[25] A variable was considered to be a confounder if it could theoretically be associated with both exposure and outcome. Thus, assisted fertilization, sex of the child, plurality, gestational age, and smallness for gestational age were assessed as possible confounders. In addition, we also assessed the confounding effect of being born preterm or at term. Possible effects on the association between breech presentation and CP were explored for each possible confounder separately and by multivariate adjustments. In addition, confounding was assessed by stratified analyses among children born at term and preterm, and among singletons.

RESULTS

Table I shows that 29 children born after breech presentation (4.5 per 1000 live births) were diagnosed with CP, compared with 216 children (1.3 per 1000 live births) born after vertex presentation (OR 3.6; 95% CI 2.4–5.3). The increased risk was unaffected when adjusted separately for assisted fertilization and sex, but was reduced when adjusted for preterm birth, plurality, and smallness for gestational age. Multivariate adjustment only marginally affected the OR further. Moreover, in stratified analyses the increased risk persisted among children born at term and preterm (Table I).

Table II shows that among singletons with CP 24 children were born in breech presentation compared with 180 children in vertex (OR 4.1; 95% CI 2.7–6.3). Among singletons with CP, for those born at term nine children were born in breech compared with 99 in vertex (OR 3.0; 95% CI 1.5–5.9), whereas for those born preterm 12 children were born in breech compared with 64 in vertex (OR 2.6; 95% CI 1.4–5.0). Analyses stratified by mode of delivery showed that for vaginal breech delivery the increased risk for CP was confined to children born at term, whereas for those delivered in breech by Caesarean section the increased risk was only statistically significantly increased among children born preterm (Table II).

When we restricted the analyses to breech deliveries only, the relative risk for CP was 1.7 (95% CI 0.5–6.4) among singletons born at term vaginally compared with by Caesarean section.

No statistically significant differences were observed in subtype or severity of CP between children born after breech or vertex presentation (Table III).

Table IV shows that a higher proportion of children with CP born in breech than in vertex had low Apgar scores at 1 minute (p=0.040). There were no statistically significant differences between the groups in sex, plurality, gestational age, Apgar scores at 5 minutes, birthweight, pre-labour rupture of membranes, or abruptio placentae (Table IV).

Among children born in breech, 479 (7%) had a congenital birth defect compared with 4851 (3%) in children born in vertex (OR 2.7; 95% CI 2.4–3.0).

Table I: Crude and adjusted odds ratio (OR) with 95% confidence intervals (CI) for cerebral palsy (CP) among children born in breech

	All live births			Term birth[a]			Preterm birth[a]		
	CP, *n*	Not CP, *n*	OR (95% CI)	CP, *n*	Not CP, *n*	OR (95% CI)	CP, *n*	Not CP, *n*	OR (95% CI)
Birth presentation									
Breech	29	6 384	3.6 (2.4–5.3)	9	4 857	2.6 (1.3–5.1)	17	975	2.0 (1.2–3.4)
Vertex	216	170 628	1.0	103	144 169	1.0	90	10 455	1.0
OR adjusted separately for:									
Assisted fertilization			3.4 (2.3–5.0)			2.6 (1.3–5.1)			2.0 (1.2–3.4)
Sex			3.6 (2.4–5.3)			2.6 (1.3–5.1)			2.1 (1.2–3.5)
Plurality			2.3 (1.6–3.6)			2.5 (1.2–4.9)			1.8 (1.0–3.1)
Gestational age			2.9 (1.9–4.3)			2.5 (1.2–4.9)			2.2 (1.3–3.6)
Smallness for gestational age[b]			3.3 (2.2–4.9)			2.4 (1.2–4.7)			1.9 (1.1–3.3)
Preterm birth			2.2 (1.5–3.4)			NA			NA
Multivariate adjustments			2.1 (1.3–3.2)[c]			2.3 (1.2–4.7)[c]			1.9 (1.1–2.4)[c]
			2.2 (1.5– 3.3)[d]			2.4 (1.2– 4.9)[d]			1.9 (1.1–3.2)[d]

[a]Information on gestational age was missing for 552 children (9%) in breech and 16 004 (9%) in vertex. [b]Smallness for gestational age was recorded in the Medical Birth Registry of Norway for children born at gestational age >28wks. [c]Adjusted for assisted fertilization + sex + plurality + gestational age. [d]Adjusted for assisted fertilization + sex + plurality + gestational age + smallness for gestational age. NA, not available.

Table II: Crude and adjusted odds ratio (OR) with 95% confidence intervals (CI) for cerebral palsy among singeltons born in breech

	All singletons			Singletons born at term			Singeltons born preterm		
	CP, *n*	Not CP, *n*	OR (95% CI)	CP, *n*	Not CP, *n*	OR (95% CI)	CP, *n*	Not CP, *n*	OR (95% CI)
Birth presentation									
Breech									
All	24	5394	4.1 (2.7–6.3)	9	4329	3.0 (1.5–5.9)	12	606	2.6 (1.4–5.0)
Vaginal	8	2247	3.3 (1.6–6.7)	5	1826	3.9 (1.6–9.7)	3	239	1.7 (0.5–5.4)
Caesarean section	16	3147	4.7 (2.8–7.3)	4	2503	2.3 (0.8–6.2)	9	367	3.3 (1.6–6.7)
Vertex									
All	180	166 128	1.0	99	141 988	1.0	64	6625	1.0
OR adjusted separately for:									
Assisted fertilization			4.1 (2.7–6.3)			3.0 (1.5–5.9)			2.7 (1.4–5.0)
Sex (male)			4.1 (2.7–6.3)			2.9 (1.5–5.8)			2.7 (1.5–5.1)
Gestational age			3.3 (2.1–5.2)			2.9 (1.5–5.7)			2.8 (1.5–5.1)
Smallness for gestational age[a]			4.0 (2.6–6.1)			2.9 (1.4–5.7)			2.6 (1.4–5.0)
Preterm birth			2.8 (1.8–5.2)			NA			NA
Multivariate adjustments			2.8 (1.8–4.4)[b]			2.9 (1.4–5.7)[b]			2.8 (1.5–5.2)[b]
			2.8 (1.7–4.4)[c]			2.7 (1.4–5.4)[c]			2.7 (1.4–5.3)[c]

[a]Smallness for gestational age only available for gestational age >28wks. [b]Adjusted for assisted fertilization + sex + gestational age. [c]Adjusted for assisted fertilization + sex + gestational age + smallness for gestational age. NA, not available.

DISCUSSION

We found that breech presentation is a significant risk factor for CP, in particular among singletons born by vaginal delivery at term. Breech presentation was not associated with specific subtypes of CP or with the extent of fine or gross motor impairments.

For the comparison of differences in CP subtypes and motor impairments, and when we restricted the analyses to breech deliveries, the numbers were low, as is the case in most other studies.[3,12,18–20] Lack of statistically significant differences between groups must therefore be interpreted with caution. This is of particular relevance for the subanalysis restricted to children born in breech where we compared the association between CP and mode of delivery (vaginal vs Caesarean section). However, our finding of a trend towards increased risk for CP among singletons born at term in breech by vaginal delivery compared with those delivered by Caesarean section may be noteworthy, and it may be consistent with the largest study so far, the study from Sweden by Thorngren-Jerneck and Herbst.[10]

The diagnosis of CP was standardized in accordance with European guidelines,[1] and all children were at least 6 years old when the diagnosis was confirmed. However, detailed information was missing for 80 children (21%). It is very unlikely that birth presentation differed systematically between children with or without detailed information on CP.[22] However, those 80 children were misclassified into the group without CP, although in comparison with the total number of children in that group the number of misclassified children is negligible.

The prospective recording of perinatal data is a specific strength, making information bias unlikely. The results of the multivariate analyses as well as the stratified analyses suggest that our results are unlikely to be due to confounding by preterm birth, plurality, sex, or fetal growth restriction.

In general, we found strong effects of breech presentation on the risk of CP. Most noteworthy was the fourfold increased risk among singletons born at term and delivered vaginally, which may be consistent with a causal relationship.

Our results are consistent with two other cohort studies.[3,10] In one study from Sweden, the investigators found a threefold increased risk of CP in term infants born in breech presentation between 1984 and 1998,[10] whereas in a study from Denmark only a borderline increased risk was found among children born at term between 1979 and 1986.[3] In contrast, in a recent case–control study from Turkey no association was found between birth presentation and risk of CP.[17] In addition to the difference in study designs, more than 50% of the children with CP in the Turkish study were born at home, which may have obscured a possible increased risk associated with breech delivery.

Table III: Subtype and severity of cerebral palsy (CP) among children born in breech and vertex position

	Breech presentation *n*=29	Vertex presentation *n*=216	*p* value
CP subtype, *n* (%)			
Spastic unilateral	12 (41)	65 (30)	
Spastic bilateral	12 (41)	107 (50)	
Dyskinetic	4 (14)	13 (6)	
Ataxic	0	13 (6)	
Unclassified	1 (3)	18 (8)	0.189
GMFCS, *n* (%)[a]			
Level I–II	15 (52)	115 (55)	
Level III	5 (17)	35 (16)	
Level IV–V	9 (31)	59 (28)	0.940
BFMF, *n* (%)[a]			
Level 1–2	16 (55)	115 (55)	
Level 3	5 (17)	17 (8)	
Level 4–5	8 (28)	77 (37)	0.198

[a]Information on Gross Motor Function Classification System (GMFCS) and Bimanual Fine Motor Function (BFMF) is missing in seven children in vertex presentation.

Table IV: Perinatal information in children with cerebral palsy according to birth presentation

	Breech presentation *n*=29	Vertex presentation *n*=216	*p* value
Sex, *n* (%)			
Male	13 (45)	118 (55%)	
Female	16 (55)	96 (45%)	0.320
Plurality, *n* (%)[a]			
Singelton	24 (86)	180 (84%)	
Plural	4 (14)	35 (16%)	0.79
Gestational age, *n* (%)[b]			
≥37wks	9 (35)	103 (53%)	
<37wks	17 (65)	90 (47%)	0.073
Apgar score at 1min, *n* (%)[c]			
0–3	7 (26)	43 (20%)	
4–6	10 (37)	41 (19%)	
7–10	10 (37)	131 (60%)	0.040
Apgar score at 5min, *n* (%)[d]			
0–3	3 (11)	19 (9%)	
4–6	4 (15)	32 (16%)	
7–10	20 (74)	159 (76%)	0.94
Birthweight, *n* (%)[e]			
<1000g	4 (14)	18 (8%)	
1000–1499g	7 (24)	32 (15%)	
1500–2499g	5 (17)	52 (24%)	
≥2500g	13 (45)	113 (53%)	0.408
Pre-labour rupture of membrane >24h, *n* (%)	2 (7)	19 (9%)	0.731
Abruptio placentae, *n* (%)	2 (7)	21 (10%)	0.469

[a]Information on plurality missing in two children. [b]Information on gestational age missing in 26 children. [c]Information on Apgar score at 1min missing in three children. [d]Information on Apgar score at 5min missing in eight children. [e]Information on birthweight missing in 33 children without cerebral palsy.

One possible explanation for the increased risk of CP associated with breech delivery may be that children with antenatal brain injuries are more likely to be born in breech presentation. In the present study, the lack of an association between breech delivery and a specific CP subtype and the higher proportion of children with a congenital malformation among those born in breech than in vertex position may support this interpretation. Moreover, this interpretation may be consistent with the Danish study whose investigators reported that the risk for CP was independent of delivery mode, and with their finding of a higher proportion of the diplegic and not the more severe subtypes of CP among children born after breech presentation. We found increased risk for CP among all singletons after breech Caesarean delivery. However, among those born at term the increased risk was not statistically significant.

Consistent with the larger Swedish study,[10] we found a significantly increased risk of CP among children born as singeltons in breech at term and delivered vaginally, whereas the trend towards an increased risk among those in breech delivered by Caesarean section was not statistically significant. In the larger Swedish study, elective Caesarean section was associated with a significantly reduced risk of CP. Thus, we may speculate that another possible explanation for the increased risk of CP could be that infants born in breech presentation are more likely to suffer from peripartal asphyxia. We found that children born in breech with CP had lower Apgar scores at 1 minute, but not at 5 minutes. In the Danish study the authors found that breech delivery was associated with low Apgar scores at 5 minutes,[3] whereas investigators in a more recent Dutch study found that more children born in breech had low Apgar scores at 1 minute, but not at 5 minutes.[26] However, a low Apgar score may also be a more common finding in a child with an antenatal brain insult.

Both the investigators in the Term Breech Trial[6] and the authors of a Cochrane review from 2003[7] concluded that planned Caesarean sections in term breech deliveries reduce peri- or neonatal death and serious neonatal morbidity. However, more recent studies have indicated that vaginal delivery of selected fetuses in breech presentation can be safely pursued, under specific guidelines for eligibility and

labour management.[11–16,27] Although observational studies do not allow definite conclusions, our results and those of the Swedish study[10] may be in favour of the conclusions of the Term Breech Trial and the Cochrane review.

A reasonable interpretation of the results of the present study and of the current literature may be that both antenatal and perinatal factors are responsible for the increased risk of CP associated with breech presentation. Because only a minor proportion of children with CP were born vaginally after breech presentation, and because some of these few may have suffered an antenatal brain insult, the proportion of CP cases that theoretically may be prevented if Caesarean section is performed in all term breech deliveries is low.

In conclusion, we found that breech presentation is a significant risk factor for CP. The most striking finding was a fourfold increased risk for CP in singletons in breech born vaginally at term. It is possible that a few cases of CP could have been prevented had Caesarean section been performed in all cases of term breech delivery, but to clarify this question significantly larger multicentre studies are needed.

REFERENCES

1. Surveillance of Cerebral Palsy in Europe (SCPE) Collaborative Group. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol* 2000; **42:** 816–24.
2. Koo MR, Dekker GA, van Geijn HP. Perinatal outcome of singleton term breech deliveries. *Eur J Obstet Gynecol Reprod Biol* 1998; **78:** 19–24.
3. Krebs L, Topp M, Langhoff-Roos J. The relation of breech presentation at term to cerebral palsy. *Br J Obstet Gynaecol* 1999; **106:** 943–47.
4. Herbst A, Thorngren-Jerneck K. Mode of delivery in breech presentation at term: increased neonatal morbidity with vaginal delivery. *Acta Obstet Gynecol Scand* 2001; **80:** 731–37.
5. Belfrage P, Gjessing L. The term breech presentation. A retrospective study with regard to the planned mode of delivery. *Acta Obstet Gynecol Scand* 2002; **6:** 544–50.
6. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet* 2000; **356:** 1375–83.
7. Hofmeyr GJ, Hannah ME. Planned caesarean section for term breech delivery. *Cochrane Database Syst Rev* 2003; **3:** CD000166.
8. Pradhan P, Mohajer M, Deshpande S. Outcome of term breech births: 10-year experience at a district general hospital. *BJOG* 2005; **112:** 218–22.
9. Molkenboer JFM, Roumen FJME, Smits LJM, Nijhuis JG. Birth weight and neurodevelopmental outcome of children at 2 years of age after planned vaginal delivery for breech presentation at term. *Am J Obstet Gynecol* 2006; **194:** 624–29.
10. Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. *Obstet Gynecol* 2006; **108:** 1499–1505.
11. Doyle LW, Anderson PJ, Victorian Infant Collaborative Study Group. Improved neurosensory outcome at 8 years of age of extremely low birth weight children born in Victoria over three distinct eras. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F484–88.
12. Krupitz H, Arzt W, Ebner T, Sommergruber M, Steininger E, Tews G. Assisted vaginal delivery versus caesarean section in breech presentation. *Acta Obstet Gynecol Scand* 2005; **84:** 588–92.
13. Uotila J, Tuimala R, Kirkinen P. Good perinatal outcome in selective vaginal breech delivery at term. *Acta Obstet Gynecol Scand* 2005; **84:** 578–83.
14. Håheim LL, Albrechtsen S, Berge LN, et al. Breech birth at term: vaginal delivery or elective cesarean section? A systematic review of the literature by a Norwegian review team. *Acta Obstet Gynecol Scand* 2004; **83:** 126–30.
15. Alarab M, Regan C, O'Connell MP, Keane DP, O'Herlihy C, Foley ME. Singleton vaginal breech delivery at term: still a safe option. *Obstet Gynecol* 2004; **103:** 407–12.
16. Hellsten C, Lindqvist PG, Olofson P. Vaginal breech delivery: is it still an option? *Eur J Obstet Gynecol Reprod Biol* 2003; **111:** 122–28.
17. Öztürk A, Demirci F, Yavuz T, et al. Antenatal and delivery risk factors and prevalence of cerebral palsy in Duzce (Turkey). *Brain Dev* 2007; **29:** 39–42.
18. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. *Am J Dis Child* 1985; **139:** 1031–08.
19. Scheller JM, Nelson KB. Does caesarean delivery prevent cerebral palsy or other neurological problems of childhood? *Obstet Gynecol* 1994; **83:** 624–30.
20. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94. *Acta Paediatr* 2001; **90:** 271–77.
21. Rosenbloom L. Dyskinetic cerebral palsy and birth asphyxia. *Dev Med Child Neurol* 1994; **36:** 285–89.
22. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. *Eur J Paediatr Neurol* 2008; **12:** 4–13.
23. Skjærven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000; **79:** 440–49.
24. Altman DG. Practical Statistics for Medical Research. London: Chapman & Hall, 1997.
25. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. *Int J Epidemiol* 1997; **26:** 224–27.
26. Molkenboer JF, Vencken PM, Sonnemans LG, et al. Conservative management in breech deliveries leads to similar results compared with cephalic deliveries. *J Matern Fetal Neonatal Med* 2007; **20:** 599–603.
27. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 340. Mode of term singleton breech delivery. *Obstet Gynecol* 2006; **108:** 235–37.

Paper III

OBSERVATIONAL STUDY

Induction of labor and cerebral palsy: a population-based study in Norway

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Key words
Cerebral palsy, labor induction, children, birth, etiology

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Abstract

Objective. To investigate the association between labor induction and later development of cerebral palsy (CP). *Design.* Registry-based cohort study. *Setting.* Perinatal data on all children born in Norway 1996–1998 were obtained from the Medical Birth Registry of Norway (MBRN). Neurodevelopmental data were collected from the Norwegian Cerebral Palsy Registry (CPRN). *Population.* A total of 176,591 children surviving the neonatal period. Of 373 children with CP, detailed data were available on 241. *Methods.* Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated as estimates of the relative risk that a child with CP was born after labor induction. *Main outcome measures.* Total CP and spastic CP subtypes. *Results.* Bilateral cerebral palsy was more frequently observed after induced labor (OR: 3.1; 95% CI 2.1–4.5). For children born at term the association between bilateral CP and labor induction was stronger (OR: 4.4; 95% CI 2.3–8.6). The association persisted after adjustment for maternal disease, gestational age, standard deviation score for birthweight (z-score) and prelabor rupture of membranes (PROM) (adjusted OR: 3.7; 95%CI 1.8–7.5). Among children with CP born at term, four-limb involvement (quadriplegia) was significantly more frequent after induced (45.5%) compared with non-induced labor (8.0%). There was no significant association between labor induction and unilateral CP subtype or CP in preterm born children. *Conclusions.* In this study population, we found that labor induction at term was associated with excess risk of bilateral spastic CP and in particular CP with four-limb involvement.

Introduction

Cerebral palsy (CP) is the most common physical disability in children comprising a heterogeneous group of conditions with different etiological pathways (1,2). The processes leading to CP are still poorly understood although a number of antenatal and perinatal risk factors have been studied (3). Perinatal risk factors and events such as intrapartum asphyxia (4), breech presentation (5) and hyperbilirubinemia (6,7) are of particular interest, since they may theoretically be preventable.

While the proportion of births following induction of labor has been fairly stable (~15%) over years in Norway (8), this proportion has increased in a number of other developed countries during the last decade (9–12). In the USA, induction of labor more than doubled between 1990 and 2005 (from 9.5% to 22.3%) (13). Labor is usually induced for maternal or fetal medical indications, but in the recent years there has been a trend toward elective labor induction on maternal request with no medical indications (14–16). Such practice has been questioned (17) due to mounting evidence of adverse neurological outcome even among children born slightly preterm (at 34–36 weeks) (18–20). However, few studies have addressed induction of labor as a possible independent risk factor for CP and the results have been conflicting. While Nielsen et al. (21) found increased risk of CP

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among children after induction of labor, Gaffney et al. (22) and Nelson (23) found no such association.

Since CP is a heterogeneous group of disorders, it is likely that different CP subtypes have different etiologies. Unilateral spastic CP in children born at term is most likely caused by a cerebrovascular insult (24,25). Bilateral spastic CP, mainly diplegia, is more common among preterm born children (3,26,27). Ataxic subtypes are more likely caused by brain maldevelopment (28), while dyskinetic and quadriplegic CP are associated with acute perinatal hypoxia (29,30). Thus, in the search for specific causes and risk factors for CP, it is important to study possible associations with specific CP subtypes.

In this study, we aimed to study labor induction as an independent risk factor for CP in general, and for unilateral and bilateral spastic CP in particular.

Material and methods

In this registry-based cohort study, we linked data from the Medical Birth Registry of Norway (MBRN) with data from the Norwegian Cerebral Palsy Registry (CPRN). Data from the two registries were matched by the MBRN using each child's unique 11-digit personal identification number. An unchanged birth notification form was in use from 1967 to 1 December 1998. Notification is mandatory and data on each pregnancy are recorded on standard forms by birth attendants within one week of delivery for all deliveries after 16 weeks of gestation. The record includes information about the mother's health before and during pregnancy as well as data on labor and characteristics of the newborn within the first week after delivery.

The CPRN has recorded data on all children born in Norway with CP since 1996 (31). Briefly, this is an informed consent based register where all the 19 child rehabilitation centers in Norway provide detailed clinical data on children with CP. These centers serve all children with neuro-developmental disabilities in Norway. To ensure ascertainment of all cases, the centers provide summary data on how many children with CP are identified at each center. The detailed clinical data include subtypes of CP, severity of motor dysfunction and associated impairments.

In all 177,272 children were born in Norway during 1996–1998. Among these children, data were missing for 293, and 388 children died in the perinatal period. Thus, the total study population comprised 176,591 children who survived the early neonatal period.

Based on summary data, 373 children were diagnosed with CP among all children born 1996–1998 (prevalence: 2.0 per 1000 births). The CPRN has collected detailed clinical data on 293 (79%) of all children with CP. Among the 80 missing cases, parents of only eight (2%) children refused to participate while some participating centers could not provide detailed data on 72 cases due to work overload. Among the remaining 293 children, we could not technically merge data with the MBRN in 22 cases, 15 children were born abroad and another 15 children had a post-neonatal etiology and were excluded from the study, leaving 241 children with CP for further analysis.

The outcome variable, CP, was defined as a 'group of permanent and non-progressive disorders of movement and posture caused by a central nervous lesion, damage or dysfunction originating early in life' according to the definition proposed by the European CP network, Surveillance of Cerebral Palsy in Europe (SCPE) (32). Applying these criteria, unilateral spastic CP involves one side of the body and includes hemiplegia or hemiparesis. In bilateral spastic CP both sides of the body are involved. Furthermore, we used the Swedish classification to divide bilateral CP into diplegia (lower limbs most affected) and quadriplegia (four limbs affected with upper limbs more affected) (33,34). The diagnosis was confirmed by a child neurologist when a child was at least 4-year old before inclusion in CPRN. Mean age at confirmed diagnosis was 6.9 years.

As exposure variable, we studied induction as a dichotomous yes/no variable. Induction of labor is recorded in the MBRN as amniotomy, oxytocin (Syntocinon®) infusion and prostaglandin analogues. Data on dosages or sequence of procedures were not detailed enough to study each induction method separately and we therefore decided in the main analyses and presentation of the results to exclude cases where cesarean section was listed as the method of induction. However, we have also analyzed our data including cases where cesarean section was listed under labor induction.

Other, in the MBRN available variables, included maternal diseases such as diabetes, anemia, hypertension, preeclampsia, eclampsia, epilepsy, thyroid dysfunction, chronic renal disease, urinary tract infection, venereal diseases and rubella. In the present study, we have studied each maternal disease separately as well as maternal disease as a group. Assisted fertilization included in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) methods. Congenital malformations detected in the first week of life are reported in the MBRN. Gestational age (GA) is recorded in completed weeks based on the last menstrual period (LMP) and was included in the multivariable analyses as a continuous variable as well as dichotomized in preterm birth (i.e. born before 37 completed weeks) and term (i.e. equal to or above 37 weeks of gestation). Birthweight is recorded in the birth registry and we calculated standard deviation scores (z-score = (actual birth weight − mean)/standard deviation (SD)) for birthweight, corrected for GA and sex, using Norwegian reference curves (35). The z-score as a continuous variable was used as a proxy for fetal growth. In addition, small-for-gestational age (SGA), recorded in the registry as a birthweight of less than the 10th percentile for GA adjusted for sex and parity,

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was used as another approach to study fetal growth restriction. Moreover, we also defined large-for-gestational age as a birthweight z-score higher than +2 SD.

Prolonged prelabor rupture of membranes (PROM) was defined as rupture of membranes 24 hours or longer prior to delivery. Preterm prelabor rupture of membranes (PPROM) was defined as rupture of membranes earlier than 37 weeks of gestation. Finally, Apgar scores at 1 and 5 minutes are recorded in the birth registry, and we categorized the scores into three groups; (group 1: 0–3, group 2: 4–6 and group 3: 7–10).

The study was approved by the Norwegian Data Inspectorate and the Regional Ethical Committee (REC) for medical research in the Central Norway Regional Health Authority. Written informed consent was obtained from the parents to record detailed data in the register and to link data from CPRN with data from the MBRN. Ethical approval for the CPRN and linking to the birth register was granted by Norwegian Data Inspectorate and the Regional Ethical Committee (REC) for medical research in Mid-Norway; reference number: 046–02 (2002).

Statistical analyses

Data analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 17. Chi-squared statistics or Fisher's exact test were performed to explore differences in proportions. Logistic regression analyses were used to calculate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) for CP among children born after labor induction compared with children born after non-induced labor.

Covariates evaluated as possible confounders were selected based upon theoretical considerations as well as upon bivariate statistical analyses. The variables were entered in the model according to the conceptual hierarchal framework approach proposed by Victora et al. (36). Briefly, according to this framework, variables are included by first adjusting for the variable being most apart and 'ahead' of the relevant exposure in a time-line leading to the outcome. In this study, this was considered to be maternal age and parity. However, none of these factors had any effect on the OR. Then, the next variable would be maternal disease, assisted fertilization, multiple pregnancy, child's sex, congenital malformations, preeclampsia, fetal lie, prolonged rupture of membranes, SGA or LGA then preterm birth, in this order. Finally, risk factors that changed the OR by at least 10% were included in our multivariable model. We also explored if these variables could be confounders of the association between CP and labor induction in term and preterm born children separately. Apgar scores at 1 and 5 minutes were not included as potential confounders as it is likely to be an intermediate variable. A p-value of <0.05 was chosen as the level of significance

Results

Table 1 displays the prevalence of some risk factors for children with and without CP. Induction of labor had been performed in 24.1% of children with CP compared with 13.4% among children without CP ($p < 0.001$).

Table 2 shows the distribution of some risk factors in births after labor induction compared to non-induced births. Bilateral spastic CP was more frequent after labor induction

Table 1. Occurrence (%) of risk factors for cerebral palsy (CP) in CP births and non-CP births, Norway 1996–1998.

	CP ($n = 241$) n (%)	Controls ($n = 176{,}350$) n (%)	p–value
Maternal disease	104 (43.2%)	38, 837 (22.0%)	<0.001
Nulliparity	105 (43.9%)	71, 271 (40.5%)	0.29
Assisted fertilization	13 (5.4%)	2, 011 (1.1%)	<0.001
Multiple pregnancy	20 (8.3%)	2, 747 (1.6%)	<0.001
Boys	126 (52.3%)	90, 920 (51.6%)	0.85
Congenital malformations	8 (3.3%)	5, 183 (2.9%)	0.70
Pre-eclampsia	12 (5.0%)	5, 640 (3.2%)	0.14
Preterm birth	105 (48.8%)	11, 349 (7.1%)	<0.001
SGA*	34 (14.1%)	12, 075 (6.8%)	0.07
LGA	9 (4.7%)	6, 282 (4.1%)	0.59
Breech	27 (11.2%)	6, 249 (3.5%)	<0.001
PROM/ PPROM	24 (10.0%)	2, 860 (1.6%)	<0.001
Labor induction	58 (24.1%)	23, 543 (13.4%)	<0.001
Placental abruption	21 (8.7%)	933 (0.5%)	<0.001
Low Apgar score**	23 (12.8%)	818 (0.5%)	<0.001

Note: *SGA: Small for gestational age, recorded only for pregnancies >28 weeks.

**Low Apgar is defined as Apgar score of 3 or less at 5 minutes after birth compared with Apgar score of 7 or higher.

PROM, Prelabor rupture of membranes ≥24 hours before delivery.

PPROM, Preterm prelabor rupture of membranes ≥24 hours before delivery.

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Table 2. Occurrence (%) of risk factors for cerebral palsy in births after labor induction compared with non-induction, Norway 1996–1998.

	Induction ($n = 23,601$) *n* (%)	No induction ($n = 176,350$) *n* (%)	*p*–value
Maternal disease	9, 309 (39.4%)	29, 632 (19.4%)	<0.001
Nulliparity	11, 006 (46.8%)	60, 370 (39.6%)	<0.001
Assisted fertilization	490 (2.1%)	1, 534 (1.0%)	<0.001
Multiple pregnancies	842 (3.6%)	1, 925 (1.3%)	<0.001
Boys	12, 834 (54.6%)	78, 212 (51.1%)	<0.001
Congenital malformation	1, 063 (4.5%)	4, 128 (2.7%)	<0.001
Pre-eclampsia	3, 229 (13.7%)	2, 423 (1.6%)	<0.001
Preterm birth	3, 073 (14.6%)	8, 381 (6.0%)	<0.001
SGA*	2, 390 (10.1%)	9, 719 (6.4%)	0.064
LGA	1, 222 (6.3%)	5, 069 (3.7%)	<0.001
Breech	889 (3.8%)	5, 387 (3.5%)	0.058
PROM/PPROM	1, 189 (5.0%)	1, 695 (1.1%)	<0.001
Placental abruption	368 (1.6%)	586 (0.4%)	<0.001
Low Apgar**	408 (1.9%)	433 (0.3%)	<0.001

Note: *SGA: Small for gestational age, recorded only for pregnancies >28 weeks.
**Low Apgar is defined as Apgar score of 3 or less at 5 minutes after birth compared with Apgar score of 7 or higher.
PROM: Prelabor rupture of membranes ≥24 hours before delivery.
PPROM: Preterm prelabor rupture of membranes ≥24 hours before delivery.

compared with non- induced labor (OR 3.08; CI 2.09–4.54) (Table 3). Adjustment for maternal disease, GA, z-score for birthweight and PROM/ PPROM in the same model reduced the OR, but the association between induction of labor and CP remained significant. In contrast, unilateral spastic CP was not associated with labor induction (Table 3). Multiple pregnancy, placental abruption and fetal lie were significantly associated with CP but did not affect the association between labor induction and CP assessed by multiple logistic regression (data not shown). Maternal age, parity, preeclampsia, LGA, congenital malformations and the sex of the child were not associated with CP in this study population (data not shown).

The OR for bilateral CP when labor induction was performed among children born at term was 4.42(CI: 2.27–8.59) compared with an OR of 1.31 among children born preterm. This risk was marginally reduced after adjustment for confounding effect of maternal disease, GA, z-score for birthweight and PROM/ PPROM in the same model (OR: 3.65; CI: 1.78–7.49). For preterm children, there was no association between CP and induction (Table 4).

Table 5 shows the classification of CP in children born after induced versus non-induced deliveries, according to CP subtype. Among children with CP born at term ($n = 100$), four-limb involvement (i.e. quadriplegia) was significantly more frequent after labor induction (45.5%) compared with non-induced deliveries (8.0%).

Children born between 37 and 40 gestational weeks had an OR for bilateral CP (adjusted OR: 3.74; CI: 1.54–9.04) that was comparable to the OR for children born at 40 weeks of gestation or more (crude OR: 5.33; CI: 2.24–12.65).

Among children born after labor induction with CP seven (12%) had Apgar scores equal to or below 3, and eight (12%) had Apgar scores between 4 and 7. In contrast, among children born after labor induction who did not develop CP 410 (1.8%) had Apgar score equal to or below 3, and 330 (1.5%) had scores between 4 and 7 ($p < 0.001$ vs. CP-group).

When we re-analyzed our data including cesarean section as mode of induction, the results were essentially unchanged or even higher (data not shown).

Discussion

In this Norwegian birth cohort, we found that labor induction at term was associated with an excess risk of bilateral spastic CP, in particular with the quadriplegic subtype.

The exposure data were recorded prospectively in the MBRN and the CP data were collected when the children were at least 4 years of age and without knowledge of the exposure data. Thus, the risk of information bias is low. However, detailed data on 80 children (21%) with CP were missing in CPRN. The reason for missing cases was mainly work overload of the neuropediatricians in some centers, while only eight families (2%) refused to have their children registered. Most likely these dropouts were therefore at random, and we find it most unlikely that missing children with CP differed systematically in mode of delivery from the cases included. Finally, the misclassification of these children as non-CP cases is negligible compared with the 176,591 other control children included. Another potential bias in our study could be that we excluded cases where cesarean section was listed as the method of induction in the birth register. However, when

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Table 3. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk that children with bilateral and unilateral spastic cerebral palsy were born after labor induction compared with children born without induction of labor, Norway 1996–1998.

	All CP					Bilateral CP					Unilateral CP				
N = 176,590	CP *n*	Not CP *n*	OR	(95% CI)	*p*	CP *n*	Not CP *n*	OR	(95% CI)	*p*	CP *n*	Not CP *n*	OR	(95% CI)	*p*
Induction of labor	58	23,543	2.06	(1.53–2.76)	<0.001	38	23,543	3.08	(2.09–4.54)	<0.001	14	23,543	1.47	(0.82–2.62)	0.20
Labor not induced	183	152,807				80	152,807	1.00			62	152,807			
OR for CP after labor induction adjusted separately for:															
Maternal disease			1.67	(1.24–2.26)	<0.001			2.28	(1.54–3.39)	<0.001			1.27	(0.70–2.30)	0.42
Preterm birth			1.50	(1.10–2.05)	0.01			1.92	(1.28–2.89)	0.002			1.32	(0.71–2.47)	0.38
Birth weight z-score			2.26	(1.66–3.08)	<0.001			3.34	(2.23–4.99)	<0.001			1.73	(0.94–3.20)	0.08
SGA*			1.98	(1.47–2.66)	<0.001			2.97	(2.02–4.38)	<0.001			1.40	(0.79–2.51)	0.25
PROM/PPROM			1.76	(1.30–2.38)	<0.001			2.45	(1.64–3.67)	<0.001			1.36	(1.36–2.45)	0.31
Gestational age			1.27	(0.91–1.79)	0.16			1.62	(1.03–2.55)	0.04			1.16	(0.60–2.26)	1.16
Multivariable adjustment**:			1.24	(0.90–1.73)	0.19			1.56	(1.01–2.40)	0.04			1.13	(0.59–2.17)	0.70

Note: *SGA: Small for gestational age, recorded only for pregnancies > 28 weeks

**Odds ratio for CP after labor induction adjusted for: maternal disease, gestational age, z-score for birth weight and PROM/PPROM.

PROM, Prelabor rupture of membranes ≥ 24 hours before delivery.

PPROM, Preterm prelabor rupture of membranes, ≥ 24 hours before delivery.

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Table 4. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) as estimates of the relative risk that children with bilateral spastic cerebral palsy were born after labor induction compared with children born without labor induction analyzed separately for children born preterm and at term, Norway 1996–1998.

	Preterm					Term				
	CP *n*	Non-CP *n*	OR	(CI)	*p-value*	CP *n*	Non-CP *n*	OR	(CI)	*p-value*
Induction of labor	23	3,039	1.31	(0.80–2.16)	0.29	14	17,939	4.42	(2.27–8.59)	<0.001
Labor not induced	48	8,310	1.00			23	130,303	1.00		
OR for CP after labor induction adjusted separately for:										
Maternal disease			1.12	(0.68–1.86)	0.65			4.32	(2.19–8.53)	<0.001
Birth weight z-score			1.44	(0.89–2.44)	0.14			3.96	(2.00–7.85)	<0.001
SGA*			1.33	(0.81–2.20)	0.26			3.91	(2.00–7.64)	<0.001
PROM/ PPROM			1.28	(0.77–2.10)	0.34			4.14	(2.10–8.16)	<0.001
Gestational age			0.86	(0.56–1.62)	0.86			4.50	(2.31–8.75)	<0.001
Multivariable adjustment**:			1.02	(0.61–1.71)	0.94			3.65	(1.78–7.49)	<0.001

Note; *SGA: Small for gestational age, recorded only for pregnancies >28 weeks.
**Odds ratio for CP after labor induction adjusted for: maternal disease, gestational age, z-score for birth weight and PROM/ PPROM.
PROM, Prelabor rupture of membranes, ≥24 hours before delivery.
PPROM, Preterm prelabor rupture of membranes, ≥24 hours before delivery.

Table 5. Classification of CP in children born after induced compared with non-induced labor by gestational age, presented for children born preterm and at term separately, Norway 1997–1998.

	Preterm			Term		
	Induced labor *n* = 34(%)	Non-induced labor *n* = 71(%)	*p*-value	Induced labor *n* = 22(%)	Non-induced labor *n* = 88(%)	*p*-value
CP subtype:						
Unilateral	5 (14.7)	15 (21.1)	0.60	8 (36.4)	34 (38.6)	1.00
Bilateral						
Diplegic	21 (61.8)	35 (49.3)	0.30	4 (18.2)	16 (18.2)	1.00
Quadriplegic	2 (5.9)	13 (18.3)	0.14	10 (45.5)	7 (8.0)	<0.001
Dyskinetic	0	3 (4.2)	0.55	0 (0)	12 (13.6)	0.12
Ataxic	1 (2.9)	2 (2.8)	1.00	0 (0)	9 (10.2)	0.20
Not classified	5 (14.7)	3 (4.2)	0.11	0 (0)	10 (11.4)	0.21

we re-analyzed our data including cesarean section the OR for CP in the induction group was even higher.

Multivariable analysis showed that the excess risk of CP persisted after adjustment for a number of potential confounders available in the medical birth registry. Moreover, we controlled for preterm birth by applying stratified analyses. Nonetheless, confounding by variables not available to us cannot be excluded.

Results from the few studies addressing the link between CP and induction of labor have been conflicting (21,22). Consistent with our results, a registry-based study in Denmark by Nielsen et al. (21) showed that labor induction carried an excess risk of CP (OR: 2.5). In contrast, Gaffney et al. (22) in UK found no association (OR: 1.2). The latter study used data abstracted from hospital records, and was restricted to children born at term. Both studies were case–control studies; however, they did not assess the association between induction and specific CP subtypes separately. Thus, differences in study design and population may partly explain the different results.

Another significant difference between our study and the previous studies was the considerable difference in the proportion of labor induction in the control groups varying from 3.2% in the Danish to 25.7% in the British study. In our registry-based cohort study induction of labor was recorded in 13.4% of all children and in 17.6% if cesarean section was included. These differences are most likely explained by variations in clinical practice. Usually induction of labor follows a stepwise procedure. The first step often involves administration of cervical ripening agents such as local prostaglandin

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E analogues. When the cervix is ripe, the common procedure would be amniotomy followed by oxytocin infusion (10,37,38).

Labor induction is mainly performed to rescue the mother and the offspring from harmful effects of continuation of pregnancy such as in maternal disease, restricted or excessive intrauterine growth, prolonged rupture of membranes and prolonged pregnancy. Since such complications are risk factors for death in utero, it should be emphasized that induction of labor may have saved lives in some of the cases with CP, and also that it may have saved other children from developing CP.

Post-term pregnancies account for a significant proportion of induced deliveries. The definitions of post-term pregnancy (41 or 42 completed pregnancy weeks) and the policies of induction (induction at 41 weeks or expectant management) may vary. Thus, differences in clinical practice may also explain the different results in different studies (21,22). However, we found that even children born between gestational weeks 37 and 40 had higher odds for CP after labor induction, making this explanation seems less likely.

Even if one should be cautious in a causal inference from epidemiological studies, some findings of the present study may be in favor of such a relation. This applies for the magnitude of the association, indicated by a four-fold increased risk of CP among children born after labor induction, as well as the predominance of the quadriplegic spastic CP subtype.

We are only able to speculate on possible mechanisms leading to CP after labor induction due to lack of detailed data. One possible mechanism could be that induction of labor is more often required in children with an antenatal brain insult. This assumption could be supported by animal studies showing that labor starts late in pregnancies where the offspring had an antenatal brain insult (39,40).

Alternatively, induction of labor may directly or indirectly compromise the child during birth and may lead to, or exaggerate, a global brain insult. All drugs used for labor induction may lead to deceleration of the fetal heart rate, tachycardia or decreased short-term variability; most likely through hyperstimulation of the uterus (10,41,42). Hyperstimulation of the uterus, or excessive uterine activity, leads to less oxygen supply to the fetal brain (43) and development of metabolic acidosis (44). This could be consistent with the lower Apgar score at 5 minutes observed in the CP group, and is further supported by the predominance of the bilateral spastic subtype with four-limb affection (quadriplegia).

Also in favor of this explanation, studies addressing the short-term outcome of labor induction have described associations with neonatal seizures (45) and encephalopathy (46,47) after labor induction. Encephalopathy and seizures may be early signs of brain injury and an Australian study have suggested that newborn encephalopathy is the single most common precursor of CP at term (48) (49). In a study by Heimstad et al., induction of labor was associated with poor outcome measured in terms of low Apgar score, low pH and hypoglycaemia in the newborn (50). However, in other studies the association between labor induction and encephalopathy was not statistically significant (22,51).

In conclusion, in this study population labor induction at term was associated with excess risk of bilateral spastic CP and in particular CP with four-limb involvement. However, studies including more detailed clinical data are needed to explore if induction of labor per se may lead or contribute to a cerebral insult.

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References

1. Aicardi J. Diseases of the nervous system in childhood. London: Mac Keith Press, 2009.
2. Blair E, Stanley F. Aetiological pathways to spastic cerebral palsy. Paediatr Perinat Epidemiol. 1993;7:302–17.
3. Nelson KB. Causative factors in cerebral palsy. Clin Obstet Gynecol. 2008;51:749–62.
4. Rennie JM, Hagmann CF, Robertson NJ. Outcome after intrapartum hypoxic ischaemia at term. Seminars in fetal and neonatal medicine. [doi: 10.1016/j.siny.2007.07.006]. 2007;12:398–407.
5. Andersen GL, Irgens LM, Skranes J, Salvesen KA, Meberg A, Vik T. Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study. Dev Med Child Neurol. 2009;51:860–5.
6. Simard-Tremblay E, Shevell M, Dagenais L. Determinants of ambulation in children with spastic quadriplegic cerebral palsy: a population-based study. J Child Neurol. 2010;25:669–73.
7. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. Aust J Physiother. 2003;49:7–12.
8. The medical birth registry in Norway. Annual report. Oslo: Norwegian Institute of Public Health, 2010.
9. Information Services NHS Scotland. NHS board variations in maternity care and outcomes. Edinburgh: NHS National Services Scotland, 2005.
10. RCOG Royal College of Obstetricians and Gynaecologists. Labour Induction, clinical guidlines. 2 edn. London: RCOG Press, 2008.
11. Robson S, Pridmore B, Dodd J. Outcomes of induced labour. Aust N Z J Obstet Gynaecol. 1997;37:16–19.

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12. Le Ray C, Carayol M, Breart G, Goffinet F. Elective induction of labor: failure to follow guidelines and risk of cesarean delivery. Acta Obstet Gynecol Scand. 2007;86:657–65.
13. Martin JA, Kirmeyer S, Osterman M, Shepherd RA. Born a bit too early: recent trends in late preterm births. NCHS Data Brief. 2009:1–8.
14. Mealing NM, Roberts CL, Ford JB, Simpson JM, Morris JM. Trends in induction of labour, 1998–2007: a population-based study. Aust N Z J Obstet Gynaecol. 2009;49:599–605.
15. Simpson KR, Thorman KE. Obstetric "Conveniences": elective induction of labor, cesarean birth on demand, and other potentially unnecessary interventions. J Perinat Neonatal Nurs. 2005;19:134–44.
16. Lerchl A, Reinhard S. Where are the Sunday babies? II. Declining weekend birth rates in Switzerland. Naturwissenschaften. [10.1007/s00114-007-0305-4]. 2008;95:161–4.
17. Kramer MS. Late preterm birth: appreciable risks, rising incidence. J Pediatr. 2009;154:159–60.
18. Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. J Pediatr. 2009;154:169–76.e3.
19. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R, et al. The contribution of mild and moderate preterm birth to infant mortality. JAMA. 2000;284:843–9.
20. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371:75–84.
21. Nielsen LF, Schendel D, Grove J, Hvidtjorn D, Jacobsson B, Josiassen T, et al. Asphyxia-related risk factors and their timing in spastic cerebral palsy. Br J Obstet Gynaecol. 2008;115:1518–28.
22. Gaffney G, Sellers S, Flavell V, Squier M, Johnson A. Case-control study of intrapartum care, cerebral palsy, and perinatal death. BMJ. 1994;308:743–50.
23. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. Am J Dis Child. 1985 Oct;139:1031–8.
24. Lee J, Croen LA, Lindan C, Nash KB, Yoshida CK, Ferriero DM, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. Ann Neurol. 2005;58:303–8.
25. Nelson KB. Perinatal ischemic stroke. Stroke. 2007;38:742–5.
26. Alberman E. Birth weight and length of gestation in cerebral palsy. Dev Med Child Neurol. 1963;5:388–94.
27. Polani PE. Prematurity and cerebral palsy. Br Med J. 1958;2:1497–9.
28. Miller G. Ataxic cerebral palsy and genetic predisposition. Arch Dis Child. 1988;63:1260–1.
29. Himmelmann K, Hagberg G, Wiklund LM, Eek MN, Uvebrant P. Dyskinetic cerebral palsy: a population-based study of children born between 1991 and 1998. Dev Med Child Neurol. 2007;49:246–51.
30. Himmelmann K, McManus V, Hagberg G, Uvebrant P, Krageloh-Mann I, Cans C, et al. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity. Arch Dis Child. 2009;94:921–6.
31. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. Eur J Paediatr Neurol. 2008;12:4–13.
32. Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2000;42:816–24.
33. Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954–1970. I. Analysis of the general changes. Acta Paediatr Scand. 1975;64:187–92.
34. Mutch L, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol. 1992;34:547–51.
35. Skjaerven R, Gjessing HK, Bakketeig LS. New standards for birth weight by gestational age using family data. Am J Obstet Gynecol. 2000;183:689–96.
36. Victora C, Huttly S, Fuchs S, Olinto M. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol. 1997;26:224–7.
37. ACOG American College of Obstetricians and Gynecologists. Induction of labor. Obstetrics Gynecol Practice Bull. 2009;107.
38. Care in normal birth: a practical guide. Birth. 1997;24:121–3.
39. Gersting J, Schaub CE, Keller-Wood M, Wood CE. Inhibition of brain prostaglandin endoperoxide synthase-2 prevents the preparturient increase in fetal adrenocorticotropin secretion in the sheep fetus. Endocrinology. 2008;149:4128–36.
40. Liggins GC, Kennedy PC, Holm LW. Failure of initiation of parturition after electrocoagulation of the pituitary of the fetal lamb. Am J Obstet Gynecol. 1967;98:1080–6.
41. Hofmeyr GJ, Gulmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2010;10:CD000941.
42. Crane JM, Young DC, Butt KD, Bennett KA, Hutchens D. Excessive uterine activity accompanying induced labor. Obstet Gynecol. 2001;97:926–31.
43. Peebles DM, Spencer JA, Edwards AD, Wyatt JS, Reynolds EO, Cope M, et al. Relation between frequency of uterine contractions and human fetal cerebral oxygen saturation studied during labour by near infrared spectroscopy. Br J Obstet Gynaecol. 1994;101:44–8.
44. Bakker PCAM, Kurver PHJ, Kuik DJ, Van Geijn HP. Elevated uterine activity increases the risk of fetal acidosis at birth. Am J Obstet Gynecol. [doi: 10.1016/j.ajog.2006.11.035]. 2007;196:313e1–e6.
45. Minchom P, Niswander K, Chalmers I, Dauncey M, Newcombe R, Elbourne D, et al. Antecedents and outcome of very early neonatal seizures in infants born at or after term. Br J Obstet Gynaecol. 1987;94:431–9.
46. Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal

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encephalopathy in full-term infants. BMJ. 1995;311: 598–602.
47. Gaffney G, Flavell V, Johnson A, Squier M, Sellers S. Cerebral palsy and neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed. 1994;70:F195–200.
48. Badawi N, Felix JF, Kurinczuk JJ, Dixon G, Watson L, Keogh JM, et al. Cerebral palsy following term newborn encephalopathy: a population-based study. Dev Med Child Neurol. 2005;47:293–8.
49. Dixon G, Badawi N, Kurinczuk JJ, Keogh JM, Silburn SR, Zubrick SR, et al. Early developmental outcomes after newborn encephalopathy. Pediatrics. 2002;109: 26–33.
50. Heimstad R, Romundstad PR, Eik-Nes SH, Salvesen KA. Outcomes of pregnancy beyond 37 weeks of gestation. Obstet Gynecol. 2006;108(3, Part 1):500–8.
51. Dale A, Stanley FJ. An epidemiological study of cerebral palsy in western Australia, 1956–1975. ii: spastic cerebral palsy and perinatal factors. Dev Med Child Neurol. 1980;22:13–25.

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Paper IV

The effects of multiple risk factors on cerebral palsy. A register based study.

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Keywords: Cerebral palsy, risk factors, interaction, epidemiology, risk.

Abbreviations: AP-attributable proportion, CI-confidence interval, CP-Cerebral palsy, CPRN-Norwegian Cerebral Palsy Registry, ICR-interaction contrast ratio, MBRN-Medical Birth Registry of Norway, OR-odds ratio, RF-Risk factor, SGA-small for gestational age.

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Guro L Andersen and Areej I Elkamil initially explored and analyzed the data, while Magne Stoknes performed the final as well as the advanced statistical analyses.

Guro L Andersen and Magne Stoknes together wrote the first version of the paper, and completed the final version. They have contributed equally to the completion of the manuscript.

Lorentz M Irgens was principal responsible for the data from the medical birth registry, and contributed significantly to the design of the study as well as interpretation of the data.

Jon Skranes and Kjell Å Salvesen contributed significanly to the interpretation of the data, Jon Skranes as neuropaediatrician and Kjell Å Salvesen as obstetrician.

Torstein Vik initiated the project, supervised the analyses, was main responsible for the interpretation of the data and drafting the manuscript.

All authors have contributed significantly to the drafting and critically reviewed the final version of the article.

ABSTRACT

Objective: To examine the effects of multiple risk factors on cerebral palsy (CP).

Materials/methods: For 176 591 Norwegian infants born 1996-98 and surviving the early neonatal period, data on a number of pre- and perinatal risk factors (RFs) for CP were available in the Medical Birth Registry of Norway. For 241 children with CP detailed clinical data were available in the Norwegian CP registry.

Results: 43 (18 %) children with CP had none of the available RFs, 22 % had one, 51 % had two to four, and 10 % had five or more RFs. The odds ratio for CP increased exponentially from 2.4 (CI: 1.6; 3.6) for one to 124 (CI: 59; 258) if six or more RFs were registered. For children born at term, 30 % had no RF, and none had five or more, while in children born preterm, 9 % had no additional RF and another 9 % had five or more ($p<0.001$ vs. term). In both groups, few children shared the same combination of RFs. The most detrimental effect was observed for the combination of maternal disease and low 5-minute Apgar score, registered in 11.2 % of children with CP. The combination of maternal disease and premature birth had an interaction contrast ratio of 9.25 (CI: 3.56; 14.94), suggesting biological interaction.

Conclusions: We found an exponentially increased risk for CP with increasing number of RFs. Combinations of RFs were more common in children born preterm than at term. However, few children shared the same combination.

INTRODUCTION

Cerebral palsy (CP) comprises a group of disorders of movement, posture and motor functions due to non-progressive lesions or abnormalities in the immature brain[1]. Several authors have proposed that CP probably is the result of a cascade of events[2-7]. These events may be associated with a number of risk factors occurring before (i.e. pre-pregnancy risk factors) or during pregnancy, or at birth and in the first days of life. A number of pre-pregnancy risk factors has been described including maternal age[7], parity[7,8] and maternal diseases including epilepsy[9], diabetes[7] and thyroid disease[9-12]. In addition a recent study has proposed a genetic background by identifying certain single polymorphisms associated with cerebral palsy[13]. Risk factors occurring early or late in pregnancy are assisted fertilization[14], male gender[7], congenital malformation[9-11,15,16], multiple pregnancy[17,18] and intrauterine growth restriction[19] Finally, potential risk factors at birth include preterm delivery[20,21], breech presentation[7,22,23], induction of labour[24], placental abruption[25] and low Apgar score[26,27].

Theoretically each of the above mentioned risk factors may reflect events that could either trigger, or be part of a cascade leading to an early brain insult. Blair and Stanley, in 1993 concluded that many possible routes may lead to CP, however each route contributed only to a small proportion of cases[10,11]. More recently, Keogh and Badawi concluded that the future of CP research lies in understanding the complex interactions of multiple risk factors[3]. In this study, we aimed to examine the combined effects of multiple risk factors for CP using data from the Norwegian Cerebral Palsy Registry and the Medical Birth Registry of Norway.

Materials and methods

Study design

This register study included all live born children in Norway between 1st of January 1996 and 31st of December 1998 surviving the neonatal period. Data on risk factors were recorded in the Medical Birth Registry of Norway (MBRN)[28], and the Norwegian Cerebral Palsy Registry (CPRN) provided clinical data on children diagnosed with CP. The MBRN linked their data with the data from CPRN using each child`s unique 11-digit personal identification code. The CP registry is an informed consent based registry collecting data from the 20 pediatric habilitation centers in Norway. Details on the registry have been published earlier[22]. The data used in this study were collected between January the 1st of 2003 and 31st of March 2006, when the children were at least four years old.

Study population

During the study period, 176 591 children survived the early neonatal period, and 373 of them were diagnosed with CP. Parents of six (2 %) children with CP refused to participate, while some participating centers could not provide detailed data on 72 cases mainly due to work overload. Fifteen children with CP were born abroad and were not registered by the MBRN. Another 15 children had a post-neonatal cause of their CP, and for 22 children the MBRN was not able to link the data, probably due to an an error in the 11-digit personal identification code. Thus, the final study population comprises 241 children with CP and 176 350 control children.

Study variables

CP was diagnosed and classified according to the recommendations by the Surveillance of Cerebral Palsy in Europe[1].

Among the items of data available in the MBRN, twelve risk factors for CP were chosen based on the literature (table 1).

Maternal disease (diabetes, anemia, hypertension, preeclampsia, eclampsia, epilepsy, thyroid dysfunction, chronic renal disease, urinary tract infection, venereal diseases or rubella), assisted fertilization (*in vitro* fertilisation and/or intra cytoplasmic sperm injection), plurality (number of children born ≥ 2), abnormal placental structure (defined as presence of fibrin or calcium depositions, placental oedema, bleeding in placenta, infarction in placenta, necrotic placenta or other pathological conditions in placenta), bleeding in pregnancy, small for gestational age (SGA, birth weight below the 10th percentile for gestational age), abnormal presentation (occipital, abnormal cephalic, breech or transverse presentation), rupture of membranes 24 hours or more prelabour, placental abruption, induction of labour (use of prostaglandin, oxytocin, amniotomy, sectio, methylergonovine/Pathergin or other provocation), Apgar score < 7 at five minutes and preterm birth (length of gestation < 37 weeks based on last menstrual period). The associations between these risk factors and CP are shown in table 1.

Ethics

Written informed consent to record detailed data in the register and to link data from the MBRN with data from the CPRN was obtained from the parents. The

study was approved by the Norwegian Data Inspectorate and the Regional Ethical Committee (REC) for medical research in Mid-Norway.

Statistical methods

Statistical analyses were carried out using SPSS (The Statistical Package for Social Sciences) for Windows, version 17.0 (SPSS Inc, Chicago, IL, USA). Sun Java was applied to generate the syntax used in SPSS, and Eclipse 3.4.0 for Windows was used as compiler.

Odds ratios (OR) with 95 % confidence intervals (CI) were calculated as estimates of the relative risk for CP if a specific risk factor was present, using children without this risk factor as reference. Odds ratios were also calculated for the combinations of two up to seven risk factors, using children without any of the recorded risk factors as reference. We also counted the number of cases with each specific combination of risk factors in order to identify if some combinations were more common than others. For the most common combinations we estimated their combined OR and their interaction using the interaction contrast ratio $ICR = OR(AB) - OR(A\overline{B}) - OR(\overline{A}B) + 1$ where OR(AB) denotes the OR for the combination of risk factor A and B, OR($A\overline{B}$) denotes the OR for the presence of A, but not B, and OR($\overline{A}B$) denotes the OR for the presence of B, but not A. An ICR-value above 0 indicates that the odds for CP for a given combination of risk factors is higher than the additive effect of each of the factors, and may suggest biological interaction. For combinations with a positive ICR we calculated the proportion attributable (AP) to interaction as AP = ICR/ OR(AB)[29,30]. For both

ICR and AP the confidence intervals were calculated according to the methodology described by Hosmer and Lemeshow (1992)[31].

All analyses were done for the total study population as well as for children born at term (≥ 37 weeks) and preterm (< 37 weeks) separately.

RESULTS

Among all children, 43 (18 %) had no risk factors, 22 % had one, 51 % had two to four, and 10 % had five or more risk factors (table 2) . The odds ratio for CP increased exponentially ($p < 0.001$) from 2.4 (CI: 1.6; 3.6) if one risk factor was present to 2240 (CI: 138; 36395) if eight of the selected risk factors were present (table 2).

Among children born at term 33 (30 %) had no risk factors, 37 % had one, 33 % had two or more, and none had five or more risk factors (table 2). The odds ratio for CP increased exponentially ($p < 0.001$) from 2.6 (CI: 1.6; 4.0) if one risk factor was observed to 15.9 (CI: 6.2; 40.7) if four risk factors were observed (table 2).

Among children born preterm, 9 % had no additional risk factor ($p < 0.001$ vs. term), 21 % had one, and 70 % had two or more ($p <0.001$ vs. term) risk factors. Overall 9 % had five or more additional risk factors ($p = 0.001$ vs. term). The odds ratio for CP in this group increased exponentially ($p < 0.001$) from 2.5 (CI: 1.2; 5.5) if one additional risk factor was present to 340 (CI: 177; 654) if seven risk factors were present (table 2). However, only one child with CP had seven risk factors in the preterm group, and only two children had six risk factors.

Among all children the four most common combinations of risk factors were maternal disease and preterm delivery, preterm delivery and induction, maternal disease and induction, and maternal disease and 5-minute Apgar score < 7 (table 3). Maternal disease and 5-minute Apgar score < 7 was the combination with the highest OR among both term and preterm born children. The only combination with an ICR significantly different from zero was the combination of maternal disease and preterm birth (table 3). However, the proportion attributable to interaction when these two risk factors were present was not statistically significantly different from zero (AP = 0.51, CI: -0.34; 1.35). Among children born at term (figure 1) as well as for children born preterm (figure 2) very few shared the same combinations of risk factors.

DISCUSSION

We found an exponentially increasing risk for CP with increasing number of risk factors. The combination of several risk factors was more common among children born preterm than among those born at term. However, overall very few children shared the same combination of risk factors. The most detrimental effects of combined risk factors were observed for the combinations of maternal disease and low Apgar score at five minutes, maternal disease and preterm delivery and preterm delivery and induction of labour. For the combination of maternal disease and preterm delivery we found evidence for biological interaction between the two risk factors.

The increasing risk for CP with increasing number of risk factors as well as for specific combinations is unlikely to be due to chance, as indicated by the very low p-values. The prospective recording of risk factors is a strength of the study. The diagnosis of CP was in accordance with European guidelines[1], and all children were at least four years old when the diagnosis was confirmed. A potential limitation may be that clinical data were missing for 80 children in the CPRN. However, the reason for missing cases was mainly work overload on the neuropediatricians in some centers, while only six families (2 %) refused to have their children registered. We find it most unlikely that perinatal data on children with CP differed systematically between neuropediatric centres able and unable to provide detailed clinical data. These drop outs were therefore most likely at at random. Finally the misclassification of these children as non-CP cases is negligible compared with the 176 350 other control children included. The wide confidence intervals for ICR and AP, probably due to the fact that very few

children shared the same combination of risk factors, suggest that the interaction observed should be interpreted with caution. The excess risks for CP associated with each risk factor separately (table 1) is consistent with a number of previous studies suggesting that our CP population is representative[4, 13, 14].

A number of previous studies have explored risk factors for CP[7-9,12-27], however we have found only one study addressing the risk associated with combinations of risk factors[10,11]. Consistent with our study, Blair and Stanley found that the risk for spastic CP increased exponentially with increasing number of risk factors, that risk factors were more common in preterm than in term born children, that some combinations increased the risk for spastic CP when occurring together, and that each route leading to CP contributed only a small proportion of all cases[10,11]. However, even if they included a number of peri- and neonatal clinical risk factors not available to us, the proportion without identified risk factors in their study was higher (35 %) than in our study (18 %). This difference may partly be explained by differences in design, since their study was a nested case- control study of children with spastic CP, but also to differences in the quality and availability of the recorded risk factors.

The high and exponentially increasing ORs associated with increasing number of risk factors may be consistent with the concept of a "causal pathway", meaning that the brain injury leading to CP probably is a consequence of several consecutive interdependent events; a cascade of events[6]. This interpretation may also be consistent with our finding of detrimental effects of the consecutive combinations of maternal disease and low Apgar score at five minutes, and of

maternal disease and preterm delivery, and in particular with the evidence for biological interaction between the latter combination.

On the other hand, Nelson (2008) has proposed that the multiplicity of risk factors in the etiology of CP means that a causal *web* is a more realistic model[4], meaning that multiple risk factors converge concurrently without an evident linear causal chain[32,33]. Our finding of a large number of different combinations of risk factors, but with increasing risk with increasing number may also be consistent with this interpretation.

Overall, the finding that very few children shared the same combinations of risk factors suggests that children may have different vulnerability to different risk factors[4], and that some children in general are more vulnerable to insults than others. Consistent with this, recent studies have reported on associations between cerebral palsy and a number of candidate genes[4,11,32]. Further, familial aggregation of CP has been reported in populations with high rates of consanguinity[4]. Thus, we speculate that a child's immanent vulnerability to one or more adverse events *in utero* or at birth represent be the etiological background of CP.

Multiple risk factors were present in 70 % of children born preterm and in 90 % if prematurity is included.as one of the risk factors. Thus, in preterm children the theory of a "causal pathway" may be more probable, since it is reasonable to assume that the immature brain (in general) is more susceptible to damage[34]. In contrast, among children born at term only 1/3 of the children had more than one risk factor, and in this group individual susceptibility, perhaps explained by gene polymorphisms, may play a larger role. Thus, in children born at term the causal web- theory may be the best model.

In conclusion, we found that the risk for CP increased exponentially with increasing number of risk factors. However, few children shared the same combination of risk factors. Our results may be consistent with the notion that CP in preterm children is the result of a cascade of events while in children born at term, the child's individual vulnerability to an adverse event, may play a larger role.

REFERENCES

1. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). *Dev Med Child Neurol.* Dec 2000;42(12):816-824.

2. Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. *Best Pract Res Clin Obstet Gynaecol.* Jun 2004;18(3):425-436.

3. Keogh JM, Badawi N. The origins of cerebral palsy. *Curr Opin Neurol.* Apr 2006;19(2):129-134.

4. Nelson KB. Causative factors in cerebral palsy. *Clin Obstet Gynecol.* Dec 2008;51(4):749-762.

5. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. *Aust J Physiother.* 2003;49(1):7-12.

6. Stanley F, Blair E, Alberman E. *Cerebral palsies : epidemiology and causal pathways*. London: Mac Keith; 2000.

7. Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. *Obstet Gynecol.* Dec 2006;108(6):1499-1505.

8. Topp M, Langhoff-Roos J, Uldall P. Preterm birth and cerebral palsy. Predictive value of pregnancy complications, mode of delivery, and Apgar scores. *Acta Obstet Gynecol Scand.* Oct 1997;76(9):843-848.

9. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med.* Jul 10 1986;315(2):81-86.

10. Blair E, Stanley F. Aetiological pathways to spastic cerebral palsy. *Paediatr Perinat Epidemiol.* Jul 1993;7(3):302-317.

11. Blair E, Stanley F. When can cerebral palsy be prevented? The generation of causal hypotheses by multivariate analysis of a case-control study. *Paediatr Perinat Epidemiol.* Jul 1993;7(3):272-301.

12. Pharoah PO, Buttfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet.* Feb 13 1971;1(7694):308-310.

13. Gibson CS, Maclennan AH, Dekker GA, et al. Candidate genes and cerebral palsy: a population-based study. *Pediatrics.* Nov 2008;122(5):1079-1085.

14. Hvidtjorn D, Grove J, Schendel DE, et al. Cerebral palsy among children born after in vitro fertilization: the role of preterm delivery--a population-based, cohort study. *Pediatrics.* Aug 2006;118(2):475-482.

15. Croen LA, Grether JK, Curry CJ, Nelson KB. Congenital abnormalities among children with cerebral palsy: More evidence for prenatal antecedents. *J Pediatr.* Jun 2001;138(6):804-810.

16. Torfs CP, van den Berg B, Oechsli FW, Cummins S. Prenatal and perinatal factors in the etiology of cerebral palsy. *J Pediatr.* Apr 1990;116(4):615-619.

17. Pharoah PO. Risk of cerebral palsy in multiple pregnancies. *Clin Perinatol.* Jun 2006;33(2):301-313.

18. Topp M, Huusom LD, Langhoff-Roos J, Delhumeau C, Hutton JL, Dolk H. Multiple birth and cerebral palsy in Europe: a multicenter study. *Acta Obstet Gynecol Scand.* Jun 2004;83(6):548-553.

19. Jarvis S, Glinianaia SV, Torrioli MG, et al. Cerebral palsy and intrauterine growth in single births: European collaborative study. *Lancet.* Oct 4 2003;362(9390):1106-1111.

20. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. *Acta Paediatr.* Mar 2001;90(3):271-277.

21. Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. *Acta Paediatr.* Mar 2005;94(3):287-294.

22. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. *Eur J Paediatr Neurol.* Jan 2008;12(1):4-13.

23. Krebs L, Topp M, Langhoff-Roos J. The relation of breech presentation at term to cerebral palsy. *Br J Obstet Gynaecol.* Sep 1999;106(9):943-947.

24. Nielsen LF, Schendel D, Grove J, et al. Asphyxia-related risk factors and their timing in spastic cerebral palsy. *BJOG.* Nov 2008;115(12):1518-1528.

25. Jacobsson B, Hagberg G, Hagberg B, Ladfors L, Niklasson A, Hagberg H. Cerebral palsy in preterm infants: a population-based case-control study of antenatal and intrapartal risk factors. *Acta Paediatr.* 2002;91(8):946-951.

26. Blair E, Stanley FJ. Intrapartum asphyxia: a rare cause of cerebral palsy. *J Pediatr.* Apr 1988;112(4):515-519.

27. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics.* Jul 1981;68(1):36-44.

28. Medical Birth Registry of Norway, Statistics database. http://mfr-nesstar.uib.no/mfr/. Accessed 01/05, 2010.

29. Rothman KJ. *Modern Epidemiology*. Boston: Little; 1998.

30. Ahlbom A, Alfredsson L. Interaction: A word with two meanings creates confusion. *Eur J Epidemiol.* 2005;20(7):563-564.

31. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology.* Sep 1992;3(5):452-456.

32. Krieger N. Epidemiology and the web of causation: has anyone seen the spider? *Soc Sci Med.* Oct 1994;39(7):887-903.

33. Vineis P, Kriebel D. Causal models in epidemiology: past inheritance and genetic future. *Environ Health.* 2006;5:21.

34. Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol.* Feb 2007;49(2):144-151.

TABLES

Table 1: Occurence of risk factors among children with and without cerebral palsy (CP) in a national cohort of 176 591 children. The table als shows odds ratio (OR) with 95 % confidence intervals (CI) for CP in the presence of one of the risk factors using children without the selected risk factor as reference.

Risk factor	CP cases (%)		Cases in control group (%)		All cases OR (CI)	Term (≥ 37 weeks) OR (CI)	Preterm (< 37 weeks) OR (CI)
1. Maternal disease	104	(43.1)	39020	(22.1)	2.7 (2.1; 3.5)	1.3 (0.8; 2.0)	2.1 (1.4; 3.1)
2. Assisted fertilization	13	(5.4)	2031	(1.5)	4.9 (2.8; 8.6)	1.0 (1.0; 1.0)	2.5 (1.3; 5.1)
3. Plurality	20	(8.3)	2781	(1.6)	5.7 (3.6; 9.0)	0.9 (0.1; 7.0)	1.6 (0.9; 2.8)
4. Placental structure	25	(10.0)	10684	(6.0)	1.8 (1.2; 2.7)	1.1 (0.5; 2.4)	1.8 (1.1; 3.2)
5. Bleeding in pregnancy	19	(7.8)	2344	(1.3)	6.4 (4.0; 10.1)	0.9 (0.1; 6.4)	3.1 (1.8; 5.3)
6. Preterm birth	105	(43.6)	11573	(6.5)	11.0 (8.5; 14.2)	-	-
7. SGA	34	(14.1)	12135	(6.9)	2.2 (1.5; 3.2)	3.6 (2.3; 5.7)	0.9 (0.5; 1.9)
8. Abnormal presentation	31	(12.9)	8871	(5.0)	2.8 (1.9; 4.1)	2.0 (1.1; 3.9)	1.9 (1.1; 3.1)
9. Rupture of membranes 24 hours prelabour	24	(10.0)	2898	(1.6)	6.6 (4.3; 10.1)	1.8 (0.4; 7.1)	2.2 (1.4; 3.6)
10. Placental abruption	21	(8.7)	949	(0.5)	17.7 (11.3; 27.8)	16.0 (6.5; 39.5)	4.4 (2.5; 7.9)
11. Induction	73	(30.3)	31203	(17.7)	2.0 (1.5; 2.7)	1.8 (1.2; 2.7)	1.3 (0.9; 1.9)
12. 5-minute Apgar score < 7	57	(23.7)	2420	(1.4)	22.8 (16.9; 30.8)	38.0 (24.5; 58.9)	4.0 (2.5; 6.2)

Table 2: Odds ratios (OR) with 95% confidence intervals (CI) for CP by number of risk factors (versus none) in term and preterm births, Norway 1996-98.

	All cases			Term (≥ 37 weeks)			Preterm (< 37 weeks)		
Number of risk factors	CP cases (%)	OR	CI	CP cases (%)	OR	CI	CP cases (%)	OR	CI
0	43 (17.9 %)	1.0		33 (30.3 %)	1.0		9 (8.9 %)	1.0	
1	52 (21.6 %)	2.4	1.6; 3.6	40 (36.7 %)	2.6	1.6; 4.0	21 (20.8 %)	2.5	1.2; 5.5
2	51 (21.2 %)	5.6	3.7; 8.4	20 (18.3 %)	3.5	2.0; 6.0	30 (29.7 %)	3.8	1.8; 7.9
3	45 (18.7 %)	13.6	8.9; 20.6	11 (10.1 %)	7.5	3.8; 14.8	18 (17.8 %)	4.3	1.9; 9.7
4	26 (10.8 %)	23.1	14.2; 37.7	5 (4.6 %)	15.9	6.2; 40.7	14 (13.9 %)	9.6	4.1; 22.2
5	15 (6.2 %)	48.7	26.9; 88.1	0	N/A		6 (5.9 %)	15.7	5.5; 44.7
6-8	9 (3.7 %)	123.7	59.3; 257.9	0	N/A		3 (3.0 %)	59.9	14.9; 240.6
Sum cases	241			109*			101*		

* Gestational age was missing in 26 (10.8 %) of the cases, and information about risk factors was missing in 5 (2 %) of the cases.

Table 3: Odds ratios (OR) and interaction contrast ratio (ICR) with 95% confidence intervals (CI) for CP in the most common combinations of two risk factors, using children without the same combination as reference, Norway 1996-98.

All cases (n=241)

Combination of risk factors	CP cases (%)	OR	CI	ICR	CI
Maternal disease and preterm delivery	66 (27.4 %)	18.2	13.2; 25.2	9.25	3.56; 14.94
Preterm delivery and induction	43 (17.8 %)	16.3	11.3; 23.6	3.11	-2.89; 9.10
Maternal disease and induction	41 (17.0 %)	3.9	2.7; 5.6	0.38	-1.22; 1.99
Maternal disease and 5-minute Apgar score < 7	27 (11.2 %)	39.1	25.5; 60.0	12.50	-8.75; 33.76

Term (≥ 37 weeks) (n=109)

Combination of risk factors	CP cases (%)	OR	CI	ICR	CI
Maternal disease and induction	11 (10.9 %)	2.1	1.1; 3.9	0.21	-1.48; 1.90
SGA and induction	9 (8.3 %)	6.3	3.1; 12.7	2.49	-2.15; 7.13
Maternal disease and 5-minute Apgar score < 7	8 (7.3 %)	47.0	22.3; 98.8	9.70	-32.62; 52.01
Maternal disease and SGA	8 (7.3 %)	4.3	2.1; 9.0	0.58	-3.27; 4.42

Preterm (< 37 weeks) (n=101)

Combination of risk factors	CP cases (%)	OR	CI	ICR	CI
Maternal disease and induction	29 (28.7 %)	2.3	1.4; 4.0	-0.78	-2.35; 0.79
Maternal disease and 5-minute Apgar score < 7	17 (16.8 %)	7.0	3.8; 12.8	1.25	-4.46; 6.96
Maternal disease and bleeding in pregnancy	15 (14.9 %)	4.1	2.3; 7.6	N/A	-
Maternal disease and abnormal presentation	11 (10.9 %)	4.0	2.0; 8.0	0.98	-2.14; 4.09

Figure 1: The distribution of combinations of risk factors for children with CP born at term (1: Maternal disease, 2: Assisted fertilization, 3: Plurality, 4: Placental structure, 5: Bleeding in pregnancy, 6: Birth weight below the 10th percentile for gestational age (SGA), 7: Abnormal presentation, 8: Rupture of membranes 24 hours prelabour, 9: Placental abruption, 10: Induction, 11: 5-minute Apgar score < 7).

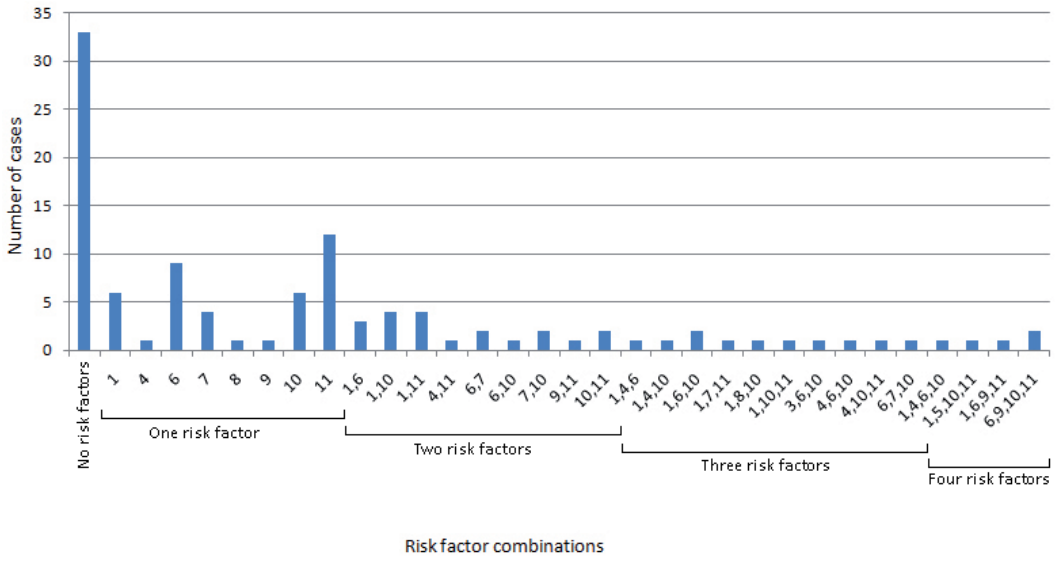
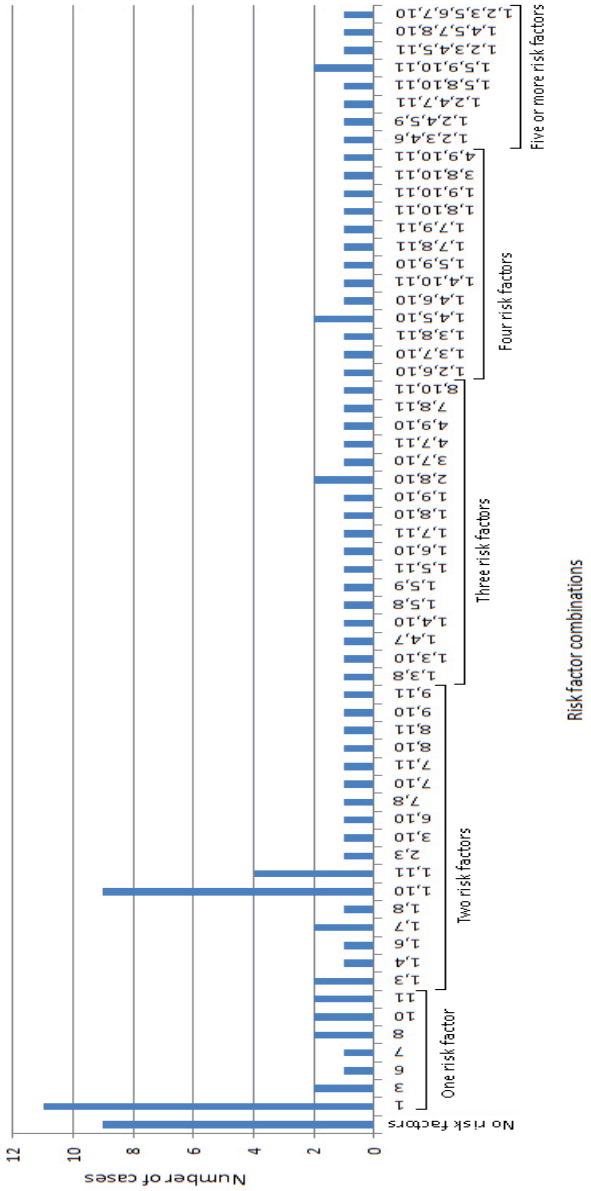


Figure 2: The distribution of combinations of risk factors for children with CP born preterm (1: Maternal disease, 2: Assisted fertilization, 3: Plurality, 4: Placental structure, 5: Bleeding in pregnancy, 6: SGA (birth weight below the 10th percentile for gestational age), 7: Abnormal presentation, 8: Rupture of membranes 24 hours prelabour, 9: Placental abruption, 10: Induction, 11: 5-minute Apgar score < 7).



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56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.

66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.

134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
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