Title
Maternal Risk Factors for Congenital Cerebral Palsy

Author
Streja, Elani

Publication Date
2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Maternal Risk Factors for Congenital Cerebral Palsy

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Epidemiology

by

Elani Streja

2012

ABSTRACT OF THE DISSERTATION

Maternal Risk Factors for Congenital Cerebral Palsy

by

Elani Streja

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2012

Professor Jørn Olsen, Chair

Congenital Cerebral Palsy (CP) is the most common physical disability in children. In spite of major advances in medical technology, the etiology of CP is still not well understood. There is growing evidence that brain damage leading to CP development occurs during pregnancy and that maternal phenotype contributes to this intrauterine environment. We hypothesized that maternal factors such as infections, smoking, comorbidities and genetics can increase the risk of CP in children. Additionally, we hypothesized the relationship between birth weight and placenta weight is a proxy for placenta insufficiency, which may be an important factor in the pathology leading to CP. The aim of this dissertation is to examine the associations between these maternal factors and CP in the child.

We carried out studies using both Danish national registries and the Danish National Birth Cohort. Diagnoses of CP in the child were ascertained using the Danish

National Cerebral Palsy Register. Cox proportional hazard ratios were calculated to estimate risk of CP or risk of cardiovascular disease. For studies on placental disorders, placenta weight, and birth weight, we identified 1,874,653 singleton births occurring between January 1st 1973 and December 31st 2003, of which 2,547 had CP. We found the risk of CP decreased with increasing continuous placenta weight (/100g) (aHR 0.68; 95% CI: 0.64-0.71). However, adjustment for continuous birth weight (kg) reversed this association (aHR 1.15; 95% CI: 1.07-1.22). Associations with CP were additionally found for vaginal bleeding, diabetes in pregnancy and hypertensive disorders in pregnancy, but associations were no longer significant after adjustment for both birth weight (kg) and placenta weight (/100g). The association between placenta abruption and CP risk remained significant after adjustment for both placenta weight and birth weight. After stratification on several birth weight groups, continuous placenta weight was not significantly associated with CP.

For the study on cardiovascular risk in parents of children with CP, we used the children in Study 1, and identified the mothers of 1,021,955 singleton firstborns, of whom 2,508 had CP. After adjustment for demographic confounders, child being born small for gestational age and maternal hypertensive disorder during pregnancy, the “all cardiovascular disease” endpoint was significantly associated with CP (aHR 1.32; 95% CI: 1.04-1.68). However, after additional adjustment for preterm birth the association was no longer significant (aHR 1.11; 95% CI: 0.87-1.42). In cardiovascular subtypes, however, cerebrovascular disease and thrombosis did remain significant in adjusted models including preterm birth (aHR 2.08; 95% CI: 1.11-3.91 and aHR 3.23; 95% CI:

1.19-8.78 respectively). For fathers, the adjusted hazard ratios were much lower and did not reach the level of significance for any of the endpoints.

In the study of self reported maternal infections, maternal smoking and CP risk we included 81,066 singletons who were born between August 1996 and June 2003 in the Danish National Birth Cohort. Self-reported vaginal infections were associated with an increased risk of overall CP and spastic CP (aHR: 1.52; 95% CI: 1.04-2.24 and aHR: 1.73; 95% CI: 1.16-2.60). In particular untreated vaginal infections were associated with an increased risk of spastic CP (aHR: 1.95; 95% CI: 1.16-3.26). Fever was associated with the risk of CP (aHR: 1.53; 95% CI: 1.06-2.21). Smoking 10 or more cigarettes per day during pregnancy was also associated with spastic CP (aHR: 1.80; 95% CI: 1.10-2.94). There were interactions on a multiplicative scale for the outcome spastic CP between untreated vaginal infections and either smoking 10 or more cigarettes per day or preterm delivery. Urinary tract infections were not associated with having a child with CP.

In conclusion, maternal factors may affect the intratuterine environment and play a role in the etiology of CP.

The dissertation of Elani Streja is approved.

Catherine Sugar

Onyebuchi Arah

Beate Ritz

Jørn Olsen, Committee Chair

University of California, Los Angeles

2012

DEDICATIONS

To the Streja family: past, present, and future.

Thanks Dad!

In loving memory of my grandparents Dr. Marcel Streja, professor of urology, Dr. Eugenia Streja, professor of ob/gyn who would have loved to discuss the contents of this thesis with me, Dr. Elazar Sternhell, after whom I am named and who has always looked out for me and guided me to my doctorate and Mrs. Hinda Sternhell, who loved me more than anyone in this world.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

aHR	Adjusted Hazard Ratio
ADHD	Attention Deficit Hyperactivity Disorder
CP	Congenital Cerebral Palsy
DNBC	Danish National Birth Cohort
HDP	Hypertensive Disorders of Pregnancy
HR	Hazard Ratio
ICD	International Classification of Disease
IUGR	Intrauterine Growth Restriction
N	Number
PVL	Periventricular Leukomalacia
sCP	Spastic Cerebral Palsy
SCPE	Surveillance Cerebral Palsy in Europe
SGA	Small for gestational age

ACKNOWLEDGMENTS

Many thanks to Dr. Jørn Olsen, my advisor and committee chair for making this research possible and for his direction, guidance, encouragement, patience and wisdom. Thank you to my doctoral committee Dr. Beate Ritz, Dr. Onyebuchi Arah, and Dr. Catherine Sugar for their insight and mentorship.

This dissertation would not be possible without the assistance and support of my family: my father Dr. Dan Streja, my mother: MOE Lidia Streja, my brother CFO David Streja MBA, my sister Dr. Leanne Streja, my sister-in-law CD Stephanie Streja, and special appearance by Muscat Streja. Thank you also to Hilda, Jorge, and FDr. Viviana Marroquin and Andrea Tanchez.

Thank you to Dr. Jakob Grove from University of Aarhus, Denmark for your unending patience and being with me from the beginning of this journey.

I would also like to thank from University of Aarhus, Denmark, Dr. Chunsen Wu, Dr. Lars Henning Pedersen, Dr. Bodil H. Bech, Ms. Gitte Nielsen, and Mr. Antonio Sylvester, from the Danish National Cerebral Palsy Register, Dr. Peter Uldall, and from the Danish National Birth Cohort Ms. Inge Bente Laue Eisensee for answering my numerous questions, and for supporting me, encouraging me and helping me with these projects.

I would like to acknowledge my coauthors from the Center for Disease Control and Prevention National Center on Birth Defects and Developmental Disabilities, Dr. Diana

E. Schendel, Dr. Marshalyn Yeargrin-Allsopp, Dr. Kim Van Naarden Braun, and Dr. Deborah Christensen who provided much detailed assistance on these projects.

Thank you to Ms. Joy Miller for being my guide and holding my hand through every step of this journey. I would also like to thank my UCLA coauthors Dr. Jessica E. Miller (my epi sister), Dr. Naomi Greene, Dr. Shannon L. Rhodes, Dr. Jasveer Virk, Dr. Joni Ricks, and FDr. Zeyan Liew. An additional thank you goes to my epi family study buddies Dr. Jodie Katon, Dr. Ximena Vergara, FDr. Rhodri Dierst-Davies, and FDr. Robin Jeffries (Biostatistics) who helped me study, laughed with me, and encouraged me through the 200 series and doctoral exam.

Thank you to Dr. Simin Liu, Dr. Luisa Iruela-Arispe, and Dr. Mark Litwin for helping me enter into UCLA SPH, to Dr. Lisa Smith for all your love, laughter, and support, and to Drs. Linda and Ed McCabe who taught me so much about how to look at my research from a social perspective and gave me so many opportunities through the UCLA Center for Society and Genetics.

Thank you to Dr. Kam Kalantar-Zadeh, Dr. Miklos Molnar, and Ms. Jennie Jing from LA Biomed who taught me so much of the fundamentals of epi research and provided the most productive and fun work environment for the past 5 ½ years. Thank you for laughing with me!

Finally thank you to my friends who kept me laughing and inspired every day: Kimberly Wathen/Mills, Christian Medina, Dorian Ovalle, Sgt. Jeff Graham, Mario Alaniz (thank you for my nickname), Mike Burton, Elio Plascencia, Patrick Kenny, Kaiyana Rain,

Leslie Maltz, mi Borrachos, KM families, Dr. Elizabeth Stordeur Pryor, Amanda Goldberg, Dr. Sean Owen, Dr. Antigone Oreopoulos, Melissa and Addison Bakewell families, Joslyn and Hernandez family, Steve, Rowan, Taryn, Anwyn and Benson family, David Goldstein and family, the Feder family and my cousins Merav Inbar, Ben Amit, and Gad Inbar (so lucky my travels to Denmark allowed me to see you!).

Final thanks again to my sister Leanne who brings both knowledge and silliness to everything I do! You're so next!

This dissertation was funded by grants from the Center for Disease Control and Prevention National Center on Birth Defects and Developmental Disabilities, and fellowships from UCLA FSPH Department of Epidemiology, and UCLA Center for Society and Genetics.

VITA

2000	B. S., Biochemistry University of California, Davis Davis, California
2006	M. P. H., Epidemiology University of California, Los Angeles Los Angeles, California

PUBLICATIONS

1: Molar MZ, Streja E, Kovesdy CP, Hoshino J, Hatamizadeh P, Glassrock RJ, Ojo AO, Kalantar-Zadeh K. Estimated glomerular filtration rate at reinitiation of dialysis and mortality in failed kidney transplant recipients. Nephrol DialTransplant. 2012 Apr 20. PubMed PMID: 22523118.

2: Kalantar-Zadeh K, Streja E, Molnar MZ, Lukowsky LR, Krishnan M, Kovesdy CP, Greenland S. Mortality Prediction by Surrogates of Body Composition: An Examination of the Obesity Paradox in Hemodialysis Patients Using Composite Ranking Score Analysis. A J Epidemiol. 2012 Mar 16. PubMed PMID: 22427612.

3: Molar MZ, Kovesdy CP, Rosivall L, Bunnapradist S, Hoshino J, Streja E, Krishnan M, Kalantar-Zadeh K. Associations of pre-transplant anemia management with post-transplant delayed graft function in kidney transplant recipients. Clin Transplant. 2012 Mar 12. doi: 10.1111/j.1399-0012.2012.01598.x. PubMed PMID: 22443414.

4: Molnar MZ, Streja E, Kovesdy CP, Shah A, Huang E, Bunnapradist S, Krishana M, Kopple JD, Kalantar-Zadeh K. Age and the Associations of Living Donor and Expanded Criteria Donor Kidneys with Kidney Transplant Outcome. Am J Kidney Dis. 2012 Feb 3. PubMed PMID: 22305759.

5: Streja E, Molnar MZ, Kovesdy CP. Race, age, and mortality among patients undergoing dialysis. JAMA. 2011 Nov 23; 306(20):2215; author reply 2215-6. PubMed PMID: 22110100.

6: Molnar MZ, Streja E, Kovesdy CP, Budoff MJ, Nissenson AR, Krishnan M, Anker SD, Norris KC, Fonarow GC, Kalantar-Zadeh K. High platelet count as a link between renal cachexia and cardiovascular mortality in end-stage renal disease patients. Am J Clin Nutr: 2011 Sep; 94(3):945-54. PubMed PMID: 21813809.

7: Molnar MZ, Kovesdy CP, Bunnapradist S, Streja E, Krishnan M, Kalantar-Zadeh K. Higher recipient body mass index is associated with post-transplant delayed kidney graft function. Kidney Int. 2011 Jul; 80(2):218-24. doi:10.1038/ki 2011.114. PubMed PMID: 21525853.

8: Streja E, Kovesdy CP, Molnar MZ, Norris KC, Greenland S. Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. Am J Kidney Dis. 2011 Jun; 57(6):883-93. PubMed PMID: 21239093.

9: Streja E, Molnar MZ, Kovesdy CP, Bunnapradist S, Jing J, Nissenson AR, Mucsi I, Danovitch GM, Kalantar-Zadeh K. Associations of pretransplant weight and muscle mass with mortality in renal transplant recipients. Clin J Am Soc Nephrol. 2011 Jun; 6(6): 1463-73. PubMed PMID: 21415312.

10: Molnar MZ, Kovesdy CP, Bunnapradist S, Streja E, Mehrotra R, Krishnan M, Nissenson AR, Kalantar-Zadeh K. Associations of pretransplant serum albumin with post-transplant outcomes in kidney transplant recipients. Am J Transplant 2011 May; 11(5):1006-25. Doi: 10.1111/j 1600-6143.2011.03480.x. PubMed PMID: 21449945.

11: Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krishnan M, Nissenson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss and mortality in transplant-

waitlisted maintenance hemodialysis patients. Am J Transplant 2011 Apr;11(4):725-36 doi: 10.1111/j. 1600-1643.2011.03468.x. PubMed PMID: 21446975
12: Kalantar-Zadeh K, Miller JE, Kovesdy CP, Mehrotra R, Lukowsky LR, Streja E, Ricks J, Jing J, Nissenson AR, Greenland S, Norris KC. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. J Bone Miner Res. 2010 Dec; 25(12):2448-58. doi: 10.1002/jbmr.177. Epub 2010 Jul 7. PubMed PMID: 20614473.
13: Molnar MZ, Lukowsky LR, Streja E, Dukkipati R, Jing J, Nissenson AR, Kovesdy CP, Kalantar-Zadeh K. Blood pressure and survival in long-term hemodialysis patients with and without polycystic kidney disease. J Hypertens. 2010 Aug 17. [Epub ahead of print] PubMed PMID: 20720499.
14: Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, Nissenson AR, Krishnan M, Kopple JD, Mehrotra R, Anker SD. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc. 2010 Nov; 85(11):991-1001. PubMed PMID: 21037042; PubMed Central PMCID: PMC2966362.
15: Kalantar-Zadeh K, Golan E, Shohat T, Streja E, Norris KC, Kopple JD. Survival disparities within American and Israeli dialysis populations: learning from similarities and distinctions across race and ethnicity. Semin Dial. 2010 Nov; 23(6):586-94. doi: 10.1111/j.1525-139X.2010.00795.x. PubMed PMID: 21175833.
16: Park JC, Kovesdy CP, Duong U, Streja E, Rambod M, Nissenson AR, Sprague SM, Kalantar-Zadeh K. Association of serum alkaline phosphatase and bone mineral density in maintenance hemodialysis patients. Hemodial Int. 2010 Apr; 14(2):182-92. Epub 2010 Mar 24. PubMed PMID: 20345388.
17: Miller JE, Kovesdy CP, Nissenson AR, Mehrotra R, Streja E, Van Wyck D, Greenland S, Kalantar-Zadeh K. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis. 2010 Jan; 55(1):100-12. Epub 2009 Oct 22. PubMed PMID: 19853336; PubMed Central PMCID: PMC2803335.
18: Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, Kovesdy CP. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. Am J Kidney Dis. 2009 May; 53(5):823-34. Epub 2009 Apr 1. PubMed PMID: 19339087; PubMed Central PMCID: PMC2691452.
19: Kalantar-Zadeh K, Streja E, Miller JE, Nissenson AR. Intravenous iron versus erythropoiesis-stimulating agents: friends or foes in treating chronic kidney disease anemia? Adv Chronic Kidney Dis. 2009 Mar; 16(2):143-51. Review. PubMed PMID: 19233073.
20: Streja E, Kovesdy CP, Greenland S, Kopple JD, McAllister CJ, Nissenson AR, Kalantar-Zadeh K. Erythropoietin, iron depletion, and relative thrombocytosis: a possible explanation for hemoglobin-survival paradox in hemodialysis. Am J Kidney Dis. 2008 Oct; 52(4):727-36. Epub 2008 Aug 29. PubMed PMID: 18760517.
21: Clark P, Freeman DJ, Streja E, Sattar N, Walker ID, Greer IA. The G-to-T point mutation in codon 34 of the factor XIII gene and the risk of pre-eclampsia. Blood Coagul Fibrinolysis. 2003 Feb; 14(2):155-7. PubMed PMID: 12632025.
22: Streja DA, Hui RL, Streja E, McCombs JS. Selective contracting and patient outcomes: a case study of formulary restrictions for selective serotonin reuptake inhibitor antidepressants. Am J Manag Care. 1999 Sep;5(9):1133-42. PubMed PMID: 10621079.

I. BACKGROUND

1. Introduction to Congenital Cerebral Palsy (CP)

1.1 History

Congenital cerebral palsy (CP) has been recognized and described since antiquity as deformities of the limbs, often occurring since birth (Obladen 2011). It was envisionedthat the Greek blacksmith god Hephaistos had a form of CP, and at the time he was described as lame, deformed, and grotesque in the eyes of the Greeks. Persons with cerebral palsy were victims of society's ignorance and were submitted to cruel discriminations including a wide range of punishments from mockery to executions. Deformation or paralysis at birth and its consequences were attributed to supernatural causes from the "evil eye" to "God's wrath" until the 19th century, and even attributed to inadequate swaddling of the infant in 4th century BC (Obladen 2011). Although in the 15th century anatomists began to examine and describe the brain in persons with these disabilities, it was not until 1801 that a male British surgeon midwife described spastic diplegia and its link to fever and prematurity (Underwood 1801): ***''Palsy of the lower extremities is not a common disorder anywhere, I believe, and seems to occur seldomer in London than in other parts of this kingdom . . . it seems to arise from debility prematurity, and usually attacks children previously reduced by fever; seldom those under one, or more than four or five years old . . . so that the first thing observed is a debility of the lower extremities, which gradually become more infirm, and after a few weeks are unable to support the body.''***

Leipzig obstetrician Johann Christian Gottfried Jorg then further described the

neurodevelopmental disorders and the link to prematurity in 1826. However, William John Little, the founder of modern orthopedics was credited with the initial clinical description of the disease: first in 1843 as a case report and then as a summary of his experiences in an influential lecture to the Royal Society of Obstetrics in 1861. Spastic Cerebral Palsy (SCP) was named after him in the medical literature until the second part of the 20th century. Little who was a victim of the disease himself, attributed CP to birth trauma and this theory was predominant until modern times.

French pathologist Parrot and German pathologist Wirchov described periventricular leukomalacia in 1867 and attributed it to asphyxic lesions of the brain. In 1897, Sigmund Freud published an extensive monograph including 63 autopsy reports. He found little evidence to support Little's theory concerning pathogenesis of the disease and concluded asphyxia neonatorum is not the causal factor for spastic cerebral paralysis but rather that antenatal factors have a predominant role in the pathogenesis. Nearly 100 years later, in 1981, Nelson and Ellenberg compared the Apgar scores at birth with the neurodevelopmental status of the children at age 7 and found almost no association (Nelson and Ellenberg 1981). In 1986 the same authors published a landmark study in the New England Journal of Medicine on analysis of the antecendents of cerebral palsy and concluded that maternal mental retardation, birth weight below 2001g and fetal malformation were the main predictors while "inclusion of information about the events of birth and the neonatal period" added little to information provided by characteristics available before the labor began (Nelson and Ellenberg 1986).

1.2 Definition, classification and prevalence

1.2.1 Definition

The 2006 Report on the definition and classification of cerebral palsy (Rosenbaum et al. 2007) states: "***Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems".***

This definition might appear vague but provides a unifying concept:

- The terms "palsy" and "group" were retained in spite of the fact that paralysis is not a common denominator of the disease and the condition is heterogeneous.
- Cerebral palsy should be differentiated from:
    - transient neurological disorders occurring during the early stages of post natal neurodevelopment,
    - phenotypically similar disorders due to lesions acquired after basic motor development is relatively well established.
- Cerebral palsy does not include:
    - Neurodevelopmental disabilities that do not primarily affect movement and posture,
    - Conditions associated with disorders of movement and posture that are not associated with activity limitations leading to functional disability,
    - Conditions arising from a single, inciting event or discrete series of events which are still active at the time of diagnosis,
    - Conditions occurring from disturbances occurring later than infancy,

- Disorders solely of spinal, peripheral nerve, muscular or mechanical origin,
- Severely impaired cognition but no motor signs.

- Cerebral palsy might be accompanied by disorders other than impairment of movement and/or posture including:
  - Vision, hearing and other sensory modalities resulting from either the 'primary' disturbance to which CP is attributed, or as a secondary consequence of activity limitations that restrict learning and perceptual development experiences,
  - The capacity to incorporate and interpret sensory and/or cognitive information,
  - Global and specific cognitive processes, including attention,
  - Impairment of expressive and/or receptive communication and/or social interaction skills,
  - Psychiatric or behavioral problems such as autism spectrum disorders, attention deficit hyperactivity disorders (ADHD), sleep disturbances, mood disorders and anxiety disorders,
  - Virtually every seizure type and many epileptic syndromes,
  - Musculoskeletal problems, such as muscle/tendon contractures, bony torsion, hip displacement and spinal deformity.

In spite of this detailed definition of the disorder, it is still recommended that the diagnosis be confirmed by a neurologist. Exclusion of genetic/metabolic disorders presenting with CP-like findings by laboratory tests is important. Brain imaging can be helpful in

pinpointing the location of the underlying brain abnormality and sometimes provides etiologically useful information (Paneth 2008). In order to differentiate cerebral palsy from transient neurological disorders of the neonate, it is recommended that the diagnosis is not established until after at least one year, with most studies recommending between ages 3 to5 for diagnosis confirmation (Topp, Uldall and Greisen 2001), (Krageloh-Mann and Cans 2009).

1.2.2 Classification of Cerebral Palsy

The same document proposed a new approach to the classification of cerebral palsy, which is detailed and dynamic. The classification should be precise enough to propose characteristics operationally defined so that, in general, "competent examiners will classify the same individual in the same way, given identical information".

- First, the nature of the problem and its severity should be described. It is recommended that cases continue to be classified by the dominant type of tone or movement abnormality, categorized as spasticity, dystonia, choreoathetosis, or ataxia, but that any additional tone or movement abnormalities present should be listed as secondary (see Table V of Rosenbaum, 2007). At the same time, the functional consequences of involvement of the upper and lower extremities should be separately classified using objective functional scales.

Table V: Definitions adopted for European classification of cerebral palsy

Spastic CP is characterized by at least two of:
Abnormal pattern of posture and/or movement
Increased tone (not necessarily constant)
Pathological reflexes (increased reflexes: hyperreflexia and/or pyramidal signs e.g. Babinski response)
Spastic CP may be either bilateral or unilateral
Spastic bilateral CP is diagnosed if:
Limbs on both sides of the body are involved
Spastic unilateral CP is diagnosed if:
Limbs on one side of the body are involved
Ataxic CP is characterized by both:
Abnormal pattern of posture and/or movement
Loss of orderly muscular coordination so that movements are performed with abnormal force, rhythm, and accuracy
Dyskinetic CP is dominated by both:
Abnormal pattern of posture and/or movement
Involuntary, uncontrolled, recurring, occasionally stereotyped movements
Dyskinetic CP may be either dystonic or choreo-athetotic
Dystonic CP is dominated by both:
Hypokinesia (reduced activity, i.e. stiff movement)
Hypertonia (tone usually increased)
Choreo-athetotic CP is dominated by both:
Hyperkinesia (increased activity, i.e. stormy movement)
Hypotonia (tone usually decreased)

Table of subtypes from SCPE report, Rosenbaum 2007

- The classification should also include the presence or absence of later-developing musculoskeletal problems and/or accompanying non-motor neurodevelopmental or sensory problems, such as seizures, hearing or vision impairments, or attentional, behavioral, communicative and/or cognitive deficits, and the extent to which impairments interact.
- The classification should include the anatomical distribution of the parts of the body affected by motor impairment or limitations and the neuroimaging studies. Although the American Academy of Neurology recommends obtaining neuroimaging studies in all children with cerebral palsy, there is no current classification based on these studies.
- Cause and timing is not developed sufficiently to justify a classification based etiology, but for the present, timing of insult should be noted when reasonably firm evidence indicates that the causative agent, or a major component of the cause, was operative in a specific time-window.

For practical purposes, in epidemiologic studies the classification is limited to a description of the dominant type of tone or movement abnormality. Since spastic cerebral palsy is the most prevalent form, some studies are limiting patient classification to spastic and non-spastic cerebral palsy.

In addition to congenital cerebral palsy, there is also acquired cerebral palsy which is an triggored by an incident such as injury after birth or later on in life. This thesis focuses only on congenital cerebral palsy, and therefore cerebral palsy will refer to the congenital form throughout the manuscript.

1.2.3 Incidence, prevalence, and trends of cerebral palsy

Overall, the incidence of cerebral palsy is between 2 and 3 per 1000 live births (Krageloh-Mann and Cans 2009, Odding, Roebroeck and Stam 2006, Pakula, Van Naarden Braun and Yeargin-Allsopp 2009). This rate increases to 40–100 per 1000 live births among babies born very early or with very low birth weight. The lower the birth weight or the gestational age the higher the incidence of the disorder. The overall incidence of cerebral palsy varies little between different geographical areas. The Surveillance of Cerebral Palsy in Europe report indicated incidences varying between 1.5 and 3.0 per 1000 live births across Europe (2000b). Recent reviews from Denmark estimate the incidence between 2.1 and 2.4 per 1000 live births (Topp et al. 2001, Ravn, Flachs and Uldall 2010). Data from Australia (Reid, Carlin and Reddihough 2011) and Northern England (Glinianaia, Rankin and Colver 2011) show similar prevalence of CP to Denmark. In China, Liu et al report an incidence of 1.6 per thousand live births, comparable with that of developed countries, but with a higher birth weight specific incidence, attributable to poor survival of low birth weight children (Liu et al. 2000).

Prevalence of cerebral palsy is established in the US by surveys addressing the health of the children. In 1997–2008 National Health Interview Surveys, Boyle et al reported prevalence of 3.9 per 1000 children aged 3 to 17 years (Boyle et al. 2011). In another U.S. study, Kirby et al reported prevalence of CP in 8 year-old children varying between 2.9 per 1000 in Wisconsin to 3.8 per 1000 in Georgia (Kirby et al. 2011). Additionally, by race or ethnicity, the lowest prevalence was for Hispanics (1 per 1000) and the highest for Native Americans (55 per 1000), both in Wisconsin. In California, the incidence of cerebral palsy seems to be lower overall and also varies according to the ethnicity from 1.09 per 1000 live births in Asians to 1.75 per 1000

live births in African Americans, 1.36 per 1000 live births in Whites and 1.46 per 1000 live births in Hispanics (Wu et al. 2011)

Spastic is the predominant form of CP. In the Kirby U.S. study, the prevalence of CP differed according to the type of tone and movement abnormality with the spastic form including 80-82% of the CP patients and non-spastic including for 18-20% of CP patients (Kirby et al. 2011). In Sweden spasic cerebral palsy account for 95% of the patients and non-spastic cerebral paralysis accounted for 5% of the patients (Hagberg et al. 2001) and similar numbers were reported in Northern England (Glinianaia et al. 2011). In Denmark, in term deliveries, spastic account for 84.8% of CP cases and non-spastic cerebral palsy accounted for 15.2% of CP cases, while in preterm spastic accounted for 91.4% of CP cases and non-spastics for only 8.6% of the CP cases (Ravn et al. 2010).

Trends in incidence of cerebral palsy are illustrated in Figure 1 of Hagberg et al, 2001 (Hagberg et al. 2001). The incidence declined in the fifties and sixties, increased in the late seventies and eighties with a zenith in 1990 and then declined again. Since 1990 the incidence of cerebral palsy has been stable (Reid et al. 2011) or decreased (Glinianaia et al. 2011) The incidence of cerebral palsy among preterm children showed a decreasing trend after 1990 (van Haastert et al. 2011). The SCPE also noted increases in CP complicated with

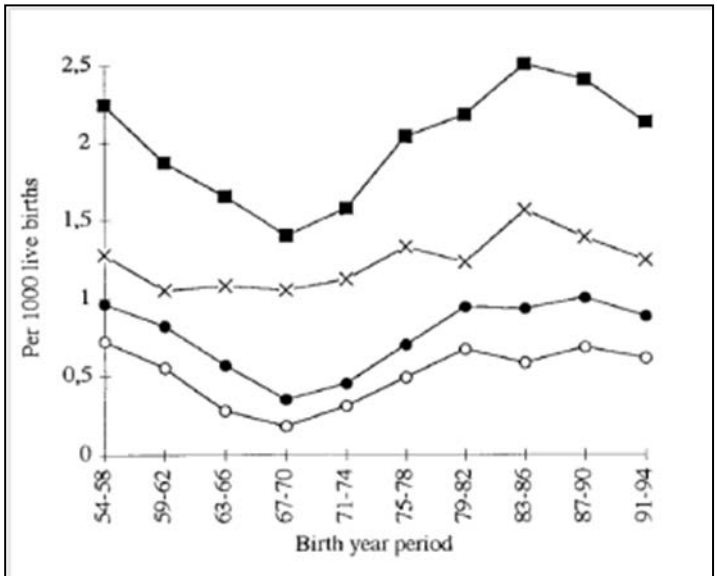


Fig. 1. Crude prevalence of CP per 1000 live births in 1954–94. —■— Total CP; —×— Term CP; —●— Preterm CP; —○— Preterm diplegia. (From Hagberg et al)

epilepsy between 1976- 1983 followed by a decrease in incidence afterward, from 1984- 1998 (Sellier et al. 2012).

Varying trends have also been noted for certain CP subtypes. In another Surveillance of Cerebral Palsy in Europe report (Himmelmann et al. 2009), a progressive increase of dyskinetic cerebral palsy among term deliveries was reported. While another report has shown that there has been a steady decrease in spastic cerebral paralysis (Andersen et al. 2008).

The SCPE attributes trends as due to changes in medical practice (2000b, Himmelmann et al. 2009) :

- Between 1950 and 1975 there was a decrease in neonatal injury and infection leading to a decrease in the incidence of cerebral palsy.
- Starting from the 1970s, there was an increase in neonatal morbidity and rates of cerebral palsy associated with the increased survival of extremely low birth weight and low gestation infants.
- From 1990 further improvement in prenatal and perinatal care have resulted in stabilization or decrease of the incidence of cerebral palsy.
- However, within CP there has been an increase in dyskinetic cerebral palsy subtype, a more rare and severe form of CP. The increase has been attributed to the improved survival (or decreased neonatal mortality) in children born with normal birth weight and/or at term, but who have experienced perinatal adverse events.

The above statistics are derived from data on singleton births. The incidence of cerebral palsy in multiple pregnancies is much higher. Twin pregnancies have a risk from 4 to 12

times the risk of singleton pregnancies (Topp et al. 2004, Liu et al. 2000, Grether, Nelson and Cummins 1993). At least in part this is due to the fact that twin pregnancies are over-represented in the low gestational age and low birth weight groups. There is disagreement concerning the gestational age or birth weight adjusted risk of cerebral palsy in twin pregnancies. Grether et al showed that risk in twins with birth weight under 1,500g was comparable with that of very low birth weight singletons (Grether et al. 1993). Twins born weighing 2,500 g and more had a CP risk 3.6 times that of singletons of similar weight. Similar data were reported by Liu et al (Liu et al. 2000) who showed that, compared with singletons, multiple births had higher incidence of cerebral palsy with the difference in incidence increasing with increasing birth weight. In a Surveillance of Cerebral Palsy in Europe study (Topp et al. 2004) the risk of cerebral palsy was not significantly different between singletons and multiple births after stratification for gestational age. The pathogenesis of cerebral palsy in twins has additional risk factors (Bonellie, Currie and Chalmers 2005) and is not the subject of this thesis.

2. Pathophysiology

2.1 Imaging

Imaging studies are the best available method for understanding the macroscopic pathology of cerebral palsy. Krageloh-Mann et al (Krageloh-Mann and Cans 2009, Krageloh-Mann and Horber 2007) classified the type of lesions can be as grey matter lesions, periventricular white matter lesions, brain maldevelopments and miscellaneous. The prevalence of lesions depends on the gestational age and the clinical form of the disease. Figure 2 (Krageloh-Mann and Horber 2007) shows the difference in prevalence of lesions between the more severe forms of spastic cerebral palsy.

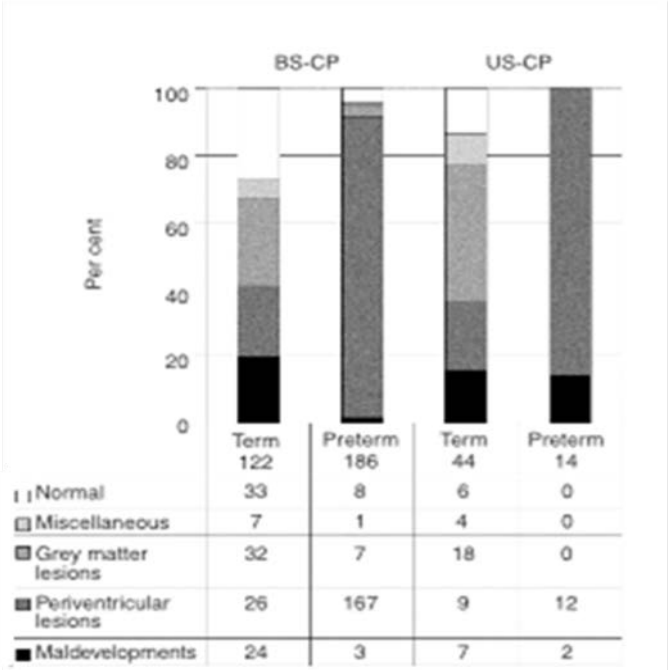


Figure 2: *MRI pattern distribution in two major CP subtypes. Bilateral spastic cerebral palsy (BS-CP) and unilateral spastic cerebral palsy (US-CP) according to gestational age grouping term/preterm.*

From Krageloh-Mann & Korber

- Grey matter lesions typically occur in the late third trimester or in the intrapartum period. These lesions include middle cerebral artery infarcts, multicystic encephalomalacia (which is the pathology equivalent of brain status post infarction), and basal ganglia/thalamus lesions. Grey matter lesions were reported in 18% of CP cases and also appeared more frequently in cerebral palsy children delivered at term (33%) than in preterm cerebral palsy children (3.5%). CP subtypes in the term-born children with gray matter lesions were mainly severe forms of bilateral spastic -CP such as tetraplegia, quadriplegia or athetoid cerebral palsy.

- Periventricular white matter lesions occur mostly in the early 3rd trimester of pregnancy, and include periventricular leukomalacia (PVL) and periventricular haemorrhagic infarctions. Periventricular white matter lesions were reported in 56% of cases, and were highly prevalent in children born preterm (90% in comparison to 20% in term-born). CP subtypes most frequently seen with periventricular white matter lesions were spastics, of mostly milder bilateral forms.

- Brain maldevelopments were reported in 9% of cases. They occurred more often in term than in preterm-born children with cerebral palsy. CP subtypes most frequently seen with brain maldevelopments were especially severe forms of spastic cerebral palsy.

- Miscellaneous imaging studies were rare and did not fit in any of the groups described.

In 85-90% of cerebral palsy cases the magnetic resonance imaging scan (MRI) of the brain will show an abnormality. Among children admitted to neonatal intensive care units, MRI will predict cerebral palsy in preterm newborns with 79% sensitivity and 94% specificity while in term newborns with hypoxic ischemic encephalopathy it will predict cerebral palsy with 71% sensitivity and 94% specificity(de Vries et al. 2011). However, in dyskinetic and ataxic cerebral palsy the MRI is often normal or shows “miscellaneous” results (Towsley et al. 2011).

2.2 Molecular biology

Research on CP development has focused mostly on understanding injuries involving the white matter. The most prevalent white matter lesion is periventricular leukomalacia. Pathogenesis of periventricular leukomalacia involves cerebral hypoxia/ischemia and inflammation. Evidence for ischemia as a major pathogenic mechanism in periventricular leukomalacia emanates from a variety of animal models in which induction of decreased cerebral blood flow (and thereby induced hypoxia) leads to predominantly white matter injury (Deng, Pleasure and Pleasure 2008). Furthermore, assisted ventilation during hypoxic events can lead to hypocarbia. Hypocarbia is a potent cerebral vascoconstrictor and can thereby also lead to reduced cerebral blood flow. In a recent study of 905 infants weighing less than 1250 g cumulative hypocarbia during the first week of life was associated with an odds ratio of 5.6 for development of periventricular leukomalacia (Shankaran et al. 2006). Hypoxic-ischemic events lead to necrosis of brain tissue, but can also activate a subsequent inflammatory response.

Inflammation is the second axis for pathogenesis. Neuropathological observations provide

stronger evidence for cytokine-mediated white matter injury in the premature brain. Several cytokines (especially interferon γ and tumor necrosis factor (TNF- α)) have been detected directly in human periventricular leukomalacia lesions, expressed principally in microglia/macrophages (Kadhim et al. 2003). Hypoxia-ischemia and infection/inflammation, the two principal initiating mechanisms in pathogenesis of PVL, may act separately or in concert to activate the two principal downstream mechanisms: free radical attack by reactive oxygen and nitrogen species and excitotoxicity (neuronal damage). Microglia, the resident macrophages in the brain responsible for immune defense, may play a central role in the generation of reactive oxygen and nitrogen species involved in periventricular leukomalacia, and this role may be greatest under conditions of the combination of hypoxia/ischemia and infection/ inflammation.

The neuropathologic hallmarks of periventricular leukomalacia are microglial activation and focal and diffuse periventricular depletion of premyelinating oligodendroglia (Deng et al. 2008). During weeks 24 to 32 of pregnancy, when infants are at greatest risk for periventricular leukomalacia, premyelinataing oligodendrocyte progenitor cells (cells responsible for creating myelin) predominate in cerebral white matter (Back et al. 2001). Upon injury, the brain's immune defense system's microglia can become activated and produce damaging reactive oxygen and nitrogen species in order to destroy harmful organisms and rebuild damaged tissue. However, these activated microglia cells can also lead to further damage and depletion of the oligodendrocytes responsible for myelination (Billiards et al. 2008).

Upon further investigation however, Billard et. al found no significant difference in cell density markers for this type of oligodendrocytes in the periventricular white matter of periventricular leukomalacia cases versus controls, meaning that damage from microglia did not actually lead to diminished cell density of oligodendrocytes responsible for myelinataion. The

authors did find an increase in cell density at the necrotic foci compared with distant areas, and qualitative differences in the immunostains of myelin proteins in both the diffuse and necrotic components of periventricular leukomalacia. From these findings, the authors suggest that oligodendrocytes may migrate to the “core” of an injury after inflicted damage to replenish oligodendrocyte cell number, and therefore overall cell densities are unchanged. However, despite preserved cell density, the oligodendrocyes may still have arrested in ability to produce myelin and lead to impaired axon-oligodendrocyte signaling.

2.3 Role of Inflammation

The central nervous system is capable of responding with innate and adaptive immune responses, mainly through microglial cells. Perinatal infection alone or combined with hypoxia–ischemia, and the subsequent activation of the innate immunity (including proinflammatory cytokine releases), might be implicated in the genesis of brain lesions of cerebral palsy. The cytokines, interleukin 1-beta and tumor necrosis factor alpha can be released from bacterial endotoxin-activated macrophages at sites of infection, as in maternal chorioamnionitis or can be produced by glial cells and activated monocytes infiltrating the fetal brain—or both mechanisms can be active (Girard et al. 2009). Cytokines released within brain tissues could then inflict direct deleterious effects to the brain. Proinflammatory cytokines, through their signaling pathways could modulate a prolonged inflammatory response and the production of neurotoxic mediators. Figure 3 from Carlo et al. shows

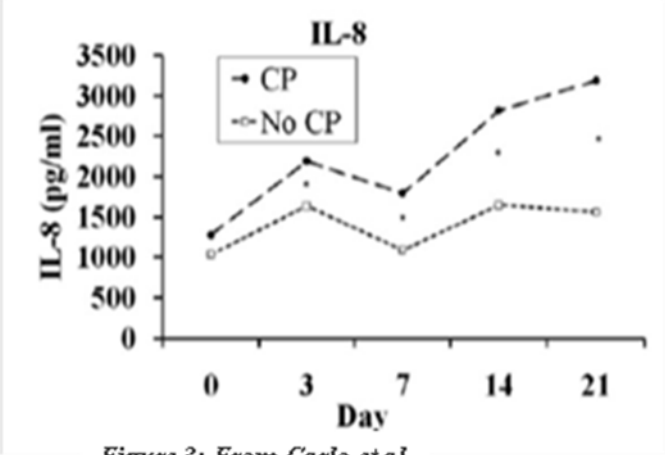


Figure 3: From Carlo et al

interleukin-8 levels continuing to rise even after the child's birth (Carlo et al. 2011). Interleukins are involved in apoptosis, which acts to remodel and repair the structure of the central nervous system. Interleukins -6, -9 and tumor necrosis factor alpha enhance excitotoxicity, whereas the anti-inflammatory cytokine interleukin-10 is protective (Hagberg, Mallard and Jacobsson 2005). Leviton et al have reported on the association between interleukins measured in the cord blood in days following birth and imaging studies in preterm newborns showing cerebral white matter damage (Leviton et al. 2011) . Elevated concentrations of vascular endothelial growth factor receptor 1, serum amyloid A, and macrophage inflammatory protein 1b on day 1 and interleukin-8 on day 7 were associated with increased risk of ventriculomegaly. Elevated concentrations of macrophage inflammatory protein 1b on day 1 and intercellular adhesion molecule 1 on day 7 were associated with increased risk of an echolucent (cystic) lesion. This mechanism involving the inflammatory response seems to be the link between maternal infection and neurodegenerative disorders.

2.4 Role of Coagulation

Inflammation acts bidirectionally with coagulation pathways. Proinflammatory cytokines upregulate proteins involved in blood clot formation, which in turn can further promote coagulation and inflammation. Thrombin, a protein involved in the coagulation cascade, can itself also contribute to brain damage via production of free radicals that destroy oligodendrocyte precursors (Xi, Reiser and Keep 2003). In addition thrombin additionally further upregulates production of proinflammatory markers which can also cause the oxidative damage.

It has been suggested that coagulation plays a role in CP development since markers of coagulation, especially indicators of coagulation disorders have been found in the neonatal blood of children with CP (Nelson et al. 1998). Nelson et al. found higher concentrations of

antithrobmin III, translational products for Factor V Leiden mutation, and proteins C and S in children with CP than in controls. Further evidence has identified placental thrombotic lesions, thrombi in the fetal vessels (Kraus and Acheen 1999), and perinatal arterial stroke (Nelson 2006) in children with CP. Studies of genetic factors of coagulation such as Factor V Leiden, MTHFR, and prothrombin have suggested that inherited thrombophilias may be responsible for a thrombosis in relation to CP development (Gibson et al. 2006, O'Callaghan et al. 2012). However, it has also been postulated that it is really the proinflammatory action of these coagulants that cause the brain damage related to CP (Leviton and Dammann 2004).

3. Who is the mother?

3.1 Maternal Genetic Factors

3.1.1 Genes associated with Congenital Cerebral Palsy

There are a few reports of association between maternal genes and CP. Since inflammation and thrombosis play an important role in the pathogenesis of cerebral palsy, candidate genes are genes encoding coagulation factors or factors associated with the inflammatory response. A review paper by O'Callaghan (O'Callaghan et al. 2009)- which includes data from their own research- lists polymorphisms in genes, most of which are also associated with cardiovascular risk: mannose binding lectin (Rugonfalvi-Kiss et al. 2002) , inducible nitric oxide synthetase (Oksala et al. 2008), transforming growth factor beta-1 (Sie et al. 2006), plasminogen activating factor 2 (Buyru et al. 2003), matrix metalloproteinase-2 (Hlatky et al. 2007), toll-like receptor 4 (Enquobahrie et al. 2008), methylene-tetrahydrofolate reductase (Xuan et al. 2011), tumor necrosis factor alpha (Ria et al. 2011), (Hou et al. 2009),

interleukin 8 (Zhang et al. 2011) , interleukin-10 (Munshi et al. 2010) and neuropeptide Y (Lee and Kong 2007). However, O'Callaghan argues that all these associations with cerebral palsy are questionable since the data are not significant after adjustment for multiple comparisons.

A number of studies have shown evidence for the association of cerebral palsy with the Factor V Leiden mutation. The mutation is a single G (glutamine) to A (arginine) base substitution (G1691A), which prevents the inactivation of factor V by activated protein C, a component of the anticoagulant system. Reid et al compared the frequency of Factor V Leiden mutation in mothers of children with cerebral palsy with the frequency obtained from a normal population of blood donors (Reid et al. 2011). The frequency was 10.4% in mothers of cerebral palsy children and 3.6% in controls. O'Callaghan showed that maternal Factor V Leiden mutation was significantly associated with CP in cases born before 32 weeks and hemiplegic cases (O'Callaghan et al. 2009). Like other candidate genes, Factor V Leiden mutation has also been associated with cardiovascular disorders (Gohil, Peck and Sharma 2009, Wu and Tsongalis 2001).

3.1.2 Genes Associated with Hypertensive Disorders of Pregnancy (HDP)

Similar to Cerebral Palsy, there are candidate genes, but no genetic test predicting the risk for the group of disorders included in the "hypertensive disorders of pregnancy". This group includes gestational hypertension and preeclampsia. Although these conditions are similar, there are a number of risk factors that differ for these two disorders. In a previous study, large-for gestational age birth, uterine surgery, antepartum hemorrhage and uro-genital infection increased the risk for gestational hypertension only, while primiparity was a risk factor only for preeclampsia (Villar et al. 2006). Studies have repeated shown that these disorders are also heriditary. An analysis of phenotypic covariance between twins of different zygosity in the

Summary of findings:

Maternal candidate genes for CP are also associated with cardiovascular disease. Other disorders of pregnancy associated with cardiovascular risk have the same type of association. It is not known if CP is associated with maternal risk of cardiovascular disease later in life.

Swedish Twin Register and the Swedish Medical Birth Register (Salonen Ros et al. 2000) estimated the heritability and non-shared environmental effect were 0.54 (95% confidence interval 0–0.71) and 0.46 (0.29–0.67), respectively; corresponding estimates for gestational hypertension were 0.24 (0–0.53) and 0.76 (0.47–1.00), respectively.

Candidate genes for hypertensive disorders of pregnancy that were similarly shown to be associated with CP were also selected among genes associated with thrombophilic and proinflammatory factors. Factor V Leiden has been reported to be associated with hypertension disorders of pregnancy. In the Avon Longitudinal Study of Parents and Children, Factor V Leiden was significantly associated with preeclampsia, with a pooled OR of 1.49 (95% CI 1.13–1.96) (Dudding et al. 2008). Having the T allele of C677T polymorphism of the methylene tetrahydofolate reductase (MTHFR) gene increased the odds of hypertensive disorders of pregnancy by 1.21-fold in a meta-analysis of 23 studies (Kosmas, Tatsioni and Ioannidis 2004). Statistically significant associations with preeclampsia were identified for the Met235Thr/AGT polymorphism under the dominant genetic and recessive models and for insertion–deletion angiotensin converting enzyme polymorphism, under the recessive model (Medica, Kastrin and Peterlin 2007). Polymorphism at position 2670 in the Fas gene increased the risk of hypertensive disorders of pregnancy in preterm deliveries (Sziller et al. 2005). A meta-analysis of the angiotensinogen gene M235T polymorphism showed a doubling of the risk for hypertensive disorders of pregnancy in Caucasians (Zafarmand et al.

2008). These genes have been shown to be also associated with the risk of cardiovascular disease (Bentley et al. 2010), (Wu and Tsongalis 2001), (Bis et al. 2003), (Schnabel et al. 2008).

3.1.3 Genes associated with Preterm Birth and Small for Gestational Age (SGA)

Delivery of a preterm or small for gestational age infant is associated with a high risk of cerebral palsy. Preterm birth is a condition with a strong hereditary component, (Porter et al. 1997), (Kistka et al. 2008). Mothers with gene polymorphism of prostaglandin E receptor 3 gene (PTGER3; rs977214) showed a high risk for preterm delivery (Ryckman et al. 2010). Preterm labor risk was significantly increased in mothers homozygous for the IL-1b -511T allele and carriers of IL-1a 4845-T allele in (Yilmaz et al. 2012). Other studies showed associations between COL5A2 gene (Myking et al. 2011), polymorphisms in KCNN3 (Day et al. 2011), IGF1R gene (Haataja et al. 2011) and preterm delivery. These genes have been associated with an increased risk of cardiovascular disorders (Sober et al. 2009), martin (Martin et al. 2006), (Ellinor et al. 2010), (Cheng et al. 2008).

Cardiovascular events have also been associated with genetic polymorphisms associated with the birth of small for gestational age infant (Yamada et al. 2005) including: Factor V Leiden (Ye et al. 2006), prothrombin G20210A (Ye et al. 2006), MTFHR C677T (Kim and Becker 2003), CYP1A1 (Cornelis, El-Sohemy and Campos 2004), IGF-I (Aoi et al. 2010), Angiotensinogen Thr235 (Mehri et al. 2011, Schelleman et al. 2007).

3.2 Prepregnancy Risk Factors

3.2.1 Obstetric history

Past history of obstetric difficulties, such as multiple miscarriage, neonatal death or stillbirth, have been associated with cerebral palsy (Stelmach, Pisarev and Talvik 2005, O'Callaghan et al. 2011). Rooney (Rooney 2001) has suggested that there may be an association of CP with mothers who a previous elective abortion based on a reports of an association between previous elected abortion and preterm birth. However, no study has officially reported an association between prior elective abortion and CP. Repeated cesarean section also does not appear to increase the risk of cerebral palsy (Ozturk et al. 2007); however, it is associated with CP risk factors lower birth weights and lower Apgar scores (Gedikbasi et al. 2010).

3.2.2. Past medical history

Maternal prepregnancy morbidity is important for evaluation of risk of cerebral palsy and its prevention. Of the conditions with preventable potential, the most common are thyroid disorders. Thyroid hormone is known to be involved in nervous system development, both in utero and first years of life and congenital hypothyroidism has been recognized as one of the principal known causes of mental deficiency. Although the O'Callaghan cohort does not associate hypothyroidism with the risk of cerebral palsy (O'Callaghan et al. 2011), a review by Hong et. al summarized that an increased risk of either cerebral palsy or "neurological dysfunction" is found in children born to hypothyroid mothers (Hong and Paneth 2008). The review includes the findings by Nelson that showed mothers of children with CP were more likely to have hyperthyroidism before pregnancy and thyroid treatment during pregnancy, (which may render them hypothyroid) (Nelson and Ellenberg 1985, Nelson and Ellenberg 1986). Maternal hypothyroidism is also associated with preterm delivery, gestational hypertension, preeclampsia, placental abruption, preterm labor and perinatal hemorrhage all risk factor for cerebral palsy (Yazbeck and Sullivan 2012). The risk of preterm delivery and placenta abruption

is present also in women with “normal” thyroid function but positive thyroid autoantibodies. The relationship between thyroid function, thyroid hormone replacement therapy and neurodevelopmental outcomes is being explored in the Extremely Low Gestational Age Neonate Study (La Gamma and Paneth 2012).

Association between cerebral palsy and diabetes during the pregnancy has also been debated. O’Callaghan cohort does not show a significant association (O'Callaghan et al. 2011) but a Swedish study showed an association between neurodevelopmental disorders and diabetes with significant odd ratios of 1.36 for gestational diabetes and 2.30 for prepregnancy diabetes (Aberg and Westbom 2001). Ornoy et al showed that gestational diabetes, as a result of the metabolic abnormalities in the second half of pregnancy, induces long term minor neurological deficits, including decreased motor proficiencies, which are more pronounced in younger children (Ornoy et al. 1999). Diabetes during the pregnancy has also been associated with schizophrenia in offspring (Van Lieshout and Voruganti 2008) and “metabolic disorders during pregnancy” have been associated with autism (Krakowiak et al. 2012). The relationship between maternal diabetes and CP needs further exploration.

In the landmark study of Nelson and Ellenberg ((Nelson and Ellenberg 1985) maternal mental retardation was significantly associated with cerebral palsy. In another study, cerebral palsy risk was markedly increased if the mother suffered from psychiatric illness (Stelmach et al. 2005). Risk of developmental disorders, including autism, was significantly elevated for children of mothers with bipolar disorder and risk of epilepsy was doubled for children of mothers with unipolar depression (Morgan et al. 2012). The risk of giving birth preterm or to a small for gestational age infant is increased in mothers with schizophrenia and not affected by antipsychotic use (Lin et al. 2010). The association of maternal mental illness with

neurodevelopmental disorders or their risk factors is probably not related only to an aberrant lifestyle of the mother and deserves more studies.

Anemia and maternal rheumatic disease have also been associated with cerebral palsy in some studies (Stelmach et al. 2005), but this relationship is not consistent (O'Callaghan et al. 2011).

3.2.3 Psychological and socio-economic factors

Cerebral palsy has been associated with a lower socioeconomic status of the parents. Sundrum et al reported that this association can be only partly accounted for by the known social gradients in association with birth weight and gestational age (Sundrum et al. 2005). Hjern et al corroborated these data showing that children in households with low socioeconomic status had odds ratio of CP of 1.49 compared with higher socioeconomic status and that after adjustment for perinatal indicators with preterm birth, the odds ratio decreased to 1.36 (Hjern and Thorngren-Jerneck 2008). In a recent study, Dolk et al showed that the evidence for a socio-economic gradient was strongest for spastic bilateral cases and cases with severe intellectual impairment (Dolk, Pattenden and Johnson 2001). In California, maternal education was associated with cerebral palsy in a dose-response fashion among white and Hispanic women (Wu et al. 2011).

Maternal psychological factors are equally important in determining CP risk. Li et al reported that extremely severe stress in prenatal life (loss of child, spouse, parent, and sibling) could increase the susceptibility for cerebral palsy among children born preterm or with impaired fetal growth (Li et al. 2009). One of the possible mediators of this association could be placenta weight since life stress (but not emotional symptoms) during pregnancy is associated with increased placenta weight at birth (Tegethoff et al. 2010b). In a different report, the same group

(Tegethoff et al. 2010a) showed a positive association between life stress and birth weight, but placenta weight changes and birth weight changes were never compared.

3.2.4 Family history

Although CP is not known as a inherited disorder, having a relative with cerebral palsy has been reported to increase the risk of the offspring to have cerebral palsy (O'Callaghan et al. 2011). This study is consistent with hypothesis of a strong hereditary component in the etiology of cerebral palsy. Parents of one affected child had a 4.8-fold risk of having a second affected child, and where the siblings were twins, the risk was 29-fold (Hemminki et al. 2007). The genetic contribution to athetoid cerebral palsy is smaller, with an overall risk of recurrence in siblings of about 1% (Amor et al. 2001).

3.3. Timing and Mode of Pregnancy

3.3.1 Parental age

The risk of cerebral palsy in different maternal ages has been the subject of a long discussion. In 1963, Nabors noted that the risk of cerebral palsy increases in mother over age 35 years with the exception of primigravidas (Nabors 1963). In 1986 Nelson and Ellenberg (Nelson and Ellenberg 1986) did not find higher maternal age associated with increase CP risk. O'Callaghan et al further corroborated these results (O'Callaghan et al. 2011). However, Wu et al (Wu et al. 2006) reported that maternal age over 35 years doubled the risk of cerebral palsy. Similarly, Thorngren-Jerneck et al reported an increased risk in women delivering between 35 and 40 years with further increase in risk in women aged 40 years or more (Thorngren-Jerneck and Herbst 2006). Fraser reported an increased risk of preterm birth, low birth weight, and small for gestational age in teenage mothers ages 13-17 when compared with mothers ages 20-24

(Fraser, Brockert and Ward 1995). All three reproductive outcomes are additionally risk factors for cerebral palsy, which suggests that there is a possible U-shaped association of maternal age and CP, in that both older age and very young age are associated with increased risk.

Paternal age has been associated with other disorders considered to have a neurodevelopmental pathogenesis: epilepsy, schizophrenia and autism (Vestergaard et al. 2005), (Perrin, Brown and Malaspina 2007), (Reichenberg et al. 2006). Fletcher et al reported that no parental age or birth order effects were observed in spastic quadriplegia or diplegia, but a paternal age effect was detected in those with athetoid/ dystonic cerebral palsy and congenital hemiplegia (Fletcher and Foley 1993).

3.3.2. Parity and interpregnancy time

Primiparity increases the risk of cerebral palsy by 20% (Thorngren-Jerneck and Herbst 2006). It is also associated with an increased risk of small for gestational age or small birth weight (Shah and Ohlsson 2009). However, another study has shown that parity of three or more previous children increases the risk of cerebral palsy (Topp et al. 2004).

Other studies have shown that risk of cerebral palsy is also increased with decreasing interpregnancy interval (Grether et al. 1996, Torfs et al. 1990), even after adjustment for amnionitis and neonatal brain injury interval (Pinto-Martin, Cnaan and Zhao 1998). Short interpregnancy interval has also been reported to be associated with preterm birth and small for gestational age infants (Grisaru-Granovsky et al. 2009). However, a study in the Danish National Birth Cohort, did not find an association between interpregnancy duration and CP (Zhu et al. 2010).

3.3.3 Year and season

In earlier chapters, we reported finding from previous studied that CP has varied slightly in incidence over the years, so that year of birth of the child may be a factor when estimating CP risk. Seasonal variations were also reported for the incidence of cerebral palsy children. The peaks in cerebral palsy births occurred in May and August and the lowest number of CP births occurred in February and December (Kulak and Sobaniec 2005, Kant, Dewan and Jain 1986).

3.3.4 Assisted fertilization

Assisted fertilization has been shown to markedly increase the risk of cerebral palsy (Hvidtjorn et al. 2010, Zhu et al. 2010) in Danish registries; however some studies suggest that this association is accounted for by the increase in multiple births and preterm delivery from using assisted fertilization technologies (Hvidtjorn et al. 2010, Kallen et al. 2010).

4. What is happening during the pregnancy?

4.1 Number, sex and presentation of fetuses

The presence of multiple births increases markedly the risk of cerebral palsy. In the O'Callaghan et al and Liu et al cohorts the presence of twins increases the risk more than six times (O'Callaghan et al. 2011), (Liu et al. 2000). Grether et. al found that twin pregnancies produce a child with CP 12 times more than singletons, but this relationship is in part explained that twins are more likely to be low birth weight and normal weight children are at higher risk of CP(Grether et al. 1993). The risk for triplets is not statistically different from the risk of twins (Wadhawan et al. 2011). However, subtypes of cerebral palsy and the risk factors might be different for twin pregnancies (Bonellie et al. 2005).

There is also a higher risk for male infants to develop cerebral palsy with a ratio approaching 60/40 in preterm births (Thorngren-Jerneck and Herbst 2006). This higher risk of CP for males is also seen in the US (Boyle et al. 2011), but risk ratios vary between 1.0 to1.6 from state to state (Kirby et al. 2011).

Breech delivery is a significant risk factor for CP, in particular among singletons born by vaginal delivery at term (Andersen et al. 2008). It has been shown to increase the risk of cerebral palsy 3-6 fold (Thorngren-Jerneck and Herbst 2006, Ozturk et al. 2007, Stelmach et al. 2005, O'Callaghan et al. 2011). It is not clear if cesarean section could decrease this risk (Morken, Kallen and Jacobsson 2007), (Badawi and Keogh 2009).

4.2 Disorders of pregnancy

4.2.1 Preterm and Intrauterine Growth Restriction (IUGR)

As described earlier, preterm delivery was identified very early on as a risk factor for CP. In the Nelson and Ellenberg analysis, preterm delivery was reported to be an independent risk factor for CP with a small but significant predictive value (Nelson and Ellenberg 1986). Jacobson and Hagberg reviewed the antenatal factors for cerebral palsy and estimated that 4% of the children who are born between 32 and 36 weeks gestation account for 15% cases of CP and 1% children born at less than 32 weeks gestation account for 28% of children with CP with a total prevalence of 42% CP children being born preterm (Jacobsson and Hagberg 2004). In Figure 4 these authors show a logarithmic decrease in risk with increasing

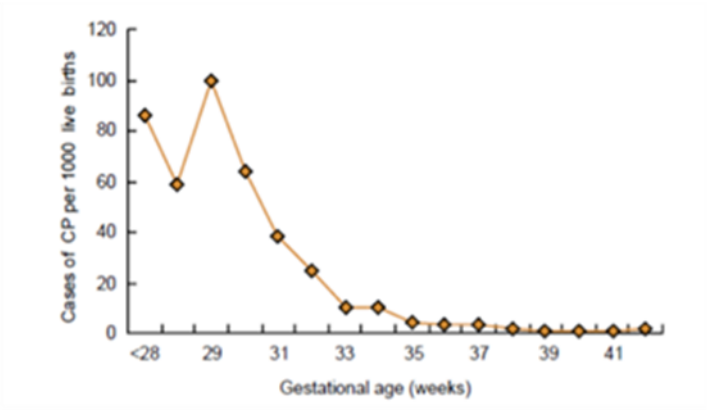


Fig 4: Prevalence of CP per 1,000 live births
From Jacobsson & Hagberg

gestational age. Infants born preterm have a 35% increased risk of CP demonstrated in the Thorngren-Jerneck and Herbst cohort (Thorngren-Jerneck and Herbst 2006). O'Callaghan et al estimate that being born before 32 weeks gestation compared with being born after 36 weeks gestation increases the risk of CP more than 70 times (O'Callaghan et al. 2011).

In 1963 Allison Mcdonald published the first series of cases separating low birth weight from gestational age, showing what looks like an independent contribution to the risk of CP (McDonald 1963). She also observed a difference in risk of spastic versus nonspastic CP by getstional age. Pharoah et al., in 1987 reported frequency distributions of risk of cerebral palsy by gestational age and by birth weight (Pharoah et al. 1987). The authors observed that frequency distributions and prevalence of birth weight and gestational age differed for those with hemiplegia, diplegia, and quadriplegia. Jarvis et al used gestational age adjusted values of birth weight for the calculation of CP risk which automatically adjusted for the association between gestational age and birth weight (Jarvis, Glinianaia and Blair 2006). Jarvis et al reported that the greater the degree to which growth deviates either up or down from optimal weight-for gestational age, the higher is the rate of cerebral palsy, the larger is the proportion of male cases, and the more severe is the functional disability.

What is the definition of a small child? In the Nelson & Ellenberg analysis the definition is given as a birth weight below 2001g (Nelson and Ellenberg 1986). By this definition and in this study, low birth weight along with maternal mental retardation and fetal malformation are the leading risk factors for CP. In the Thorngren-Jerneck cohort, the lower threshold for a normal weight is 2500g and this seems to be the most commonly used definition (Thorngren-Jerneck and Herbst 2006). More recently most authors have defined weight with adjustment for gestational age. A small for gestational age is usually defined conservatively as an infant weighing below

the tenth percentile for the gestational week or more stringently two standard deviations below the mean. In multivariate analysis, SGA defined as two standard deviations below the mean for gestational age was reported to increase the risk of CP by 4.1 times (Lindqvist and Molin 2005) or 3.36 times (Hjern and Thorngren-Jerneck 2008). When the definition of SGA was set as "lower than the first percentile" , the risk of CP increased 6.6 times(Jacobsson et al. 2008).

Another criteria used for definition of low birth weight is by comparison with sibs' weight at birth. The basic principle is that the birth weight-specific mortality of a second child depends on the birth weight of an older sibling. A failure to achieve the biologically intended size appears to increase the risk of adverse outcome even in babies who are not classified as small for gestation (Pedersen et al. 2007), (Basso and Wilcox 2010). This customized birth weight standard appears useful but does not always increase the predictive value of the measurement. Customized standards categorized a higher absolute number of preterm infants who are still-born as small for gestational age. However, infants classified by population references were at higher risk of perinatal mortality than infants classified as small for gestational age by customized standards (Hemming et al. 2008). Customization could lead to a large artifactual increase in the proportion of small for gestational age infants born preterm leading to a large increase in perinatal mortality risk among infants classified as small for gestational age (Zhang et al. 2007). A recent Cochrane analysis concluded that further randomized trials are required to accurately assess whether the improvement in detection of small for gestational age shown is secondary to customized charts alone or an effect of the policy change (Carberry et al. 2011).

Using the term intrauterine growth restriction (IUGR) is another way of increasing the ability to predict of small of gestational age measurements and defines a small fetus in distress.

IUGR is defined as "a birth weight below the 10th percentile for the reference population (SGA), and a longitudinal decrease of abdominal circumference measured in-utero by ultrasound of more than 40-percentiles"(Cetin and Alvino 2009). A small abdominal circumference is in an indication of asymmetric growth, which is usually due to a compromised blood supply of oxygen and nutrients through the placenta to the fetus as seen in 80-90% of cases of IUGR (Sankaran and Kyle 2009). Others have included in the definition of IUGR, an evaluation of umbilical vascular flow on the grounds that "umbilical artery Doppler evaluation of the fetus with suspected IUGR can help differentiate the hypoxic growth-restricted fetus from the non-hypoxic small fetus" (Society for Maternal-Fetal Medicine Publications et al. 2012). Although intrauterine growth restriction has varied in definition across studies, a number of studies have reported an association of intrauterine growth restriction and CP indicating that a mechanism inhibiting the fetus from growing to its full potential size is related to CP development (Jarvis et al. 2006, O'Callaghan et al. 2011).

4.2.2 Role of the Placenta in the Pathogenesis of Cerebral Palsy

Summary of findings:
In patients with CP, placenta pathology is frequently abnormal and showing extensive lesions, suggesting the possibility of placenta malfunction.

The placenta plays a major role in the development and growth of the fetus, as it is the sole source for the fetus' nutrients and oxygen. If placenta function is impaired, the fetus can become hypoxic and malnourished, leading to poor pregnancy outcome(Cetin and Alvino 2009).

Placenta vascular pathology in CP has been extensively studied by previous authors. Two

reviews by Redline summarize the knowledge of the chronic placenta changes associated with disorders of neurodevelopment and specifically with CP (Redline 2006, Redline 2009). The placenta changes are degenerative, thrombotic and inflammatory and all occur with a high frequency. A circulatory abnormality of the placenta such as fetal thrombotic vasculopathy, chronic villitis with obliterative fetal vasculopathy, chorioamnionitis with severe fetal vasculitis, and meconium-associated fetal vascular necrosis was present in 52% cases of CP (Redline 2005). There has also been evidence of blood clots in the placenta tissues, as diffuse chorioamnionic hemosiderosis and intervillous fibrin deposition have also been reported as associated with CP (Redline 2006, Redline 2008). Studies of pathology of the placenta in periventricular leukomalacia, showed a significant increase for diffuse capsular deciduitis and capsular decidual plasma cells, meaning the placenta was infected and inflammed (Maleki et al. 2009). Circulatory disorders of the placenta may result in infarcts which are strongly associated with the risk of CP (Blair, de Groot and Nelson 2011) and particularly with the risk of spastic quadriplegia(Nielsen et al. 2008). In a small study, 11 out of 15 children with CP had thrombi in the placenta(Kraus 1997). In another small study 7 out of 8 placentas of children with perinatal stroke showed abnormalities (Curry et al. 2007). Although there studies are small in number, they show high incidence of placenta lesions in CP cases they did have and suggest an important role for malfunction of this organ in the pathogenesis of the disease.

Placenta disorders such as placenta abruption and placenta previa were reported to be associated with CP. (Spinillo et al. 1997, Matsuda, Maeda and Kouno 2005, Thorngren-Jerneck and Herbst 2006). Placenta abruption is associated with maternal age and/or smoking, which could also affect the risk of CP (Budde et al. 2007, Hung et al. 2007, Odibo et al. 2007, Tikkanen et al. 2006b, Tikkanen et al. 2006a, Yang et al. 2009). Placenta previa is associated with an

increased risk of cerebral palsy with odds ratio of 2.4 (Kulak et al. 2010) but its risk is smaller in other studies when compared with the risk associated with placenta abruption (Matsuda, Maeda and Kouno 2003).

Because the placenta provides nutrients for the fetus' growth, and low birth weight is a risk factor for CP, the relationship between placenta weight, birth weight and neurodevelopment is of interest. Studies have also demonstrated that placenta weight is proportional to birth weight in normal fetal growth (Salafia et al. 2008). Hasegawa et. al. and Thompson et al have published standardized measurement curves of placental weight and birth weight in order to assess fetal growth (Hasegawa et al. 2011) (Thompson et al. 2007).

An abnormal placenta weight can be attributed to environmental conditions of pregnancy that may also result in effects to the fetus (Sedlis et al. 1967). Of the conditions which may increase placenta growth the most prevalent are higher pre-pregnancy body mass index, gestational diabetes and pregnancy weight gain, while African American ethnicity and anemia reduce placenta growth (Baptiste-Roberts et al. 2008). Other factors that have been shown to be associated with both cerebral palsy and smaller placenta size include maternal age (Haavaldsen, Samuelsen and Eskild 2011, Thorngren-Jerneck and Herbst 2006, Ozturk et al. 2007), smoking (Williams, Evans and Newnham 1997, Collier and Hogue 2007), parity(Warburton and Naylor 1971, Thorngren-Jerneck and Herbst 2006), child sex(Thompson et al. 2007, Thorngren-Jerneck and Herbst 2006) and socioeconomic status(Salafia et al. 2008, Dolk et al. 2001, Hjern and Thorngren-Jerneck 2008).

A summary of the work by Ted Kloosterman on the relation between placenta weight and birth weight (Bleker et al. 2006) demonstrated that changes in placenta growth preceded changes in fetal growth and concluded that poor fetal growth is not the cause, but the result of poor

placental growth. Placenta function and not placenta weight is the main factor determining the growth of the fetus. A small birth weight relative to placenta size would be an indication of placental insufficiency leading to intrauterine growth restriction. The relationship between birth weight and placental weight may be a proxy for placenta function. In pregnancies with placenta insufficiency the fetal weight is lower than predicted by gestational age. An early definition of placenta insufficiency states: "In clinical practice obstetricians generally speak of placental insufficiency when they observe at birth an *immature* newborn, that is a newborn whose weight, length and physiological development are lower than expected for the time of the gestation, or when they think that during pregnancy a fetus fails to grow normally as the pregnancy advances" (Wilkin 1961). In normal pregnancies, placenta weight and birth weight are strongly correlated (Almog et al. 2011, Pathak et al. 2010). Infants' small for gestational age could be adequate for placenta weight or small for placenta weight. Most of the reports of low birth weight for placenta size are referring to pathologic conditions resulting in infants small for gestational age (Bortolus et al. 1998, Eskild, Romundstad and Vatten 2009, Vedmedovska et al. 2011), diabetes (Heinonen, Taipale and Saarikoski 2001, Kucuk and Doymaz 2009), uterine abnormalities (Heinonen et al. 2001, Hasegawa et al. 2011), cord abnormalities (Hasegawa et al. 2011) and chorioamnionitis (Shatrov et al. 2010). Children with a birth weight small relative to placenta size represent a high risk group and have increased rates of admission to the neonatal intensive care unit, APGAR scores < 7 at 5 minutes and need for caesarean section (Shehata et al. 2011). A low birth weight for

Summary of findings:
The delivery of an infant with a lower weight than predicted for placenta weight is considered an indicator of placenta function associated with higher risk of pregnancy complications

placenta size is also associated with an increased incidence of meconium stained liquor, hypocalcaemia, hypomagnesaemia and phototherapy even after exclusion of the preterm infants (Lao and Wong 1999). Preterm children born with this characteristic are more likely to have hypospadias (abnormal penile and urethral development) (Fujimoto et al. 2008). The main consequence of a low birth for placenta weight is a long-term increase risk of cardiovascular disease, which will be described further. In a sample of children, birth weights and placenta weights may each look similar across births, but per child a different causal structure may change the relationship between birth weight and placenta weight and thus this relationship may need to be analyzed diffently.

4.2.3 Hypertensive Disorders of Pregnancy.

Gestational hypertension and pre-eclampsia have been studied mostly together as hypertension disorders of pregnancy even if the severity and the pathogenesis might be to a certain extent different. There is disagreement concerning the association of this group and the risk of cerebral palsy. The association was reported by some studies (Thorngren-Jerneck and Herbst 2006), (Lee et al. 2005) but not by another (O'Callaghan et al. 2011). Studies have shown a decreased risk of CP in preeclampsia in preterm delivery, and increased risk of CP in term deliveries (Wu et al. 2009, Mann et al. 2011). A possible interpretation has been that the associations of preeclampsia with lower CP risk in preterm delivery may represent the modifying effect of gestational age and method of delivery rather than an effect of preeclampsia itself (Greenwood et al. 2005, Mann et al. 2011). Spontaneous preterm delivery is associated with increased risk of CP while preeclamptic mothers are more likely to deliver preterm because they undergo cesarean section in order to protect the child (Hogberg and Holmgren 2007).

Consequently, children born preterm to preeclamptic mothers are more likely to have preterm delivery for reasons other than intrauterine or fetal pathology; the decreased risk for CP in this group is actually does not actually represent protection from CP risk, but a collider-stratification bias. As described by Mann et al. (Mann et al. 2011), when looking at the preterm strata alone, because preelcamptic children are more likely to be delivered earlier but are also more likely to be healthier than other children born preterm. The stratification creates a comparison group that has a higher rate of intrauterine infection (as well as other risk factors for preterm birth that may be associated with CP). This results in an elevated risk of CP in the 'controls' and thereby reduces the observed effect of pre-eclampsia, as most pre-eclamptic women who deliver preterm probably do not have these other, unmeasured risk factors for preterm birth and CP. Another interpretation is that the analysis was done not controlling for unmeasured intermediate-outcome confounding (Vanderweele and Hernandez-Diaz 2011). The association between CP and maternal hypertensive disorder during pregnancy requires further analysis.

4.2.4 Vaginal bleeding during pregnancy

Vaginal bleeding during the pregnancy has been reported to increase the risk of cerebral palsy in a 1952 review (Deaver 1952) and again documented by Nelson & Ellenberg 33 years later (Nelson and Ellenberg 1985). Newer cohorts are reporting significant associations with odds ratios of 2.04 (O'Callaghan et al. 2011) and 6.72 (Stelmach et al. 2005). The risk reported seem to be associated with preterm delivery (O'Shea 2002), (Grether et al. 1996), (Stoknes et al. 2012) but not with term delivery (Stoknes et al. 2012).

4.2.5 Maternal infection

To date, maternal infection is one of the most well known risk factors for CP. In the O'Callaghan cohort the odds ratio for cerebral palsy for "any maternal infection" was 1.55. (95% CI: 1.26-1.91) (O'Callaghan et al. 2011). Maternal fever (Grether et al. 2003, Impey et al. 2001) and maternal infections (Nelson and Ellenberg 1986, Schendel 2001, Himmelmann et al. 2011) have been associated with an increased risk of CP irrespective of gestational age.

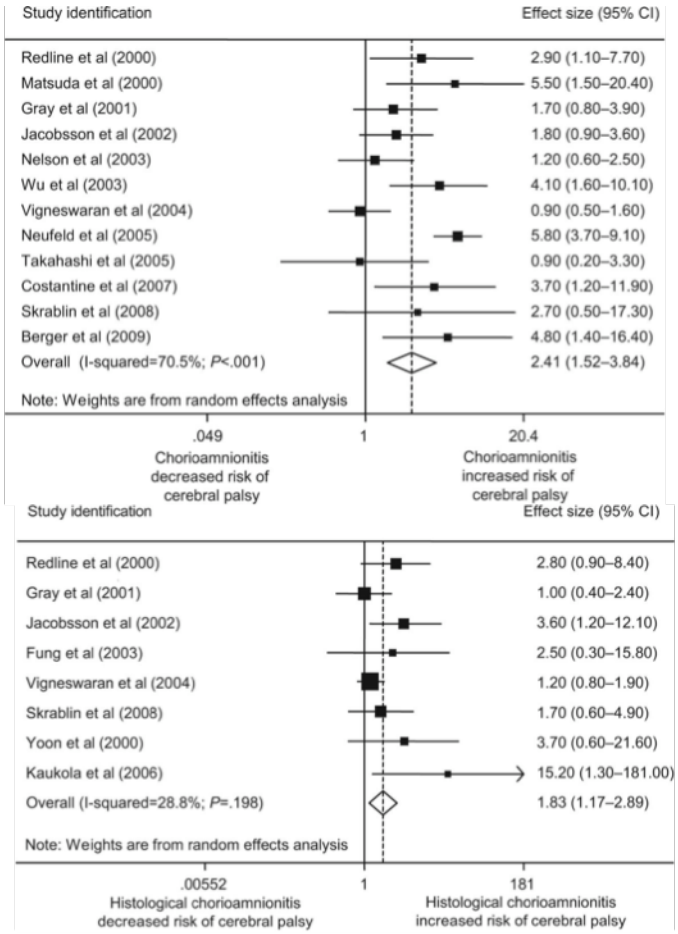


Figure 6 Risk of cerebral palsy in chorioamnionitis

Fever is a non-specific symptom, usually caused by systemic infection. In a case control study, Grether et al. found that maternal fever>38C at admission of delivery or within 24 hours postpartum was associated with CP in very preterm infants (Grether et al. 2003). Hyperthermia earlier during pregnancy has been associated with other neurological disorders in children (Lieberman et al. 2000, Ghi et al. 2010). Sun et al found associations between childhood epilepsy and maternal fever, but not hyperthermia as reported in the Danish National Birth Cohort (Sun et al. 2008, Sun et al. 2011) indicating that maternal infection may also be involved in the etiology of epilepsy.

Of the maternal infections the strongest association with the risk of cerebral palsy is

chorioamnionitis. As shown before, intrauterine infection can cause bacterial infections in the fetus but also result in a potentially life threatening and disabling fetal inflammatory response. Shatrov et al (Shatrov et al. , Shatrov et al. 2010) have published a meta-analysis of all the studies associating chorioamnionitis and cerebral palsy (Fig 6). Overall, the association of CP with chorioamnionitis is significant with an odds ratio of 2.41 if the diagnosis is made clinically and 1.83 if the diagnosis is made histologically. Chorioamnionitis can occur with intact membranes, and this appears to be especially common for the very small fastidious genital mycoplasmas such as *Ureaplasma* species and *Mycoplasma hominis*, found in the lower genital tract of over 70% of women (Tita and Andrews 2010). In a multivariate analysis of term or near term infants, Wu et al found a 4-fold increased risk of cerebral palsy and additionally reported a 11% population attributable fraction of chorioamnionitis for CP (Wu et al. 2003). However, Grether et. al found that chrioamnionitis was not an independent risk factor for CP in very premature infants when gestational age and other confounders were tightly controlled (Grether et al. 2003).

Summary of findings:
Maternal fever and maternal infections are associated with CP. Chorioamnionitis is a strong risk factor for CP and may occur with intact membranes.

Because chorioamnionitis is seldom attributable to hematogenous bacterial contamination, infections of the vagina or urinary tract have been of special interest because of their proximity to the fetus (Tita and Andrews 2010). In most studies these are not clearly separated from each other.

Mann et.al found an association of CP with exposure to genitourinary infection, which included vaginal infections, when exposed in the first two trimesters of pregnancy (Mann et al.

2009). In their study, the association was limited to infants born preterm and urinary tract infections that were not separated from vaginal infections. Similarly, another study showed an increased risk of spastic CP in preterm birth in the presence of "severe infections in close relation to the genital tract" such as pyelonephritis or chorioamnionitis (Jacobsson et al. 2002). Stelmach et. al. found an association between CP and clinically and bacteriologically diagnosed genital infection before or during pregnancy (Stelmach et al. 2005). However, because the methodology for selecting and defining these conditions was not documented, one cannot ascertain the type of infection. In another study from the same group, bacterial vaginosis combined with impending abortion in the first trimester was reported to be associated with poorer neurological outcome (Stelmach et al. 2004). A study in a Danish population found that exposure to bacterial vaginosis early in pregnancy was associated with preterm birth and/or low birth weight and clinical chorioamnionitis, all risk factors for CP(Svare et al. 2006). The O'Callaghan et al cohort did not find a statistically significant association of urinary tract infections and CP (O'Callaghan et al. 2011). In a case control study, Polivka et al found urinary tract infections to be associated with CP (Polivka, Nickel and Wilkins 1997); however, the information on infection was obtained through telephone interviews with an average time of 4.2 years after delivery, subjecting the study to differential recall bias. Camp et al also found urinary tract infections to be associated with intellectual disability (mental retardation) including cases with CP, but gave no definition of urinary tract infections and no mention of genital infections (Camp et al. 1998). Similarly, in a study by McDermott et al., mental retardation or developmental delay was associated with

Summary of findings:
In most studies vaginal infections are not separated from urinary infections when assessing their association with CP

untreated urinary tract infections compared with either no urinary tract infections or treated urinary tract infections. In both these studies the cohort included both CP and other neurologic diagnoses.

Other infections are less studied. In the Stelmach et al cohort, the presence of at least one episode of acute respiratory tract infection (with a temperature ≥ 38°C) either in the first or second half of pregnancy was related to cerebral palsy. Infections in pregnancy, including the most common congenital infections (TORCH: toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus), are known causes of long-term neurodevelopmental disabilities, although the proportion of children with specific disabilities attributable to TORCH infections appears to be 5% to 10% or less (Schendel 2001)

For any analysis of the associations between maternal infections and cerebral palsy, maternal age (Ozturk et al. 2007, Thorngren-Jerneck and Herbst 2006, Matsuda et al. 2011), smoking during pregnancy (Collier and Hogue 2007, Thorsen et al. 2006), alcohol consumption(Thorsen et al. 2006, Abel 2010a), socio-economic status (Cammack et al. 2011, Dolk et al. 2001, Hjern and Thorngren-Jerneck 2008), household size during pregnancy (Hjern and Thorngren-Jerneck 2008, Thorsen et al. 2006), season pregnancy started (Morris 1971, Kulak and Sobaniec 2005), and calendar year of birth (Evans et al. 1995, Ravn et al. 2010) have been shown to be associated with an increased risk of CP as well as being associated with increased risk of infections. These factors can act as confounders in studies of the association of infections with CP should be taken into account.

Summary of findings:
Smoking is associated with the vaginal infections and CP. Their interaction in the risk of CP has not been studied.

Smoking 10 or more cigarettes during the pregnancy is a particularly important confounder since it has been associated with vaginal infections (Thorsen et al. 2006) and with CP (Thorngren-Jerneck and Herbst 2006, O'Callaghan et al. 2011).

4.3 Smoking

In the Thorngren Jerneck cohort of 2,300 infants with CP and 1.6 million infants without CP in Sweden, an association between CP and smoking in pregnancy was also found (Thorngren-Jerneck and Herbst 2006). Collier et al estimate that 1.7% of cases of CP in Georgia, USA are attributable to smoking. Maternal smoking during pregnancy is also associated with a 20–30% higher likelihood for stillbirth, a 40% elevation in the risk for infant mortality and a 2-fold increase in the incidence of sudden infant death syndrome (Salihu and Wilson 2007). There is also a relationship between maternal smoking and fetal growth restriction including significant reductions in growth of head circumference, (-0.56 mm/week; 95% confidence interval (CI): -0.73, -0.40), abdominal circumference (-0.58 mm/week; 95% CI: -0.81, -0.34), and femur length (-0.19 mm/week; 95% CI: -0.23, -0.14) (Salihu and Wilson 2007, Jaddoe et al. 2007). In a US cohort, prenatal smoking was present in 11.5% of all births and was significantly associated with preterm deliveries, term low birth weight deliveries and preterm-related deaths (Dietz et al. 2010). These data were corroborated in the Danish National Birth Cohort while also showing that women who used nicotine replacement therapy had no such increased risk (Lassen et al. 2010). Furthermore, smoking has been shown to induce degenerative lesions on the placenta causing placental malformation and malfunction (Zdravkovic et al. 2005).

4.4 Alcohol

Abel in a letter to the editor entitled “Cerebral Palsy and Alcohol Consumption during

Pregnancy: Is There a Connection?" listed common features of cerebral palsy and fetal-alcohol syndrome (Abel 2010b). However, in spite of the similarities, the O'Callaghan et al cohort shows no association between alcohol use during the pregnancy and cerebral palsy (O'Callaghan et al. 2011). Similarly, no association was found for alcohol use during the pregnancy and autistic spectrum disorders (Eliasen et al. 2010). In a systematic review of 14 relevant papers, Henderson et al found no association between binge drinking during the pregnancy (most often defined as 5 drinks or more on an single occasion) and pregnancy outcomes, including intrauterine growth restriction, preterm birth, and small for gestational age (Henderson, Kesmodel and Gray 2007). Contrary to all these reports, a recent publication by O'Leary et al shows a significant association between alcohol and cerebral palsy in Australian nonaboriginals (O'Leary et al. 2009). The exposure was for "alcohol related diagnosis", indicating that only subjects with heavy maternal alcohol abuse were included.

5. What's happening during the birth?

Traditionally, cerebral palsy has been attributed to birth trauma as noted by Dr. William John Little and his school. As the mounting evidence pointed to a very limited contribution for birth trauma in a otherwise normally developed infant a cause for CP, Most studies have focused on prenatal risk factors of cerebral palsy. In spite of the current belief that birth trauma has little pathogenic role in the causation of cerebral palsy a recent Google search for the terms "cerebral palsy" and "lawyer" resulted in 239,000 hits! These lawyers are usually seeking to file law suits against physicians blaming birth trauma related to faulty physician practices at delivery as the cause for the child's cerebral palsy.

Lie et al reported that 11% of the children with Apgar score of less than 3 at birth were diagnosed with cerebral palsy, compared with only 0.1% of the children with Apgar score of 10 (Lie, Groholt and Eskild 2010). In this study, low Apgar score was strongly associated with each of the three subgroups of spastic cerebral palsy, although the association was strongest for quadriplegia. A document of the international cerebral palsy task force recommended that an intrapartum hypoxic to whom the pathogenesis of cerebral palsy could be attributed should include: 1) evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord or very early neonatal blood samples; 2) early onset of severe or moderate neonatal encephalopathy in infants of 34 weeks gestation or more, and 3) cerebral palsy is of the spastic quadriplegic or dyskinetic type (MacLennan 2000). A California study reported that 31.3% of children with CP had 1 or more of the 6 adverse intrapartum events versus only 12.9% in controls (Gilbert et al. 2010). The events were placental abruption, uterine rupture during labor, fetal distress , birth trauma , cord prolapsed, and mild-severe birth asphyxia. Prepartum pathology might have contributed to some of these events. Other events associated with increased risk are: premature rupture of membranes, (Ozturk et al. 2007, Stoknes et al. 2012), prolonged labor (Ozturk et al. 2007), emergency cesarean delivery (Stelmach et al. 2005), (Thorngren-Jerneck and Herbst 2006), and instrumental delivery (Stelmach et al. 2005), (Thorngren-Jerneck and Herbst 2006). A study in Turkey found home births are risk factor for CP (Ozturk et al. 2007)), but similar studies have not been conducted in countries where home births are less frequent such as the US and Scandinavian countries.

6. What's happening after birth, during lifetime?

Is CP associated with maternal cardiovascular disease?

Having a child with CP is extremely stressful and costly for a caregiver who in the vast majority of situations is the mother. Maternal stress associated with the care of a child with CP may act as an intermediate and lead to an increase in the level of cardiovascular risk factors and ultimately to cardiovascular disease. Caregiver stress has been recognized as a risk factor for cardiovascular events (Lee et al. 2003). Caregivers of children with CP, as compared with parents of children without disabilities, have been documented to have a very high "parental stress index" (Wang and Jong July 2004), high salivary cortisol as objective index of marked stress (Bella, Garcia and Spadari-Bratfisch 2011) and a greater likelihood of a variety of physical problems, including back problems, migraine headaches peptic ulcer, asthma and rheumatic disorders (Brehaut et al. 2004). These studies suggest that it is likely that caregiving for a CP child might lead to an increase in cardiovascular risk.

In a previous chapter, I have documented previous results that maternal candidate genes for CP are also associated with cardiovascular risk. The possibility of a common maternal phenotype leading to cardiovascular disorders and to CP in the offspring could be another mechanism linking the two outcomes. To date, there is no study to our knowledge exploring the association between having a child with CP and parental cardiovascular risk.

6.1 Cardiovascular risk in women with risk factors for CP

Pregnancy related factors have been identified as important risk factors for cardiovascular diseases in women. Recently, the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women recommend that "healthcare professionals who meet women for the first time later in their lives should take a careful and detailed history of pregnancy complications with focused questions about a history of gestational diabetes mellitus,

preeclampsia, preterm birth, or birth of an infant small for gestational age" (Mosca et al. 2011), all risk factors for cardiovascular disease. Additionally, Gestational diabetes (Watanabe 2011), preeclampsia (Williams and Pipkin 2011), preterm birth (DeFranco, Teramo and Muglia 2007) and preterm delivery (Porter et al. 1997) have a familial inheritance and are considered to be associated with maternal genes.

Preterm birth, SGA and hypertensive disorders of pregnancy are major antenatal risk factors for CP and have been shown to be risk factors for cardiovascular disease. Using the same cohort as in our study, Catov et al found that women with a prior preterm birth had excess cardiovascular disease after adjustment for age, parity, and education (HR: 1.36, 95%CI: 1.31-1.41). Similarly, Lykke et al also used data from the Danish registries and showed that after mothers had a first delivery at 32–36 completed weeks of gestation, the adjusted risk of subsequent type-II diabetes increased 1.89-fold and the risk of thromboembolism increased 1.42-fold. The relationship between birth weight and cardiovascular risk has been explored in multiple studies by Davey Smith and his collaborators (Davey Smith et al. 1997, Smith et al. 2005, Davey Smith et al. 2007, Smith, Harding and Rosato 2000). In the Renfrew and Paisley Study, this group reported a doubling of the cardiovascular mortality in mothers for each kilogram lower birth weight of the offspring(Davey Smith et al. 1997). Studies have also reported this association by showing a decrease in cardiovascular risk with increase in birth weight. A meta-analysis from Davey Smith et al reported that the adjusted hazard ratio of cardiovascular disease mortality for a 1-standard deviation increase in offspring birth weight in mothers was 0.87 (Davey Smith et al. 2007). Lawlor et al showed that for every one standard deviation increase in birth weight, the risk of coronary artery disease in women was 0.84 (95%CI: 0.72- 0.97) (Lawlor et al. 2003). In the same study, lower birth weight was inversely associated with carotid artery

intima-media thickness, a strong predictor of coronary and cerebrovascular events. The association was not confounded by childhood or adulthood socioeconomic position or by adult smoking status of the participant.

Other studies have showed that delivery of a SGA infant was associated with significant changes in cardiovascular risk factors: increased cholesterol/HDL cholesterol ratio, systolic blood pressure, C-reactive protein, interleukin-6 and vascular adhesion molecules, all risk factors for cardiovascular events (Kanagalingam et al. 2009). Endothelium dependent and independent functions of the blood vessels were also impaired in mothers of SGA offspring (Kanagalingam et al. 2009). In summary both SGA and preterm birth, have a strong association with cardiovascular disease.

Hypertensive disorders of pregnancy are also a strong risk factor for cardiovascular disease later in life. Overall mortality (Bellamy et al. 2007, Funai et al. 2005) and cardiovascular mortality (Funai et al. 2005, Irgens et al. 2001, Arnadottir et al. 2005) are increased in women who had hypertensive disorders during their pregnancy. In other studies, there is an increase in the risk of ischemic heart disease (Bellamy et al. 2007, Wikstrom et al. 2005, Mann et al. 1976) and stroke (Arnadottir et al. 2005, Wilson et al. 2003) for mothers who had hypertensive disorders of pregnancy. Some of these outcomes are related to a persistent elevation of blood pressure (Wilson et al. 2003, Bellamy et al. 2007, Magnussen et al. 2011, Lykke et al. 2009) and new onset of type-2 diabetes (Lykke et al. 2009, Libby et al. 2007). A history of hypertensive disorders of pregnancy is associated with cardiovascular risk factors:

Summary of findings:
Disorders of pregnancy associated with an increased risk of CP are also associated with long-term increased risk of cardiovascular disease

increased body mass index; increased levels of cholesterol, triglycerides and insulin(He et al. 1999, Germain et al. 2007, Fraser et al. 2012); decreased flow mediated dilation of brachial artery (Germain et al. 2007); elevation of von Willebrand factor (He et al. 1999), increased fibrinogen (He et al. 1999) and C-reactive protein (Hubel et al. 2008). Some authors have summarized hypertensive disorders of pregnancy as a proinflammatory (Szarka et al. 2010) and prothrombic (Lwaleed, Dusse and Cooper 2011) state which also increases risk of venous thrombosis(Bellamy et al. 2007, Lykke et al. 2009).

Other studies have found that the excess cardiovascular risk in the fathers of affected offspring is either lower than the mothers' risk or nonexistent. Low birth weight has been shown to be associated with no increase in paternal risk of cardiovascular disease in Uppsala Birth Cohort (Manor and Koupil 2010). In the Swedish Medical Birth Cohort, for every standard deviation increase in child's birth weight, there was a decrease risk of cardiovascular mortality for parents over age 50 years: 0.94 for men and 0.69 for women (Smith et al. 2005). In the Norwegian Medical Birth Registry, there was an 8.1 fold increased risk in cardiovascular death for mothers who had preeclampsia and delivered preterm (Irgens et al. 2001). However, in this study, there was no increase in cardiovascular death risk for either exposure in fathers. The authors concluded that "a possible genetic contribution from fathers to the risk of preeclampsia was not reflected in increased risk of death from cardiovascular causes" (Irgens et al. 2001).

Lifetime risk for person with cerebral palsy, particularly for cardiovascular disease, is not well understood and future studies are needed (Haak et al. 2009), However, Barker et al has shown that the main consequence of a low birth for placenta weight is a long-term increase risk of cardiovascular disease in those children. In 1990, Barker et al wrote "The highest blood pressures occurred in men and women who had been small babies with large placentas. Such discordance between placental and fetal size may lead to circulatory adaptation in the fetus, altered arterial structure in the child, and hypertension in the adult" (Barker et al. 1990). In 1993, Barker's group developed the hypothesis that persisting changes in the levels of hormone secretion, and in the sensitivity of tissues to them, may link fetal under-nutrition with abnormal structure, function, and disease in adult life" (Barker et al. 1993). Risnes et al have also reported that children with low birth weight for placenta size have a higher risk of cardiovascular death later in life (Risnes et al. 2009). It is conceivable that neuro-hormonal changes inducing hypertension could account for this relationship. Elevation of systolic blood pressure (Blake et al. 2001, Wen et al. 2011) and pulse pressure (Hemachandra et al. 2006) are detectable in childhood in these patients, in some reports even in the first week of life (Smal et al. 2009). Brameld et al (Brameld, Hold and Pipkin 2011) showed that median angiotensin converting enzyme for each placenta was positively correlated with placental:birthweight ratio and concluded that exposure to increased placental synthesis of angiotensin II caused by higher angiotensin converting enzyme might be contributing to lifetime risk of cardiovascular disease for that child.

Summary of findings:
The delivery of an infant with a lower weight than predicted for placenta weight also associated with a higher risk of cardiovascular disease.

II. 7. Study Aims

7.1 Study 1: Placenta Disorders, Placenta Weight, Birth Weight and Congenital Cerebral Palsy

Previous Studies have shown:

1. Low birth weight is strongly associated with the risk of cerebral palsy.
2. In patients with CP, placenta pathology studies show frequently extensive lesions suggesting the possibility of placenta malfunction.
3. The delivery of an infant of lower weight than predicted by placenta weight is a proxy for placenta insufficiency.
4. The relationship between birth weight and placenta weight has not been studied in cerebral palsy.

Purpose of the study:

To investigate the relationship between placenta weight, birth weight and the risk of CP:

Hypotheses:

Assumption A: Placenta weight and birth weight are not associated with CP. They are only a proxy of placenta function.

1. ***Increasing placenta weight is negatively associated with the risk of CP (CP newborns have smaller placentas)***

2. ***After adjustment for birth weight, placenta weight is positively associated with the risk of CP (CP newborns are lower weight for placenta size, even if placenta is small)***

OR

Assumption B: Birth weight is an intermediate for placenta weight in its relationship with CP

1. ***Increasing placenta weight is negatively associated with the risk of CP (CP newborns have smaller placentas)***

2. ***After stratification by birth weight the relationship weakens or is absent***

7.2 Study 2: Cardiovascular Risk in Parent of Child with Congenital Cerebral Palsy

Previous Studies have shown:

1. Stress of the parents-caregivers for a child with cerebral palsy may increase cardiovascular risk

2. Disorders of pregnancy associated with a high risk of CP are also associated with increase cardiovascular risk

3. Maternal candidate genes for CP are also candidate genes for cardiovascular diseases.

4. The relationship between CP and cardiovascular disease has not been studied

Purpose of the study:

To investigate the relationship between cardiovascular risk in parents and CP in the offspring

Hypothesis:

1. **Mothers but not fathers of CP children have a higher risk of cardiovascular disease**
2. **This risk is independent of the presence of pregnancy disorders associated with CP.**

Assumption A: There is a strong environmental component – maternal stress as a caregiver.

The association is present with exposure starting at least after one year after the birth of the child.

Assumption B: There is no significant environmental component.

The association is present with exposure starting at the birth of the mother.

7.3 Study 3: Prenatal Exposure to Self-reported Maternal Infections, Smoking and Congenital Cerebral Palsy

Previous Studies have shown:

1. Maternal fever and maternal infection are associated with CP.
2. Intrauterine infection (chorioamnionitis) is a strong risk factor for CP.

3. Chorioamnionitis may occur with intact membranes. Urogenital infections are the likely source.

4. Vaginal and urinary infections have been associated with CP but the relationship for each infection type separately is insufficiently studied.

5. Smoking is associated with the risk of infections.

6. The relationship between smoking, infection and CP is insufficiently studied.

Purpose of the study:

To investigate the relationship between smoking, fever, vaginal and urinary infections and CP.

Hypothesis:

1. ***Vaginal infections and smoking are associated with CP independent of each other.***

2. ***Fever is associated with CP independent of smoking.***

III. 8. Methods

8.1 Danish Data Sources

This thesis was based on data obtained from the Danish registry system including the Danish Civil Registration System, the Danish Medical Birth Registry, the Danish National

Hospital Register, the Danish National Cerebral Palsy Register, and data from the Danish National Birth Cohort (DNBC).

8.1.1 Danish Civil Registration System

The Danish Civil Registration System was established for administrative use in 1968 to register information on all persons living in Denmark. The registry contains data on each person's sex, date of birth, place of birth, and continuously updated information on vital status. Data from various registries in the system can be linked via a unique personal identification number (CPR-number) that is assigned to all Danish citizens at birth. Via CPR number, a person can be linked to all listed family members (mothers, fathers, siblings, grandparents, etc.). Information is also available on numerous social and health conditions including: education, marital status, annual income, place of residence, and migration to and from Denmark.

8.1.2 Danish Medical Birth Register

The Danish Medical Birth Register was established in 1968 and computerized in 1973. It was initially intended to monitor health of the newborns and quality of antenatal and delivery care services. The registry contains data on all live births and still births in Denmark, including characteristics of mother and child related to pregnancy and delivery. From 1978, the registry began to record information on gestational age, birth weight, Apgar score at one and five minutes after birth, and congenital malformations for children born in Denmark. Birth weight was recorded in 250 gram intervals between 1973 and 1979, 10gram intervals between 1979 and 1990, and 1 gram intervals from 1991 and onward. However, many records were rounded to the nearest 10, 50, and 100 grams based on digit preference. Gestational age was recorded in the completed weeks between 1978 and 1996 and in days from 1997 onward. Information on gestational age at birth was estimated from date of last menstrual period, but ultrasound

measures during early pregnancy were mostly used in the last 20 years (Jorgensen 1999). Beginning In 1997, additional perinatal factors were added to the registry such as placenta weight, abdominal and head circumference, and body length.

8.1.3 Danish Hospital Register

The Danish National Hospital Register was established in 1977 and contains information on discharge diagnoses of all inpatients from Danish hospitals from 1977 onwards and outpatients from 1995 onwards. Diagnostic information is based on the Danish version of the International Classification of Diseases, 8^{th} revision (ICD-8) from 1977-1993, and 10^{th} revision (ICD-10) from 1994 onwards. All treatments in Danish hospitals are free of charge for all residents.

8.1.4 Danish National Birth Cohort

The Danish National Birth Cohort is a nation-wide population-based cohort of about 100,000 pregnant women and their offspring. It was designed to provide a data source for epidemiological studies of the short term and long term consequences of intrauterine exposures. Enrollment of the cohort took place between March 1996 and November 2002. General practitioners invited women to participate in the study at their first prenatal visit, usually in weeks 6-12 of pregnancy and pregnant women were included when the signed consent form was received. About 50% of general practitioners in Denmark participated in the recruitment and about 60% of their invited pregnant patients accepted the invitation. Women were invited to participate in the study if they spoke Danish well enough to complete the interviews, and intended to carry the pregnancy to term. Female interviewers conducted computer-assisted

telephone interviews, which took place at approximately pregnancy weeks 17 (interquartile range: 14–20 weeks) and 32 (interquartile range: 30–34 weeks). There were 92,892 women that participated in the first interview, 87,802 women that participated in the second interview, and together 83,935 women participated in both the first and second interviews.

8.1.5 Danish National Cerebral Palsy Register

The Danish National Cerebral Palsy Register is a population-based registry that contains a record of individuals with validated CP diagnosis from the birth year 1925 and has reported birth prevalence since 1950 (Uldall et al. 2001). Originally the database covered only patients from Eastern Denmark or about 50% of the Danish population, but in 1992 the register became a public national registry and was expanded to cover the entire Danish population. Data are collected from pediatric departments and other hospital records and before 1991 from a special institution for children with disabilities. Cases of CP are validated by a child neurologist and an obstetrician based on review of the child's physical findings recorded in medical records and information is registered in a standard form(Uldall et al. 2001).

Children are included in the register if they have CP, as defined as "a disorder of movement and posture due to a defect of lesion of the immature brain, excluding disorders which are of short duration, due to progressive disease or due solely to mental deficiency". In order to ascertain the disease is non-progressive, children must be at least 1 year of age. However, the registries reported date of diagnosis is when symptoms were first noted for the child, and in approximately 50% of CP cases, date of diagnosis is prior to the child's 1st birthday. The CP registry also contains information on disease subtypes.

8.2 Study Population and exposures

The population for study 1 and 2 was identified in the Danish Civil Registration System. See Figure 8.2.2 for information on cohort construction.

For both studies, we identified all live-born singletons born in Denmark between January 1, 1973 and December 31, 2003. Of these, 1,874,653 were alive and did not emigrate from Denmark before one year after birth and were used in the analysis for study 1. For study 1 on the association between placenta disorders, placenta weight, birth weight, and CP, information on birth weight, placenta weight, and gestational age was obtained in the Danish Medical Birth Register and information on placenta disorders and maternal disorders of pregnancy was obtained from the Danish National Hospital Register. ICD-codes used to identify these disorders are listed in 8.2.1 Table of ICD Codes. Information on gestational age, birth weight, placenta disorders, and maternal disorders during pregnancy were available for all birth years in the cohort, but data on placenta weight only began to be recorded for children born in 1997 or later. We excluded values of placenta weight $\leq$100g, n=240 or >1500g, n=114, for birth weight <500g, n=23, and for gestational age<24 weeks, n=105.

For study 2 on the association between having a child with CP and development of cardiovascular disease in the parent, we used the cohort from study 1, excluded those children who were adopted (n=12,360), and linked children with their parents' information. There were 5 non-CP children excluded who did not have parents listed in the register. We first identified mothers of CP children. If the mother had more than one child with CP (n=23), we randomly

selected either the first or second child to be used for the study. We then identified mothers without any children with CP, by removing mothers that had any CP child from the list of mothers of non-CP children. For the mother's who remained, we randomly selected one child per mother to be used as the index child.

The fathers' cohort was subsequently created from the mothers' cohort. We first removed all children where fathers could not be identified (n= 16,709). For fathers of CP children, only one father had two children with CP with different mothers, and we randomly selected one of the children and removed the other. We then removed fathers of CP children from the list of fathers of non-CP children, and randomly selected one non-CP child per father to be used as index child.

We additionally removed any parents that had errors in listing (20 non-CP moms, and 37 non-CP dads), a date of death prior to a time period where they could have conceived the child (day of birth of child -315 days). We began follow up time at day of CP diagnosis or child's 1st birthday for non-CP children, and excluded all parents that had a cardiovascular outcome prior to beginning of follow up period. Randomization of index child used per mother was performed using PROC SURVEY SELECT in SAS 9.2 (2002- 2008). Distributions of parity were similar between CP and non-CP parents: first born (53% CP, 52% non-CP), second born (32% CP, 36% non-CP), and third or later child (15% CP, 11% non-CP).

The population for study 3 was based on the Danish National Birth Cohort. We included women in our study only if they participated in both interviews (n=83,935). We additionally excluded 2,447 non-singleton children, 261 that died and 118 that emigrated prior to their first birthday, and 43 that were not in the Danish Medical Birth Register. Analysis was limited to available data on exposures of interest.

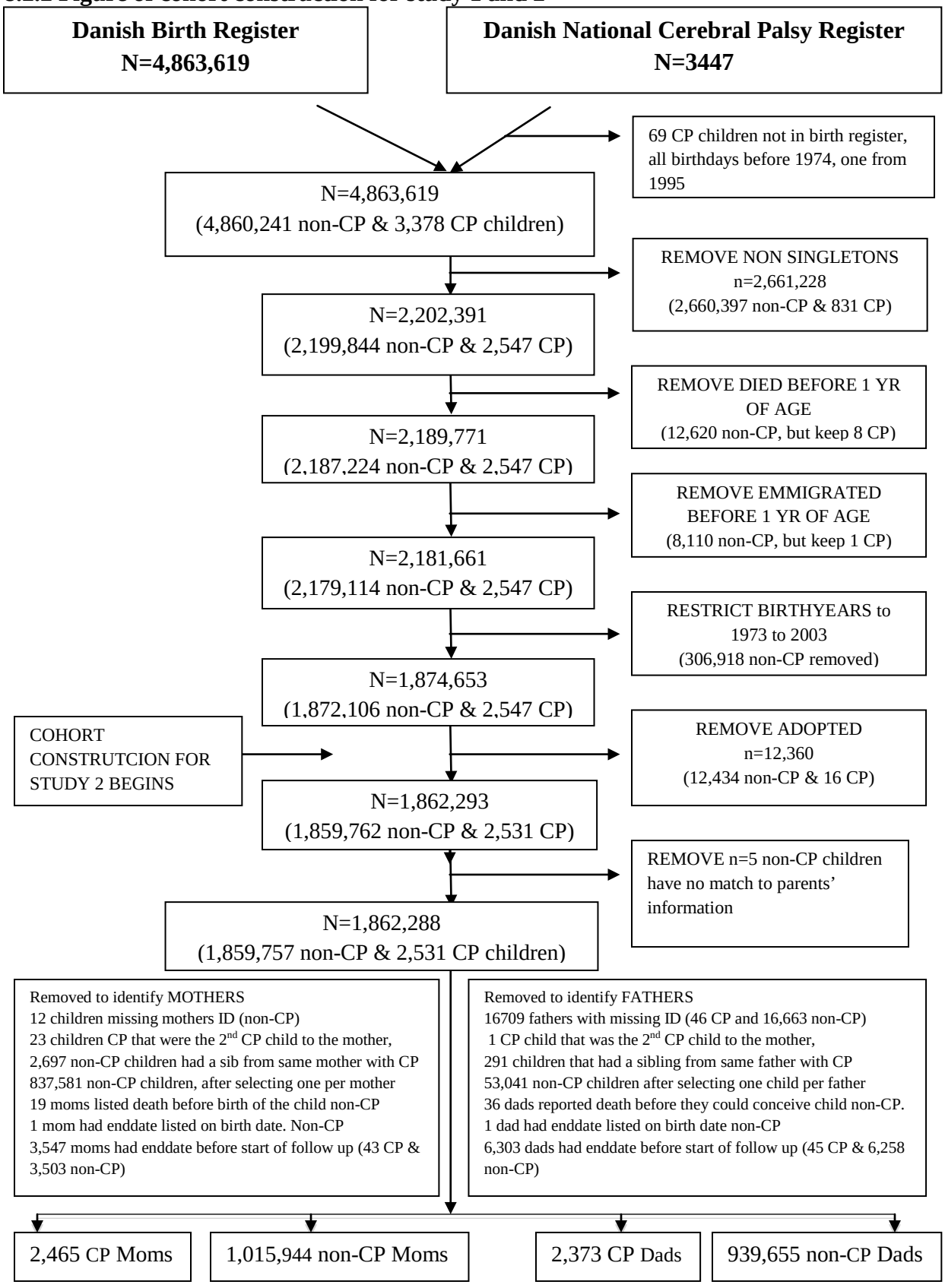
For study 3 exposures, information on exposures were obtained from two interviews during pregnancy. Information on urinary tract infections (cystitis, pyelonephritis), vaginal infections, diarrhea, fever, smoking, was obtained from the 1st and 2nd interview, while information on and cough, genital herpes, venereal warts, and herpes labialis was collected from the 2nd interview only. Women were asked directly if they had the listed infection during the time period addressed in the interview. They could either respond 'yes', 'no', 'I don't know', or 'I do not wish to answer. For exposures with information from both interviews, answers were combined. Only women who responded 'yes' or 'no' at both interviews were included in the analysis. Women were considered exposed if they said 'yes' at either or both interviews, and unexposed in they said 'no' at both interviews. Diarrhea in the questionnaire was defined as >3 defecations within 24 hours. Coughs were recorded when they lasted >1 week. Information on maternal fever episodes during pregnancy was reported independent of questions on infection. For the 'all infections' exposure group, only those women who responded 'yes' or 'no' to all above listed infections were included in the analysis. Women who responded 'no' to each and every infection exposure were defined as unexposed to any infections, while women who responded 'yes' to any of the above listed infections were considered exposed in this group. For vaginal infections, women who reported they had a vaginal infection were additionally asked in a subsequent question if they treated their infection. A further question asked about type of treatment for the vaginal infection. We defined "untreated vaginal infection" as having at least one episode of self-reported vaginal infection with no self-reported concurrent treatment. For smoking, women were asked if they smoked what kind of product they smoked, and with what frequency. Women were considered as smokers if they smoked at any time during their pregnancy. To ascertain smoking quantity, cigarettes per week was divided by 7 and added to

cigarettes per day. We only included in our analysis responses including cigarettes. Smoking during pregnancy was classified as none (no smoking reported), moderate (1-9 cigarettes per day), or heavy (10 cigarettes or more per day).

Table 8.2.1 Table of ICD Codes for Hospital Diagnoses

Hospital Diagnoses	icd-8	icd-10
All Cardiovascular Disease		
Atherosclerosis	44009: 44299, 44319, 44389:44599	I70- I74, I79
Congestive Heart Failure	42599, 42709:42719, 42799:42900	I11, I42-I43, I50
Cerebrovascular Disease	43000:43899	I60-I69
Hypertension	40009: 40499	I10, I12-I15
Ischemic Heart Disease	41009: 41499	I20- I25
Thrombosis	45099:45199	I26, I80
Other Cardiovascular	39099: 39899, 42000: 42499, 42600: 42609, 42720: 42797, 42908: 42909	I0, I27-I41, I44-I49, I51-I52,
Comorbidities		
Diabetes in pregnancy	64374	O24- O25
Hypertensive Disorder during Pregnancy	63700, 63702- 63704, 63709, 63719	O11, O13- O15
Vaginal Bleeding	62959, 65310- 65319	O46, O67
All Placenta Disorders		
Placenta Previa	63209, 65100 - 65159, 65180 - 65199, 77000 – 77009	O44
Placenta Abruption	63219, 77010- 77019	O45
Other Placenta Disorders	63430 - 63439, 65200 - 65219, 65236- 65239, 65280- 65299, 66140 - 66149, 66310 - 66319, 77020- 77029, 77080 – 77099	O365, O411D, O43, O72- O73

8.2.2 Figure of cohort construction for study 1 and 2



8.3 Information on Outcome Assessment

In all studies (outcome for study 1 and 3, and exposure for study 2), information on CP was obtained from the Danish National Cerebral Palsy Register. Time of onset for the analysis was defined as the first recorded date of diagnosis in the Danish Cerebral Palsy Registry'. If the child's date of diagnosis was prior to the age of 1 (n=1,112 for study 1) or had a missing date of diagnosis (n=425 for study 1), the child's date of diagnosis was re-centered to the date of child's 1st birthday (date of birth + 365 days).

For study 3, data on cardiovascular events as diagnosed in a hospital, either inpatient or outpatient, were obtained from the Danish National Hospital Register. The time of onset of event was defined as the first day of contact with the hospital. Prior to 1995, only inpatients were included in cardiovascular outcomes.

8.4 Confounders

Directed Acyclic Graphs (DAGs) were used to identify potential confounders and intermediates in all three studies, using information from previous studies as discussed earlier. We adjusted for confounders depending on availability.

All three studies adjusted for child sex, calendar year, combined parents' socio-economic status, and parent(s)' age.

Child Sex: For all three studies, information on child sex (male, female) was obtained from the Danish Medical Birth Registry.

Calendar Year: In study 1 and 3, calendar year was year of child's 1st birthday, while in study 2, calendar year was year of start of follow up- either diagnosis of child with CP, or age 1 of non-CP child. In study 1 and 2, calendar year was adjusted for as a dummy variable per year, whereas in study 3, calendar year was either < 2000 or ≥2000.

Combined Socioeconomic Status: In study 1 and 2, for socioeconomic status, we used information on parents' education obtained from the Danish Civil Registration System Registry. Education is one of the oldest and most commonly used markers of socioeconomic status because of its relevance as a mechanism for achievement of social position, advantageous behaviors, and occupational advancement and is highly predictive of income and wealth (Miech and Hauser 2001).We obtained each parent's education at year of birth of the child, and if not available up to five years prior and after childbirth. We then combined the parents' information, and used the higher education of the two parents as a marker of socio-economic status (low- primary, middle- secondary, high, and missing). In studies 1 and 2, 46% fathers and mothers had equal education levels, 24% fathers had higher education than mothers, and 30% mothers had higher education level than fathers; however in 5% of this latter group, fathers' identification was not available. The source year for education was from the year of birth of the child for 79% of parents, and 3%, 4%, 4%, 4%, and 5% for each year after year child's birth respectively. Less than 1% of information on parents combined education was prior to child's year of birth. Combined parents education data was missing for 11% of total in cohort.

In study 3, information of social status was based on questions from the Danish National Birth Cohort. Coding of social status was based on highest self-reported education and job titles

for both parents at the time of recruitment. Parents who had a completed education four years beyond secondary school education or were in management were classified as “high” social status. Parents with middle-range training and skilled workers were classified as “middle” social status, and unskilled workers and unemployed were classified as “low” social status.

Parent(s) age: Study 1 adjusted for both maternal age (<20, 20-25, 25-30, 30+) and paternal age (<25 25-30, 30-35, 35+), and study 3 adjusted for maternal age only (<35, 35-39, 40-44, 45+). We used age categories for parent age in studies where CP was the outcome as noted earlier from other studies both lower and higher parent age are associated with an increased risk of CP. Study 2 adjusted for parent’s age in years (mother’s for study on mother’s CVD risk and father’s for study on father’s CVD risk) at start of follow up as a continuous variable, because risk of cardiovascular outcome increases with increasing age.

Child Residence: In studies 1 and 2, our cohort included children diagnosed with CP (or were age 1 for non-CP) prior to 1992. As stated above, the Danish Nation Cerebral Palsy Registry only covered East Denmark prior to 1992. We therefore adjusted for child residence (East or West Denmark) at age of diagnosis for CP child or age 1 for non-CP child. Information on child residence was obtained from the Danish Civil Registration System Registry.

Gestational Age: Information on gestational age was collected from the Danish Medical Birth Registry, and was only available beginning in 1978. We stratified on preterm birth for studies 1 and 3, and adjusted for preterm birth in study 2. In study 2, we also adjusted for small for gestational age defined as <10% weight per child sex and gestational age weeks in our entire

cohort. Preterm Birth was defined as <37 weeks gestation. More 20% of the cohort in studies 1 and 2 had missing information on gestational age; therefore, analyses were restricted to those with available information on this covariate, complete subject analyses. Secondary analyses also used imputation methods for missing gestational age and found similar results.

Comorbidities: Information on comorbidities was collected from the Danish Hospital Registry. ICD codes used to assess presence of these disorders are listed in Table of ICD Codes. In study 1, we adjusted for maternal hypertensive disorder, diabetes and vaginal bleeding during pregnancy. In study 2, we adjusted for maternal hypertensive disorder during pregnancy in analysis on mothers' risk of cardiovascular disease.

Smoking: For study 1, data on maternal smoking (yes, no, missing) was also obtained from the Danish Medical Birth Registry. Data on maternal smoking began being collected in 1991, so all birth years prior to 1991 were coded as missing, in addition to those that did not have a yes or no response. Smoking data was missing for 58% of the total cohort. For study 3, information on smoking (none, 1-9 cigarettes per day, 10 or more cigarettes per day), was obtained from interviews as described above.

Parity: For study 1, information on parity (first live born, not first live born) was obtained from the Danish Medical Birth Registry.

Housing: In study 3, information on household size was obtained from the first interview in the Danish National Birth Cohort. Mothers were asked how many adults and how

many children lived in her household. We combined values for total household size (1, 2, 3, 4+ adults and children per household).

Season of Birth: In study 3, we adjusted for season of start of gestation, as estimated by a start date of pregnancy. We subtracted the gestational age from the child's date of birth. In all years, seasons were determined if the pregnancy start dates fell within the range: (fall: September 21st-December 20th, winter: December 21st-March 20th, spring: March 21st- June 20th, summer: June 21st- September 20th).

Alcohol/Binge drink: Information on alcohol was only available for study 3, from interviews in the Danish National Birth Cohort. At both interviews, women answered questions regarding their weekly consumption of beer, wine, and spirits while pregnant. We defined one drink as one bottle of beer, one glass of wine, or 4 cL of spirits. The total average consumption was calculated by adding the intake of beer, wine, and spirits in a total number of drinks per week. Women who reported to consume less than one drink per week were assigned a numeric value of ½. Answers from both interviews were combined, and women were classified into alcohol consumption categories based on the maximum consumption. Alcohol consumption was classified as none, light (≤1 drink per week), moderate (2-4 drinks per week), and heavy (5 or more drinks per week). Binge drinking (yes/no) was defined as having at least one episode of having five drinks or more in one night during pregnancy.

8.5 Statistical Analysis

In all three studies, we used Cox proportional hazard regression models with person-years as the time-to-event variable using PROC PHREG in SAS version 9.2. In study 1 and 3, we also used robust sandwich covariance estimates to take into account interdependency amongst women who had more than one child during the cohort time, and therefore participated more than once in the cohort

For study 1 and 3, children were followed from one year of age until a reported diagnosis of CP, death, or end of follow up (December 31st 2006 for study 1 and December 31st 2008 for study 3), whichever occurred first. As described earlier, children diagnosed with CP prior to the age of 1 were included in the analyses, and their date of diagnosis was re-centered to their 1st birthday. We chose cox proportional hazard regression models to account for the difference in disease severity. More severe CP cases may be diagnosed earlier.

For study 2, mothers and fathers were modeled separately and were followed from day of CP child's day of diagnosis or one year from the day of birth for the non-CP child studied until a reported diagnosis of cardiovascular outcome, death, emigration or December 31, 2006, whichever occurred first. We performed an additional analysis for mothers where follow up time started from mother's day of birth.

Analyses in all three studies adjusted for maternal age, child's birth year, and parents' combined socio-economic status (education in study 1 and 2). Study 1 and 2 additionally adjusted for child's sex, and child's residence. Study 1 and 3 both adjusted for maternal

smoking. Other covariates in study 1 include child's birth weight, paternal age, and parity (if child was first live born). In study 2, we additionally adjusted for age of parent at beginning of follow up, child's preterm birth and small for gestational age, and for mothers only, hypertensive disorder during pregnancy, and in study 3 we additionally adjusted for maternal alcohol consumption, binge drinking, season of birth, and number per household.

For missing data on covariates, we created a missing value category for parents' education in study 1 and 2, and maternal smoking during pregnancy in study 1. In study 3, multiple imputation methods ("PROC MI and PROC MIANALYZE" in SAS 9.2) were used to compensate for missing data in the covariates. The procedure generated 5 different simulated completed datasets, replacing each missing value with a set of plausible values based on the other available values for that variable. The multiply imputed data sets were then analyzed by using standard procedures for complete data and combining the results from these analyses. Less than 2% of the patients had missing values on covariates included in the analysis. Missing values requiring imputation included: socio-economic status (n=300), household size (n=77), season of pregnancy start (n=217), alcohol (n=413), binge drinking (n=1,233) smoking (n=671), and gestational age (n=217).

Analysis was otherwise limited to data available.

For study 3, we conducted additional analyses to test for interaction on a multiplicative scale for exposure of interest and other risk factors in the study. This test would assess if there were a greater than multiplicative risk for those children who had both of two exposures, as compared with those with only one of the two or no exposures. We created four groups of

exposure: no exposure to either factor, exposure to one factor, exposure to the other factor, and exposure to both factors. Only those in any of the 4 groups were included in the analysis. Those with missing data on either exposure groups were not included in the analyses. The group of no exposure to either factor was used as a reference group in the analyses. A similar Cox proportional hazards regression was performed to investigate the relationship of the four groups with incidence of outcome events. Models were fully adjusted as described above, but marginal hazard ratios were not adjusted for the corresponding 2nd exposure of interest.

Statistical Analysis: Study 1

In study 1, we modeled the risk of time to CP for continuous increasing placenta weight in hectograms or placenta weight (g/100). In a second model, placenta weight was additionally adjusted for continuous birth weight (kg). In order to further assess the relation between placenta weight, birth weight and CP, we divided placenta weight and birth weight into quartiles based on the data in our cohort. We then created 16 groups of placenta weight and birth weight quartile exposure group and measured the association of each group with CP, using the largest quartile for both placenta weight and birth weight as reference. This 4x4 analysis was adjusted for all above listed confounders and additionally maternal placenta disorders, hypertensive disorders, diabetes, and vaginal bleeding during pregnancy. From this 16 groups analysis, we hoped to further understand if there is a trend for placenta weight quartiles for each birth weight quartile. We additionally measured continuous placenta weight stratified on seven groups of birth weight (<1,500g, 1,500 to 1,999g, 2,000 to 2,499g, 2,500 to 2,999g, 3,000g to 3,499g, 3,500g to 3,999g, and ≥4,000g), and adjusted for model 1 confounders.

Statistical Analysis: Study 2

We modeled the risk of time to cardiovascular outcome in the mothers and fathers separately over time for parents with a CP child compared to parents having a child without CP. We also estimated separately with follow up from the date of birth of the parent considering the exposure to be genetic and with potential effects starting from birth.

Statistical Analysis: Study 3

For each infectious exposure group we modeled the risk of time to CP and to spastic CP (sCP). Certain factors significantly associated with CP were tested in pairs for interaction on a multiplicative scale. These factors include untreated and treated vaginal infection, smoking 10 or more cigarettes per day, and preterm birth.

IV. 9. Results and Interpretation

9.1 Study 1: Placenta Disorders, Placenta Weight, Birth weight, and Congenital Cerebral Palsy

9.1.1 Study 1 Results

We identified 1,874,653 singleton births that survived or did not emigrate prior to 1 year of age (date of birth+365). Among these, there were 2,547 confirmed cases of CP, and 760 cases of CP based on available placenta data. The characteristics of the subjects are presented in Table 9.1.2.1 CP infants were more likely to be first born males, born to older mothers who smoked

during their pregnancy and older fathers with a low combined parent's education level. They also had lower gestational age, lower birth weight, and lower placenta weight.

After adjustment for maternal age, paternal age, smoking, parity, child sex, calendar year, parent's education and East Denmark resident, increased placenta weight was associated with a 32% decrease in CP risk (Table 9.1.2.2). Upon stratification for preterm (<37 weeks) and term (≥37 weeks), increasing placenta weight remained associated with a decreased risk for CP, with a stronger decreased risk in preterm children and a lesser decrease in risk in term children.

Table 9.1.2.2 also shows the association of maternal gestational disorders with CP after adjustment for all above listed confounders. Mothers' that had vaginal bleeding or diabetes during their pregnancy had a more than two fold increased risk of having a child with CP, and women who had hypertensive disorders of pregnancy had a 79% increased risk of having a child with CP. After stratification by gestational age the association between vaginal bleeding during pregnancy and CP remained significant only in preterm children, while having diabetes or hypertensive disorders of pregnancy remained associated with increased risk of CP only in term children.

We studied disorders associated with placenta pathology in this cohort and the results are also in Table 9.1.2.2. After restricting to participants with available data on confounders, there were 86,810 cases of placenta disorders and among them 278 cases in mothers of subjects with CP. In adjusted analysis, the occurrence of a placental disorder or specifically of placenta previa and placenta abruption was associated with CP. Placenta abruption, increased CP risk more than 7 fold. The group labeled "other placental disorders" was also associated with increased risk of CP.

Table 9.1.2.3 shows that after adjustment for birth weight as a continuous variable the association between placenta weight and CP reversed overall and similarly within each gestational age strata. Table 9.1.2.3 shows also the hazard ratios for the same variables as Table 2 after simultaneous adjustment for placenta weight and birth weight. The results show that the association with CP remained significant only for placenta disorders and placenta abruption.

In addition to adjustment for birth weight as a continuous variable, we tested the association between placenta weight and CP in different birth weight strata. The results are shown in tables 9.1.2.4 and 9.1.2.5. The association of placenta weight with CP appeared to present only in the lowest quartile of birth weight (table 4) or non-significant in all strata (table 9.1.2.5).

9.1.2 Study 1 Tables

Table 9.1.2.1: Characteristics of the cohort according to the presence of CP in the infant.

		ALL	CP	NO CP
		n=1,874,653	n=2,547	n=1,872,106
Variable	**N**	**mean±SD**	**mean±SD**	**mean±SD**
Preterm (%)	1,481,976	4.4	35	4.4
SGA (%)	1,478,328	7.3	16.7	7.3
Birthweight (g)	1,868,067	3,462±562	2,759±1,035	3,463±560
Placental weight (g)	418,845	663±147	586±179	663±147
Vaginal Bleeding (%, [n])	1,874,246	0.73 [13,595]	1.73 [44]	0.72 [13,551]
Gestational Diabetes (%, [n])	1,874,246	0.45 [8,488]	1.22 [31]	0.45 [8,457]
Preeclampsia (%, [n])	1,874,246	3.62 [67,804]	6.60 [168]	3.61 [67,636]
Child Gender (% female)	1,874,653	48.7	40.6	48.7
Maternal Age (%)				
<20 years	1,874,248	3.6	3.8	3.6
20 to 25 years	1,874,248	23.6	23	23.6
25 to 30 years	1,874,248	38.7	33.9	38.7
30 to 35 years	1,874,248	24.8	27.6	24.8
≥35 years	1,874,248	9.3	11.7	9.3
First Liveborn (%)	1,871,575	52.8	56.4	52.8
Paternal Age (%)				
<25 years	1,848,260	13.2	13.9	13.2
25 to 30 years	1,848,260	33.9	30.2	33.9
30 to 35 years	1,848,260	31.4	29.9	31.4
35 to 40 years	1,848,260	14.7	17.3	14.7
≥40 years	1,848,260	6.8	8.6	6.8
Maternal Smoker:				
Smoking - NO (%)	1,874,653	31.1	33.6	31.1
Smoking - YES (%)	1,874,653	10.9	15.6	10.9
Smoking - Missing data (%)	1,874,653	58	50.8	58
Parent Education (%)				
Low	1,874,653	12.8	16.1	12.8
Middle	1,874,653	23.8	24.8	23.8
High	1,874,653	18.2	19.4	18.2
Missing	1,874,653	45.2	39.7	45.2
East Denmark Resident (%)	1,874,565	51.5	76.3	51.5

Table 9.1.2.2: Hazard Ratios (HR) for cerebral palsy according to prenatal risk factors, placenta weight and placenta disorders, stratified by gestational age group.

						Stratified by gestational age							
						preterm <37 weeks				term or later ≥37 weeks			
	N used	N CP	HR crude	aHR	95% CI	N used	N CP	aHR	95% CI	N Used	N CP	aHR	95% CI
Placenta weight (g/100)	409,590	760	0.67	**0.68**	**(0.64-0.71)**	18,211	204	**0.60**	**(0.54- 0.66)**	389,916	552	**0.88**	**(0.83- 0.94)**
Vaginal Bleeding	1,846,955	42	2.41	**2.15**	**(1.59- 2.92)**	63,820	32	**1.86**	**(1.30- 2.66)**	1,397,157	10	0.80	(0.43- 1.50)
Diabetes in pregnancy	1,846,955	29	2.72	**2.18**	**(1.51- 3.15)**	63,820	13	0.99	(0.57- 1.72)	1,397,157	16	**1.94**	**(1.19- 3.19)**
Hypertensive disorder during pregnancy	1,846,955	164	1.88	**1.79**	**(1.53- 2.10)**	63,820	80	1.09	(0.86- 1.37)	1,397,157	76	**1.38**	**(1.09- 1.74)**
Placenta Disorders (all)	1,846,955	278	2.54	**2.56**	**(2.26- 2.90)**	63,820	156	**1.47**	**(1.23- 1.75)**	1,397,157	110	**1.63**	**(1.34- 1.98)**
Placenta Previa	1,769,520	73	6.10	**6.42**	**(5.08- 8.11)**	57,442	53	**1.50**	**(1.12- 1.99)**	1,331,543	19	**3.90**	**(2.48- 6.15)**
Placenta Abruption	1,765,650	63	9.15	**7.70**	**(5.99- 9.90)**	56,714	53	**1.96**	**(1.48- 2.60)**	1,329,159	10	**3.01**	**(1.62- 5.61)**
Other Placenta Disorders	1,832,746	151	1.65	**1.68**	**(1.43- 1.99)**	58,695	59	1.23	(0.94- 1.61)	1,389,153	81	**1.36**	**(1.09- 1.70)**

*aHR: adjusted for maternal age (<20, 20-25, 25-30, 30+), paternal age (<25 25-30, 30-35, 35+), smoking (yes, no, missing), first live born (yes, no), child sex (male, female), parents' education (low, middle, high, missing), and East Denmark resident (yes, no), calendar year.

Table 9.2.1.3: Hazard Ratios (HR) for cerebral palsy according to prenatal risk factors, placenta weight and placenta disorders, stratified by gestational age group and adjusted for placenta weight.

						Stratified by gestational age							
						preterm <37 weeks				term or later ≥37 weeks			
	N used	N CP	HR crude	aHR	95% CI	N used	N CP	aHR	95% CI	N Used	N CP	aHR	95% CI
Placenta weight (g/100)	418,845	760	0.67	**1.15**	**(1.07-1.22)**	18,109	200	**1.16**	**(1.02-1.33)**	389,284	540	**1.10**	**(1.02-1.19)**
Vaginal Bleeding	408,238	27	2.41	1.21	(0.82-1.79)	18,109	19	1.18	(0.73-1.90)	389,284	8	0.95	(0.47-1.91)
Diabetes in pregnancy	408,238	15	2.72	1.42	(0.85-2.38)	18,109	6	1.32	(0.58-3.00)	389,284	9	1.47	(0.76-2.86)
Hypertensive disorder during pregnancy	408,238	50	1.88	0.87	(0.65-1.18)	18,109	31	0.68	(0.65-1.01)	389,284	19	0.97	(0.61-1.54)
Placenta Disorders (all)	408,238	52	2.54	**1.44**	**(1.08-1.91)**	18,109	30	**1.58**	**(1.07-2.34)**	389,284	22	1.11	(0.73-1.71)
Placenta Previa	392,586	6	6.10	1.69	(0.75-3.79)	16,904	4	1.29	(0.48-3.51)	374,853	2	2.57	(0.64-10.4)
Placenta Abruption	393,721	24	9.15	**2.00**	**(1.31-3.04)**	17,386	21	**1.72**	**(1.09-2.73)**	375,503	3	1.52	(0.49-4.72)
Other Placenta Disorders	405,902	23	1.65	1.11	(0.73-1.68)	65,270	6	1.46	(0.65-3.30)	387,931	17	0.99	(0.61-1.61)

All adjusted for maternal age (<20, 20-25, 25-30, 30+), paternal age (<25 25-30, 30-35, 35+), smoking (yes, no, missing), first live born (yes, no), child sex (male, female), parent's education (low, middle, high, missing), and East Denmark resident (yes, no), calendar year, and birth weight. All also adjusted for placenta weight (/100g) except for placenta weight as exposure.

Table 9.2.1.4: Hazard Ratios (HR) for cerebral palsy according to quartiles of placental weight and birth weight

BIRTH WEIGHT QUARTILES			PLACENTA WEIGHT QUARTILES			
			1	2	3	4
		aHR	**5.57 (4.18- 7.43)**	**3.39 (2.36- 4.87)**	**2.74 (1.66- 4.53)**	**2.83 (1.29- 6.20)**
	1	N CP	279	62	21	7
		No CP	51,711	19,372	7,921	2525
		aHR	1.23 (0.81- 1.87)	1.34 (0.90- 2.01)	1.29 (0.79- 2.09)	**1.93 (1.09- 3.41)**
	2	N CP	35	40	23	15
		No CP	31,440	32,904	19,620	8413
		aHR	1.57 (0.99- 2.50)	1.45 (0.99- 2.13)	1.07 (0.71- 1.63)	1.47 (0.95- 2.27)
	3	N CP	26	48	35	31
		No CP	18,068	36,533	35,949	22951
		aHR	1.52 (0.70- 3.34)	1.04 (0.61- 1.76)	1.12 (0.74- 1.69)	1.00 (reference)
	4	N CP	7	18	37	58
		No CP	4,835	18,658	35,598	61277

Data adjusted for maternal age (<20, 20-25, 25-30, 30+), paternal age (<25 25-30, 30-35, 35+), smoking (yes, no, missing), first live born (yes, no), child sex (male, female), parent's education (low, middle, high, missing), East Denmark resident (yes, no), calendar year, vaginal bleeding during pregnancy(yes, no), hypertension disorders during pregnancy (yes, no), gestational diabetes (yes, no), and placenta disorders (yes, no).

Table 9.2.1.5: Hazard Ratios (HR) for association between placenta weight and cerebral palsy stratified by birth weight

Birthweight (g) Group	N Used	N CP	HR unadjusted	HR adjusted	95% CI
<1500g	1,825	83	1.06	1.05	(0.87- 1.28)
1,500 to 1,999	2,639	73	1.15	1.16	(0.94- 1.43)
2,000 to 2,499	8,438	64	1.03	1.05	(0.83- 1.33)
2,500 to 2,999	40,592	109	1.12	1.11	(0.92- 1.32)
3,000 to 3,499	126,259	165	1.16	1.14	(0.99- 1.31)
3,500 to 3,999	143,696	159	0.99	0.99	(0.86- 1.13)
4000+	84,889	89	1.02	1.03	(0.89- 1.19)
All	408,238	742	0.67	**0.68**	**(0.64-0.71)**

Data adjusted for maternal age (<20, 20-25, 25-30, 30+), paternal age (<25 25-30, 30-35, 35+), smoking (yes, no, missing), first live born (yes, no), child sex (male, female), parent's education (low, middle, high, missing), calendar year, and East Denmark resident (yes, no).

9.1.3 Study 1 Interpretation:

1. We have shown that a lower placenta weight is associated with the risk of cerebral palsy
2. We have confirmed that vaginal bleeding, diabetes and hypertension disorders of/during pregnancy are associated with CP
3. We have confirmed that placenta disorders and specifically placenta previa and placenta abruption are associated with increased CP risk.
4. After stratification by gestational age:
    a. Low placenta weight continues to be associated with CP in term and preterm births
    b. Placenta disorders, previa and abruption continues to be associated with CP in term and preterm births
    c. Diabetes during pregnancy and hypertensive disorders of pregnancy are associated with CP only in term delivery. For hypertensive disorders of pregnancy this is a confirmation of previous data, which were presented in previous chapters. For diabetes it is a new finding. A possible interpretation is that gestational age is an intermediate and a collider bias becomes apparent after adjustment for the exposure and unknown confounders. The same interpretation is applicable for vaginal bleeding which is associated with CP only in preterm. Another interpretation is the presence of a selection bias. We discussed this for hypertensive disorders of pregnancy. For diabetes it is conceivable that the known increases in risk related to macrosomia towards the end of the pregnancy account for the results. In vaginal bleeding selection could operate by placing the medical

disasters in the preterm group while minor bleeding occurred in children delivered at term.

5. After adjustment for birth weight, placenta weight was positively associated with CP. These results were predicted by the assumption A: *Placenta weight and birth weight are not associated with CP. They are only a proxy of placenta function.* This is not a confirmation of its validity, but a working hypothesis for further studies. After adjusting for both birth weight and placenta weight the association of CP with vaginal bleeding, diabetes during pregnancy and hypertensive disorders of pregnancy are no longer significant. This suggests that placenta function is part of the pathogenetic mechanism for the association. The fact that placenta abruption is still significant after adjustment for both birth weight and placenta weight suggests placenta function prior to delivery is not part of the mechanism for the association between placenta abruption and CP.

6. When the data were stratified by birth weight on the assumption that birth weight was an intermediate, a weak trend for association between placenta weight and birth weight was seen only in the low birth weight group for the method used in Table 4 and no significant association was seen when for the method used in Table 5. This is not a confirmation of the validity of assumption B: *Birth weight is an intermediate for placenta weight in its relationship with CP,* but a working hypothesis. It would suggest that the literature on birth weight/placenta weight ratio is based on a methodology of adjusting on an intermediate and thereby inducing collider bias. Alternative explanations should be examined.

9.2 Study 2: Cerebral Palsy and Parent Cardiovascular Risk

9.2.1 Study 2 Results

We identified 1,021,955 mothers of singletons that survived or did not emigrate prior to 1 year of age (date of birth + 365), did not result in CP in the infant and had information concerning the mother. There were 2,508 mothers of confirmed cases of CP selected by the same criteria.

We used two methods for the entry time in the study. The entry time began either at day of diagnosis for children with CP and 1st birthday (day of birth +365) for non-CP children (Method 1), or at the time of mother's birth for all participants (Method 2). For Method 1, 43 CP mothers and 3,504 non-CP mothers ended follow up prior to day of diagnosis for CP child or child's 1st birthday for non-CP child, and were removed for analysis. Of those that were removed, 22 CP mothers and 2,695 non-CP mothers had a cardiovascular outcome prior to child's diagnosis or child's 1st birthday. From Method 1, we had an average follow up time of 16.8 ± 9.7 years for non-CP mothers and 13.9± 8.8 for CP mothers with a maximum of 33 years of follow up time for both. At end of follow up, maternal age averaged at 46 ± 10 years for non-CP mothers and 44 ± 9 with less than 20% of mothers over age 55 for non-CP mothers and less than 10% for CP mothers.

After adjustment for mother's age, year of child's birth, child's residence, parent's education and child sex, the "all cardiovascular disease" endpoint was significantly associated with CP (Table 9.2.2.2) irrespective of the method used for the point of entry. After additional adjustment for small for gestational age offspring and hypertension disorder of pregnancy, the association remained significant for both methods. After adjustment for preterm the association was no longer significant, irrespective of the method used.

Table 9.2.2.3 shows the associations of CP with different types of cardiovascular disease and all cause mortality. For method 1, after adjustment for mother's age, year of child's birth, child's residence, parent's education and child sex, all cardiovascular endpoints and all cause mortality were significantly associated with CP with the exception of ischemic heart disease. For method 2 only cerebrovascular disease, thrombosis and "others were significantly associated with CP. The group of "other cardiovascular disease" included six cases of arrhythmias, two cases of peripheral arterial disease, one case of pulmonary hypertension, one case of bacterial endocarditis and one case of cardiomyopathy.

The fully adjusted model, including small for gestational age offspring, hypertension disorder of pregnancy and preterm delivery showed a significant association between CP and cerebrovascular disease and thrombosis in the model with method 1 and also between CP and thrombosis in method 2. An analysis of the ICD codes for thrombosis and cerebrovascualar disease in the mothers of CP children showed in the cerebrovascular disease group nine ischemic strokes, three hemorrhagic strokes and one transient ischemic attack. In the thrombosis group, all six subjects had deep vein thrombosis and one had also a pulmonary embolism.

We similarly identified 942, 028 fathers of singleton children of which 2,373 had CP children and the data are shown in tables 9.2.2.4. We had an average follow up time of 16.3 ± 9.5 years for non-CP and 13.4± 8.6 years for CP fathers with a maximum of 33 years of follow up for both father groups. At end of follow up, paternal age averaged at 48 ± 10 years for non-CP, 46 ± 9 for CP fathers with less than 25% of non-CP and 15% of CP fathers over age 55. For fathers, the adjusted hazard ratios were much lower and did not reach the level of significance for any of the endpoints.

9.2.2 Study 2 Tables

Table 9.2.2.1: Characteristics of maternal cohort

VARIABLE	ALL	NO CP	CP
N	1,018,409	1,015,944	2,465
Child Gender (% female)	49	49	41
Maternal Age (years)*	29±5	29±5	30±5
Education (%)			
Low	19	19	24
Medium	39	39	40
High	31	31	31
Education: missing values	11	11	5
East Denmark Resident (%)	53	53	76
Preterm (%)**	4.7	4.7	34.6
Small for Gestational Age (%)**	7.7	7.7	16.5
Hypertensive Disorders of Pregnancy (%)	4.1	4.1	6.8

**** Mean ± SD***

*****Based on ALL n=763,384 NO CP n=761,284 and CP n=2,100.***

Table 9.2.2.2: Hazard Ratios (HR) for all cardiovascular disease in mothers by different levels of adjustment and entry time

	Method 1						Method 2					
	Number			CP			Number			CP		
	All	CVD	CP	CVD	aHR	95%CL	All	CVD	CP	CVD	aHR	95%CL
Unadjusted	1,018,409	38,724	2,465	97	**1.51**	**(1.24-1.84)**	1,021,955	41,440	2,508	119	**1.59**	**(1.33-1.90)**
Model 1	1,018,409	38,724	2,465	97	**1.35**	**(1.10-1.64)**	1,021,955	41,440	2,508	119	**1.45**	**(1.21-1.74)**
Model 2	1,018,409	38,724	2,465	97	**1.32**	**(1.09-1.62)**	1,021,955	41,440	2,508	119	**1.41**	**(1.18-1.68)**
Model 3	763,384	18,976	2,100	66	**1.32**	**(1.04-1.68)**	766,538	21,586	2,142	88	**1.44**	**(1.17-1.77)**
Model 4	763,384	18,976	2,100	66	1.11	(0.87-1.42)	766,538	21,586	2,142	88	1.16	(0.94-1.43)

Model 1: adjusted for at entry time: mother's age, calendar year, child's residence, parent's education, child sex.

Model 2: adjusted for Model 1 + hypertensive disorder during pregnancy (yes, no).

Model 3: adjusted for Model 2 + small for gestational age (<10% percentile weight per gestational age (yes, no).

Model 4: adjusted for Model 3 + preterm delivery (yes, no).

Table 9.2.2.3: Hazard Ratios (HR) for cardiovascular disease types in mothers 1,018,409 using Method 1 and two levels of adjustment

			Crude	Model 1				Model 4	
	All	CP	HR	aHR	95%CL	All	CP	aHR	95%CL
Hypertension	18,754	43	1.34	1.24	(0.92-1.67)	9,840	29	1.02	(0.71-1.47)
Ischemic Heart Disease	16,877	36	1.31	1.12	(0.80-1.55)	7,494	23	0.88	(0.59-1.33)
Cerebrovascular Disease	2,896	13	2.83	**2.49**	**(1.45-4.30)**	1,241	10	**2.08**	**(1.11-3.91)**
Thrombosis	752	4	2.99	**2.69**	**(1.00-7.20)**	396	4	**3.23**	**(1.19-8.78)**
Congestive Heart Failure	1,040	4	2.48	2.15	(0.81-5.76)	406	2	1.09	(0.27-4.43)
Other Cardiovascular Disorders	3,630	12	2.05	**2.05**	**(1.15-3.58)**	1,582	6	1.20	(0.53-2.69)
All Cause Mortality	27,118	64	1.39	**1.34**	**(1.05-1.71)**	10,604	41	1.17	(0.86-1.60)

Model 1: adjusted for at entry time: mother's age, calendar year, child's residence, parent's education, child sex.

Model 4: adjusted for Model 1 + hypertensive disorder during pregnancy, small for gestational age and preterm delivery

Table 9.2.2.4: Hazard Ratios (HR) for cardiovascular disease (all and types) in 942, 028 fathers of which 2,373 father of CP children

	Model 1					Model 4			
	All	CP	Unadj	aHR	95%CL	All	CP	aaHR	95%CL
All Cardiovascular Disease	71,549	142	1.14	1.03	(0.87-1.21)	33,666	98	1.03	(0.84-1.26)
Hypertension	20,992	40	1.09	0.96	(0.71-1.31)	10,657	31	1.08	(0.76-1.53)
Ischemic Heart Disease	45,668	86	1.08	0.98	(0.79-1.21)	20,796	56	0.92	(0.71-1.20)
Cerebrovascular Disease	5,925	11	1.15	1.00	(0.55-1.81)	2,361	8	1.21	(0.60-2.42)
Thrombosis	968	3	1.76	1.56	(0.50-4.84)	462	2	1.27	(0.31-5.16)
Congestive Heart Failure	3,682	10	1.69	1.45	(0.78-2.70)	1,408	6	1.41	(0.63-3.16)
Other Cardiovascular Disorders	9,148	19	1.29	1.21	(0.77-1.90)	3,611	13	1.27	(0.31-5.16)
All Cause Mortality	49,326	94	1.08	0.99	(0.81-1.22)	19,809	53	0.88	(0.67-1.16)

Model 1: adjusted for at child's birth- father's age, calendar year, child's residence, parents' education and child sex
Model 4: adjusted for Model 1 + small for gestational age and preterm delivery

9.2.3 Study 2 Interpretations:

1. Cerebral palsy is associated with an increased risk of cardiovascular disease in the mother.
2. These associations were still significant after adjustment for potential confounders: mother's age, year of child's diagnosis (or 1 year of age for non-CP), child's residence, parents' education and child sex, preterm birth, small for gestational age and hypertensive disorders of pregnancy
3. The association was no longer significant after adjustment for preterm. This indicates that preterm is a very strong confounder and that the association between overall cardiovascular disease and CP could be mediated by preterm delivery.
4. There is no significant difference between the method using the point of entry at the time of the diagnosis of CP or at the birth of the mother.
5. Thrombosis and cerebrovascular disease but no other disease endpoints were significantly associated with CP after a fully adjusted model, including preterm delivery. These diseases have in common a prothrombotic predisposition. Their association with CP is consistent with a common genetic etiology.

9.3 Study 3: Prenatal Exposure to Self-reported Maternal Infections, Smoking and Congenital Cerebral Palsy.

9.3.1 Study 3 Results

All together 81,066 singletons were included in the analysis. Children were followed to a maximum of 11.4 years and the mean length of follow-up time was 7.2 $\pm$ 1.5 years (Mean $\pm$ SD), respectively. A total of 139 children were identified as having CP of which 121 had the spastic form. The characteristics of the subjects are presented in Table 9.3.2.1. We provided characteristics for the exposure groups of interest (vaginal infections, fever, and smoking) and for the entire cohort, for factors associated significantly with CP or sCP. Characteristics of the exposed and unexposed children were rather similar. Mothers who smoked 10 or more cigarettes per day were more likely to be binge drinkers, and less likely to be of higher socio-economic status.

The association between infections and the primary outcome are shown in Table 9.3.2.2.There were 45,192 women reporting an infection during the pregnancy in the first two interviews. Their risk of delivering an infant with CP overall or sCP specifically was not significantly different for women reporting an infection compared to women not reporting any infection. When the data were analyzed according to the type of infection, there was an association between vaginal infections and both overall CP and sCP risk and no significant association for other infections. When vaginal infections were separated into untreated and treated groups, a significant association was noted for untreated vaginal infections and sCP. There was no significant association of urinary tract infections with either CP or sCP. Maternal fever was also significantly associated with having a child with CP overall, but not sCP alone although the association was in the same direction (Table 9.3.2.2).

We did observe a significant association between maternal smoking during pregnancy and risk of sCP in their children. When we separated maternal smokers into those who smoked 10 or more cigarettes per day and those who smoked less at any time during their pregnancy, we detected an association with sCP for smoking 10 or more cigarettes per day but no association for women who smoked less than 10 cigarettes per day.

Table 9.3.2.3 presents the results of the interaction analysis of smoking 10 or more cigarettes per day with untreated and treated vaginal infections for sCP outcome. No significant deviation from the multiplicative model was detected between smoking 10 or more cigarettes per day and treated vaginal infections; however, untreated vaginal infections did have a significant multiplicative interaction with smoking 10 or more cigarettes per day for the sCP outcome, which may indicate they operate within the same causal field.

There were only 3,176 (3.9%) preterm births in our cohort but they accounted for 32 cases of CP (23%), and 29 cases of sCP (24%). Table 9.3.2.4 shows the of the interactions between preterm delivery with untreated and treated vaginal infections for sCP outcome. There was a multiplicative interaction between preterm and untreated vaginal infections for sCP.

9.3.2 Study 3 Tables (next page).

Table 9.3.2.1: Characteristics of Cohort According to Selected Self-Reported Maternal Infections

Covariate	Vaginal infections		Fever		Smoking			All
	NO	YES	NO	YES	NO	1-9 cigs/day	10+cigs/day	
N	n=62,788	n=16,719	n=56,493	n=24,744	n=59,285	n=10,768	n=10,342	n= 81,066
MATERNAL AGE								
15-24	9.4	8.7	9.2	9.5	7.3	12.7	17.0	9.3
25-29	39.1	37.4	39.1	37.9	38.8	40.0	36.7	38.7
30-34	37.1	38.2	36.8	38.4	38.8	34.4	31.6	37.3
≥35	14.4	15.7	14.9	14.2	15.1	12.9	14.7	14.7
SOCIO-ECONOMIC STATUS								
High	66.6	68.7	66.4	68.3	71.7	62.1	45.3	67.0
Middle	29.5	27.7	29.7	27.9	25.7	33.4	44.5	29.1
Low	3.9	3.6	3.9	3.8	2.6	4.5	10.2	3.9
HOUSEHOLD SIZE DURING PREGNANCY								
1 person	1.1	1.4	1.1	1.2	0.7	1.9	2.6	1.2
2 person	45.5	39.5	46.4	38.8	43.6	48.7	43.4	44.3
3 person	36.9	39.3	35.6	41.8	38.4	35.1	33.9	37.3
4+ person	16.5	19.8	16.9	18.2	17.3	14.3	20.1	17.2
SEASON PREGNANCY STARTED								
Fall	26.8	26.0	24.9	31.0	26.7	26.8	26.1	26.6
Winter	23.5	23.6	25.0	19.9	23.4	23.4	24.3	23.5
Spring	24.6	25.0	26.8	19.5	24.5	25.1	25.6	24.8
Summer	25.1	25.4	23.3	29.6	25.4	24.7	24	25.2
BIRTH YEAR								
1996-1999	34.7	33.8	33.9	35.7	33.9	35.5	36.6	34.3
2000-2003	65.3	66.2	66.1	64.3	66.1	64.5	63.4	65.7
MATERNAL SMOKING								
None	73.9	73.2	74.4	72.2	x	x	x	73.7
1-9 cigarettes/day	13.3	13.7	13.2	13.9	x	x	x	13.4
>10 cigarettes/day	12.8	13.1	12.4	13.9	x	x	x	12.9
MATERNAL ALCOHOL								
None	42.7	39.9	42.1	42.2	41	40.1	50.0	41.9
light (≤1 drinks/wk)	34.8	35.5	35.0	35.0	36.3	34	28.3	35.1
moderate (2-4 drinks/wk)	20.5	22.3	20.9	20.8	21	23.4	18.1	20.9
heavy (5+ drinks/wk)	2.0	2.3	2.0	2.0	1.7	2.5	3.6	2.1
Any episode of binge drinking ≥5 drinks in one	30.4	32.3	30.5	31.4	27.1	42.8	39.7	30.8
GESTATIONAL AGE								
Term or later (≥37 weeks)	96.5	96.5	96.4	96.6	96.7	96.3	95.6	96.1
Preterm (<37 weeks)	3.5	3.5	3.6	3.4	3.3	3.7	4.4	3.9

Table 9.3.2.2: Hazard Ratios (HR) for CP according to infections and smoking

	All Cerebral Palsy (N = 139)							Spastic Cerebral Palsy (N = 121)						
	Number							Number						
	Non-CP Exposed		CP Exposed		Crude HR	aHR*	95% CI	Non-CP Exposed		CP Exposed		Crude HR	aHR*	95% CI
FACTORS	NO	YES	YES	NO				NO	YES	NO	YES			
All Infections	30,145	45,197	48	71	0.99	0.98	(0.68- 1.41)	30,138	45,188	41	62	1.01	1.00	(0.67- 1.48)
Vaginal Infections	62,788	16,719	37	93	1.50	**1.52**	**(1.04- 2.24)**	62,772	16,717	35	77	1.71	**1.73**	**(1.16- 2.60)**
Untreated	71,910	7,597	18	112	1.60	1.62	(0.98- 2.69)	71,892	7,597	18	94	1.93	**1.95**	**(1.16- 3.26)**
Treated	70,385	9,122	19	111	1.41	1.44	(0.88- 2.37)	70,369	9,120	17	95	1.52	1.55	(0.91-2.64)
Urinary Infections	70,848	9,202	11	116	0.73	0.74	(0.40- 1.38)	70,832	9,201	10	100	0.77	0.79	(0.41- 1.50)
Cystitis	68,049	9,084	11	112	0.74	0.74	(0.40- 1.38)	68,033	9,083	10	96	0.78	0.79	(0.41- 1.51)
Pyelonephritis	79,621	292	1	125	2.19	2.29	(0.32- 16.45)	79,604	292	1	108	2.53	2.56	(0.35- 18.51)
Diarrhea	61,258	18,822	32	98	1.06	1.03	(0.69- 1.54)	61,244	18,818	28	84	1.09	1.04	(0.68- 1.59)
Cough	67,513	12,842	23	107	1.13	1.11	(0.71- 1.75)	67,498	12,839	20	92	1.14	1.11	(0.69- 1.81)
Herpes Labialis.	70,146	10,016	11	117	0.66	0.66	(0.35- 1.22)	70,130	10,014	9	101	0.62	0.62	(0.32- 1.24)
Genital Herpes	79,085	1,273	5	124	2.51	2.38	(0.97- 5.83)	79,070	1271	3	109	1.71	1.63	(0.52- 5.13)
Venereal Warts	79,631	733	1	129	0.84	0.77	(0.11- 5.53)	79,613	733	1	111	0.98	0.89	(0.12- 6.35)
Fever	56,493	22,632	49	80	1.53	**1.53**	**(1.06- 2.21)**	56,487	22,620	37	74	1.25	1.23	(0.82- 1.86)
Smoking (all)	59,285	21,110	36	94	1.08	1.11	(0.75- 1.65)	59,269	21,108	34	78	1.22	1.26	(0.83- 1.91)
1-9 cig/day	69,627	10,768	12	118	0.70	0.71	(0.39- 1.30)	69,610	10,767	11	101	0.78	0.79	(0.42- 1.49)
10+ cig/day	70,053	10,342	24	106	1.46	1.57	(0.98- 2.54)	70,036	10,341	23	89	1.69	**1.80**	**(1.10- 2.94)**

All adjusted for maternal age (<35, 35-39, 40-44, 45+), alcohol drink per week (never, ≤ 1, 2-4, 5+), binge drinking, combined socioeconomic status group (1,2,3), season of birth (fall, winter, spring summer), number per household (1,2,3,4+), birth year (<2000, ≥2000), smoking (0, 1-9, 10+)

Table 9.3.2.3: Hazard Ratios for sCP based on combined exposures to smoking 10 cigarettes or more per day and vaginal infections

		Smoking 10 cigarettes or more per day						
		NO			YES			
Exposure	values	N	N sCP	OR	N	N sCP	OR	ALL
Vaginal Infections	**No**	54,707	60	1	8,034	17	**2.06 (1.17- 3.62)**	1
	Untreated	6,641	14	**1.95 (1.08- 3.49)**	953	4	**3.99 (1.45- 11.00)**	**1.95 (1.17- 3.26)**
	Treated	7,880	15	**1.78 (1.00- 3.16)**	1,229	2	1.62 (0.40- 6.65)	1.56 (0.92- 2.65)
All				1			**1.86 (1.15- 3.03)**	

All adjusted for maternal age (<35, 35-39, 40-44, 45+), alcohol drink per week (never, ≤ 1, 2-4, 5+), binge drinking, combined socioeconomic status group (1,2,3), season of birth (fall, winter, spring summer), number per household (1,2,3,4+), and birth year (<2000, ≥2000).

Table 9.3.2.4: Hazard Ratios for sCP based on combined exposures to preterm and vaginal infections

		PRETERM						
		TERM 37+ weeks			PRETERM <37 weeks			
Exposure	values	N	N sCP	OR	N	N sCP	OR	ALL
Vaginal Infections	**No**	60,402	63	1	2,205	14	**5.88 (3.27- 10.55)**	1
	Untreated	7,307	13	1.71 (0.94- 3.11)	264	4	**14.25 (5.12- 39.63)**	**1.84 (1.09- 3.11)**
	Treated	8,784	15	1.66 (0.94- 2.93)	314	2	**6.23 (1.52- 25.58)**	1.55 (0.91- 2.64)
All				1			**5.89 (3.59- 9.68)**	

All adjusted for maternal age (<35, 35-39, 40-44, 45+), alcohol drink per week (never, ≤ 1, 2-4, 5+), binge drinking, combined socioeconomic status group (1,2,3), season of birth (fall, winter, spring summer), number per household (1,2,3,4+), and birth year (<2000, ≥2000).

9.3.3 Interpretation:

1. Vaginal infections were associated with CP and spastic CP.
2. Urinary tract infections based on maternal report as defined for this analysis were not associated with an increased risk of CP.
3. Untreated but not treated vaginal infections were associated with spastic CP. This suggests a possible role for the treatment and for differences in risk factors for CP subtypes, but the data are not conclusive. Additional studies will be necessary to understand if the data are due to the intervention or due to unknown confounders.
4. Vaginal infection and preterm birth, or untreated vaginal infection and preterm birth both had multiplicative interactions for the risk of sCP indicating that these exposures may be risk factors for sCP in the same causal field and possibly with preterm as a downstream consequence of the infection.
5. We confirm that fever is associated with the risk of CP. The information is obtained in majority of cases before birth and vaginal infections are not usually associated with fever. Hence, the data suggest a role for systemic infections other than vaginal infections occurring prior to the perinatal period.
6. Smoking more than 10 cigarettes per day is associated with risk of spastic CP. This identified a relationship with smoking quantity and CP subtype.

V. 10. Strengths and Limitations

10.1 Sample size

The main strengths of these studies are their population-based longitudinal design. The first two studies are based on data from nationwide registers, which have provided a large study

size and comprehensive population coverage. Health care delivery in Denmark is free of charge and therefore hospital data is more likely to represent the base population. Additionally, the medical birth register covers information on all births in Denmark, since 1973, including home and non-hospital deliveries. The Birth Registry data are obtained from official reports filed by midwives in attendance at all deliveries.

CP is a rare disorder and there are always difficulties in collecting enough cases in order to obtain significant results. The Danish National Cerebral Palsy Registry is one of the largest national databases for this condition. We had available data from over 2,500 children with CP, while the majority of studies have included a few hundred cases. This is another strength of the studies presented. However, because the number of available CP cases was further reduced by the availability of the data on exposures and confounders, the confidence intervals in all three studies are quite large.

10.2 Subjectivity of the data:

For study 3 we used data collected from telephone interviews in the Danish National Birth Cohort database. The fact that our data were self-reported during pregnancy means that we could capture pathology for which no physician was consulted, which may include milder cases of infections. This may increase sensitivity but decrease specificity of our infections exposure. Questions on urinary infections asked specifically about exposure cystitis and pyelonephritis as diagnosed by a physician, which may decrease misclassification of this exposure. However, questions on vaginal infection did not differentiate between bacterial and fungal. Furthermore, smoking and alcohol use during the pregnancy may have been underreported because of the known recommendation for abstinence during pregnancy. We did not have any data to validate the patient's report for any exposure. Therefore, non-differential misclassification of the

exposure is possible. Conversely, the interviews were conducted during pregnancy, prior to the diagnosis of CP, and therefore information on exposures was most likely free of differential recall bias.

10.3 Availability of the data

Although, our study was strengthened by the use of multiple Danish National databases with a large amount of data on confounders, our analyses were still limited by amount of data available. Unmeasured confounding may explain associations in our results. Furthermore, in study 1, information on placenta weight was only available after 1997, and we could therefore only do analyses on placenta weight for 1/3 of the children in our study, and only in 22% of the children in whom the birth weight was available. Information on gestational age was only available after 1978, and even after this time still had more than 20% missing data. In adjustment for preterm birth, our cohort size was truncated for analyses based on available data for preterm.

In order to maximize numbers used in our analysis we created missing categories for smoking and education. We believe that these two variables were not missing completely at random, and imputation of such a large number would have biased our results toward the null.

For study 1, data on smoking was collected in the birth registry beginning in 1991, but even after 1991, more than 50% of mothers in our cohort were missing data on smoking. Because we found differences in education level between mothers' with missing smoking data and the rest of our cohort, we decided that data on smoking may not have been missing at completely at random and therefore created a missing smoking category for analysis.

Similarly, in studies 1 and 2, we used education as a measurement of socioeconomic status. Even though we assessed socioeconomic status combining information from both parents

in up to 5 years before and after pregnancy, we only had information on parents' education for 55% of our cohort. For education, we also believed those that had missing data were not random and therefore created a missing category. For both smoking and education, creating a missing may have biased our results. However, we additionally repeated our analysis without missing categories in complete subject analysis, and found little difference with our reported results.

In study 3, we used multiple imputation methods to fill in missing values on covariates (<2%) in order to maximize the number of observations used in each analysis, which may have also led to some loss of precision. In study 3, we only used women that participiated in both interviews, we found that women who missed an interview (particularly those who attended the 1st and missed the 2nd interview) were more likely to be younger mothers who lived alone, smoked, drank alcohol, and of lower socioeconomic status. There 5,195 women of which 21 had children with CP that attended the 1st interview only, and 3,671 women that attended the 2nd interview only of which 5 had a child with CP.

In study 2, we used the hospital database as our only source for cardiovascular disease diagnoses which might not have captured a large number of events not occurring within this system. The hospital database only included outpatient diagnoses since 1995, and a number of events such as hypertension may not have necessitated a visit to the hospital.

The Danish National Cerebral Palsy Register only covered East Denmark prior to 1992. Therefore, in study 1, there may be non-differential misclassification of the outcome of CP for those children at diagnostic age, prior to 1992. Our study adjusted for East vs. West Denmark residence at diagnostic age to account for this bias. The majority of CP cases were born or diagnosed after 1992 when the registry covered all of Denmark. Study 2 may be limited by short

follow up time available to have cardiovascular diagnosis occurrences for this relatively young cohort of parents, especially those with CP children.

10.4 Data collection methods

One of the strengths of the study was that the diagnosis of CP was obtained through a standardized methodology. The cases of CP in the Danish National Cerebral Palsy Registry have been evaluated and confirmed by two physicians making misclassification of the outcome less likely. Cases of CP in the register were about half the number total collected from hospital registries, and eliminated misdiagnosed cases of CP which included a range of conditions from flat-footedness and toe walking to psychomotor delay and progressive neurometabolic diseases.

In addition, cardiovascular outcomes were assessed using standardized ICD codes, and there was little variation over time in the diagnosis of main cardiovascular disorders. A limitation of the study is that diagnostic criteria for ischemic heart disease have changed since 2000(2000a), so a number of parents with this outcome in prior years may have been misclassified. Information on placenta weight determination was not standardized and this could lead to important variations in results (Asfour and Bewley 2011). Also the method for determination of gestational age varied in time (Jorgensen 1999) and this could also lead to non-directional misclassification bias.

10.5 Generalizability of the results

Our study was strengthened by use on an ethnically homogeneous Danish population and adjustment for ethnicity was not necessary. However, use of this population can also be a study limitation, as the data cannot be extrapolated to ethnicities other than North-Europeans. Other

ethnicities may have different placenta and birth weight and other risk for cardiovascular disorders at young age.

In study 3, although over 100,000 women were recruited into the Danish National Birth Cohort, only 60% of invited women participated, which represented only 30% of the eligible population. It has also been noted that the cohort underrepresented lower socioeconomic status women (Jacobsen, Nohr and Frydenberg 2010), and questions may arise concerning selection bias and the generalizability of the results. However, studies on the Danish National Birth Cohort showed that the effect of low participation on results was small and studies using these cohorts were reliable(Nohr et al. 2006).

VI. **Perspectives for future research**

Relationship between placenta weight and birth weight in different ethnicities

One of the limitations of our study is the restriction of the cohort to Caucasians. As discussed in the introduction, Asians and African Americans have different sizes for both placenta and birth weight. In order to extend the data to these populations it would be interesting to perform the same study in a different cohort including or limited to minorities.

Finding best perinatal predictors of CP.

The Danish Medical Birth Registry additionally contains measurement at birth of other perinatal factors such as birth length, abdominal and head circumferences, and Apgar scores. I am working at the present time to evaluate which combination of measurements could best predict CP. Results from these studies could give insight on how to use ultrasound to determine risk of poor pregnancy outcomes.

Placenta ultrasound correlation with CP.

Low birth weight has a strong association with CP. We believe that in reality intrauterine growth restriction rather than low birth weight is the factor associated with the pathogenesis of CP. In order to differentiate intrauterine growth restriction from low birth weight, prospective longitudinal measurements of fetal growth would be necessary. These measurements should be accompanied by evaluation of placenta function through determinations of fetal blood flow in different territories [umbilical artery, ductus venous, middle cerebral artery, etc].

Placenta pathology correlation with CP in large studies

My study was based on a limited number of reports on the association between placenta pathology and CP risk. Future studies should collect information on placenta pathology at birth for a large number of children and then continue follow up over time to evaluate outcome risk. The rationale for such study has been discussed in the medical literature recently (Blair et al. 2011).

Revisit data with longer follow up.

One of the limitations of the cardiovascular data is the very short term follow up. It would be of interest to explore this or similar cohorts in 10 years as cardiovascular events will continue to accumulate.

Future studies on thrombosis and cerebrovascular disease

In our studies, women who had a child with CP had an increased risk for thrombosis or cerebrovascular disease, even after adjustment for preterm birth. It would be of interest to see if

there were other factors mediating this relationship, such as higher level of coagulants due to smoking, birth control, or genetic factors.

Lifestyle of mothers/caregivers

The interpretation of our data is that cerebral palsy in the offspring is associated with cardiovascular risk in the mother but not in the father. This can be explained either by genetic factors or by a caregiver effect in the mother. A large amount of information is necessary in order to understand the latter:

- Does the mother have a different lifestyle in terms of diet, exercise, and smoking?
- Is the stress and the psychological impact that different between mothers and fathers of the CP child?

Screening for vaginitis during pregnancy

One of the strengths of our study is the fact that we captured low grade infections for which no physician was consulted since data were obtained by questionnaire. The only way to validate the data would be through prospective periodic screening for bacterial, fungal and trichomoniasis, starting in the first trimester. This could enable the investigators to create a profile for the high risk patients and suggest measures of prevention.

Association of treatment of vaginal infections and CP

We have shown that untreated vaginal infections are strongly associated with CP. It is not clear from our data whether treatment is the reason for the difference or the risk is attributable to unknown confounders. Although, our questionnaires asked about treatment type,

we did not have a large enough sample to evaluate if treatment type affected CP risk. It would also be of interest to obtain prospective information concerning sexual activity, sexual partners and condom use, etc. during pregnancy.

Screening for interleukins in amniotic fluid

Fetal inflammatory syndrome has an important role in the pathogenesis of CP. It would be of interest to obtain a battery of cytokine tests during routine amniocenthesis and to test for association with pregnancy outcome and risk of CP.

Further studies on smoking and CP risk

Smoking during the pregnancy is done against strong physician advice. It is conceivable that data on smoking obtained from the patient underestimate the true exposure. The Danish National Birth Cohort asks if the woman's husband smokes, but additional data on second hand smoking is limited. It would be of interest to further evaluate if 2nd hand smoke is a risk factor for CP, and obtain data on urinary cotinine in pregnant women to measure exposure. Furthermore, the Danish National Birth Cohort does not ask questions regarding drug use during pregnancy. It may of interest to look at the association of drug use (marijuana and others) and risk of CP.

VII. Concluding Remarks

Our studies have shown:

1. Placenta disorders and / or the birth of a child with lower weight than predicted by placenta weight is a strong risk factor for cerebral palsy and an intermediate for the main disorders of pregnancy associated with CP.
2. CP in the offspring is associated with increased cardiovascular risk in the mother.
3. Preterm delivery is an important confounder for this association with the exception of cerebrovascular disease and thrombosis.
4. Self-reported vaginal infections, fever and smoking 10 or more cigarettes per day during pregnancy were associated with a higher risk of overall CP and/or spastic CP. Untreated vaginal infections in mothers smoking 10 or more cigarettes per day or delivered preterm identified a group at very high risk of CP.

This thesis is a contribution towards the understanding of congenital cerebral palsy etiology. Findings from this work should be followed up in other study populations as suggested above. My hope is that these studies contribute to further understanding of this disease and initiates new research directions.

VIII. References

(2000a) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J,* 21**,** 1502-13.

(2000b) 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,* 42**,** 816-24.

2002- 2008. SAS® 9.2. SAS Institute Inc., Cary, NC, USA.

Abel, E. L. (2010a) Alcoholism's evolutionary and cultural origins. *Curr Drug Abuse Rev,* 3**,** 197-204.

---. 2010b. Cerebral palsy and alcohol consumption during pregnancy: is there a connection? In *Alcohol Alcohol*, 592-4. England.

Aberg, A. & L. Westbom (2001) Association between maternal pre-existing or gestational diabetes and health problems in children. *Acta Paediatr,* 90**,** 746-50.

Almog, B., F. Shehata, S. Aljabri, I. Levin, E. Shalom-Paz & A. Shrim (2011) Placenta weight percentile curves for singleton and twins deliveries. *Placenta,* 32**,** 58-62.

Amor, D. J., J. E. Craig, M. B. Delatycki & D. Reddihough (2001) Genetic factors in athetoid cerebral palsy. *J Child Neurol,* 16**,** 793-7.
Andersen, G. L., L. M. Irgens, I. Haagaas, J. S. Skranes, A. E. Meberg & T. Vik (2008) Cerebral palsy in Norway: prevalence, subtypes and severity. *Eur J Paediatr Neurol,* 12**,** 4-13.
Aoi, N., T. Nakayama, M. Soma, K. Kosuge, A. Haketa, M. Sato, N. Sato, S. Asai & K. Matsumoto (2010) Association of the insulin-like growth factor1 gene with myocardial infarction in Japanese subjects. *Hereditas,* 147**,** 215-24.
Arnadottir, G. A., R. T. Geirsson, R. Arngrimsson, L. S. Jonsdottir & O. Olafsson (2005) Cardiovascular death in women who had hypertension in pregnancy: a case-control study. *BJOG,* 112**,** 286-92.
Asfour, V. & S. Bewley (2011) Cord clamping practice could affect the ratio of placental weight to birthweight and perinatal outcomes. *BJOG,* 118**,** 1539-40; author reply 1540.
Back, S. A., N. L. Luo, N. S. Borenstein, J. M. Levine, J. J. Volpe & H. C. Kinney (2001) Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci,* 21**,** 1302-12.
Badawi, N. & J. M. Keogh. 2009. The vexed issue of cerebral palsy and breech presentation. In *Dev Med Child Neurol,* 846. England.
Baptiste-Roberts, K., C. M. Salafia, W. K. Nicholson, A. Duggan, N. Y. Wang & F. L. Brancati (2008) Maternal risk factors for abnormal placental growth: the national collaborative perinatal project. *BMC Pregnancy Childbirth,* 8**,** 44.
Barker, D. J., A. R. Bull, C. Osmond & S. J. Simmonds (1990) Fetal and placental size and risk of hypertension in adult life. *BMJ,* 301**,** 259-62.
Barker, D. J., P. D. Gluckman, K. M. Godfrey, J. E. Harding, J. A. Owens & J. S. Robinson (1993) Fetal nutrition and cardiovascular disease in adult life. *Lancet,* 341**,** 938-41.
Basso, O. & A. Wilcox (2010) Mortality risk among preterm babies: immaturity versus underlying pathology. *Epidemiology,* 21**,** 521-7.
Bella, G. P., M. C. Garcia & R. C. Spadari-Bratfisch (2011) Salivary cortisol, stress, and health in primary caregivers (mothers) of children with cerebral palsy. *Psychoneuroendocrinology,* 36**,** 834-42.
Bellamy, L., J. P. Casas, A. D. Hingorani & D. J. Williams (2007) Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ,* 335**,** 974.
Bentley, P., G. Peck, L. Smeeth, J. Whittaker & P. Sharma (2010) Causal relationship of susceptibility genes to ischemic stroke: comparison to ischemic heart disease and biochemical determinants. *PLoS One,* 5**,** e9136.
Billiards, S. S., R. L. Haynes, R. D. Folkerth, N. S. Borenstein, F. L. Trachtenberg, D. H. Rowitch, K. L. Ligon, J. J. Volpe & H. C. Kinney (2008) Myelin abnormalities without oligodendrocyte loss in periventricular leukomalacia. *Brain Pathol,* 18**,** 153-63.
Bis, J. C., N. L. Smith, B. M. Psaty, S. R. Heckbert, K. L. Edwards, R. N. Lemaitre, T. Lumley & F. R. Rosendaal (2003) Angiotensinogen Met235Thr polymorphism, angiotensin-converting enzyme inhibitor therapy, and the risk of nonfatal stroke or myocardial infarction in hypertensive patients. *Am J Hypertens,* 16**,** 1011-7.
Blair, E., J. de Groot & K. B. Nelson (2011) Placental infarction identified by macroscopic examination and risk of cerebral palsy in infants at 35 weeks of gestational age and over. *Am J Obstet Gynecol,* 205**,** 124 e1-7.
Blake, K. V., L. C. Gurrin, L. J. Beilin, F. J. Stanley, L. I. Landau & J. P. Newnham (2001) Placental weight and placental ratio as predictors of later blood pressure in childhood. *J Hypertens,* 19**,** 697-702.
Bleker, O. P., M. Buimer, J. A. van der Post & F. van der Veen (2006) Ted (G.J.) Kloosterman: on intrauterine growth. The significance of prenatal care. Studies on birth weight, placental weight and placental index. *Placenta,* 27**,** 1052-4.

Bonellie, S. R., D. Currie & J. Chalmers (2005) Comparison of risk factors for cerebral palsy in twins and singletons. *Dev Med Child Neurol,* 47**,** 587-91.

Bortolus, R., L. Chatenoud, E. Di Cintio, P. Rossi, G. Benzi, M. Surace & F. Parazzini (1998) Placental ratio in pregnancies at different risk for intrauterine growth. *Eur J Obstet Gynecol Reprod Biol,* 80**,** 157-8.

Boyle, C. A., S. Boulet, L. A. Schieve, R. A. Cohen, S. J. Blumberg, M. Yeargin-Allsopp, S. Visser & M. D. Kogan (2011) Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics,* 127**,** 1034-42.

Brameld, J. M., R. Hold & F. B. Pipkin (2011) Regional variation in angiotensin converting enzyme activity in the human placenta. *Placenta,* 32**,** 906-8.

Brehaut, J. C., D. E. Kohen, P. Raina, S. D. Walter, D. J. Russell, M. Swinton, M. O'Donnell & P. Rosenbaum (2004) The health of primary caregivers of children with cerebral palsy: how does it compare with that of other Canadian caregivers? *Pediatrics,* 114**,** e182-91.

Budde, M. P., T. E. De Lange, G. A. Dekker, A. Chan & A. M. Nguyen (2007) Risk factors for placental abruption in a socio-economically disadvantaged region. *J Matern Fetal Neonatal Med,* 20**,** 687-93.

Buyru, N., J. Altinisik, C. B. Gurel & T. Ulutin (2003) PCR-RFLP detection of PAI-2 variants in myocardial infarction. *Clin Appl Thromb Hemost,* 9**,** 333-6.

Cammack, A. L., C. Buss, S. Entringer, C. J. Hogue, C. J. Hobel & P. D. Wadhwa (2011) The association between early life adversity and bacterial vaginosis during pregnancy. *Am J Obstet Gynecol,* 204**,** 431 e1-8.

Camp, B. W., S. H. Broman, P. L. Nichols & M. Leff. 1998. Maternal and neonatal risk factors for mental retardation: defining the 'at-risk' child. In *Early Hum Dev*, 159-73. Ireland.

Carberry, A. E., A. Gordon, D. M. Bond, J. Hyett, C. H. Raynes-Greenow & H. E. Jeffery (2011) Customised versus population-based growth charts as a screening tool for detecting small for gestational age infants in low-risk pregnant women. *Cochrane Database Syst Rev***,** CD008549.

Carlo, W. A., S. A. McDonald, J. E. Tyson, B. J. Stoll, R. A. Ehrenkranz, S. Shankaran, R. N. Goldberg, A. Das, D. Schendel, P. Thorsen, K. Skogstrand, D. M. Hougaard, W. Oh, A. R. Laptook, S. Duara, A. A. Fanaroff, E. F. Donovan, S. B. Korones, D. K. Stevenson, L. A. Papile, N. N. Finer, T. M. O'Shea, B. B. Poindexter, L. L. Wright, N. Ambalavanan, R. D. Higgins & N. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research (2011) Cytokines and neurodevelopmental outcomes in extremely low birth weight infants. *J Pediatr,* 159**,** 919-25 e3.

Cetin, I. & G. Alvino (2009) Intrauterine growth restriction: implications for placental metabolism and transport. A review. *Placenta,* 30 Suppl A**,** S77-82.

Cheng, J., J. Liu, X. Li, J. Peng, S. Han, R. Zhang, Y. Xu & S. Nie (2008) Insulin-like growth factor-1 receptor polymorphism and ischemic stroke: a case-control study in Chinese population. *Acta Neurol Scand,* 118**,** 333-8.

Collier, S. A. & C. J. Hogue (2007) Modifiable risk factors for low birth weight and their effect on cerebral palsy and mental retardation. *Matern Child Health J,* 11**,** 65-71.

Cornelis, M. C., A. El-Sohemy & H. Campos (2004) Genetic polymorphism of CYP1A2 increases the risk of myocardial infarction. *J Med Genet,* 41**,** 758-62.

Curry, C. J., S. Bhullar, J. Holmes, C. D. Delozier, E. R. Roeder & H. T. Hutchison (2007) Risk factors for perinatal arterial stroke: a study of 60 mother-child pairs. *Pediatr Neurol,* 37**,** 99-107.

Davey Smith, G., C. Hart, C. Ferrell, M. Upton, D. Hole, V. Hawthorne & G. Watt (1997) Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study. *BMJ,* 315**,** 1189-93.

Davey Smith, G., E. Hypponen, C. Power & D. A. Lawlor (2007) Offspring birth weight and parental mortality: prospective observational study and meta-analysis. *Am J Epidemiol,* 166**,** 160-9.

Day, L. J., K. L. Schaa, K. K. Ryckman, M. Cooper, J. M. Dagle, C. T. Fong, H. N. Simhan, D. C. Merrill, M. L. Marazita, J. C. Murray & S. K. England (2011) Single-nucleotide polymorphisms in the KCNN3 gene associate with preterm birth. *Reprod Sci,* 18**,** 286-95.

de Vries, L. S., I. C. van Haastert, M. J. Benders & F. Groenendaal (2011) Myth: cerebral palsy cannot be predicted by neonatal brain imaging. *Semin Fetal Neonatal Med,* 16**,** 279-87.

Deaver, G. G. (1952) Etiological factors in cerebral palsy. *Bull N Y Acad Med,* 28**,** 532-6.

DeFranco, E., K. Teramo & L. Muglia (2007) Genetic influences on preterm birth. *Semin Reprod Med,* 25**,** 40-51.

Deng, W., J. Pleasure & D. Pleasure (2008) Progress in periventricular leukomalacia. *Arch Neurol,* 65**,** 1291-5.

Dietz, P. M., L. J. England, C. K. Shapiro-Mendoza, V. T. Tong, S. L. Farr & W. M. Callaghan (2010) Infant morbidity and mortality attributable to prenatal smoking in the U.S. *Am J Prev Med,* 39**,** 45-52.

Dolk, H., S. Pattenden & A. Johnson (2001) Cerebral palsy, low birthweight and socio-economic deprivation: inequalities in a major cause of childhood disability. *Paediatr Perinat Epidemiol,* 15**,** 359-63.

Dudding, T., J. Heron, A. Thakkinstian, E. Nurk, J. Golding, M. Pembrey, S. M. Ring, J. Attia & R. J. Scott (2008) Factor V Leiden is associated with pre-eclampsia but not with fetal growth restriction: a genetic association study and meta-analysis. *J Thromb Haemost,* 6**,** 1869-75.

Eliasen, M., J. S. Tolstrup, A. M. Nybo Andersen, M. Gronbaek, J. Olsen & K. Strandberg-Larsen (2010) Prenatal alcohol exposure and autistic spectrum disorders--a population-based prospective study of 80,552 children and their mothers. *Int J Epidemiol,* 39**,** 1074-81.

Ellinor, P. T., K. L. Lunetta, N. L. Glazer, A. Pfeufer, A. Alonso, M. K. Chung, M. F. Sinner, P. I. de Bakker, M. Mueller, S. A. Lubitz, E. Fox, D. Darbar, N. L. Smith, J. D. Smith, R. B. Schnabel, E. Z. Soliman, K. M. Rice, D. R. Van Wagoner, B. M. Beckmann, C. van Noord, K. Wang, G. B. Ehret, J. I. Rotter, S. L. Hazen, G. Steinbeck, A. V. Smith, L. J. Launer, T. B. Harris, S. Makino, M. Nelis, D. J. Milan, S. Perz, T. Esko, A. Kottgen, S. Moebus, C. Newton-Cheh, M. Li, S. Mohlenkamp, T. J. Wang, W. H. Kao, R. S. Vasan, M. M. Nothen, C. A. MacRae, B. H. Stricker, A. Hofman, A. G. Uitterlinden, D. Levy, E. Boerwinkle, A. Metspalu, E. J. Topol, A. Chakravarti, V. Gudnason, B. M. Psaty, D. M. Roden, T. Meitinger, H. E. Wichmann, J. C. Witteman, J. Barnard, D. E. Arking, E. J. Benjamin, S. R. Heckbert & S. Kaab (2010) Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet,* 42**,** 240-4.

Enquobahrie, D. A., N. L. Smith, J. C. Bis, C. L. Carty, K. M. Rice, T. Lumley, L. A. Hindorff, R. N. Lemaitre, M. A. Williams, D. S. Siscovick, S. R. Heckbert & B. M. Psaty (2008) Cholesterol ester transfer protein, interleukin-8, peroxisome proliferator activator receptor alpha, and Toll-like receptor 4 genetic variations and risk of incident nonfatal myocardial infarction and ischemic stroke. *Am J Cardiol,* 101**,** 1683-8.

Eskild, A., P. R. Romundstad & L. J. Vatten (2009) Placental weight and birthweight: does the association differ between pregnancies with and without preeclampsia? *Am J Obstet Gynecol,* 201**,** 595 e1-5.

Evans, B. A., S. M. McCormack, P. D. Kell, J. V. Parry, R. A. Bond & K. D. MacRae (1995) Trends in female sexual behaviour and sexually transmitted diseases in London, 1982-1992. *Genitourin Med,* 71**,** 286-90.

Fletcher, N. A. & J. Foley (1993) Parental age, genetic mutation, and cerebral palsy. *J Med Genet,* 30**,** 44-6.

Fraser, A., S. M. Nelson, C. Macdonald-Wallis, L. Cherry, E. Butler, N. Sattar & D. A. Lawlor (2012) Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the avon longitudinal study of parents and children. *Circulation,* 125**,** 1367-80.

Fraser, A. M., J. E. Brockert & R. H. Ward (1995) Association of young maternal age with adverse reproductive outcomes. *N Engl J Med,* 332**,** 1113-7.

Fujimoto, T., T. Suwa, K. Kabe, T. Adachi, M. Nakabayashi & T. Amamiya (2008) Placental insufficiency in early gestation is associated with hypospadias. *J Pediatr Surg,* 43**,** 358-61.
Funai, E. F., Y. Friedlander, O. Paltiel, E. Tiram, X. Xue, L. Deutsch & S. Harlap (2005) Long-term mortality after preeclampsia. *Epidemiology,* 16**,** 206-15.
Gedikbasi, A., A. Akyol, B. Bingol, D. Cakmak, A. Sargin, R. Uncu & Y. Ceylan (2010) Multiple repeated cesarean deliveries: operative complications in the fourth and fifth surgeries in urgent and elective cases. *Taiwan J Obstet Gynecol,* 49**,** 425-31.
Germain, A. M., M. C. Romanik, I. Guerra, S. Solari, M. S. Reyes, R. J. Johnson, K. Price, S. A. Karumanchi & G. Valdes (2007) Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? *Hypertension,* 49**,** 90-5.
Ghi, T., S. Giunchi, G. Pilu, A. Youssef, A. M. Morselli-Labate, T. Arcangeli, M. C. Meriggiola, C. Pelusi, G. Ancora, G. Cocchi, G. Faldella & G. Pelusi. 2010. Neonatal hypoxic-ischemic encephalopathy in apparently low risk pregnancies: retrospective analysis of the last five years at the University of Bologna. In *J Matern Fetal Neonatal Med,* 516-21. England.
Gibson, C. S., A. H. MacLennan, N. G. Janssen, W. J. Kist, W. M. Hague, E. A. Haan, P. N. Goldwater, K. Priest & G. A. Dekker (2006) Associations between fetal inherited thrombophilia and adverse pregnancy outcomes. *Am J Obstet Gynecol,* 194**,** 947 e1-10.
Gilbert, W. M., B. N. Jacoby, G. Xing, B. Danielsen & L. H. Smith. 2010. Adverse obstetric events are associated with significant risk of cerebral palsy. In *Am J Obstet Gynecol,* 328 e1-5. United States: Inc.
Girard, S., H. Kadhim, M. Roy, K. Lavoie, M. E. Brochu, A. Larouche & G. Sebire (2009) Role of perinatal inflammation in cerebral palsy. *Pediatr Neurol,* 40**,** 168-74.
Glinianaia, S. V., J. Rankin & A. Colver. 2011. Cerebral palsy rates by birth weight, gestation and severity in North of England, 1991-2000 singleton births. In *Arch Dis Child,* 180-5. England.
Gohil, R., G. Peck & P. Sharma (2009) The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. *Thromb Haemost,* 102**,** 360-70.
Greenwood, C., P. Yudkin, S. Sellers, L. Impey & P. Doyle. 2005. Why is there a modifying effect of gestational age on risk factors for cerebral palsy? In *Arch Dis Child Fetal Neonatal Ed,* F141-6. England.
Grether, J. K., K. B. Nelson & S. K. Cummins (1993) Twinning and cerebral palsy: experience in four northern California counties, births 1983 through 1985. *Pediatrics,* 92**,** 854-8.
Grether, J. K., K. B. Nelson, E. S. Emery, 3rd & S. K. Cummins (1996) Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. *J Pediatr,* 128**,** 407-14.
Grether, J. K., K. B. Nelson, E. Walsh, R. E. Willoughby & R. W. Redline. 2003. Intrauterine exposure to infection and risk of cerebral palsy in very preterm infants. In *Arch Pediatr Adolesc Med,* 26-32. United States.
Grisaru-Granovsky, S., E. S. Gordon, Z. Haklai, A. Samueloff & M. M. Schimmel (2009) Effect of interpregnancy interval on adverse perinatal outcomes--a national study. *Contraception,* 80**,** 512-8.
Haak, P., M. Lenski, M. J. Hidecker, M. Li & N. Paneth (2009) Cerebral palsy and aging. *Dev Med Child Neurol,* 51 Suppl 4**,** 16-23.
Haataja, R., M. K. Karjalainen, A. Luukkonen, K. Teramo, H. Puttonen, M. Ojaniemi, T. Varilo, B. P. Chaudhari, J. Plunkett, J. C. Murray, S. A. McCarroll, L. Peltonen, L. J. Muglia, A. Palotie & M. Hallman (2011) Mapping a new spontaneous preterm birth susceptibility gene, IGF1R, using linkage, haplotype sharing, and association analysis. *PLoS Genet,* 7**,** e1001293.
Haavaldsen, C., S. O. Samuelsen & A. Eskild (2011) The association of maternal age with placental weight: a population-based study of 536,954 pregnancies. *BJOG,* 118**,** 1470-6.
Hagberg, B., G. Hagberg, E. Beckung & P. Uvebrant (2001) Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. *Acta Paediatr,* 90**,** 271-7.
Hagberg, H., C. Mallard & B. Jacobsson. 2005. Role of cytokines in preterm labour and brain injury. In *BJOG,* 16-8. England.

Hasegawa, J., K. Arakawa, M. Nakamura, R. Matsuoka, K. Ichizuka, O. Katsufumi, A. Sekizawa & T. Okai (2011) Analysis of placental weight centiles is useful to estimate cause of fetal growth restriction. *J Obstet Gynaecol Res,* 37**,** 1658-65.

He, S., A. Silveira, A. Hamsten, M. Blomback & K. Bremme (1999) Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. *Thromb Haemost,* 81**,** 538-42.

Heinonen, S., P. Taipale & S. Saarikoski (2001) Weights of placentae from small-for-gestational age infants revisited. *Placenta,* 22**,** 399-404.

Hemachandra, A. H., M. A. Klebanoff, A. K. Duggan, J. B. Hardy & S. L. Furth (2006) The association between intrauterine growth restriction in the full-term infant and high blood pressure at age 7 years: results from the Collaborative Perinatal Project. *Int J Epidemiol,* 35**,** 871-7.

Hemming, K., A. Colver, J. L. Hutton, J. J. Kurinczuk & P. O. Pharoah. 2008. The influence of gestational age on severity of impairment in spastic cerebral palsy. In *J Pediatr*, 203-8, 208 e1-4. United States.

Hemminki, K., X. Li, K. Sundquist & J. Sundquist (2007) High familial risks for cerebral palsy implicate partial heritable aetiology. *Paediatr Perinat Epidemiol,* 21**,** 235-41.

Henderson, J., U. Kesmodel & R. Gray (2007) Systematic review of the fetal effects of prenatal binge-drinking. *J Epidemiol Community Health,* 61**,** 1069-73.

Himmelmann, K., K. Ahlin, B. Jacobsson, C. Cans & P. Thorsen (2011) Risk factors for cerebral palsy in children born at term. *Acta Obstet Gynecol Scand,* 90**,** 1070-81.

Himmelmann, K., V. McManus, G. Hagberg, P. Uvebrant, I. Krageloh-Mann & C. Cans. 2009. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity. In *Arch Dis Child*, 921-6. England.

Hjern, A. & K. Thorngren-Jerneck (2008) Perinatal complications and socio-economic differences in cerebral palsy in Sweden - a national cohort study. *BMC Pediatr,* 8**,** 49.

Hlatky, M. A., E. Ashley, T. Quertermous, D. B. Boothroyd, P. Ridker, A. Southwick, R. M. Myers, C. Iribarren, S. P. Fortmann, A. S. Go & V. F. a. G. E. S. Atherosclerotic Disease (2007) Matrix metalloproteinase circulating levels, genetic polymorphisms, and susceptibility to acute myocardial infarction among patients with coronary artery disease. *Am Heart J,* 154**,** 1043-51.

Hogberg, U. & P. A. Holmgren (2007) Infant mortality of very preterm infants by mode of delivery, institutional policies and maternal diagnosis. *Acta Obstet Gynecol Scand,* 86**,** 693-700.

Hong, T. & N. Paneth (2008) Maternal and infant thyroid disorders and cerebral palsy. *Semin Perinatol,* 32**,** 438-45.

Hou, L., J. Huang, X. Lu, L. Wang, Z. Fan & D. Gu (2009) Polymorphisms of tumor necrosis factor alpha gene and coronary heart disease in a Chinese Han population: interaction with cigarette smoking. *Thromb Res,* 123**,** 822-6.

Hubel, C. A., R. W. Powers, S. Snaedal, H. S. Gammill, R. B. Ness, J. M. Roberts & R. Arngrimsson (2008) C-reactive protein is elevated 30 years after eclamptic pregnancy. *Hypertension,* 51**,** 1499-505.

Hung, T. H., C. C. Hsieh, J. J. Hsu, L. M. Lo, T. H. Chiu & T. T. Hsieh (2007) Risk factors for placental abruption in an Asian population. *Reprod Sci,* 14**,** 59-65.

Hvidtjorn, D., J. Grove, D. Schendel, C. Svaerke, L. A. Schieve, P. Uldall, E. Ernst, B. Jacobsson & P. Thorsen (2010) Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: a population-based cohort study. *Hum Reprod,* 25**,** 2115-23.

Impey, L., C. Greenwood, K. MacQuillan, M. Reynolds & O. Sheil (2001) Fever in labour and neonatal encephalopathy: a prospective cohort study. *BJOG,* 108**,** 594-7.

Irgens, H. U., L. Reisaeter, L. M. Irgens & R. T. Lie (2001) Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ,* 323**,** 1213-7.

Jacobsen, T. N., E. A. Nohr & M. Frydenberg (2010) Selection by socioeconomic factors into the Danish National Birth Cohort. *Eur J Epidemiol,* 25**,** 349-55.

Jacobsson, B., K. Ahlin, A. Francis, G. Hagberg, H. Hagberg & J. Gardosi. 2008. Cerebral palsy and restricted growth status at birth: population-based case-control study. In *BJOG*, 1250-5. England.
Jacobsson, B. & G. Hagberg (2004) Antenatal risk factors for cerebral palsy. *Best Pract Res Clin Obstet Gynaecol,* 18**,** 425-36.
Jacobsson, B., G. Hagberg, B. Hagberg, L. Ladfors, A. Niklasson & H. Hagberg (2002) Cerebral palsy in preterm infants: a population-based case-control study of antenatal and intrapartal risk factors. *Acta Paediatr,* 91**,** 946-51.
Jaddoe, V. W., B. O. Verburg, M. A. de Ridder, A. Hofman, J. P. Mackenbach, H. A. Moll, E. A. Steegers & J. C. Witteman (2007) Maternal smoking and fetal growth characteristics in different periods of pregnancy: the generation R study. *Am J Epidemiol,* 165**,** 1207-15.
Jarvis, S., S. V. Glinianaia & E. Blair. 2006. Cerebral palsy and intrauterine growth. In *Clin Perinatol*, 285-300. United States.
Jorgensen, F. S. (1999) Epidemiological studies of obstetric ultrasound examinations in Denmark 1989-1990 versus 1994-1995. *Acta Obstet Gynecol Scand,* 78**,** 305-9.
Kadhim, H., B. Tabarki, C. De Prez & G. Sebire (2003) Cytokine immunoreactivity in cortical and subcortical neurons in periventricular leukomalacia: are cytokines implicated in neuronal dysfunction in cerebral palsy? *Acta Neuropathol,* 105**,** 209-16.
Kallen, A. J., O. O. Finnstrom, A. P. Lindam, E. M. Nilsson, K. G. Nygren & P. M. Olausson (2010) Cerebral palsy in children born after in vitro fertilization. Is the risk decreasing? *Eur J Paediatr Neurol,* 14**,** 526-30.
Kanagalingam, M. G., S. M. Nelson, D. J. Freeman, W. R. Ferrell, L. Cherry, G. D. Lowe, I. A. Greer & N. Sattar. 2009. Vascular dysfunction and alteration of novel and classic cardiovascular risk factors in mothers of growth restricted offspring. In *Atherosclerosis*, 244-50. Ireland.
Kant, L., S. Dewan & B. K. Jain (1986) Cerebral palsy--is it a seasonal disorder? *J Epidemiol Community Health,* 40**,** 92-3.
Kim, R. J. & R. C. Becker (2003) Association between factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations and events of the arterial circulatory system: a meta-analysis of published studies. *Am Heart J,* 146**,** 948-57.
Kirby, R. S., M. S. Wingate, K. Van Naarden Braun, N. S. Doernberg, C. L. Arneson, R. E. Benedict, B. Mulvihill, M. S. Durkin, R. T. Fitzgerald, M. J. Maenner, J. A. Patz & M. Yeargin-Allsopp (2011) Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network. *Res Dev Disabil,* 32**,** 462-9.
Kistka, Z. A., E. A. DeFranco, L. Ligthart, G. Willemsen, J. Plunkett, L. J. Muglia & D. I. Boomsma (2008) Heritability of parturition timing: an extended twin design analysis. *Am J Obstet Gynecol,* 199**,** 43 e1-5.
Kosmas, I. P., A. Tatsioni & J. P. Ioannidis (2004) Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. *J Hypertens,* 22**,** 1655-62.
Krageloh-Mann, I. & C. Cans (2009) Cerebral palsy update. *Brain Dev,* 31**,** 537-44.
Krageloh-Mann, I. & V. Horber (2007) The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol,* 49**,** 144-51.
Krakowiak, P., C. K. Walker, A. A. Bremer, A. S. Baker, S. Ozonoff, R. L. Hansen & I. Hertz-Picciotto (2012) Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics,* 129**,** e1121-8.
Kraus, F. T. (1997) Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. *Hum Pathol,* 28**,** 246-8.
Kraus, F. T. & V. I. Acheen (1999) Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol,* 30**,** 759-69.

Kucuk, M. & F. Doymaz (2009) Placental weight and placental weight-to-birth weight ratio are increased in diet- and exercise-treated gestational diabetes mellitus subjects but not in subjects with one abnormal value on 100-g oral glucose tolerance test. *J Diabetes Complications,* 23**,** 25-31.

Kulak, W., B. Okurowska-Zawada, D. Sienkiewicz, G. Paszko-Patej & E. Krajewska-Kulak. 2010. Risk factors for cerebral palsy in term birth infants. In *Adv Med Sci*, 216-21. Poland.

Kulak, W. & W. Sobaniec (2005) Seasonal variations of cerebral palsy births in northeastern Poland. *Arch Med Res,* 36**,** 178-82.

La Gamma, E. F. & N. Paneth (2012) Clinical importance of hypothyroxinemia in the preterm infant and a discussion of treatment concerns. *Curr Opin Pediatr,* 24**,** 172-80.

Lao, T. T. & W. Wong (1999) The neonatal implications of a high placental ratio in small-for-gestational age infants. *Placenta,* 20**,** 723-6.

Lassen, T. H., M. Madsen, L. T. Skovgaard, K. Strandberg-Larsen, J. Olsen & A. M. Andersen (2010) Maternal use of nicotine replacement therapy during pregnancy and offspring birthweight: a study within the Danish National Birth Cohort. *Paediatr Perinat Epidemiol,* 24**,** 272-81.

Lawlor, D. A., G. Davey Smith, P. Whincup, G. Wannamethee, O. Papacosta, S. Dhanjil, M. Griffin, A. N. Nicolaides & S. Ebrahim (2003) Association between offspring birth weight and atherosclerosis in middle aged men and women: British Regional Heart Study. *J Epidemiol Community Health,* 57**,** 462-3.

Lee, C. & M. Kong (2007) An interactive association of common sequence variants in the neuropeptide Y gene with susceptibility to ischemic stroke. *Stroke,* 38**,** 2663-9.

Lee, J., L. A. Croen, K. H. Backstrand, C. K. Yoshida, L. H. Henning, C. Lindan, D. M. Ferriero, H. J. Fullerton, A. J. Barkovich & Y. W. Wu (2005) Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA,* 293**,** 723-9.

Lee, S., G. A. Colditz, L. F. Berkman & I. Kawachi (2003) Caregiving and risk of coronary heart disease in U.S. women: a prospective study. *Am J Prev Med,* 24**,** 113-9.

Leviton, A. & O. Dammann. 2004. Coagulation, inflammation, and the risk of neonatal white matter damage. In *Pediatr Res*, 541-5. United States.

Leviton, A., K. Kuban, T. M. O'Shea, N. Paneth, R. Fichorova, E. N. Allred & O. Dammann (2011) The relationship between early concentrations of 25 blood proteins and cerebral white matter injury in preterm newborns: the ELGAN study. *J Pediatr,* 158**,** 897-903 e1-5.

Li, J., M. Vestergaard, C. Obel, D. H. Precht, J. Christensen, M. Lu & J. Olsen (2009) Prenatal stress and cerebral palsy: a nationwide cohort study in Denmark. *Psychosom Med,* 71**,** 615-8.

Libby, G., D. J. Murphy, N. F. McEwan, S. A. Greene, J. S. Forsyth, P. W. Chien, A. D. Morris & D. M. C. for the (2007) Pre-eclampsia and the later development of type 2 diabetes in mothers and their children: an intergenerational study from the Walker cohort. *Diabetologia,* 50**,** 523-30.

Lie, K. K., E. K. Groholt & A. Eskild (2010) Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study. *BMJ,* 341**,** c4990.

Lieberman, E., J. Lang, D. K. Richardson, F. D. Frigoletto, L. J. Heffner & A. Cohen (2000) Intrapartum maternal fever and neonatal outcome. *Pediatrics,* 105**,** 8-13.

Lin, H. C., I. J. Chen, Y. H. Chen, H. C. Lee & F. J. Wu (2010) Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? *Schizophr Res,* 116**,** 55-60.

Lindqvist, P. G. & J. Molin (2005) Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol,* 25**,** 258-64.

Liu, J., Z. Li, Q. Lin, P. Zhao, F. Zhao, S. Hong & S. Li (2000) Cerebral palsy and multiple births in China. *Int J Epidemiol,* 29**,** 292-9.

Lwaleed, B. A., L. Dusse & A. J. Cooper (2011) Tissue factor dependent pathway and the diagnosis of pre-eclampsia. *Semin Thromb Hemost,* 37**,** 125-30.

Lykke, J. A., J. Langhoff-Roos, B. M. Sibai, E. F. Funai, E. W. Triche & M. J. Paidas (2009) Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension,* 53**,** 944-51.

MacLennan, A. (2000) A template for defining a causal relationship between acute intrapartum events and cerebral palsy: international consensus statement. International Cerebral Palsy Task Force. *Aust N Z J Obstet Gynaecol,* 40**,** 13-21.

Magnussen, E. B., L. J. Vatten, K. Myklestad, K. A. Salvesen & P. R. Romundstad (2011) Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. *Am J Obstet Gynecol,* 204**,** 526 e1-8.

Maleki, Z., A. J. Bailis, C. H. Argani, F. B. Askin & E. M. Graham. 2009. Periventricular leukomalacia and placental histopathologic abnormalities. In *Obstet Gynecol*, 1115-20. United States.

Mann, J. I., R. Doll, M. Thorogood, M. P. Vessey & W. E. Waters (1976) Risk factors for myocardial infarction in young women. *Br J Prev Soc Med,* 30**,** 94-100.

Mann, J. R., S. McDermott, H. Bao & A. Bersabe (2009) Maternal genitourinary infection and risk of cerebral palsy. *Dev Med Child Neurol,* 51**,** 282-8.

Mann, J. R., S. McDermott, M. I. Griffith, J. Hardin & A. Gregg (2011) Uncovering the complex relationship between pre-eclampsia, preterm birth and cerebral palsy. *Paediatr Perinat Epidemiol,* 25**,** 100-10.

Manor, O. & I. Koupil (2010) Birth weight of infants and mortality in their parents and grandparents: the Uppsala Birth Cohort Study. *Int J Epidemiol,* 39**,** 1264-76.

Martin, J. J., I. Hausser, P. Lyrer, O. Busse, R. Schwarz, R. Schneider, T. Brandt, M. Kloss, M. Schwaninger, S. Engelter & C. Grond-Ginsbach (2006) Familial cervical artery dissections: clinical, morphologic, and genetic studies. *Stroke,* 37**,** 2924-9.

Matsuda, Y., Y. Kawamichi, K. Hayashi, A. Shiozaki, S. Satoh & S. Saito (2011) Impact of maternal age on the incidence of obstetrical complications in Japan. *J Obstet Gynaecol Res,* 37**,** 1409-14.

Matsuda, Y., T. Maeda & S. Kouno (2003) Comparison of neonatal outcome including cerebral palsy between abruptio placentae and placenta previa. *Eur J Obstet Gynecol Reprod Biol,* 106**,** 125-9.

--- (2005) Fetal/neonatal outcome in abruptio placentae during preterm gestation. *Semin Thromb Hemost,* 31**,** 327-33.

McDonald, A. D. (1963) CEREBRAL PALSY IN CHILDREN OF VERY LOW BIRTH WEIGHT. *Arch Dis Child,* 38**,** 579-88.

Medica, I., A. Kastrin & B. Peterlin (2007) Genetic polymorphisms in vasoactive genes and preeclampsia: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol,* 131**,** 115-26.

Mehri, S., S. Mahjoub, A. Farhati, R. Bousaada, S. Ben Arab, B. Baudin & M. Hammami (2011) Angiotensinogen gene polymorphism in acute myocardial infarction patients. *J Renin Angiotensin Aldosterone Syst,* 12**,** 42-7.

Miech, R. A. & R. M. Hauser (2001) Socioeconomic status and health at midlife. A comparison of educational attainment with occupation-based indicators. *Ann Epidemiol,* 11**,** 75-84.

Morgan, V. A., M. L. Croft, G. M. Valuri, S. R. Zubrick, C. Bower, T. F. McNeil & A. V. Jablensky (2012) Intellectual disability and other neuropsychiatric outcomes in high-risk children of mothers with schizophrenia, bipolar disorder and unipolar major depression. *Br J Psychiatry,* 200**,** 282-9.

Morken, N. H., K. Kallen & B. Jacobsson. 2007. Outcomes of preterm children according to type of delivery onset: a nationwide population-based study. In *Paediatr Perinat Epidemiol*, 458-64. England.

Morris, C. A. (1971) Seasonal variation of streptococcal vulvo-vaginitis in an urban community. *J Clin Pathol,* 24**,** 805-7.

Mosca, L., E. J. Benjamin, K. Berra, J. L. Bezanson, R. J. Dolor, D. M. Lloyd-Jones, L. K. Newby, I. L. Pina, V. L. Roger, L. J. Shaw, D. Zhao, T. M. Beckie, C. Bushnell, J. D'Armiento, P. M. Kris-Etherton, J. Fang, T. G. Ganiats, A. S. Gomes, C. R. Gracia, C. K. Haan, E. A. Jackson, D. R. Judelson, E. Kelepouris, C. J. Lavie, A. Moore, N. A. Nussmeier, E. Ofili, S. Oparil, P. Ouyang, V. W. Pinn, K. Sherif, S. C. Smith, Jr., G. Sopko, N. Chandra-Strobos, E. M. Urbina, V. Vaccarino & N. K. Wenger (2011) Effectiveness-based guidelines for the prevention of

cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation,* 123**,** 1243-62.
Munshi, A., K. Rajeshwar, S. Kaul, A. Al-Hazzani, A. A. Alshatwi, M. Sai Babu, A. Usha & A. Jyothy (2010) Interleukin-10-1082 promoter polymorphism and ischemic stroke risk in a South Indian population. *Cytokine,* 52**,** 221-4.
Myking, S., R. Myhre, H. K. Gjessing, N. H. Morken, V. Sengpiel, S. M. Williams, K. K. Ryckman, P. Magnus & B. Jacobsson (2011) Candidate gene analysis of spontaneous preterm delivery: new insights from re-analysis of a case-control study using case-parent triads and control-mother dyads. *BMC Med Genet,* 12**,** 174.
Nabors, G. C. (1963) Maternal age and parity in relation to cerebral palsy in their infants. *South Med J,* 56**,** 282-3.
Nelson, K. B. 2006. Thrombophilias, perinatal stroke, and cerebral palsy. In *Clin Obstet Gynecol,* 875-84. United States.
Nelson, K. B., J. M. Dambrosia, J. K. Grether & T. M. Phillips (1998) Neonatal cytokines and coagulation factors in children with cerebral palsy. *Ann Neurol,* 44**,** 665-75.
Nelson, K. B. & J. H. Ellenberg (1981) Apgar scores as predictors of chronic neurologic disability. *Pediatrics,* 68**,** 36-44.
--- (1985) Antecedents of cerebral palsy. I. Univariate analysis of risks. *Am J Dis Child,* 139**,** 1031-8.
--- (1986) Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med,* 315**,** 81-6.
Nielsen, L. F., D. Schendel, J. Grove, D. Hvidtjorn, B. Jacobsson, T. Josiassen, M. Vestergaard, P. Uldall & P. Thorsen (2008) Asphyxia-related risk factors and their timing in spastic cerebral palsy. *BJOG,* 115**,** 1518-28.
Nohr, E. A., M. Frydenberg, T. B. Henriksen & J. Olsen (2006) Does low participation in cohort studies induce bias? *Epidemiology,* 17**,** 413-8.
O'Callaghan, M. E., A. H. MacLennan, C. S. Gibson, G. L. McMichael, E. A. Haan, J. L. Broadbent, P. N. Goldwater, G. A. Dekker & G. Australian Collaborative Cerebral Palsy Research (2011) Epidemiologic associations with cerebral palsy. *Obstet Gynecol,* 118**,** 576-82.
O'Callaghan, M. E., A. H. Maclennan, C. S. Gibson, G. L. McMichael, E. A. Haan, J. L. Broadbent, P. N. Goldwater, J. N. Painter, G. W. Montgomery, G. A. Dekker & G. Australian Collaborative Cerebral Palsy Research (2012) Fetal and maternal candidate single nucleotide polymorphism associations with cerebral palsy: a case-control study. *Pediatrics,* 129**,** e414-23.
O'Callaghan, M. E., A. H. MacLennan, E. A. Haan & G. Dekker (2009) The genomic basis of cerebral palsy: a HuGE systematic literature review. *Hum Genet,* 126**,** 149-72.
O'Leary, C. M., N. Nassar, J. J. Kurinczuk & C. Bower (2009) The effect of maternal alcohol consumption on fetal growth and preterm birth. *BJOG,* 116**,** 390-400.
O'Shea, T. M. (2002) Cerebral palsy in very preterm infants: new epidemiological insights. *Ment Retard Dev Disabil Res Rev,* 8**,** 135-45.
Obladen, M. (2011) Lame from birth: early concepts of cerebral palsy. *J Child Neurol,* 26**,** 248-56.
Odding, E., M. E. Roebroeck & H. J. Stam (2006) The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil,* 28**,** 183-91.
Odibo, A. O., A. G. Cahill, D. M. Stamilio, E. J. Stevens, J. F. Peipert & G. A. Macones (2007) Predicting placental abruption and previa in women with a previous cesarean delivery. *Am J Perinatol,* 24**,** 299-305.
Oksala, N. K., A. Oksala, T. Erkinjuntti, T. Pohjasvaara, T. Kunnas, R. Vataja, M. Kaste & P. J. Karhunen (2008) Long-term survival after ischemic stroke in postmenopausal women is affected by an interaction between smoking and genetic variation in nitric oxide synthases. *Cerebrovasc Dis,* 26**,** 250-8.
Ornoy, A., A. Wolf, N. Ratzon, C. Greenbaum & M. Dulitzky (1999) Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes. *Arch Dis Child Fetal Neonatal Ed,* 81**,** F10-4.

Ozturk, A., F. Demirci, T. Yavuz, S. Yildiz, Y. Degirmenci, M. Dosoglu & Y. Avsar (2007) Antenatal and delivery risk factors and prevalence of cerebral palsy in Duzce (Turkey). *Brain Dev,* 29**,** 39-42.

Pakula, A. T., K. Van Naarden Braun & M. Yeargin-Allsopp (2009) Cerebral palsy: classification and epidemiology. *Phys Med Rehabil Clin N Am,* 20**,** 425-52.

Paneth, N. 2008. Establishing the diagnosis of cerebral palsy. In *Clin Obstet Gynecol,* 742-8. United States.

Pathak, S., F. Jessop, L. Hook, N. J. Sebire & C. C. Lees (2010) Placental weight, digitally derived placental dimensions at term and their relationship to birth weight. *J Matern Fetal Neonatal Med,* 23**,** 1176-82.

Pedersen, C. B., Y. Sun, M. Vestergaard, J. Olsen & O. Basso (2007) Assessing fetal growth impairments based on family data as a tool for identifying high-risk babies. An example with neonatal mortality. *BMC Pregnancy Childbirth,* 7**,** 28.

Perrin, M. C., A. S. Brown & D. Malaspina (2007) Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophr Bull,* 33**,** 1270-3.

Pharoah, P. O., T. Cooke, L. Rosenbloom & R. W. Cooke (1987) Effects of birth weight, gestational age, and maternal obstetric history on birth prevalence of cerebral palsy. *Arch Dis Child,* 62**,** 1035-40.

Pinto-Martin, J. A., A. Cnaan & H. Zhao (1998) Short interpregnancy interval and the risk of disabling cerebral palsy in a low birth weight population. *J Pediatr,* 132**,** 818-21.

Polivka, B. J., J. T. Nickel & J. R. Wilkins, 3rd (1997) Urinary tract infection during pregnancy: a risk factor for cerebral palsy? *J Obstet Gynecol Neonatal Nurs,* 26**,** 405-13.

Porter, T. F., A. M. Fraser, C. Y. Hunter, R. H. Ward & M. W. Varner (1997) The risk of preterm birth across generations. *Obstet Gynecol,* 90**,** 63-7.

Ravn, S. H., E. M. Flachs & P. Uldall (2010) Cerebral palsy in eastern Denmark: declining birth prevalence but increasing numbers of unilateral cerebral palsy in birth year period 1986-1998. *Eur J Paediatr Neurol,* 14**,** 214-8.

Redline, R. W. (2005) Severe fetal placental vascular lesions in term infants with neurologic impairment. *Am J Obstet Gynecol,* 192**,** 452-7.

---. 2006. Placental pathology and cerebral palsy. In *Clin Perinatol,* 503-16. United States.

--- (2008) Placental pathology: a systematic approach with clinical correlations. *Placenta,* 29 Suppl A**,** S86-91.

--- (2009) Disorders of placental circulation and the fetal brain. *Clin Perinatol,* 36**,** 549-59.

Reichenberg, A., R. Gross, M. Weiser, M. Bresnahan, J. Silverman, S. Harlap, J. Rabinowitz, C. Shulman, D. Malaspina, G. Lubin, H. Y. Knobler, M. Davidson & E. Susser (2006) Advancing paternal age and autism. *Arch Gen Psychiatry,* 63**,** 1026-32.

Reid, S. M., J. B. Carlin & D. S. Reddihough (2011) Rates of cerebral palsy in Victoria, Australia, 1970 to 2004: has there been a change? *Dev Med Child Neurol,* 53**,** 907-12.

Ria, M., J. Lagercrantz, A. Samnegard, S. Boquist, A. Hamsten & P. Eriksson (2011) A common polymorphism in the promoter region of the TNFSF4 gene is associated with lower allele-specific expression and risk of myocardial infarction. *PLoS One,* 6**,** e17652.

Risnes, K. R., P. R. Romundstad, T. I. Nilsen, A. Eskild & L. J. Vatten (2009) Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. *Am J Epidemiol,* 170**,** 622-31.

Rooney, B. 2001. Elective surgery boosts cerebral palsy risk. In *Eur J Obstet Gynecol Reprod Biol,* 239-41. Ireland.

Rosenbaum, P., N. Paneth, A. Leviton, M. Goldstein, M. Bax, D. Damiano, B. Dan & B. Jacobsson (2007) A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl,* 109**,** 8-14.

Rugonfalvi-Kiss, S., V. Endresz, H. O. Madsen, K. Burian, J. Duba, Z. Prohaszka, I. Karadi, L. Romics, E. Gonczol, G. Fust & P. Garred (2002) Association of Chlamydia pneumoniae with coronary

artery disease and its progression is dependent on the modifying effect of mannose-binding lectin. *Circulation,* 106**,** 1071-6.
Ryckman, K. K., N. H. Morken, M. J. White, D. R. Velez, R. Menon, S. J. Fortunato, P. Magnus, S. M. Williams & B. Jacobsson (2010) Maternal and fetal genetic associations of PTGER3 and PON1 with preterm birth. *PLoS One,* 5**,** e9040.
Salafia, C. M., J. Zhang, A. K. Charles, M. Bresnahan, P. Shrout, W. Sun & E. M. Maas (2008) Placental characteristics and birthweight. *Paediatr Perinat Epidemiol,* 22**,** 229-39.
Salihu, H. M. & R. E. Wilson (2007) Epidemiology of prenatal smoking and perinatal outcomes. *Early Hum Dev,* 83**,** 713-20.
Salonen Ros, H., P. Lichtenstein, L. Lipworth & S. Cnattingius (2000) Genetic effects on the liability of developing pre-eclampsia and gestational hypertension. *Am J Med Genet,* 91**,** 256-60.
Sankaran, S. & P. M. Kyle (2009) Aetiology and pathogenesis of IUGR. *Best Pract Res Clin Obstet Gynaecol,* 23**,** 765-77.
Schelleman, H., O. H. Klungel, J. C. Witteman, M. M. Breteler, M. Yazdanpanah, A. H. Danser, A. Hofman, C. M. van Duijn, A. de Boer & B. H. Stricker (2007) Angiotensinogen M235T polymorphism and the risk of myocardial infarction and stroke among hypertensive patients on ACE-inhibitors or beta-blockers. *Eur J Hum Genet,* 15**,** 478-84.
Schendel, D. E. (2001) Infection in pregnancy and cerebral palsy. *J Am Med Womens Assoc,* 56**,** 105-8.
Schnabel, R., M. G. Larson, J. Dupuis, K. L. Lunetta, I. Lipinska, J. B. Meigs, X. Yin, J. Rong, J. A. Vita, C. Newton-Cheh, D. Levy, J. F. Keaney, Jr., R. S. Vasan, G. F. Mitchell & E. J. Benjamin (2008) Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension,* 51**,** 1651-7.
Sedlis, A., H. Berendes, H. S. Kim, D. F. Stone, W. Weiss, J. Deutschberger & E. Jackson (1967) The placental weight-birthweight relationship. *Dev Med Child Neurol,* 9**,** 160-71.
Sellier, E., P. Uldall, E. Calado, S. Sigurdardottir, M. G. Torrioli, M. J. Platt & C. Cans (2012) Epilepsy and cerebral palsy: characteristics and trends in children born in 1976-1998. *Eur J Paediatr Neurol,* 16**,** 48-55.
Shah, P. S. & A. Ohlsson (2009) Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. *CMAJ,* 180**,** E99-108.
Shankaran, S., J. C. Langer, S. N. Kazzi, A. R. Laptook, M. Walsh & N. National Institute of Child Health and Human Development Neonatal Research (2006) Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. *Pediatrics,* 118**,** 1654-9.
Shatrov, J. G., S. C. Birch, L. T. Lam, J. A. Quinlivan, S. McIntyre & G. L. Mendz Chorioamnionitis and cerebral palsy: a meta-analysis. 116**,** 387-92.
--- (2010) Chorioamnionitis and cerebral palsy: a meta-analysis. *Obstet Gynecol,* 116**,** 387-92.
Shehata, F., I. Levin, A. Shrim, B. Ata, B. Weisz, R. Gamzu & B. Almog (2011) Placenta/birthweight ratio and perinatal outcome: a retrospective cohort analysis. *BJOG,* 118**,** 741-7.
Sie, M. P., A. G. Uitterlinden, M. J. Bos, P. P. Arp, M. M. Breteler, P. J. Koudstaal, H. A. Pols, A. Hofman, C. M. van Duijn & J. C. Witteman (2006) TGF-beta 1 polymorphisms and risk of myocardial infarction and stroke: the Rotterdam Study. *Stroke,* 37**,** 2667-71.
Smal, J. C., C. S. Uiterwaal, H. W. Bruinse, P. Steendijk & F. van Bel (2009) Inverse relationship between birth weight and blood pressure in growth-retarded but not in appropriate for gestational age infants during the first week of life. *Neonatology,* 96**,** 86-92.
Smith, G. D., S. Harding & M. Rosato (2000) Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ,* 320**,** 839-40.
Smith, G. D., J. Sterne, P. Tynelius, D. A. Lawlor & F. Rasmussen (2005) Birth weight of offspring and subsequent cardiovascular mortality of the parents. *Epidemiology,* 16**,** 563-9.
Sober, S., E. Org, K. Kepp, P. Juhanson, S. Eyheramendy, C. Gieger, P. Lichtner, N. Klopp, G. Veldre, M. Viigimaa, A. Doring, S. Kooperative Gesundheitsforschung in der Region Augsburg, M. Putku, P. Kelgo, H. Y. i. E. Study, S. Shaw-Hawkins, P. Howard, A. Onipinla, R. J. Dobson, S. J.

Newhouse, M. Brown, A. Dominiczak, J. Connell, N. Samani, M. Farrall, M. R. C. B. G. o. H. Study, M. J. Caulfield, P. B. Munroe, T. Illig, H. E. Wichmann, T. Meitinger & M. Laan (2009) Targeting 160 candidate genes for blood pressure regulation with a genome-wide genotyping array. *PLoS One,* 4**,** e6034.

Society for Maternal-Fetal Medicine Publications, C., E. Berkley, S. P. Chauhan & A. Abuhamad (2012) Doppler assessment of the fetus with intrauterine growth restriction. *Am J Obstet Gynecol,* 206**,** 300-8.

Spinillo, A., E. Capuzzo, S. Orcesi, M. Stronati, M. Di Mario & E. Fazzi. 1997. Antenatal and delivery risk factors simultaneously associated with neonatal death and cerebral palsy in preterm infants. In *Early Hum Dev*, 81-91. Ireland.

Stelmach, T., E. Kallas, H. Pisarev & T. Talvik (2004) Antenatal risk factors associated with unfavorable neurologic status in newborns and at 2 years of age. *J Child Neurol,* 19**,** 116-22.

Stelmach, T., H. Pisarev & T. Talvik (2005) Ante- and perinatal factors for cerebral palsy: case-control study in Estonia. *J Child Neurol,* 20**,** 654-60.

Stoknes, M., G. L. Andersen, A. I. Elkamil, L. M. Irgens, J. Skranes, K. A. Salvesen & T. Vik (2012) The effects of multiple pre- and perinatal risk factors on the occurrence of cerebral palsy. A Norwegian register based study. *Eur J Paediatr Neurol,* 16**,** 56-63.

Sun, Y., M. Vestergaard, J. Christensen, A. J. Nahmias & J. Olsen (2008) Prenatal exposure to maternal infections and epilepsy in childhood: a population-based cohort study. *Pediatrics,* 121**,** e1100-7.

Sun, Y., M. Vestergaard, J. Christensen & J. Olsen (2011) Prenatal exposure to elevated maternal body temperature and risk of epilepsy in childhood: a population-based pregnancy cohort study. *Paediatr Perinat Epidemiol,* 25**,** 53-9.

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

Svare, J. A., H. Schmidt, B. B. Hansen & G. Lose. 2006. Bacterial vaginosis in a cohort of Danish pregnant women: prevalence and relationship with preterm delivery, low birthweight and perinatal infections. In *BJOG*, 1419-25. England.

Szarka, A., J. Rigo, Jr., L. Lazar, G. Beko & A. Molvarec (2010) Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. *BMC Immunol,* 11**,** 59.

Sziller, I., D. Nguyen, A. Halmos, P. Hupuczi, Z. Papp & S. S. Witkin (2005) An A > G polymorphism at position -670 in the Fas (TNFRSF6) gene in pregnant women with pre-eclampsia and intrauterine growth restriction. *Mol Hum Reprod,* 11**,** 207-10.

Tegethoff, M., N. Greene, J. Olsen, A. H. Meyer & G. Meinlschmidt (2010a) Maternal psychosocial adversity during pregnancy is associated with length of gestation and offspring size at birth: evidence from a population-based cohort study. *Psychosom Med,* 72**,** 419-26.

--- (2010b) Maternal psychosocial stress during pregnancy and placenta weight: evidence from a national cohort study. *PLoS One,* 5**,** e14478.

Thompson, J. M., L. M. Irgens, R. Skjaerven & S. Rasmussen (2007) Placenta weight percentile curves for singleton deliveries. *BJOG,* 114**,** 715-20.

Thorngren-Jerneck, K. & A. Herbst (2006) Perinatal factors associated with cerebral palsy in children born in Sweden. *Obstet Gynecol,* 108**,** 1499-505.

Thorsen, P., I. Vogel, K. Molsted, B. Jacobsson, M. Arpi, B. R. Moller & B. Jeune (2006) Risk factors for bacterial vaginosis in pregnancy: a population-based study on Danish women. *Acta Obstet Gynecol Scand,* 85**,** 906-11.

Tikkanen, M., M. Nuutila, V. Hiilesmaa, J. Paavonen & O. Ylikorkala (2006a) Clinical presentation and risk factors of placental abruption. *Acta Obstet Gynecol Scand,* 85**,** 700-5.

--- (2006b) Prepregnancy risk factors for placental abruption. *Acta Obstet Gynecol Scand,* 85**,** 40-4.

Tita, A. T. & W. W. Andrews (2010) Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol,* 37**,** 339-54.

Topp, M., L. D. Huusom, J. Langhoff-Roos, C. Delhumeau, J. L. Hutton & H. Dolk (2004) Multiple birth and cerebral palsy in Europe: a multicenter study. *Acta Obstet Gynecol Scand,* 83**,** 548-53.
Topp, M., P. Uldall & G. Greisen (2001) Cerebral palsy births in eastern Denmark, 1987--90: implications for neonatal care. *Paediatr Perinat Epidemiol,* 15**,** 271-7.
Torfs, C. P., B. van den Berg, F. W. Oechsli & S. Cummins (1990) Prenatal and perinatal factors in the etiology of cerebral palsy. *J Pediatr,* 116**,** 615-9.
Towsley, K., M. I. Shevell, L. Dagenais & R. Consortium (2011) Population-based study of neuroimaging findings in children with cerebral palsy. *Eur J Paediatr Neurol,* 15**,** 29-35.
Uldall, P., S. I. Michelsen, M. Topp & M. Madsen (2001) The Danish Cerebral Palsy Registry. A registry on a specific impairment. *Dan Med Bull,* 48**,** 161-3.
Underwood, M. 1801. A Treatise on the Disorders of Childhood, and Management of Infants From the Birth; Adapted to Domestic Use., ed. J. Matthews, 89-90. London, UK.
van Haastert, I. C., F. Groenendaal, C. S. Uiterwaal, J. U. Termote, M. van der Heide-Jalving, M. J. Eijsermans, J. W. Gorter, P. J. Helders, M. J. Jongmans & L. S. de Vries (2011) Decreasing incidence and severity of cerebral palsy in prematurely born children. *J Pediatr,* 159**,** 86-91 e1.
Van Lieshout, R. J. & L. P. Voruganti (2008) Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J Psychiatry Neurosci,* 33**,** 395-404.
Vanderweele, T. J. & S. Hernandez-Diaz (2011) Is there a direct effect of pre-eclampsia on cerebral palsy not through preterm birth? *Paediatr Perinat Epidemiol,* 25**,** 111-5.
Vedmedovska, N., D. Rezeberga, U. Teibe, I. Melderis & G. G. Donders (2011) Placental pathology in fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol,* 155**,** 36-40.
Vestergaard, M., A. Mork, K. M. Madsen & J. Olsen (2005) Paternal age and epilepsy in the offspring. *Eur J Epidemiol,* 20**,** 1003-5.
Villar, J., G. Carroli, D. Wojdyla, E. Abalos, D. Giordano, H. Ba'aqeel, U. Farnot, P. Bergsjo, L. Bakketeig, P. Lumbiganon, L. Campodonico, Y. Al-Mazrou, M. Lindheimer, M. Kramer & G. World Health Organization Antenatal Care Trial Research (2006) Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol,* 194**,** 921-31.
Wadhawan, R., W. Oh, B. R. Vohr, L. Wrage, A. Das, E. F. Bell, A. R. Laptook, S. Shankaran, B. J. Stoll, M. C. Walsh, R. D. Higgins, H. Eunice Kennedy Shriver National Institute of Child & N. Human Development Neonatal Research (2011) Neurodevelopmental outcomes of triplets or higher-order extremely low birth weight infants. *Pediatrics,* 127**,** e654-60.
Wang, H.-Y. & Y.-J. Jong. July 2004. PARENTAL STRESS AND RELATED FACTORS IN PARENTSOF CHILDREN WITH CEREBRAL PALSY. 334- 340. Kaohsiung J Med Sci.
Warburton, D. & A. F. Naylor (1971) The effect of parity on placental weight and birth weight: an immunological phenomenon? A report of the Collaborative Study of Cerebral Palsy. *Am J Hum Genet,* 23**,** 41-54.
Watanabe, R. M. (2011) Inherited destiny? Genetics and gestational diabetes mellitus. *Genome Med,* 3**,** 18.
Wen, X., E. W. Triche, J. W. Hogan, E. D. Shenassa & S. L. Buka (2011) Association between placental morphology and childhood systolic blood pressure. *Hypertension,* 57**,** 48-55.
Wikstrom, A. K., B. Haglund, M. Olovsson & S. N. Lindeberg (2005) The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG,* 112**,** 1486-91.
Wilkin, P. (1961) Placental insufficiency. *Ir J Med Sci,* 425**,** 200-10.
Williams, L. A., S. F. Evans & J. P. Newnham (1997) Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant. *BMJ,* 314**,** 1864-8.
Williams, P. J. & F. B. Pipkin (2011) The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol,* 25**,** 405-17.

Wilson, B. J., M. S. Watson, G. J. Prescott, S. Sunderland, D. M. Campbell, P. Hannaford & W. C. Smith (2003) Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ,* 326**,** 845.

Wu, A. H. & G. J. Tsongalis (2001) Correlation of polymorphisms to coagulation and biochemical risk factors for cardiovascular diseases. *Am J Cardiol,* 87**,** 1361-6.

Wu, C. S., E. A. Nohr, B. H. Bech, M. Vestergaard, J. M. Catov & J. Olsen (2009) Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol,* 201**,** 269 e1-269 e10.

Wu, Y. W., L. A. Croen, S. J. Shah, T. B. Newman & D. V. Najjar (2006) Cerebral palsy in a term population: risk factors and neuroimaging findings. *Pediatrics,* 118**,** 690-7.

Wu, Y. W., G. J. Escobar, J. K. Grether, L. A. Croen, J. D. Greene & T. B. Newman (2003) Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA,* 290**,** 2677-84.

Wu, Y. W., G. Xing, E. Fuentes-Afflick, B. Danielson, L. H. Smith & W. M. Gilbert (2011) Racial, ethnic, and socioeconomic disparities in the prevalence of cerebral palsy. *Pediatrics,* 127**,** e674-81.

Xi, G., G. Reiser & R. F. Keep. 2003. The role of thrombin and thrombin receptors in ischemic, hemorrhagic and traumatic brain injury: deleterious or protective? In *J Neurochem*, 3-9. England.

Xuan, C., X. Y. Bai, G. Gao, Q. Yang & G. W. He (2011) Association between polymorphism of Methylenetetrahydrofolate reductase (MTHFR) C677T and risk of myocardial infarction: a meta-analysis for 8,140 cases and 10,522 controls. *Arch Med Res,* 42**,** 677-85.

Yamada, H., F. Sata, Y. Saijo, R. Kishi & H. Minakami (2005) Genetic factors in fetal growth restriction and miscarriage. *Semin Thromb Hemost,* 31**,** 334-45.

Yang, Q., S. W. Wen, K. Phillips, L. Oppenheimer, D. Black & M. C. Walker (2009) Comparison of maternal risk factors between placental abruption and placenta previa. *Am J Perinatol,* 26**,** 279-86.

Yazbeck, C. F. & S. D. Sullivan (2012) Thyroid disorders during pregnancy. *Med Clin North Am,* 96**,** 235-56.

Ye, Z., E. H. Liu, J. P. Higgins, B. D. Keavney, G. D. Lowe, R. Collins & J. Danesh (2006) Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. *Lancet,* 367**,** 651-8.

Yilmaz, Y., H. Verdi, A. Taneri, A. C. Yazici, A. N. Ecevit, N. M. Karakas, A. Tarcan, A. Haberal, N. Ozbek & F. B. Atac (2012) Maternal-fetal proinflammatory cytokine gene polymorphism and preterm birth. *DNA Cell Biol,* 31**,** 92-7.

Zafarmand, M. H., M. E. Nijdam, A. Franx, D. E. Grobbee & M. L. Bots (2008) The angiotensinogen gene M235T polymorphism and development of preeclampsia/eclampsia: a meta-analysis and meta-regression of observational studies. *J Hypertens,* 26**,** 1726-34.

Zdravkovic, T., O. Genbacev, M. T. McMaster & S. J. Fisher (2005) The adverse effects of maternal smoking on the human placenta: a review. *Placenta,* 26 Suppl A**,** S81-6.

Zhang, X., R. W. Platt, S. Cnattingius, K. S. Joseph & M. S. Kramer (2007) The use of customised versus population-based birthweight standards in predicting perinatal mortality. *BJOG,* 114**,** 474-7.

Zhang, X., B. Zhang, M. Zhang, Y. Han, Y. Zhao, Z. Meng, X. Li, J. Kang & C. Yan (2011) Interleukin-8 gene polymorphism is associated with acute coronary syndrome in the Chinese Han population. *Cytokine,* 56**,** 188-91.

Zhu, J. L., D. Hvidtjorn, O. Basso, C. Obel, P. Thorsen, P. Uldall & J. Olsen (2010) Parental infertility and cerebral palsy in children. *Hum Reprod,* 25**,** 3142-5.