Risk factors and outcomes of preterm birth

A study of the associations of preterm birth with cerebral palsy and atopic diseases

Håvard Trønnes

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Genetic Epidemiology research group
Department of Global Public Health and Primary Care
University of Bergen, Norway

Department of Pediatrics
Haukeland University Hospital
Bergen, Norway

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ABSTRACT

Background: Children born preterm are at increased risk for a number of chronic diseases, including cerebral palsy and asthma. Asthma is usually categorised among the atopic diseases, but whether preterm birth also affects the risk for other atopic diseases, is less explored. Furthermore, it is known that women with asthma are at increased risk of too early delivery, but the knowledge on risk of preterm birth for mothers with atopic dermatitis or allergic rhinoconjunctivitis is limited.

Preterm birth may be caused by interactions between disorders of pregnancy and conditions related to mother and fetus. Whether these pathologic conditions influence the risk of later chronic diseases for preterm children, is still largely unknown.

Objectives: We wanted to assess how preterm birth and pregnancy disorders relate to risk of cerebral palsy and severe asthma and atopic dermatitis. In addition, we aimed to explore the risk of preterm birth with maternal atopic diseases.

Methods: Prospective national cohort studies were performed by linking data from the Medical Birth Registry of Norway to other compulsory national registries.

Results: Preterm birth and several pregnancy disorders were strongly associated with cerebral palsy. Preterm birth was associated with increased risk of severe asthma and decreased risk of severe atopic dermatitis. The two diseases were differently related to pregnancy disorders and other risk factors. Maternal asthma was associated with increased risk of preterm birth, but maternal atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk.

Conclusions: Risk of cerebral palsy with or without a recorded pregnancy disorder varied within categories of gestational age. Our findings suggest a protective effect of preterm birth on atopic dermatitis and a reduced risk of preterm delivery for mothers with other atopic diseases than asthma. This may shed light on mechanisms of preterm birth, but further studies are needed to confirm and explore these findings.

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1. LIST OF PUBLICATIONS

I Trønnes H, Wilcox AJ, Lie RT, Markestad T, Moster D.

Risk of cerebral palsy in relation to pregnancy disorders and preterm birth: a national cohort study

Developmental Medicine & Child Neurology (E-pub ahead of print, published online 13 March 2014)

II Trønnes H, Wilcox AJ, Markestad T, Lie RT, Moster D.

The association of preterm birth with severe asthma and atopic dermatitis: a national cohort study

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III Trønnes H, Wilcox AJ, Lie RT, Tollånes MC, Markestad T, Moster D.

Associations of maternal atopic diseases with adverse pregnancy outcomes: a national cohort study

Submitted

2. ABBREVIATIONS

CI – confidence interval

CP – cerebral palsy

DAG – directed acyclic graph

GA – gestational age

ICD – International Classification of Diseases

MBRN – Medical Birth Registry of Norway

NIS – National Insurance Scheme

OR – odds ratio

RR – relative risk

SD – standard deviation

SGA – small for gestational age

Th1 – T-lymphocyte helper cell type 1

Th2 – T-lymphocyte helper cell type 2

WHO – World Health Organization

3. INTRODUCTION

3.1 Preterm birth

3.1.1 Definition

The word *preterm* is derived from the Latin word *prae* (before) and the Greek word *terma* (limit). In 1977, the World Health Organization (WHO) defined preterm birth as birth before 37 completed weeks of gestation or fewer than 259 days from the first day of the last menstrual period.[1]

3.1.2 Historical background

There are few tales of preterm birth or preterm children in ancient history. Obviously, part of the explanation lies in the fact that gestational age mostly was not known. Even though the Hippocratic writers (450-350 B.C.) described quite accurately the length of a normal pregnancy,[2] preterm children were not defined as a specific group. Instead, preterm children were categorised together with children with low birth weight and children who were feeble of other reasons. This is reflected in the medical literature in the 19th century with a frail child of any reason classified as *weakling, lebensswach* (German, weak for life), or *débile* (French, weak).[2, 3]

Throughout history, the viability of the newborn has been emphasized. Infanticide was a widespread practice in order to remove weak and deformed children.[4] In Sparta, a council of elders decided the fate of newborns based on criteria of strength and viability in order to create a physically strong society.[5] During the Roman Empire, it was custom to lay the newborn on the ground, and if the father lifted up the child, he signalled a desire to preserve its life.[6] The expressions *to raise a child* and *élever un infant* (French) stem from this ritual.

The historical disinterest in the care for preterm or other feeble infants may be explained by the combination of high infant mortality and limited resources. We can only speculate what the infant mortality rates were in earlier periods, but in 1881-

1885, the European rates were estimated to 10-20 %.[7] For a family with low resources, raising a sick child would be a significant burden. It is likely that many preterm babies died of hypothermia, respiratory failure, and feeding difficulties, in addition to the common causes of neonatal death. Still, there are credible reports of very preterm children that survived with a good outcome, with the birth of Sir Isaac Newton (1643) as an example:

"(…)*when he was born he was so little they could have put him in a quart pot and so unlikely to live that two women who were sent to My Lady Packenham at North Witham for some thing for him sate down on a stile on the way and said to one another they need not make haste for the child would certainly be dead before they could be back*."[8]

With declining birth rates in Europe in the 19th century, a politically motivated interest in reducing infant mortality began to rise. This interest also included care of preterm and other weak children. The invention of the incubator by the French obstetrician Tarnier in 1880 was a breakthrough in neonatal care.[9] The incubator prevented hypothermia, but more importantly, it spotlighted the nursing care of the weak newborn. The efforts of saving preterm and weak children were still highly controversial, because of high expenses, high mortality, and uncertain outcomes. Challenged by difficult fundraising for expensive neonatal care units, the physicians Lion and Couney introduced *incubator baby shows* in 1896. In these shows, visitors could watch small and weak infants being nursed in their incubators for an entrance fee.[9] Even though the idea of an exhibition of immature children may seem odd for the modern reader, these shows were important in developing neonatal care in the early 20th century.

With the acknowledgement of preterm birth as a public health issue, interest in causes and prevention of preterm birth increased. Already in 1916, the physician La Fétra [10] suggested that preterm birth was caused by mental and physical shock, syphilis, twins, specific acute diseases, and maternal youth. These risk factors have been confirmed by research in modern times.[11-13] General improvements in public health in the beginning

of the 20th century, such as better living standards, modern sanitation, increased hygiene awareness, and introduction of vaccines and penicillin had substantial impact on infant mortality. Giant leaps in improving survival of preterm infants took place from the 1960s: The development of mechanical ventilation and continuous positive airway pressure allowed effective treatment for severe respiratory problems, and further improvements were achieved after introduction of antenatal corticosteroids in the 1970s and exogenous surfactant in the 1980s.[14]

3.1.3 The situation today

Globally, more than 10 % of all babies are born preterm.[15] Preterm birth is the most important cause of neonatal mortality and the second-leading cause of death before age of 5 (after pneumonia) worldwide.[1] Preterm birth also accounts for a great part of short- and long-term morbidity. Prevalence of preterm birth ranges from 5 to 18 % with lowest prevalence in Northern European countries and highest in sub-Saharan African countries.[15] With few exceptions, the rate of preterm birth has risen in both developed and developing countries over the last decade.[1] Possible explanations include improved registration, broader use of ultrasound-based estimation of gestational age, increased maternal age, infertility treatment, multiple pregnancies, maternal health conditions (particularly with increasing age), and changes in obstetric practice with preterm deliveries induced because of fetal or maternal indication.[1] The greatest increase in preterm births is seen among the moderate (32-33 weeks' gestation) and late preterm (34-36 weeks' gestation) deliveries.[16] In Norway, the preterm birth rate decreased from 7.2 % in 2000-2002 to 6.5 % in 2009-2011.[17]

Advances in neonatal care over the last decades have made a large impact on mortality rates for preterm infants. In the early 1970s in Norway, the survival rate of extremely preterm children (<28 weeks' gestation) was only 20 %,[18] while the corresponding survival rate in 2000 was 80 %.[19] The threshold of treating preterm infants has also shifted towards earlier gestational ages. In Norway, a 1999 consensus report considered treatment of preterm children with less than 23 weeks' gestation as experimental,[20] but several other countries offer active treatment for children born at

22 weeks' gestation.[21] Concerns about long-term outcomes of preterm children have existed in all times, but worries have been accentuated with the increasing survival of children born at extremely low gestational ages.[22, 23]

3.1.4 Risk factors of preterm birth

About one third of preterm births are medically induced before labour for maternal or fetal indications.[24] Maternal indications include pre-eclampsia, eclampsia, HELLP syndrome, previous caesarean section or uterine rupture, and maternal diseases.[25] Common fetal indications are intrauterine growth restriction, oligohydramnion, intrauterine infection, poor umbilical blood flow, abnormal fetal heart rate, placental abruption, and placenta previa.[25, 26] Approximately two thirds of preterm births are spontaneous, and the causes are largely unknown.[12] It is thought that the biological pathways are multifactorial, including maternal and fetal genetic factors, intrauterine infection, inflammation and other immunological processes, uterine distension, and placental ischaemia or haemorrhage.[12, 27] Mothers who are born preterm tend to deliver too early.[27] Male fetuses are at slightly increased risk for preterm birth,[28] and children with birth defects have a higher risk of preterm delivery.[29] Mothers of African, Caribbean, and Asian origin tend to give birth earlier than those with European origin,[30] suggesting a variation of pregnancy length with ethnicity. Several socio-demographic characteristics are associated with preterm birth. Low socio-economic and educational status, young and advanced maternal age, and single motherhood increase risk of too early birth.[11, 31, 32] Physical and psychological factors in mothers may also increase risk for preterm birth, for instance low pre-pregnancy body mass index, exposure to stressful events, and depression.[33-35]

3.1.5 Short-term outcomes

Fetal maturation is a continuum from conception to the weeks around the expected day of delivery. A preterm birth is a disruption of this process, and the preterm child is exposed to the extrauterine environment before its organs are fully developed. Preterm children may experience neonatal complications due to anatomic and functional immaturity, and brain, lungs, digestive organs, and circulatory system are particularly

vulnerable. Compared with term children, preterm children more often suffer from apnoea, respiratory distress, necrotizing enterocolitis, poor temperature regulation, hypoglycemia, intracerebral haemorrhage, feeding difficulties, and bacterial infections.[36-38] The risks of neonatal complications, morbidity, and death increase with decreasing gestational age.[19]

3.1.6 Long-term outcomes

Preterm children are at increased risk for developing a number of medical and functional disorders later in life, and risk of long-term disabilities increases with decreasing gestational age at birth.[18, 39] Preterm children are at increased risk for cerebral palsy (CP), asthma, vision and hearing deficit, epilepsy, impaired mental function, behavioural and psychological disorders, and learning disabilities.[18, 40-43] There are also concerns that adults born extremely premature may be at increased risk for early development of chronic obstructive pulmonary disease.[44]

As a group, preterm born individuals seem to differ from those born at term in social functioning. Adults born preterm tend to have lower educational level, lower income, and fewer children, and are less often married or cohabiting.[18] However, it is important to note that despite the increased risk of untoward long-term outcomes, most individuals born preterm are healthy and have a normal level of function.[18]

3.2 Cerebral palsy

3.2.1 Definition

CP has been defined as *a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems*.[45]

The definition reflects the heterogeneity of causes and phenotypes of CP. Common sub-classifications of CP include characteristics of motor disorders (spastic, ataxic, dystonic, athetotic) and their distribution (diplegic, paraplegic, quadriplegic).[46] The Gross Motor Function Classification System is a helpful tool in assessing severity of motor impairment.[47] Apart from the motor disturbances, epilepsy and impairments of cognitive abilities, vision, and hearing are common features in children with CP.[46]

3.2.2 Prevalence

The prevalence of CP is about 2 to 3 per 1000 live births with relatively little geographical variation.[48] Despite the increased survival among preterm children and advances in obstetric and neonatal care, the prevalence of CP has been surprisingly stable.[49] CP is a rare event, but it is a life-long disorder that may represent substantially increased morbidity and mortality and a significant burden for the family.[49]

3.2.3 Risk factors

A number of risk factors for CP have been consistently reported, including preterm birth, low or high maternal age, maternal chronic disease, male gender, African-American ethnicity, immigrant parents, chorioamnionitis, pre-eclampsia, placental abruption, congenital malformations, multiple pregnancy, small or large for gestational age, meconium-stained amniotic fluid, meconium aspiration, abnormal presentation, emergency caesarean section, instrumental delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, jaundice, and neonatal infections.[50] Genetic dispositions to CP have also been reported.[51]

3.2.4 Risk of cerebral palsy with preterm birth

Preterm birth is a major risk factor for CP, and the risk increases with decreasing gestational age.[18, 31, 52] The risk of CP ranges from 10 % in children born extremely preterm to 0.1 % in children born at term.[46] Compared with children born at term, children born before 28 weeks' gestation have 80-fold increased risk for developing CP, and late preterm children (34-36 weeks' gestation) have 3-fold increased risk.[18]

Moreover, the risk of CP in children born at 37-39 weeks' gestation is slightly higher than for those born at 40 weeks.[53] It seems that CP is linked to a continuum of fetal maturation towards 40 weeks' gestation. The reasons for this close relation between gestational age and CP are not clear, but may include prenatal, natal, and postnatal factors.

Prenatal risk factors

With the exception of births induced by physicians shortly before term for non-medical reasons, preterm birth is the outcome of underlying pathological processes. These pregnancy disorders may be obvious, such as clinical chorioamnionitis, placental abruption, and pre-eclampsia, but the pathologies that initiate spontaneous preterm deliveries are mostly unknown. It is feasible that both known and unknown disorders of pregnancy have harmful effects on the fetus that may influence risk of cerebral injury with later development of CP. Therefore, studies on associations between pregnancy disorders and CP in preterm infants will always be hampered by the lack of a control group of otherwise healthy and unexposed preterm children.

A number of pregnancy disorders related to preterm birth have been associated with increased risk of CP.[31, 52, 54-61] *Chorioamnionitis* or intrauterine infection has been proposed to account for more than 50 % of the earliest preterm births and 25 % of all preterm births,[62, 63] but since this disorder often lacks signs of clinical infection, it is commonly not recognised. Chorioamnionitis is usually categorised as clinical or subclinical. Both categories of chorioamnionitis induce fetal inflammatory responses, and it has been postulated that inflammation may be an important mediator for neonatal brain injury.[64] A 2000 review reported that clinical, but not histological, chorioamnionitis was associated with increased risk for CP,[61] while a review from 2010 found an increased risk with both categories.[65] *Prolonged rupture of membranes* is usually defined as rupture more than 24 hours before delivery and is commonly caused by subclinical infection or inflammation. Prolonged rupture of membranes has been reported as a risk factor of CP,[66] possibly because of increased risk of ascending infection. About 60 % of *multiple births* are preterm, and the risk of CP in multiples is 4-fold that of singletons.[12, 67] Rates of CP in multiples and singletons do not differ

significantly in gestational age categories of preterm birth,[67] suggesting that multiple birth is not more harmful for preterm children than other causes of preterm birth. *Vaginal bleeding* is a common condition in pregnancy with prevalences ranging from 1 to 26 % in different studies,[68] but the diagnosis is heterogeneous with regard to time of occurrence, causes, and severity. A large meta-analysis reported that both light and heavy bleeding and 1st and 2nd trimester bleeding were associated with preterm birth.[68] Specific causes of vaginal bleeding, such as *placenta previa* and *placental abruption*, are associated with preterm birth and CP.[69-71] Vaginal bleeding not caused by placental abruption was not associated with CP in a large, registry-based Swedish study.[52]

Small for gestational age (SGA) status may be due to constitutional factors or to incorrect calculations of gestational age, but may reflect an *intrauterine growth restriction* caused by maternal or placental failure to provide sufficient nutrition. SGA status is often used as a proxy parameter for intrauterine growth restriction and the two terms are often used interchangeably. Growth-restricted or SGA children are at risk for spontaneous and iatrogenic preterm birth,[72] and a multi-centre study in 2003 reported that children born at 32-42 weeks' gestation with a birth weight below 10th percentile for gestational age were at 4-6-fold increased risk for CP, compared with those with a birth weight in the 25th-75th percentile range.[73] The relation between SGA status and CP was less clear for children born before 32 weeks' gestation.[73] In a report from 2006, risk of CP was increased in SGA children born at term, but not preterm, compared with their gestational age peers.[52] Thus, it is not clear how SGA status or intrauterine growth restriction relate to CP in preterm children.

The association between *pre-eclampsia* and CP in preterm children has been much debated, and this discussion illustrates the problem of not having a healthy control group of preterm children. Some earlier studies have proposed that pre-eclampsia is protective against CP for preterm children.[74, 75] Pre-eclampsia is a major cause of intrauterine growth restriction and preterm birth, which considerably increases risk of CP. It is thus problematic to describe pre-eclampsia as protective against CP. The current opinion is that pre-eclampsia is not protective for CP, but less harmful than other causes of preterm birth, for example intrauterine infection.[56, 58]

Children with *congenital malformations* are at risk for preterm birth and CP.[29, 54, 76] An Australian study showed that 14 % of all children with CP had a congenital malformation in the brain.[54] This study also found a 5-fold increased risk among children with non-cerebral birth defects. Women with a pre-pregnancy *cervical conisation* are at increased risk of preterm delivery,[77, 78] possibly mediated through impaired physical barriers for bacterial infections and decreased supportive ability of the cervix. To our knowledge, the association between cervical conisation and CP has not been examined.

Natal risk factors

Birth asphyxia has been postulated to account for less than 15 % of CP cases in late preterm and term children,[79] but may be less important for earlier delivered children. Grether et al [80] reported that most very preterm children were not acidotic after birth, and that postnatal acidosis and low Apgar scores were not significantly associated with CP. This was supported by O'Shea et al [81], who found no significant relation between low Apgar score (<5 at 5 minutes after birth) and CP in very low birth weight children. These studies were hampered by small samples. A study from New Zealand found a clearly increased risk of CP (OR 3.50, 95% CI 2.83-4.31) with Apgar Score <4 one minute after birth among children with 24-30 weeks' gestation.[82] As postnatal blood samples were lacking in this study, it is uncertain whether this association may be attributed to birth asphyxia. Still, it is possible that birth asphyxia may interact with other causes of fetal depression in preterm children.

Mode of delivery of vertex-presenting preterm infants does not seem to be associated with adverse neurological outcome, but caesarean delivery appear to be beneficial for the malpresenting fetuses.[83]

Postnatal risk factors

Postnatal events may account for a substantial part of CP cases in preterm children. It has been proposed that the risk of CP attributed to immaturity is related to the increased frequency of conditions that predispose for cerebral haemorrhage and periventricular leucomalasia.[46] Children born too early are at increased risk of a

number of adverse events that may seriously disturb oxygenation, circulation, inflammation, haemostasis, and coagulation.[36-38] The cerebral vascular system in preterm infants has impaired autoregulation and arterial vascular supply,[84] which make the immature brain particularly vulnerable to inflammation and shifts in oxygenation, blood pressure, and perfusion.[84] Coagulation disturbances in preterm infants may also increase risk of cerebral haemorrhage.[85] Leversen et al [86] found that risk of CP increased 69-fold after severe cerebral haemorrhage or periventricular leucomalasia in children born extremely preterm, and Sukhov et al [31] reported that prematurity-related events such as necrotizing enterocolitis and respiratory distress syndrome were strong risk factors for CP in all categories of preterm children.

3.3 Atopic disorders

3.3.1 Definitions

Atopy may be defined as having a positive specific serum immunoglobulin E or a positive skin prick test for a food or inhalant allergen. Atopy is characterized by an imbalance of the relation between T lymphocyte helper cell type 1 (Th1) and T lymphocyte helper cell Type 2 (Th2) immune responses towards Th2 dominance.[87] Atopy is strongly related to asthma, atopic dermatitis, allergic rhinoconjunctivitis, and food allergies, commonly termed atopic diseases. In this study, we have focused on *asthma*, *atopic dermatitis*, and *allergic rhinoconjunctivitis*.

Asthma has been defined as *a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperreponsiveness, and an underlying inflammation.*[88]

The diagnosis of asthma is clinical and is based on a typical medical history of wheezy and prolonged expiration, coughing and shortness of breath, reversibility of airway obstruction with anti-asthmatic drugs, and exclusion of other diseases with similar characteristics.[89] Asthma is not a single disease, but a multifactorial syndrome with similar phenotypes.[89] It has been proposed to classify asthma according to clinical

criteria (severity, therapy-resistance, age at onset), triggers of disease (respiratory infections, exercise, environmental allergens or irritants, non-steroid anti-inflammatory substances), and inflammatory features (eosinophilic, neutrophilic).[89] These categories do to some extent overlap.

Atopic dermatitis is used synonymously with atopic eczema, and it normally manifests as chronic or recurrent dry and pruritic rash on typical sites. The disorder is characterized by impaired skin barrier and epidermal inflammation.

Allergic rhinoconjunctivitis is the combination of allergen-induced rhinitis and conjunctivitis, commonly termed hay fever. Allergic rhinitis is characterized by itching nose, sneezing, rhinorrhoea, and nasal obstruction, and allergic conjunctivitis by itching eyes, tearing, conjunctival injection, and eyelid oedema.

3.3.2 Prevalence

In general, there has been an increase in prevalence of atopy and atopic diseases over the last decades. The prevalence of atopy has increased in some countries from 15-25 % in the 1980s to 15-40 % in 1990-2000, although in other populations, the prevalence has declined or plateaued.[90] The prevalence of asthma has increased from 0-10 % in European countries in the 1970s to 5-30 % around 2000.[90] There are large geographical differences, and in some countries, the prevalence has been stable since 1990.[90] Atopic dermatitis is the most common skin disorder with a life-time prevalence ranging from 10 to 20 % in developed countries, and the prevalence has been increasing or stable in most countries since the 1990s.[91] Atopic dermatitis manifests before the first year of life in 60 % of subjects and in 90 % before 5 years of age.[92] The prevalence of allergic rhinoconjunctivitis has also been rising.[93] Allergic rhinoconjunctivitis is most frequent in adolescence with a worldwide average prevalence of 15 %.[94]

In Norway, the life-time prevalence of asthma among adults increased from 3 % in 1972 to 9% in 1999,[95] and the cumulative incidence among children increased from 7 % in 1985 to 18 % in 2008.[96] The prevalence of atopic dermatitis in children has been

stable in Norway during the last two decades, while the prevalence of allergic rhinoconjunctivitis has been rising.[96] A Norwegian study from 2003 reported that the life-time prevalence of atopic dermatitis was 21 % in adults.[97] In 2008, the cumulative incidence for children aged 7-14 years was 19 % for atopic dermatitis and 25 % for allergic rhinoconunctivitis.[96]

3.3.3 Risk factors of atopic disorders

The causes of atopy and atopic diseases are poorly understood. Genetic factors seem to be important for the development of atopy and atopic diseases. There is a strong recurrence risk of atopy among first-degree relatives,[98] and several genetic loci related to atopy and atopic diseases are identified.[99] Some of these loci are associated with one or several of the disorders, suggesting that different atopic phenotypes have shared and separate aetiological pathways.[99] Genetic predisposition of atopic dermatitis is particularly strong with a 72 % concordance rate in monozygotic twins and 23 % in dizygotic twins.[100]

However, genetics alone cannot explain the increasing prevalence of atopy and atopic disorders over the past decades. In 1989, Strachan suggested a protective effect on atopy with early life exposure of microbial diversity, also known as *the hygiene hypothesis*.[101] This theory has been supported by numerous immunological and epidemiological studies.[102] Studies have found that fetal and early life exposure to farming environment, low socio-economic status, antroposophic lifestyle, and prenatal and early life probiotic administration seem to protect from atopy,[102-105] while the protective effects of increasing parity, breast feeding, early infections, and pet exposure remain controversial.[102, 106-108] It has also been proposed that early life antibiotic exposure increases atopy risk.[109] Lifestyle factors, such as increased indoor temperature and humidity, less ventilated houses, and more indoor activity, may have contributed to the rising prevalence of atopic diseases through increased allergen exposure.[110] Although many of these hypotheses are still under debate, the current view is that atopy and atopic disorders are caused by complex interactions between genes and exposures in pregnancy and early life.[107]

There are similarities and differences in risk factors for atopy and atopic disorders. This may be due to variations of atopy component in the specific disorders. Although asthma is regarded as an atopic disorder, it has been proposed that most cases of asthma are non-atopic.[111] Risk factors for asthma differ for the various phenotypes, although tobacco smoke exposure has been consistently associated with asthma in childhood, adolescence, and adulthood.[90] Childhood asthma is associated with viral respiratory infections and early life antibiotic treatment.[109, 112] Other risk factors for asthma include obesity and exposure to air pollution.[90] Atopic dermatitis and allergic rhinoconjunctivitis are closely linked to atopy and share several risk factors, including high socioeconomic status and urban home setting.[90, 102]

3.3.4 Risk of asthma and atopic dermatitis with preterm birth

Most studies on the association between preterm birth and asthma have found an increased risk of asthma in preterm children.[42, 113] In 2006, Jaakkola et al [42] performed a meta-analysis of 19 studies from 1990 to 2005 and found that preterm children had an overall 7 % increased risk of asthma. A recent meta-analysis included almost 150,000 children of 31 birth cohort studies and found increased risk of pre-school wheezing and school-age asthma with preterm birth.[113] Risk was highest for the extremely preterm children (OR 3.9, 95% CI 2.7-5.5, for pre-school wheezing and OR 2.9, 95% CI, 1.8-4.6, for school-age asthma), but almost all preterm children were at increased risk for both outcomes.

The relation between preterm birth and asthma may be attributed to antenatal, natal and postnatal factors. Asthmatic mothers tend to deliver preterm,[114] and maternal asthma is a risk factor for asthma in offspring.[115] Smoking and maternal stress during pregnancy are associated with preterm birth and asthma.[116-118] Pregnancy complications may also have harmful effects on the fetus that predispose to later asthma development. Nafstad et al [119] reported that bleeding during pregnancy, anemia, cervix insufficiency, placenta dysfunction, rhesus immunization, hyperemesis, and preterm contractions were associated with increased risk of asthma. A large US study found increased risk of asthma with clinical chorioamnionitis in different

gestational age strata of preterm children.[120] Preterm children are more often delivered by caesarean section than term children,[121] and caesarean section is associated with increased risk of childhood asthma.[122] Respiratory distress, bronchopulmonal dysplasia, jaundice, and severe viral airway infections also occur more frequently in preterm children and have been associated with asthma.[123-126]

The relation between preterm birth and atopic dermatitis has not been explored as much as that of preterm birth and asthma, and the studies on preterm birth and atopic dermatitis report heterogeneous results. This may be due to differences in sample size, study design, populations, and outcome definition and measurement.

The possible relation between preterm birth and atopic dermatitis was first reported in 1988 by David and Ewing.[127] In this retrospective, hospital-based report with 443 children with atopic dermatitis, there were significantly fewer preterm children, and the authors speculated in a protective effect of prematurity on severe atopic dermatitis. As a response to this study, Klebanoff and Berendes [128] reported their findings from a prospective cohort study of 44,793 children born in the period 1959-1966. They found that preterm birth was not significantly associated with atopic dermatitis at one year of age (OR 0.86, 95% CI 0.66-1.11). In 1997, a birth registry- and questionnaire-based study from Denmark reported that risk of atopic dermatitis was almost similar in preterm and term children (RR 0.98, 95% CI 0.56-1.71).[129] This finding was supported by another Danish study from 2000 and a British study published in 2003.[130, 131]

Other studies have reported a significantly decreased risk of atopic dermatitis with preterm birth. Moore et al [132] found that increments of each week of gestational age increased risk of having atopic dermatitis at six months of age (OR 1.14, 95% CI 1.02-1.27). In a prospective cohort study from 2006 with 34,793 Danish mother-child pairs, Linneberg et al [115] reported a reduced risk of atopic dermatitis (OR 0.78, 95% CI 0.61-1.00) in those born preterm. Similarly, a Belgian study from 2009 reported a decreased risk of atopic dermatitis (OR 0.4, 95% CI 0.2-0.9) with preterm birth in 2,021 school-children.[133]

Some studies have even suggested that risk of atopic dermatitis may be higher after preterm delivery. Lucas et al [134] examined a British cohort of 777 preterm infants and found a 19 % cumulative incidence of atopic dermatitis after 18 months. Compared with other reports of prevalence in term infants, the authors hypothesised that preterm children were a high risk group for atopic dermatitis. A clinical, prospective study from Norway on 512 children reported a slightly higher prevalence of atopic dermatitis at 2 years of age in preterm children (18.6%) than in term children (17.9%), but the difference was not significant.[135]

3.3.5 Risk of preterm birth, stillbirth, and neonatal death with maternal atopic disorders

There are several reports on the association between asthma in pregnancy and adverse pregnancy outcomes, but the risk of poor pregnancy outcomes with other atopic disorders is not well explored.

A meta-analysis by Murphy et al [114] from 2001 included 18 publications and found that maternal asthma was associated with increased risk of preterm birth (RR 1.41, 95% CI 1.23-1.62). The association was stronger in studies where no active management was given (RR 1.50, 95% CI 1.28-1.75), and not significant in studies with active management of asthma (RR 1.07, 95% CI 0.91-1.26).

Despite the fact that atopic dermatitis and allergic rhinoconjunctivitis are among the most common chronic disorders during pregnancy, we have only identified two studies that have evaluated the risk of preterm birth with these exposures.[136, 137] A Finnish study from 2004 included 170 mothers of very low birth weight children and 306 mothers of term children.[136] In this study, maternal allergic rhinoconjunctivitis was associated with birth weight <1000g (OR 0.49, 95% CI 0.26-0.89) and more weakly with birth weight 1000-1500g (OR 0.92, 95% CI 0.56-1.51). Maternal atopic dermatitis was not significantly associated with very low birth weight (OR 0.64, 95% CI 0.36-1.15 for birth weight <1000g and OR 1.00, 95% 0.61-1.65 for birth weight 1000-1500g). As children with a birth weight below 1500 g are likely to have been born preterm, the outcomes are likely to reflect preterm birth. Somoskövi et al [137]

reported a lower rate of preterm birth among mothers with allergic rhinoconjunctivitis (3.9%) than those without (9.2%) in a cohort of 38,151 mother-children pairs ($p<0.001$). Only mothers with symptoms of allergic rhinoconjunctivitis during pregnancy were included in the study. Obviously, these two studies cannot lead to any conclusions, but may suggest a reduced risk of preterm birth with allergic rhinoconjunctivitis.

A recent meta-analysis found a significant association between maternal asthma and neonatal death (RR 1.49, 95% CI 1.10-2.00), but not stillbirth (RR 1.06, 95% CI 0.90-1.25).[138] This meta-analysis included 6 studies on neonatal death and 8 studies on stillbirth, and there were no difference in perinatal mortality risk with exacerbations or active management of asthma.

The risk of perinatal mortality with atopic dermatitis or allergic rhinoconjuntivitis has hardly been examined. Seeger et al [139] found no stillbirths among 225 pregnancies of mothers with atopic dermatitis compared with a rate of 0.6 % in the control group. In a study published in 1997, Metzger et al [140] followed 248 pregnancies of atopic mothers (with asthma or allergic rhinitis or both) and found lower rates of stillbirth and neonatal deaths than those reported for other populations. These studies do not offer any evidence for the risk of perinatal mortality with other atopic diseases.

4. AIMS

The overall aim was to explore certain risk factors and outcomes of preterm birth.

The specific aims were:

I To describe the risk of cerebral palsy with preterm birth and pregnancy disorders

II To assess the risk of severe asthma and atopic dermatitis with preterm birth

III To explore the risk of preterm birth, stillbirth, and neonatal death with maternal atopic disorders

5. METHODS

5.1 Data sources

Since 1964, every Norwegian citizen is allocated a unique personal identification number by the Norwegian Tax Administration.[141] This number is required for identification by public authorities. The personal identification number is also used to link national registries, both for official statistics and research. With the use of encrypted personal identification numbers, we were able to link the Medical Birth Registry of Norway to other national registries. All of these registries are mandatory for Norwegian citizens. Descriptions of the registries used in the current study are given in the following sections.

5.1.1 Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) has recorded all births in Norway since 1967 and is currently managed by the Norwegian Institute of Public Health.[142] The registry was established in the aftermath of the established causality between use of thalidomide in pregnancy and thousands of congenital limb deficiencies worldwide. The aims of the MBRN are to monitor birth defects and perinatal health issues for the Norwegian population and to provide data for epidemiologic research.[143]

Notification of all live births and stillbirths beyond 16 weeks' gestation (from 2003 beyond 12 weeks' gestation) is compulsory. Information on maternal health, use of drugs, and pregnancy complications before admission to maternity unit is recorded on a standardized pregnancy health chart. The health chart is brought to the maternity unit at admission, and this information, together with further data on pregnancy, birth, and postnatal health of mother and child, are recorded to the MBRN by midwives and physicians during the mothers hospital stay. From 1999, information on children admitted to neonatal departments is also reported to the MBRN.

Data about mother and child are recorded to the MBRN on standard notification forms. A new notification form was introduced in December 1998, and most of the verbatim notification boxes in the previous form (Appendix I) were replaced with specific check-boxes (Appendix II). Diagnoses of maternal and neonatal health conditions recorded in the MBRN are classified according to the International Classification of Diagnoses (ICD), version 8 for the period 1967-1998 and version 10 thereafter.

The MBRN was used to identify the study cohorts, and the registry provided information on gestational age, birth weight, pregnancy disorders, maternal health, pregnancy outcomes, mother's marital or cohabitation status, mode of delivery, and parity.

5.1.2 Population Registry

The Population Registry is linked to the MBRN and to the Cause of Death Registry for mutual update on births and deaths, and the registry contains information on immigration and emigration. The Population Registry was used to identify those who had emigrated and those with immigrant status.

5.1.3 Cause of Death Registry

The Cause of Death Registry is linked to the MBRN and the Population Registry and collects data on deaths. Causes of deaths are classified according to ICD. The registry was used to identify children who had died before one year of age.

5.1.4 The national registry of education

The national registry of education obtains annually updated information from all educational institutions and classifies attained level of education according to a 9-level scale, which ranges from 0 (no education) to 8 (Ph.D.-degree or higher). The registry provided data on the parents' educational attainments.

5.1.5 National Insurance Scheme

Norwegian residents are compulsory insured in the National Insurance Scheme (NIS).[144] Among several other social security rights, the membership in the insurance program provides a basic benefit for disabilities that confer significantly increased costs, an attendance benefit for individuals under 18 years of age with disabilities that require increased need for attendance and care, and a disability pension for individuals over 18 years of age with health conditions that reduce the working capacity with more than 50%.[145] Application for these benefits must be supplied with a health certificate from a physician, and only chronic and severe disabilities qualify for benefits. If a benefit is granted, the disability is registered by the National Insurance Scheme according to the ICD, version 9 and 10. The NIS was used to identify cases of CP, asthma, and atopic dermatitis. The registry also contributed with data on congenital malformations that were not registered by the MBRN (*paper I*) and on mothers with asthma and atopic dermatitis (*paper II*).

5.2 Study populations and design

The study designs in *paper I-III* were national cohort studies.

We used two different linked datasets for the three papers. In *paper I* and *II*, we used a data file with all births in Norway from 1967 through 2005 (Figure 1). In *paper III*, we used an updated data file with all births in Norway from 1967 through 2011 (Figure 2).

For *paper I* and *II*, the eligibility period was set to births from 1967 through 2001 to ensure a follow-up period of at least 4 years in the NIS and nearly complete data on parental education and migration.

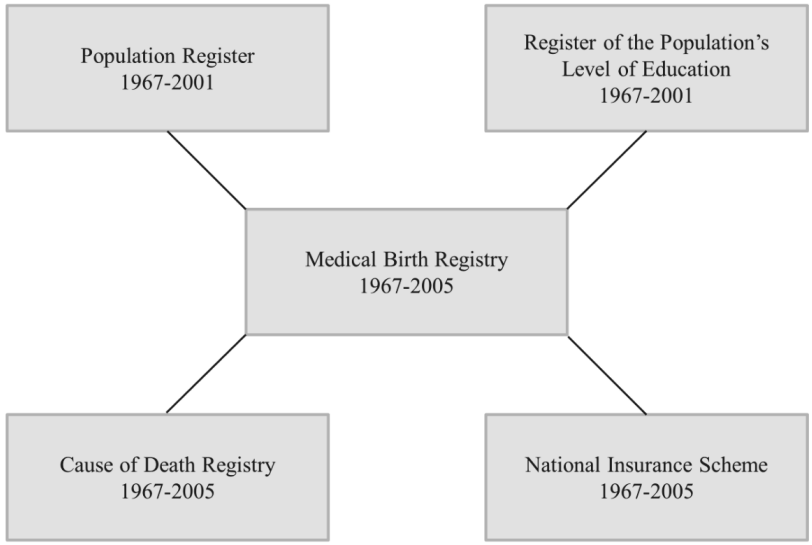

Figure 1 Linkage of national registries for *paper I* and *II*

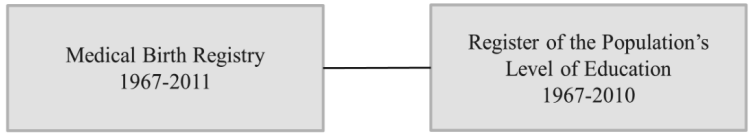

Figure 2 Linkage of national registries for *paper III*

Even though the updated data file contained information on births from 1967 through 2011, the eligibility period for *paper III* was set to births from 1967 through 2003. The reasons for this choice root in the change of the birth registry's notification forms in December 1998. After the new notification form was introduced, registration of several diagnoses changed. This resulted in substantial differences in reports of maternal atopic diseases. While records of maternal asthma and allergic rhinoconjunctivitis increased, atopic dermatitis was registered to a much lesser extent. The background for this decline in reports of maternal atopic dermatitis is not clear,

but according to the MBRN (personal message), it is probable that this diagnosis has been misclassified.

The establishment of the cohorts are shown in Figures 3-5. All live births from 1967 through 2001 were considered eligible for *paper I* and *II*, and all births from 1967 through 2003 in *paper III*. In all papers, we excluded those with missing information on gestational age and those with a probably incorrectly registered gestational age. These subjects were identified as having a birth weight more or less than three standard deviations (SDs) from the sex and gestational age specific mean birth weight.[146] Since the outcomes in *paper I* and *II* were identified through the NIS (which insures all Norwegian residents), we excluded children who had emigrated. Most children with CP, asthma, and atopic dermatitis do not receive benefits from the NIS before one year of age. For this reason, we excluded children who died before one year of age in *paper I* and *II*.

We obtained information on maternal asthma and atopic dermatitis from the NIS (*paper II)* and maternal gestational age at birth (*paper III*) with the personal identification numbers of the mothers. As a consequence, children whose mothers had missing personal identification number were excluded.

Due to a small syntax error in an analysis for *paper II*, children with probably incorrectly registered gestational age were defined as having a birth weight less or more than *and equal to* three SDs from the mean. This resulted in a discrepancy of 1,693 participants in *paper I* and *II*. The error was discovered after *paper II* was published. The analyses were repeated after the error was corrected, and the results were practically identical.

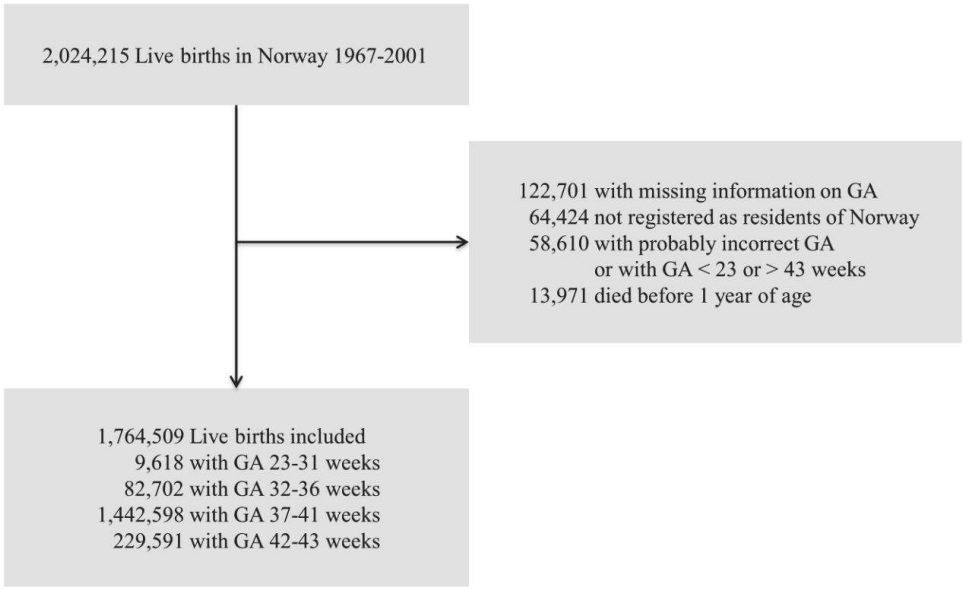

Figure 3 Establishment of the cohort in *paper I*

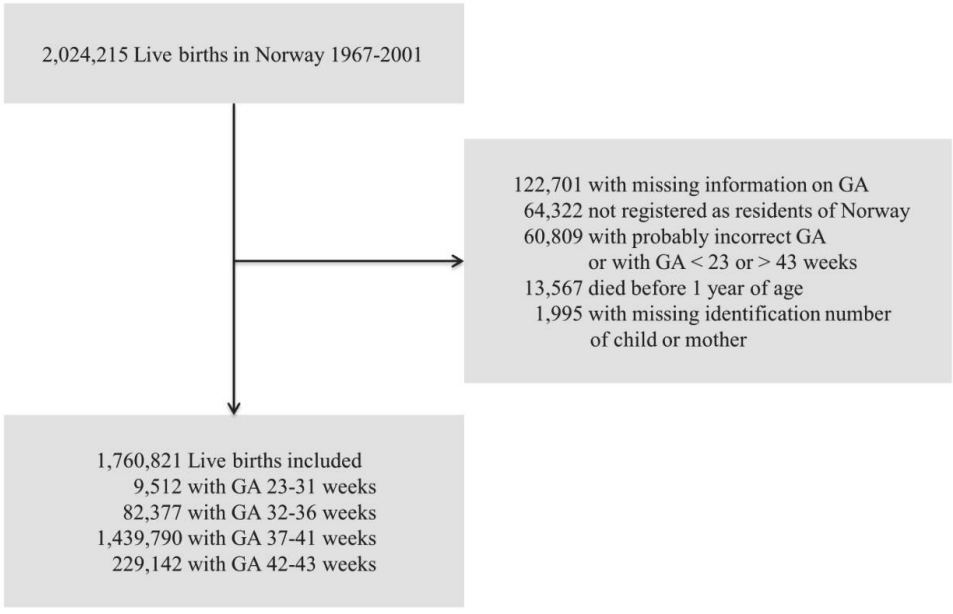

Figure 4 Establishment of the cohort in *paper II* [147]

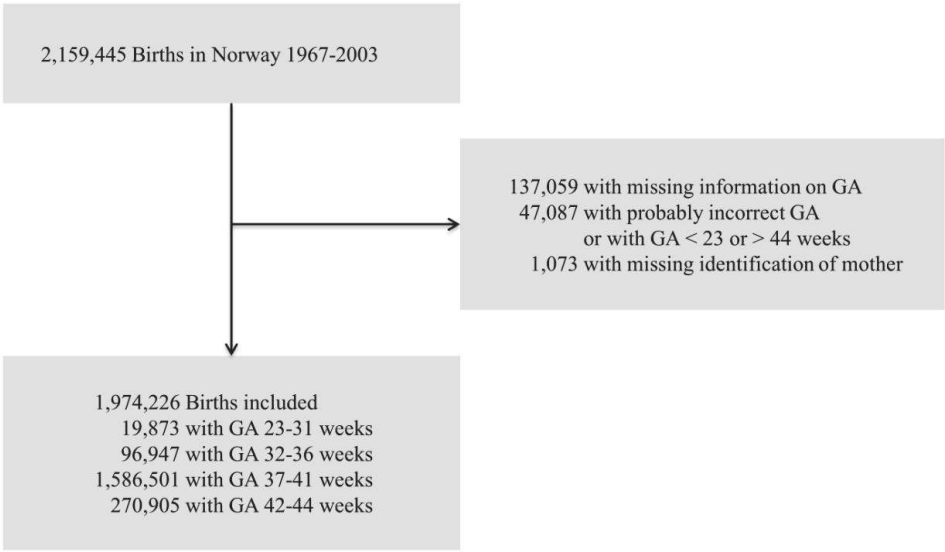

Figure 5 Establishment of the cohort in *paper III*

5.3 Variables

Asthma in offspring was identified in the NIS among recipients of basic benefit or attendance benefit registered with the ICD-codes 493 (9th version) and J45 (10th version).

Atopic dermatitis in offspring was identified in the NIS among recipients of basic benefit or attendance benefit registered with the ICD-codes 691 (9th version) and L20 (10th version).

Cerebral palsy was identified in the NIS among recipients of basic benefit, attendance benefit, or disability pension registered with the ICD-codes 342.0-344.9 (9th version) and G80-G83.9 (10th version).

Chorioamnionitis included birth registry records of chorioamnionitis and fever/sepsis during labour (without a specific diagnosis of chorioamnionitis). The MBRN data on chorioamnionitis did not discern between clinical and subclinical infection.

Congenital malformations were identified both through the MBRN and the NIS with ICD-codes. We decided not to include hip dysplasia in this variable, as only a minority of the hip dysplasias are probably true congenital malformations,[148] and the prevalence increased greatly after the introduction of ultrasound-guided screening of high risk children.

Gestational age at birth was estimated from the first day of the last menstrual period. Since 1999, gestational age at birth from ultrasound-based measurements has also been recorded in the MBRN. To ensure consequent estimations, assessment based on the last menstrual period was used for all births.

Immigrant status was defined as having both parents born abroad.

Intrauterine growth restriction was defined as birth weight less than 2 SDs from the mean according to a national standard adjusted for sex and gestational age.[146]

Maternal allergic rhinoconjunctivitis was identified in the MBRN using the ICD codes 507 (8^{th} version) and J30.1-J30.4 and H10.1 (10^{th} version).

Maternal asthma was identified in the MBRN using the ICD codes 493 (8^{th} version) and J45 (10^{th} version).

Maternal atopic dermatitis was identified in the MBRN using the ICD codes 691 and 692 (8^{th} version) and L20 (10^{th} version).

Maternal gestational age at birth was identified in the MBRN for a sub-cohort consisting of mother-child pairs with complete data on gestational age at birth for both.

Neonatal death was defined as death within 28 days after live birth.

Parental education was classified into low (less than 11 years), medium (11-14 years, reference group), and high level of education (more than 14 years).

Parity included both live births and stillbirths. We divided parity into three groups; nulliparous (reference), one previous birth, and two or more previous births.

Pre-eclampsia included eclampsia and early and late pre-eclampsia.

Preterm birth was defined as birth before 37 completed weeks of gestation.

Prolonged rupture of membranes was defined as rupture of membranes more than 24 hours before birth.

Single mother at birth was defined as not being married or cohabiting at the time of delivery.

Stillbirth was defined as birth of a child with no signs of life after 16 weeks' gestation (from 2003: after 12 weeks' gestation).

Unspecified bleeding included early and late vaginal bleeding during pregnancy with other causes than placental abruption and placenta previa.

Urinary tract infection included infectious cystitis and pyelonephritis during pregnancy.

5.4 Statistics

Prevalences and rates were estimated with contingency tables. In *paper I* and *II,* crude odds ratios with 95% confidence intervals were estimated with the use of logistic regression models. In *paper III*, we calculated crude relative risks with 95% confidence intervals with log-binomial regression models. The significance level was set to 5 % (two-sided) for all analyses.

We explored variations over time by stratifying analyses in different periods and controlling for year of birth in all adjusted analyses.

We used PASW software (Version 18.0, SPSS Inc., Chicago, IL, USA) for all statistical analyses in *paper I* and SPSS (Version 21.0, IBM corp., Armonk, NY, USA)

for all statistical analyses in *paper II* and for the contingency tables in *paper III*. Since several mothers were registered with more than one child in the birth registry, all births were not independent observations. To correct for births of the same mother, we used the robust estimation of variance option in STATA (Version 12.1, College Station, TX, USA) in the log-binomial regression models in *paper III*.

5.5 Ethical considerations

All personal identification numbers were encrypted. The dataset for *paper I* and *II* was approved by the Norwegian Data Inspectorate, the Norwegian Labour and Welfare Administration, the National Population Registry, and the Norwegian Directorate of Health. According to new legislation for registry research, the dataset for *paper III* was approved by the Regional Ethics Committee of the Western Regional Health Administration (Permission number 2010/2949-6) and by the registry administrations. These approvals included a waiver of individual consent.

6. RESULTS

6.1 Paper I

Among 1,764,509 included children, prevalence of CP was 1.8 per 1,000 live births. The prevalence increased with decreasing gestational age of birth and ranged from 1.1 per 1,000 births at 40 weeks' gestation to 90,7 per 1,000 at 26 weeks (Figure 6).

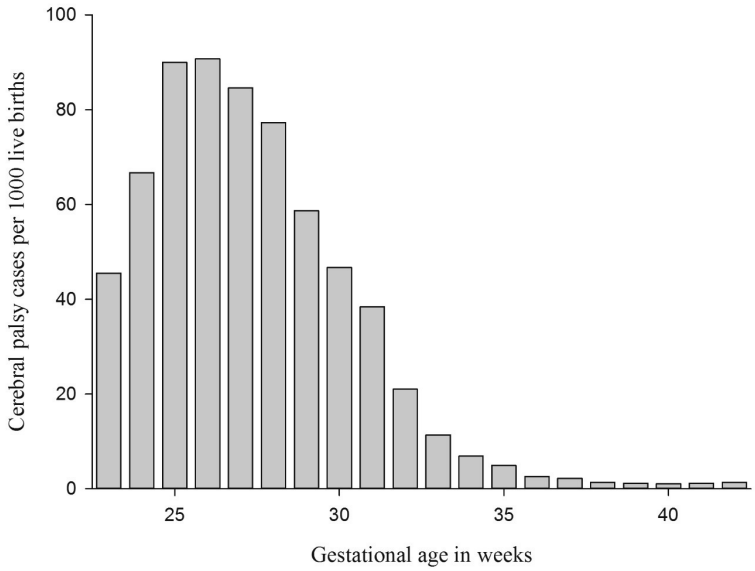

Figure 6 Risk of cerebral palsy with gestational age at birth [149]

After adjustments for pregnancy disorders, socio-demographic factors, and year of birth, the odds ratio of CP was 58.9 (95% CI 48.2-71.9) for children with 23-27 weeks' gestation, 37.1 (95% CI 32.0-43.1) with 28-30 weeks, 13.0 (95% CI 11.3-14.9) with 31-33 weeks, and 2.9 (95% 2.5-3.3) for 34-36 weeks. Pregnancy disorders were recorded in 42 % of preterm births, 12 % of term births, and 9 % of postterm births. Almost half of the children with CP (49%) were born at term or later with no record of

pregnancy complications. All included pregnancy disorders were associated with increased risk of CP.

Absolute risk of CP with a pregnancy disorder varied with categories of gestational age at birth. In children born before 32 weeks' gestation, risk was highest with chorioamnionitis (9.1%) and lowest with pre-eclampsia (3.1%). Placental abruption, chorioamnionitis, intrauterine growth restriction, and congenital malformation predicted a higher risk of CP in most gestational ages. Risk of CP was increased with most pregnancy disorders in children born after 32 completed weeks, but a recorded pregnancy disorder added less than 2 % to the absolute risk. The estimates were relatively stable over time.

6.2 Paper II

Of the 1,760,821 children included in this study, we identified 9,349 (0.5%) with severe asthma and 6,930 (0.4%) with severe atopic dermatitis. Preterm birth was associated with increased risk of severe asthma, but decreased risk of severe atopic dermatitis. Compared with term infants, the odds ratio for severe asthma was 2.37 (95% CI 2.01-2.79) for children with 23-31 weeks' gestation and 1.42 (95% CI 1.30-1.54) with 32-36 weeks. The odds ratio for severe atopic dermatitis was 0.62 (95% CI 0.42-0.92) for children with 23-31 weeks' gestation and 0.90 (95% CI 0.80-1.02) with 32-36 weeks. Postterm birth was associated with slightly increased risk of atopic dermatitis (OR 1.07, 95% CI 1.00-1.15). The absolute risk of asthma and atopic dermatitis with gestational age is displayed in Figure 7.

There were both differences and similarities in risk factors for the two diseases. Caesarean section, parity, and single motherhood were associated with increased risk of both diseases. Several pregnancy disorders and low parental education were associated with increased risk of asthma, and low or high maternal age and female gender seemed to be protective. Atopic dermatitis was generally less associated with pregnancy disorders and socio-demographic factors.

Adjustments for potential confounders weakened the association between gestational age and asthma, but slightly strengthened the association between gestational age and atopic dermatitis. Additional adjustment for smoking had no effect on the estimates in a sub-analysis of 157,149 live births from 1999 through 2001. Analyses in more narrow time strata showed stability of the associations, except that of preterm birth and asthma in the period 1967-1978. In these years, very few cases of asthma were registered.

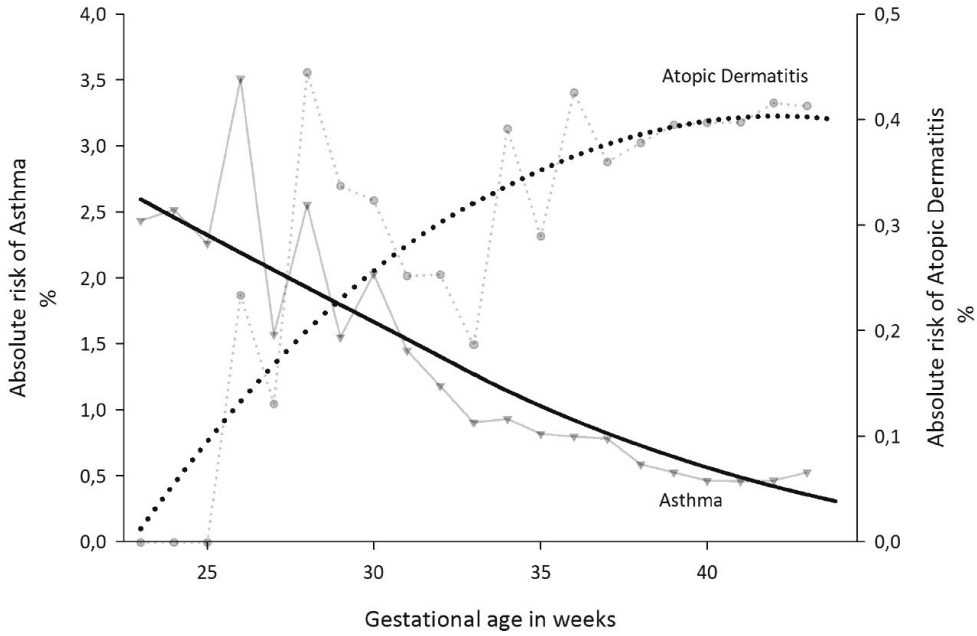

Figure 7 Absolute risks of severe asthma and atopic dermatitis according to gestational age.[147]

6.3 Paper III

We included 1,974,226 births in the study and found that 35,771 (1.8%) of these had a record of maternal asthma, 66,535 (3.4%) of maternal atopic dermatitis, and 8,505 (0.4%) of allergic rhinoconjunctivitis. The prevalence of preterm birth was 5.9 %, of stillbirth 0.6 %, and of neonatal death 0.5 %. The secular trends of these outcomes are shown in Figure 8.

Maternal asthma was associated with increased risk of preterm birth (RR 1.15, 95% CI 1.10-1.21), and more weakly with stillbirth (RR 1.10, 95% CI 0.95-1.29) and neonatal death (RR 1.13, 95% CI 0.92-1.38). In contrast, maternal atopic dermatitis was associated with decreased risk of preterm birth (RR 0.90, 95% CI 0.86-0.93), stillbirth (RR 0.70, 95% CI 0.62-0.79), and neonatal death (RR 0.76, 95% CI 0.65-0.90). Maternal allergic rhinoconjunctivitis was also associated with decreased risk of preterm birth (RR 0.84, 95% CI 0.76-0.94) and stillbirth (RR 0.40, 95% CI 0.25-0.66), but was less definitely associated with neonatal death (RR 0.83, 95% CI 0.52-1.31). Adjustments for potential confounders had relatively little impact on the risk estimates. Further adjustment for smoking in pregnancy in a sub-cohort of 267,678 births from 1999-2003 had no appreciable effect on the association between maternal asthma and preterm birth.

We assessed if maternal diagnoses were underreported after poor pregnancy outcome by exploring the associations of preterm birth, stillbirth, and neonatal death with maternal health conditions that were presumably unrelated to the outcomes (psoriasis and cystitis in pregnancy). Maternal psoriasis was associated with decreased risk of preterm birth (RR 0.89, 95% CI 0.81-0.98) and neonatal death (RR 0.78, 95% CI 0.52-1.17), but not stillbirth (RR 0.99, 95% CI 0.74-1.31). Cystitis was differently related to these outcomes with associations of decreased risk of stillbirth (RR 0.81, 95% CI 0.68-0.98) and neonatal death (RR 0.71, 95% CI 0.55-0.92), but not preterm birth (RR 0.98, 95% CI 0.94-1.03).

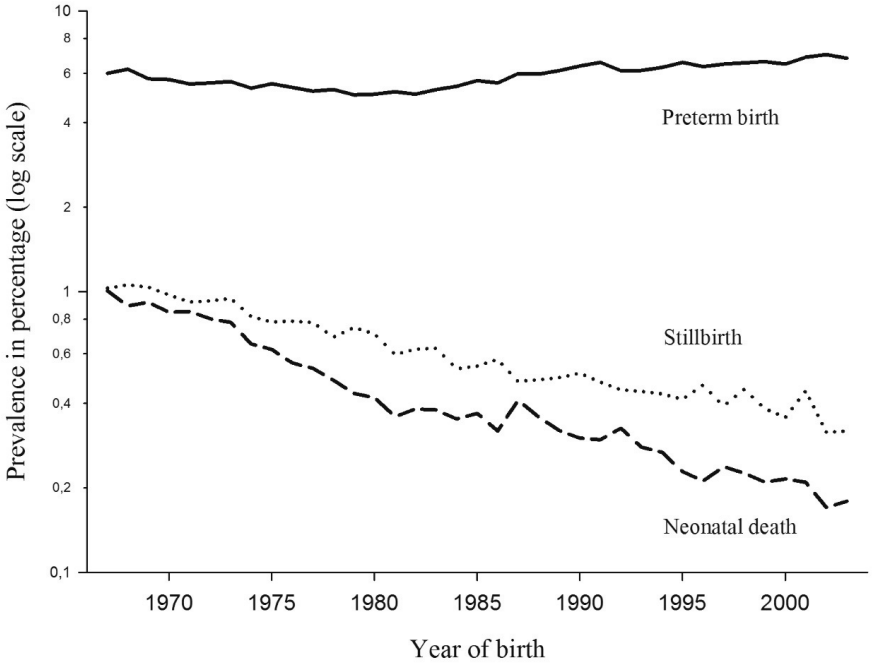

Figure 8 Secular trends of preterm birth, stillbirth, and neonatal death 1967-2003

The associations of maternal atopic diseases with preterm birth and stillbirth were largely stable in different time periods, although the association between maternal allergic rhinoconjunctivitis and stillbirth was much stronger in the most recent period. The relations between maternal atopic disorders and neonatal death varied more within time periods.

7. DISCUSSION

7.1 Discussion of methods

7.1.1 Study design

The study designs were national cohort studies in paper I-III. Data were collected from national, compulsory registries that record information prospectively.

7.1.2 Exposure and outcome identification

Paper I

The exposures in *paper I* were gestational age at birth and pregnancy disorders. Gestational age was calculated from the first day of the last menstrual period, which provides slightly longer gestational age than with ultrasound-based calculations.[150] Information on pregnancy disorders was collected from the MBRN registry, and several variables in the birth registry have been validated and found satisfactory.[151-153] The data from the MBRN are therefore considered reliable, although it is probable that underreporting and misclassification of pregnancy disorders are present to some extent.

The outcome in *paper I* was CP, which was identified in the NIS. Moster et al [154] explored the validity of CP in the NIS, and the authors reported a sensitivity of 70 % and a specificity of 99 %. The participants in this validation were 8-12 years of age, and only recipients of basic and attendance benefit were considered. The sensitivity may have been better in the present study, as we also identified those with CP who received disability pension, and the children born before 1994 were followed until a higher age. However, about 7 % of eligible births were excluded because of missing or probably incorrectly recorded gestational age, and approximately 3 % was excluded because of emigration. The exclusion of these groups, together with shorter follow-up-time for the births in the latest years of the study period, may have underestimated the

prevalence of CP. Another limitation of the outcome identification was the lack of information on subtypes of CP.

Paper II

The exposures in *paper II* were largely similar to those in *paper I*.

The outcomes asthma and atopic dermatitis were identified among recipients of basic and attendance benefits in the NIS. These diagnoses have not been validated in this registry. According to the NIS' legislation and guidelines, only severe disease qualifies for basic and attendance benefits.[155] This restricted the outcomes to severe asthma and atopic dermatitis. The time of diagnosis was not available, so we could not discern between childhood and late-onset disease.

Paper III

The exposures maternal asthma, atopic dermatitis, and allergic rhinoconjunctivits were identified in the MBRN and have not been validated. It was not possible to discern between present and previous disease, physician-verified and self-reported disease, and mild and severe disease.

The outcomes were preterm birth, stillbirth, and neonatal death. As mentioned above, estimation of gestational age with last menstrual period has probably led to some underreporting of preterm births. Registration of the variables stillbirth and neonatal death in the MBRN are not validated, but are considered reliable.

7.1.3 Internal validity

Internal validity may be defined as a study's ability to measure what it set out to. Systematic errors reduce the internal validity. Examples of such errors are *selection bias*, *information bias*, *confounding*, and *colliding bias*.

Selection bias

Selection bias occurs if participants in a study represent a group that differs from the general population with its relations to the exposures or the outcomes of the study.

Sampling bias and *susceptibility bias* are two types of selection bias. Sampling bias may occur if study participants are selectively chosen on background of an unmeasured factor that is associated with exposure and outcome. Susceptibility bias arises if an exposed group has an increased risk of an outcome as a result of the circumstances of the exposure.

The study populations in *paper I-III* are national cohorts. Sampling bias is minimized with such large study populations with compulsory participation. Possible sources of sampling bias include those who have missing or incorrectly registered gestational age (*paper I-III*) and those who have emigrated (*paper I* and *II*). Missing or wrong gestational age may be due to random errors, but also to uncertainty of last menstrual period, or to not having participated in a pregnancy health program. This may represent lifestyle factors that predict adverse outcomes. It is also possible that parents with a sick child may be prone to return to their home country. However, the rather low proportion of excluded children does not indicate that sampling bias may have substantial impact on the results.

S*urvival bias* is a type of sampling bias and occurs when a risk group for an outcome also has an increased risk of mortality, and only survivors are included. This source of bias is particularly relevant for the estimations of CP and asthma risk among the most preterm children in *paper I* and *II*, respectively.

Parents of a child born preterm may spend considerable time at the hospital. Through close contact with the health care system, parents may be more aware of possible social benefits from the NIS. This may present susceptibility bias, which may have overestimated the associations of preterm birth with CP or severe asthma. However, this type of bias cannot explain the decreased risk of severe atopic dermatitis in preterm children. Instead, a different kind of susceptibility bias may be present. Children born preterm are at risk for several long-term disorders, many of them with a large burden of disease. Parents of preterm children with other, more serious diseases may therefore be less prone to apply for NIS benefits for atopic dermatitis.

Information bias

Information bias occurs when a variable is erroneously measured or classified. This source of bias includes *misclassification*. An example of misclassification may be a wrong registration of outcome or exposure. Misclassification is differential if errors in registration of outcome or exposure depend on the other value. If misclassification occurs independently of the values of exposure and outcome, the misclassification is non-differential. It is particularly important to avoid differential misclassification, as this bias may overestimate or underestimate true values. Non-differential misclassification will weaken effects towards null value.

Non-differential misclassification due to underreporting of diagnoses and to use of gestational age based on last menstrual period is probably present. The presence of differential misclassification is less likely, since the data are collected from independent registries with prospectively recorded information. However, both exposures and outcomes were registered in the same registry (MBRN) in *paper III*. Although the MBRN generally records data prospectively, registration is retrospective in some situations. In cases of preterm birth, stillbirth, or neonatal death, the outcome is usually known before registration of exposures is completed. In these difficult situations, maternal health conditions with no known relation to the outcome may be underreported. If this is true, misclassification would be differential and could have affected the associations of adverse pregnancy outcomes with maternal atopic diseases. We pursued this possibility by analysing two other maternal health conditions with no known relation (maternal psoriasis and infectious cystitis in pregnancy) to preterm birth and perinatal mortality, but found no consistent pattern of differential misclassification.

Confounding

A confounder is a variable that may cause or correlate with both exposure and outcome. This is illustrated with a directed acyclic graph (DAG) (Figure 9). The arrows and their directions show the causal relations; the exposure causes the outcome, and the confounder causes both the exposure and the outcome.

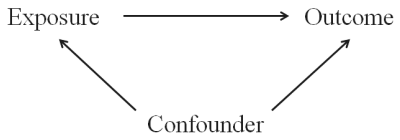

Figure 9 Causal relations between confounder, exposure, and outcome

If a confounder is not taken into account in the analysis of a relation between exposure and outcome, the association will be biased. The magnitude of this bias depends on the confounder's impact on exposure and outcome.

In *paper I*, we assessed a wide spectrum of pregnancy disorders as possible confounders, including placental abruption, chorioamnionitis, prolonged rupture of membranes, intrauterine growth restriction, pre-eclampsia, multiple births, placenta previa, unspecified bleeding, cervical conization, and congenital malformations. A number of these have been associated with both preterm birth and CP.[31, 52, 54-59, 61] We also included educational level of parents, gender, single motherhood at birth, maternal age, and immigrant status as potential confounders. These socio-demographic factors have been associated with CP risk in previous studies.[31, 52, 53, 55]

Similarly, we considered pregnancy disorders as confounders in p*aper II.* Several reports have suggested links between pregnancy complications and asthma,[119, 120, 156] while the relations between pregnancy disorders and atopic dermatitis have not been thoroughly explored. We also assessed caesarean section, parity, and maternal asthma and atopic dermatitis as possible confounders. Caesarean section is more prevalent among preterm children and is associated with increased risk of asthma. [121, 122, 157] The association between caesarean section and atopic dermatitis is unclear, and the few studies on this association are relatively small.[158-161] Parity has been associated with preterm birth and atopic diseases.[101, 129, 162, 163] Asthma and atopic dermatitis recur across generations, [117, 164] and there is convincing evidence of an association between

maternal asthma and preterm birth.[114] The association between maternal atopic dermatitis and preterm birth, however, is unclear.[136] Smoking during pregnancy is associated with preterm birth and asthma in offspring.[116, 118] Information about smoking during pregnancy was not recorded in the MBRN before December 1998. Because of this limitation in the dataset, we assessed smoking as a confounder in a sub-cohort of live births from 1999 through 2001. As in *paper I*, we considered socio-demographic factors as confounding factors.

In *paper III*, we included paternal and maternal education, single mother at birth, maternal age, and parity as potential confounders. Parental education and single motherhood at birth are indicators of socio-economic status, and high socio-economic level is associated with increased risk of atopy and decreased risk of adverse pregnancy outcomes.[102, 165] Stillbirths are, however, not assigned a personal identification number. Since Statistics Norway linked information on parents' education by the child's identification number, we lacked data from the national registry of education for parents of stillborns. Both young and advanced maternal age has been associated with poor pregnancy outcomes,[11, 166, 167] and nulliparity has been reported to increase risk of stillbirth and small for gestational age status.[168, 169] Mothers who are born preterm tend to deliver preterm,[27] and preterm birth may influence risk of atopic disease.[117, 133] We pursued this potential confounder by restricting the analysis to a sub-cohort of births of mothers who were born at term. We assessed smoking as a confounder for the association between maternal asthma and adverse pregnancy outcomes in a sub-analysis of births in the period 1999-2003.

Colliding bias

In contrast to confounding, colliding bias is not perceived intuitively. When a variable is the outcome of two or more variables that may or may not be correlated, it is termed a collider. How colliding bias may occur is exemplified with a directed acyclic graph of the possible causal pathways between exposures and outcome in *paper I* (Figure 10).

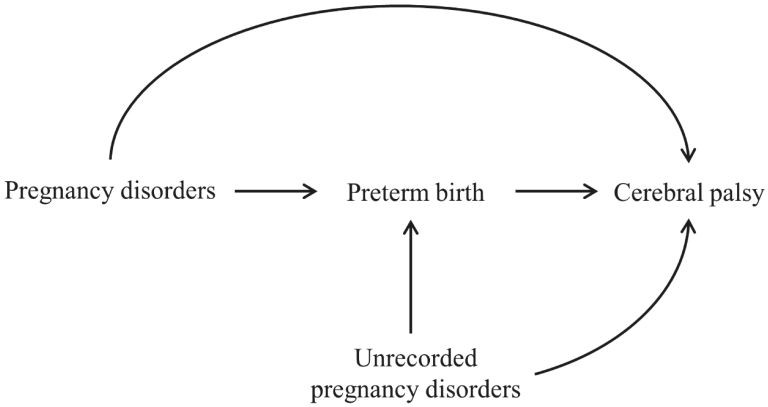

Figure 10 Causal relations between pregnancy disorders, preterm birth, and cerebral palsy

The arrows in the figure indicate the directions of the causal relations. Pregnancy disorders have a direct effect on CP and a mediated effect through preterm birth. Preterm birth is a collider, since both recorded and unrecorded pregnancy disorders cause preterm birth. Colliding bias may arise if a mediating collider (preterm birth) is adjusted for while there are unmeasured variables (unrecorded pregnancy disorders) that cause both the collider (preterm birth) and the outcome (CP). Recent causal theory has shown that adjustment on a mediating collider may result in biased estimates,[170-172] and the magnitude and the direction of this bias are unpredictable. Preterm birth or gestational age often act as a mediating collider in relations between pregnancy disorders and infant outcomes,[171] and several previous reports have not considered this in their analyses.

In the analysis of the association between preterm birth and CP, known and unknown pregnancy disorders would act as confounders (Figure 11), and could be adjusted for.

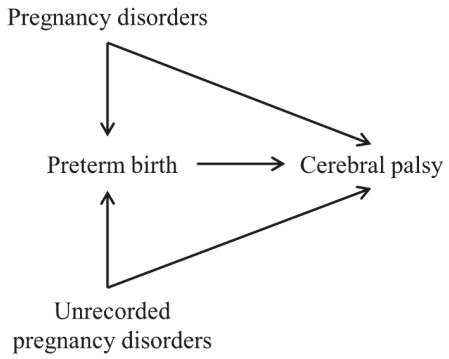

Figure 11 Causal relations between pregnancy disorders, preterm birth, and cerebral palsy

The given examples of potential colliding bias issues in *paper I* are paralleled in *paper II*, where preterm birth is a mediating collider for the associations between pregnancy disorders and atopic diseases, and in *paper III*, where preterm birth is a mediating collider for the associations of maternal atopic diseases with stillbirth and neonatal death.

7.1.4 Random errors

Random errors may occur during recording, transferring, and coding of data. In this context, such errors may have been caused by diagnostic errors, missing or erroneous registration, or misinterpretation of registration during coding. Random variations are natural fluctuations in measurements. An effective method of reducing the influence of random errors and variations on the result is to increase the sample size. With the large sample size in this study, it is expected that random errors and variation had little impact on the results. However, numbers are small in some of the stratified analyses, and the results of these may have been biased by random errors.

7.1.5 Precision and accuracy

The accuracy reflects the closeness of the result to the true value, and precision represents to which degree the results can be reproduced under the same circumstances. Accuracy and precision are influenced by study design, sample size,

and errors. Random errors and variations have greater impact on small sample sizes, and this will decrease both accuracy and precision. If there are systematic errors, a large sample size may increase precision, but not accuracy. Both the large sample size and the cohort study design in this study were likely to increase both accuracy and precision. Still, some analyses suffered from small sample sizes. The systematic error of estimating gestational age from last menstrual period has probably decreased accuracy, but not precision.

7.1.6 External validity

The external validity reflects how the results of a study can be generalised to other populations in other settings. Poor internal validity and differences in study populations, prevalences, and exposure and outcome measurements may hamper the external validity. The strengths and limitations of the internal validity of this study have already been discussed.

This study had Norwegian national cohorts as study populations. Although the study group is representative for Norway, the study population may differ from other populations with regard to prevalence of exposure and outcome, ethnicity, educational level, and health status.

Substantial loss of participants may limit the external validity. About 13 % of potential participants were excluded in *paper I* and *II* and 9 % in *paper III*. Since the registries are mandatory, the loss to follow-up was minimal. The proportions of lost participants were relatively low and should not represent a substantial limitation of the external validity.

The prevalence of atopic diseases, preterm birth, and perinatal mortality have varied over time and between countries.[15, 93, 173] This may limit the generalisability to current settings and in other populations. However, the prevalence of CP has been relatively stable with relatively little geographical variation. [48, 49]

The results from this study cannot be readily extrapolated to other populations. The consistency of CP prevalence over time and between countries, together with a

validated method of outcome measurement, argues that *paper I* has the best external validity of the three papers.

7.2 Discussion of results

7.2.1 Risk of cerebral palsy with preterm birth and pregnancy disorders

The prevalence of CP was 1.8 per 1,000 live births, which is slightly lower than in most studies, but not all.[31, 48, 52, 60] The prevalence of CP declined towards the end of the study period, possibly because of shorter follow-up-time for those born in the latest years of the study period.

Preterm birth was strongly associated with CP, and the risk increased with decreasing gestational age at birth. This association is well-established in the literature.[31, 52, 59, 174] The absolute risk of CP was highest in children with 26 weeks' gestation, probably since children born at earlier gestational ages with high risk of CP were selectively removed because of increased mortality.

Almost all socio-demographic factors were associated with both preterm birth and CP. Most studies have found that lower socio-economic status increases risk of CP.[174-177] Since educational status is closely related with socio-economic status, these studies support our finding of increased risk of CP with decreasing level of parental education. Single motherhood at birth is also a parameter for low socio-economic status, and was associated with increased CP risk. This finding was supported by a Swedish study based on hospital records.[174] Low socio-economic status is associated with preterm birth and low birthweight,[178] and it is possible that these outcomes at least partly mediate the associations with CP. Female sex was found to be protective for CP in our study. This has consistently been reported from other studies.[31, 52, 174, 177] The reasons for this difference is not known, but oestrogen and other sex hormones may have neuroprotective effects and preterm males have more respiratory and circulatory complications than the females.[179, 180] We did not find that young and advanced maternal age were risk factors for CP, which is in contrast to most reports.[31, 52, 177]

All of the included pregnancy disorders were risk factors for preterm birth and CP. Most of these have been reported in previous studies.[31, 52, 54-61] We explored how pregnancy disorders affected risk of CP in different gestational age strata and found that the risk was increased in most gestational ages in pregnancies complicated by placental abruption, chorioamnionitis, intrauterine growth restriction, and congenital malformations. Other pregnancy disorders were more likely to predict increased risk of CP after 31 weeks' gestation. This does not imply that these pregnancy disorders did not have an impact on CP risk in babies born before 32 weeks. The similar risk of CP with or without a recorded pregnancy disorder in births of 23-31 weeks' gestation suggests that the recorded pregnancy disorders were as damaging as the unrecorded ones. This may also help to explain why pregnancies with pre-eclampsia seemed to have significantly lower risk of CP among the earliest births. Considering the inflammatory and haemodynamic effects of pre-eclampsia, it is plausible to assume that this disorder has a harmful effect on the fetus. Thus, our finding suggests that pre-eclampsia is less harmful than both unrecorded and recorded pregnancy disorders in the most preterm births. This hypothesis is supported by Greenwood et al,[56] who found decreased risk of CP with pre-eclampsia (OR 0.4, 0.2-1.0) in births before 33 weeks. The authors also reported that all of these births were delivered electively, and the risk of CP for these children was not lower than that of children delivered electively for other reasons.

The low absolute risk of CP with pre-eclampsia among the most premature babies suggests that the biological contribution of immaturity to the risk of CP may be even lower than that of pre-eclampsia. It is therefore possible that pregnancy disorders may have a large impact on the risk of CP in the smallest preterm children. Since the pregnancy disorders that caused preterm births were mostly unknown, we could not determine to which extent the risk of CP in preterm children was attributed to their immaturity or to the underlying pregnancy disorders.

7.2.2 Risk of severe asthma and atopic dermatitis with preterm birth

Preterm birth was associated with increased risk of severe asthma and decreased risk of severe atopic dermatitis. Associations were generally stronger with decreasing gestational age, and the risk estimates were inverted for both diseases with postterm birth.

While the majority of the studies on preterm birth and asthma have reported increased risk of asthma with preterm birth,[42] the literature on preterm birth and atopic dermatitis has reported contradicting results. Our results are in accordance with those who have found a decreased risk of atopic dermatitis with preterm birth.[115, 127, 132, 133]

Preterm birth is normally a result of pathological processes, and it may seem counterintuitive that an abnormal condition may be associated with decreased risk of a disease. However, there is some evidence that prematurity may protect from atopy. Previous reports from Finland and Sweden have found a decreased prevalence of atopy and allergic rhinitis in preterm children.[162, 181-183] The biological pathways for a potential protective effect are unknown, but hygienic and immunological exposures may be involved. Preterm children are exposed to the extra-uterine world earlier than term children, and early exposure to microbes and antigens may protect from atopy.[101, 102] Alternatively, risk of atopy may increase with increasing length of exposure to maternal immune responses. The immune system of the fetus is modulated by the mother's immunological status,[184] and during pregnancy, the mother's immune system shifts from cellular (Th1-dominated) to humoral (Th2-dominated) immune responses. Atopic diseases are Th2-driven diseases, and it has been speculated that shorter exposure to maternal Th2-skewed immune responses in pregnancy may protect from atopy.[184, 185]

Still, a protective effect of preterm birth on atopy does not explain why prematurity is associated with increased risk of asthma. Asthma is a poorly defined diagnosis with multiple phenotypes and mostly non-atopic causes.[111] It has been suggested that asthma in preterm children may be less associated with atopy and more with respiratory complications and decreased lung function.[125] Children who are born

preterm also have particular exposures that may harm the respiratory system. Caesarean section is associated with preterm birth and later development of asthma.[121, 157] Preterm children are more often hospitalized because of respiratory virus infections, which is associated with increased risk of developing asthma.[123, 124] Neonatal jaundice is more prevalent among preterm than in term neonates,[186] and may predispose to asthma.[126] Drug use during pregnancy has been associated with asthma in offspring,[187] and it is possible that these drugs and their underlying diseases may be risk factors for preterm birth.

There seems to be a continuum of asthma risk with fetal maturation. Boyle et al reported increasing risks of asthma with decreasing gestational age.[188] Interestingly, the authors also reported that early term children (37-38 weeks' gestation) were at increased risk compared with those who were born at 39-40 weeks' gestation. In line with our study, a Finnish report found a slightly lower risk of asthma in late term and postterm infants (more than 41 weeks' gestation) than those born at 39-40 weeks.[189] Maturation of lungs and airways continue beyond term and birth, and risk of asthma may be closely related to this process. Thus, it is possible that other, non-atopic causes of asthma may overshadow a protective effect of prematurity.

We found that asthma and atopic dermatitis shared some risk factors, but the two diseases were differently related to several perinatal and socio-demographic factors. Similarly to our findings, Linneberg et al [115] found that the majority of potential risk factors differed for infant wheeze and atopic dermatitis. The differences in risk factors for asthma and atopic dermatitis suggest that the causal pathways are partly different for the two diseases.

7.2.3 Risk of preterm birth, stillbirth, and neonatal death with maternal atopic disorders

Asthma, atopic dermatitis, and allergic rhinoconjunctivitis in mothers were differently related to preterm birth, stillbirth, and neonatal death. Maternal asthma was associated with increased risk of preterm birth, while maternal atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk. We also found that maternal

atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk of stillbirth, and maternal atopic dermatitis with decreased risk of neonatal death.

Several studies have reported that maternal asthma increases risk of preterm birth,[114] but there are very few reports on risk of preterm birth with other maternal atopic diseases. A study from Finland found associations of decreased risk of extremely low birth weight with maternal atopic dermatitis and allergic rhinoconjuntivitis,[136] and a Hungarian study reported a lower rate of preterm birth in mothers with symptomatic allergic rhinoconjunctivitis during pregnancy.[137] The two studies support our findings, but clearly, the research is too limited to draw firm conclusions. The literature on the associations of perinatal mortality with maternal atopic dermatitis or allergic rhinoconjunctivitis is also scarce. We only found two small studies on this topic, but neither included statistical evaluations.

We explored various explanations for the apparently protective associations of poor pregnancy outcomes with maternal atopic dermatitis and allergic rhinoconjunctivitis. Mothers with these disorders did not have less pregnancy complications than other mothers, which could have explained more favourable outcomes. On the contrary, pre-eclampsia, unspecified bleeding, and caesarean section were more prevalent in these mothers. We did not find evidence in the literature for more favourable outcomes with drug use for atopic dermatitis and allergic rhinoconjunctivis.[190, 191] Mothers with a record of these disorders were averagely more educated and more frequently nulliparous than those without these diseases, but adjustment for these factors had minimal effect on the estimates. Restricting the analyses to mothers born at term weakened the associations, but the risk estimates were similar to those of the whole cohort. It seems that our findings cannot entirely be due to confounding, although there might be confounders that were not accounted for.

Misclassification bias may have affected the associations. After a poor pregnancy outcome, presumed unrelated health issues of the mother may be underreported. We examined how maternal psoriasis and cystitis in pregnancy (who have no reported effect on the outcomes) were related to preterm birth, stillbirth, and neonatal death.

While maternal psoriasis was significantly associated with decreased risk of preterm birth, cystitis during pregnancy was significantly associated with stillbirth and neonatal death. There is no support in the literature for a favourable effect on pregnancy with these disorders,[192-195] and the findings may suggest that maternal disorders are underreported after adverse pregnancy outcomes. Still, there was no obvious pattern of this potential bias. If there is underreporting of maternal diseases under these circumstances, the associations of pregnancy outcomes with maternal asthma may have been underestimated, and those of pregnancy outcomes with maternal atopic dermatitis and allergic rhinoconjunctivis may have been exaggerated.

If there is a protective effect of atopic dermatitis or allergic rhinoconjunctivitis against adverse pregnancy outcomes, the biological background may include immunological and genetic pathways. Immune responses in both pregnancy and atopy are shifted to Th2 dominance.[196, 197] This immunological shift in pregnancy protects the fetus from being rejected by the mother while defense against infections is maintained.[197] The ability to conserve Th2 dominant immune responses seems to influence success in pregnancy and may predict pregnancy length.[198] It is thus possible that the pre-existing Th2 deviation with atopy may be favourable for the pregnancy and protect from adverse outcomes. We can also speculate in a common genetic predisposition for atopy and pregnancy outcomes. Variants of genetic loci shared by atopic disorders have been identified,[99] but to our knowledge, potential relations of these to pregnancy outcomes have not been explored.

In contrast to maternal atopic dermatitis and allergic rhinoconjunctivitis, asthma in pregnancy seems to be harmful for the pregnancy and the fetus. Asthma in pregnancy has been associated with increased risk of preterm birth, neonatal death, congenital malformations, SGA status, decreased fetal growth, and pre-eclampsia.[114, 138] We found that maternal asthma was significantly associated with increased risk of preterm birth, but not stillbirth and neonatal death. The risk estimates for adverse pregnancy outcomes were lower than those reported in most, but not all studies.[114] Discrepancies between these studies and ours may be due to population differences, but may also be attributed to different sources of bias. Misclassification bias may have underestimated

the risk estimates, and residual confounding is possible. We did not have the possibility to adjust for smoking in pregnancy for the whole cohort, but we found minimal effects of additional adjustment for smoking in the sub-analysis of births in 1999-2003.

Several studies have explored whether asthma medication may be a culprit of unfavourable pregnancy outcomes, but the majority of studies have not found any harmful effects on perinatal events.[114] On the contrary, active management of asthma seems to lower the risk of preterm birth.[114, 138] This may suggest that features of asthma, such as inflammation, tissue hypooxygenation, and disturbances in smooth muscle tone, may have harmful effects on pregnancy and fetus. These effects may have more impact than the potential beneficial effects from atopy.

8. CONCLUSIONS

In this study, we have explored specific risk factors and outcomes of preterm birth.

In *paper I*, we found that preterm birth and several pregnancy disorders were strong risk factors for CP. Risk of CP with recorded pregnancy disorders varied within categories of gestational age.

In *paper II*, we found that preterm birth was associated with increased risk of severe asthma and decreased risk of severe atopic dermatitis. We found differences and similarities in risk factors for the two diseases, suggesting that asthma and atopic dermatitis in preterm children are partly different clinical entities.

In *paper III*, we found that maternal asthma was associated with increased risk for preterm birth, while maternal atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk. Maternal atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk of stillbirth, and maternal atopic dermatitis with decreased risk of neonatal death.

9. IMPLICATIONS AND FUTURE ASPECTS

In *paper I*, we estimated absolute risks for CP with gestational age at birth and pregnancy disorders. The estimates were relatively stable over time and may be valid for current settings. Parents who are concerned about their child's outcome after preterm birth are often interested in the probability of having a child with CP. Our findings may be useful and informative for physicians and parents who deal with preterm births and pregnancy disorders.

In *paper II*, we found that preterm birth was associated with increased risk of severe asthma. This finding emphasizes that preterm children are at risk for later development of asthma. The observed association between preterm birth and decreased risk of severe atopic dermatitis needs to be confirmed in future studies, and it is particularly interesting to clarify if this association is valid for mild and moderate disease. If this finding is reproduced, further work of identifying biological pathways is warranted. This may provide new insight in the aetiology of atopy, which may lead to new strategies for preventing atopic disorders.

In *paper III*, maternal asthma was associated with increased risk of preterm birth. The finding highlights mothers with asthma as a risk group for preterm birth. Others have shown that active management of asthma in pregnancy may decrease risk of preterm birth, and together with our study, physicians may be further encouraged to improve management of asthma in pregnant women. We also observed that maternal atopic dermatitis and allergic rhinoconjunctivitis were associated with decreased risk of preterm birth and other pregnancy outcomes. These relations need to be further explored. If the associations are verified, future research may identify specific protective factors related to atopic disorders that may result in new knowledge of adverse perinatal outcomes and new preventive strategies.

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11. APPENDICES

Appendix I

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

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

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

Barnet	Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster	Født dag, mnd., år	Klokkeslett	Personnr.	Skriv ikke her
	1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling		Kjønn 1 ☐ Gutt 2 ☐ Pike		
	Etternavn, alle fornavn (bare for levendefødte)				
	Fødested. Navn og adresse på sykehuset/fødehjemmet		Kommune		
Faren	Etternavn, alle fornavn		Født dag, mnd., år	Bostedskommune	
Moren	Etternavn, alle fornavn. Pikenavn			Født dag, mnd., år	
	Bosted. Adresse		Kommune		
	Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt			Ekteskapsår (gifte)	
	Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte	
	Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:				
Morens helse **før** svanger-skapet	1 ☐ Normal 2 ☐ Sykdom (spesifiser):				
			Siste menstruasjons første blødningsdag		
Morens helse **under** svanger-skapet	1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):				
Ble fødselen provosert	1 ☐ Nei 2 ☐ Ja				
Inngrep under fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
	Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor				
Komplika-sjoner i forbindelse med fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
Fostervann, placenta og navlesnor	1 ☐ Normalt 2 ☐ Patologisk (spesifiser):				
Barnets tilstand	Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja		Apgarscore etter 1 min.	etter 5 min.	
	For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:				
	Lengde (i cm) / Hode-omkr. (i cm) / Vekt (i g)		For døde innen 24 timer Livet varte i	Timer	Min
	For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen Dødsårsak: Seksjon? 1 ☐ Nei 2 ☐ Ja				
Alvorlige arvelige lidelser i slekten	1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:				

50 000. 5.96. SEM GRAFISK

Sted (sykehusets stempel) | Dato | Jordmor | Lege

IK - 1002.

Appendix II

Melding om avsluttet svangerskap etter 16. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Statens helsetilsyn

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: ☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei Før sv.sk. I sv.sk.
Multivitaminer ☐ ☐ Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: ☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B» ☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Røyking og yrke Forutsetter mors samtykke – se rettledning på baksiden
☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjons-metode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak ☐ Ingen ☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner ☐ Ingen ☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi: ☐ Ingen ☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta: ☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter ☐ Koagler ☐ Utskrapning ☐ Manuell uthenting
Placenta-vekt

Navlesnor ☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier ☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute
Navlesnor-lengde:

Fostervann ☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel ☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet ☐ Enkeltfødsel ☐ Flerfødsel For flerfødsel: Nr. Av totalt

Kjønn ☐ Gutt ☐ Pike Ved tvil spesifiser i «D» For dødfødte: ☐ Usikkert kjønn

Barnets vekt: | Hode-omkrets: | Total lengde: | Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var: ☐ Levendefødt

For dødfødte: ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer Livet varte: Timer | Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) ☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting

Årsak:
☐ AB0 uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato Mor: Barn:

ProtokollNr.: /

IK-1002 NT. / 19424 Sem & Stenersen PROMAN AS, OSLO 1-99