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Long-term Consequences of Preterm Birth: Swedish National Cohort Studies

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ABSTRACT

The World Health Organization defines preterm birth as birth before 37 complete weeks. The proportion of *very* preterm children with severe neurological disabilities has become smaller, but bulks of data indicate that, for many of the children born preterm, persistent subtle difficulties are evident in school age. Most studies have focused on the situation for infants born before 33 complete weeks. However, *moderately* preterm (gestational week 33–36) are much more common, and hence important from a public health perspective. In this thesis, long-term consequences of all degrees of preterm birth in school age and young adulthood have been studied. Swedish national registers have been used as data sources. The outcomes for preterm individuals have been compared with the outcomes for infants born at term (here defined as 39–41 gestational weeks).

The objective was to investigate the impact of preterm birth on social adjustment, mental health and asthma. Also, the interplay between preterm birth and socioeconomic characteristics of the childhood household has been analysed. One cohort of over half a million individuals born 1973–79 and another cohort of over a million individuals born 1987–2000 have been used for these purposes.

The risk for inhaled corticosteroid medication (our main indicator for asthma) in 6–19 year-olds born 1987–2000 increased with the degree of prematurity. For prematurely born children, compared with children with similar socioeconomic backgrounds born at term, the risk increased from 10 % in 37–38 weeks of gestation at birth, to more than a doubled risk for 23–28 weeks of gestation.

For individuals born 1987–2000, there was a stepwise increase in odds ratios for Attention-Deficit/Hyperactivity Disorder medication (our indicator for ADHD) at 6–19 years of age, with increasing degree of immaturity at birth from more than a doubled risk for infants born after 23–28 weeks of gestation, to a 20 % increased risk for 37–38 weeks of gestation compared with infants born after 39–41 weeks and with adjustment for socioeconomic confounders. Furthermore, individuals born 1973–79 were followed-up at 8–29 years of age for psychiatric hospital admissions. Compared with term infants the increase of risk varied by increasing maturity at birth, from just below 70 % for gestational week 24–32 down to just below 10 % for gestational week 37–38, with adjustment for socioeconomic confounders.

The large majority of even the most preterm (< 29 gestational weeks) born in 1973–79 led productive and independent lives in young adulthood. Very preterm individuals (< 33 gestational weeks), however, ran almost four times the risk for disability, after adjustment for socioeconomic and perinatal indicators compared with term individuals (39-41 weeks). The increased risk for disability dropped gradually with higher gestational age at birth, but was still significantly increased for gestational week 37–38 compared with gestational week 39–41.

Moderately preterm individuals to mothers of low education were more sensitive to the effect of preterm birth on the risk for ADHD. Accordingly, children growing up in socially disadvantaged households, as expressed by low socioeconomic status, were more vulnerable to the effect of preterm birth on psychiatric morbidity.

Conclusions

The risks for the unfavorable outcomes studied increased with decreasing gestational age at birth in the follow-up studies of individuals born 1973–79 and 1987–2000. The most preterm group (< 33 complete weeks) born in the seventies contributed more economically to society than they received in societal assistance/benefits. Moderately preterm and early term carried, due to their large number, most of the morbidity associated with preterm/early term birth. Hence, this group is important from a public health perspective and deserves more attention in research and clinical development.

LIST OF PUBLICATIONS

I. Lindström K, Winbladh B, Haglund B, Hjern A.
Preterm Infants as Young Adults: a Swedish National Cohort Study.
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II. Lindström K, Lindblad F, Hjern A.
Psychiatric Morbidity in Young Adults Born Preterm: a Swedish National Cohort Study.
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III. Lindström K, Lindblad F, Hjern A.
Preterm Birth and Attention-Deficit/Hyperactivity Disorder in Schoolchildren.
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IV. Vogt H, Lindström K, Bråbäck L, Hjern A
Preterm Birth and Inhaled Corticosteroid Use in 6–19-year-olds: a Swedish National Cohort Study.
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CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
ATC	Anatomic Therapeutic Chemical Classification System
BPD	Bronchopulmonary Dysplasia
CI	Confidence Interval
CLD	Chronic Lung Disease
CP	Cerebral Palsy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Edition
ICD-10	International Classification of Diseases, Tenth Edition
ICS	Inhaled Corticosteroids
IVH	Intraventricular Hemorrhage
LMP	Last Menstrual Period
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PIN	Personal Identification Number
PPROM	Preterm Premature Rupture of Membrane
PVL	Periventricular Leukomalacies
ROP	Retinopathy of Prematurity
RR	Risk Ratio
RSV	Respiratory Syncytical Virus
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small for Gestational Age
SMBR	Swedish Medical Birth Registry
VLBW	Very Low Birth Weight
WHO	The World Health Organization

1 INTRODUCTION

Preterm birth is of public health importance now that increasing numbers of children born preterm survive into youth and adulthood. Antenatal steroids, antibiotics, thermal control, intravenous fluids, total parental nutrition, surfactant and respiratory support are claimed to be some of the most important improvements in modern neonatology. Nevertheless, individuals born preterm have an increased risk for neonatal mortality, developmental disabilities and other health problems [1]. Most studies have focused on the situation for infants born before 33 complete weeks, but moderately preterm (gestational week 33–36) are much more common and important from a public health perspective [2].

In this thesis, I present four studies regarding the long-term consequences of *all* levels of preterm birth using the Swedish national registers. The aim is to investigate the long-term impact of preterm birth on social adjustment and health, controlling for a number of important socioeconomic and perinatal indicators.

2 BACKGROUND

2.1 EPIDEMIOLOGY AND DEFINITIONS

Normally, a human pregnancy has a gestational length of 40 weeks, or more precisely, 282–283 days [3]. The World Health Organization (WHO) divides the gestational age of newborn infants into *preterm* (< 37 weeks), *term* (37–41 weeks) and *post term* (≥ 42 weeks) [4]. A number of ways to categorize the different degrees of preterm birth is used in the literature [5, 6]. According to a suggestion from Engle et al., infants born after 34–36 weeks of gestation should be labeled *late preterm* infants instead of *near term* infants to emphasize their predisposal for morbidity [5]. However, subdivisions regarding the more mature group of preterm infants continue to differ [7-12].

In this thesis, perinatal variables were collected from the Swedish Medical Birth Register. Gestational age was categorized according to national Swedish perinatal statistics as shown in table 1.

Table 1. Categorization of gestational age by completed gestational weeks at birth.

Extremely preterm	< 29 weeks
Very preterm	29–32 weeks
Moderately preterm	33–36 weeks
Early term	37–38 weeks
Term	39–41 weeks
Postterm	≥ 42 weeks

As *term* comparison population in this thesis, we included individuals born after 39 to 41 weeks of gestation. *Small for Gestational Age* (SGA) was defined as less than –2 SD according to the growth chart developed by Marsal et al. [13].

Expected date of delivery is determined either by adding 280 days to the Last Menstrual Period (LMP) or, for more accuracy, by measuring the fetal size in early pregnancy by ultrasound [14, 15]. Compared to ultrasound estimates, LMP-estimates tend to overestimate gestational age by about 3 days [15].

Preterm infant's mortality rates may vary due to differences in the definitions of live born and stillborn infants. From the start of the Swedish medical birth register 1973 until June 30th 2008, the definition of intrauterine death was delivery of a dead fetus having a gestational age of at the least 28 complete weeks. In accordance with international practice, the limit was changed on July 1st 2008 to 22 complete gestational weeks [16].

Varying rates of preterm birth

The rate of preterm birth vary globally and also within high-income countries. In Sweden, 6.5 % have been reported to be born before 37 full weeks [17] compared to 12.7 % in the US (11.7 % among non-Hispanic whites, and 18.4 % among non-Hispanic blacks) [18]. Regarding the Swedish population, it has been reported that 5.2 % are born in the gestational age group 33–36 weeks and 1.3 % before 33 completed weeks of gestation [17]. Low-income countries may have higher rates of preterm birth [19].

2.2 CAUSES OF PRETERM BIRTH

Preterm birth can be grossly divided into three groups. First, there are indicated births (30–35 %), either induced or by prelabor cesarean section. The main reasons for indicated births are preeclampsia, eclampsi and intrauterine growth restriction. Second, there are births resulting from preterm labor (40–45 %), and third, births following preterm premature rupture of membranes (PPROM, 25–30 %) [20].

The causes of preterm birth are multifactorial, and vary by gestational age. The major causes of preterm births following preterm labor and PPROM are infection/inflammation, vascular disease and uterine overdistension [20]. The majority of extremely preterm births are thought to be due to intrauterine infections and maternal systemic infections involving matrix metalloproteinases in the biological pathway. Intrauterine infections and inflammation, as well as lower genital tract infections increase proinflammatory cytokine and prostaglandin cascades to cause preterm delivery through the weakening of the chorioamnion and ripening the cervix by activation of metalloproteases. Stress may induce preterm delivery by maternal-fetal hypothalamo-pituitary-adrenocortical axis leading to a cascade of increased cortisol levels, prostaglandins and metalloproteases resulting in a weakening of the chorioamnion and the start of cervical ripening. Other causes of preterm delivery are claimed to be uteroplacental thrombosis, and intrauterine vascular lesions associated with fetal stress or decidual hemorrhage, uterine over distension (in multifetal gestation and in polyhydramnios), and cervical insufficiency [20, 21].

In certain ethnic groups, preterm birth is more common, possibly due to environmental or socioeconomic factors, but perhaps also due to a genetical predisposition. For example, in American and British reports, women defined as African-American, Afro-Caribbean or black are more likely to give preterm birth [22]. Other risk factors are infections, maternal characteristics (age: low and high), reproductive history (previously induced abortions, spontaneous abortions, short interpregnancy interval), low socio-economic position, multiple-pregnancies, smoking and alcohol and substance abuse [20].

2.3 MORTALITY

Mortality rates for preterm infants increase with decreasing gestational age and are higher both during the first 28 days, and during the first year of life, compared with term infants [1, 23, 24]. As a result of advancements in obstetric and neonatal intensive care, the gestational age specific mortality has declined substantially during the last 20–30 years [25]. The Swedish EXPRESS-study demonstrates that 70 % of all live born infants born 2004–2007 at < 27 gestational weeks survived until 1 year of age [24].

There are great variations in infant's mortality rates between different regions. In 2008, there were 107 000 births in Sweden, and the infant mortality rate (under 1 year) was 2 per 1000 live births, which puts Sweden among the countries with the lowest infant mortality rates in the world together with Iceland, Lichtenstein, Luxembourg and Singapore [26]. Methodological factors are contributing to the differences in reported survival. Since so many infants born at < 24 gestational weeks die, classifying them as live births and not stillbirths may increase the infant mortality rate. The manner in which gestational age, live birth and fetal death are reported and recorded influence the international comparisons of preterm infant mortality rates [27]. Levels of perinatal care are divided into level I, II and III. An important factor contributing to lower preterm infant mortality rates are access to neonatal intensive care. Regionalized care where the mother is transferred to a center before delivery has contributed to lower infant mortality rates [28].

2.4 SHORT-TERM COMPLICATIONS

Immaturity at birth has life-long impact on various organ systems. Some of the major biological pathways behind preterm birth (inflammation, vascular mechanisms and neuroendocrine stress responses) have been suggested to play an important role in the genesis of the most important complications of prematurity, such as retinopathy of prematurity (ROP), white matter brain injury, Bronchopulmonary Dysplasia (BPD) and Necrotising Enterocolitis (NEC). Both more randomized controlled trials for new therapies and long-term follow-up studies have been called for [29].

2.4.1 Respiratory system

Towards the end of the second trimester, gas exchange is possible as a result of conducting bronchioles and capillary network having been developed. From gestational week 24 and onward until term, the alveoli and their capillary networks are developing continuously. In the type II cells of the alveoli, the surface tension decreasing factor *surfactant* is being produced.

The total lung volume is under dramatic change during the last trimester, and preterm birth during this phase may substantially alter lung function and physiology [9]. At 30 and 34 weeks of gestation, the lung volume has been calculated to be 34 % and 47 %, respectively, of the volume of a term infant. At 36 gestational weeks, the alveoli are more or less fully developed, but lung growth and development continues during until 8 years of age [30].

The norm for lung development is the hypoxic intrauterine environment. Preterm birth causes a shift to a comparatively hyperoxic atmospheric environment, which may play a role in chronic lung dysfunction. Reduced airway function at one year of age, in the absence of neonatal respiratory disease, has been demonstrated in infants born after 29–36 weeks of gestation [31]. One result of altered lung development in preterm infants is their increased vulnerability to Respiratory Syncytical virus (RSV) infection.

To induce maturity of the lung, antenatal steroids are, according to standard recommendations, given before 33 complete gestational weeks. However, according to a recent Swedish study about 60 % receive steroids in gestational week 32, and almost 40 % receive it in week 33 [10]. The steroids increase the surfactant production and reduce respiratory distress syndrome with some 50 %. Also, the risks of developing necrotising enterocolitis and intraventricular hemorrhage are decreased after this treatment [32].

2.4.1.1 Respiratory distress syndrome (RDS)

Respiratory distress syndrome is associated with surfactant deficiency and the incidence increases with decreasing gestational age. Antenatal steroids have led to a reduction in severity and incidence. Clinically, RDS-infants present with dyspnea, grunting and poor colour soon after birth. Stiff lungs requiring high pressures for ventilation results in fatigue, apnea, hypoxia or air leakage and eventually respiratory failure. RDS is a common cause of mechanical ventilation. Administration of exogenous surfactant through an endotracheal tube reduces mortality by 40 % and the risk of chronic lung disease, although long-term respiratory effects are less certain [33, 34].

2.4.1.2 Bronchopulmonary Dysplasia/Chronic Lung Disease of prematurity

Bronchopulmonary dysplasia (BPD) and Chronic Lung disease (CLD) sometimes follow RDS, and is the most severe lung disease following preterm birth. The lungs are then to a varying extent scarred, inflamed, stiff, and non-compliant. Most infants suffering from

BPD are born before 28–30 weeks. The most common definition of having severe BPD/CLD is requiring at least 30 % oxygen supplement at a time corresponding with 36 weeks of gestation [35]. BPD plays a role in increasing the risk of severe infections especially RSV infection, reactive airways (asthma), adverse neurodevelopmental outcome and poor growth in childhood [36].

2.4.1.3 Apnea

Apneas are common in preterms, especially those born after < 28 weeks. With higher maturity, the apneas of prematurity usually disappear but may recur for example during RSV-infection later in infancy. It is generally not believed that apnea of prematurity plays a role in Sudden Infant Death Syndrome although preterm birth is associated with a higher risk for Sudden Infant Death Syndrome [37].

2.4.2 Gastrointestinal system

Feeding difficulties and inability to handle large amounts of food needed for growth is common in preterm infants. The most critical gastrointestinal complication of prematurity is *necrotising enterocolitis (NEC)* including inflammation and sometimes perforation of the bowel, resulting in peritonitis and sepsis. Clinically, these infants present with swelling of the abdomen, hypotension and feeding intolerance. Treatment is antibiotics, feeding stop and sometimes surgery. Total parental nutrition is necessary during the critical illness.

Gastroesophageal reflux is common in term as well as preterm infants and presents as regurgitation of stomach content. It is manifested as wheezing, aspiration pneumonia and risk of worsening of BPD/CLD.

2.4.3 Infections and immune system

A large amount of data implies an association between maternal subclinical infection and preterm birth. Maternal infections and subsequent inflammation in the fetus have in turn been linked to white matter injury and neurodevelopmental disabilities [38, 39].

In the uterus, antibodies of the mother are protecting the fetus starting at 20 weeks of gestation, but mainly the transfer of these antibodies takes place as late as during the third trimester, resulting in a particularly immature immune system in the infants born preterm. As a consequence, infections from bacteria of low virulence and fungi in the neonatal period are a substantial clinical problem.

It seems that the complex interplay between pathogens, cytokine system, stress, neuroendocrine system, multiple gene-environment interactions have long-term consequences for survival, health, cerebral damage and neurodevelopmental outcome of preterm infants [40].

2.4.4 Cardiovascular system

There is often a delay in the transition from fetal circulation in the preterm infants, resulting in a persistent ductus arteriosus (right-to-left shunting from the pulmonary artery to the aorta in fetal life). After birth, when the vascular resistance decreases, the duct will shunt left to right if it remains open, which is quite common. A patent ductus arteriosus may be asymptomatic and close within the first week of life, or result in inadequate systematic circulatory output. It can lead to complications, and increase the risk for *intraventricular hemorrhage* (IVH), NEC, BPD/CLD and death [41]. Closing the ductus has

not been convincingly demonstrated to lower the rates of mortality and morbidity including BPD/CLD, NEC or neurodevelopmental disability [42].

2.4.5 Retinopathy of prematurity (ROP)

Retinopathy of prematurity is a neovascular retinal disorder whose incidence increases with decreasing gestational age. The causes are multifactorial but immaturity is a primary determinant. Hypoxia, blood pressure instability, sepsis and acidosis are environmental risk factors. Visual impairments are associated with severe ROP but timely diagnosis and treatment (laser therapy) improve visual outcome [43].

2.4.6 Central nervous system

The central nervous system (CNS) develops as a result of the interplay between programmed genetic and intercellular processes and intrauterine/extra uterine environment. Between the 3rd and 5th month of gestation the neuronal migration to their final destination in a particular brain layer occur. From gestational week 25 until 3 years from term, and probably longer, the synapses form as axons grow out and connects to dendrites. Different kinds of learning and sensory input determine which circuits are given added strength, while unused circuits turn weaker. Beginning at 6 months of gestation and continuing throughout childhood, the neurons are being covered by a lipid sheath, the so called myelinisation process [44].

2.4.6.1 Germinal matrix hemorrhage, intraventricular hemorrhage and, infarction of brain tissue

The white matter around the ventricles and the highly vascular germinal matrix eminence are susceptible to injury, especially in very/extremely preterm infants [45]. These infants are at risk of developing brain hemorrhages, particularly during the first week of postnatal life. The most common type, germinal matrix hemorrhage, starts in the above mentioned highly vascularised germinal matrix below the lateral ventricles. The germinal matrix is a neuronal growth zone which recesses during the middle of pregnancy. The group germinal matrix hemorrhages include the periventricular hemorrhages and intraventricular hemorrhage (hemorrhages resulting in blood being collected in the ventricles). The most severe form of "hemorrhage" is actually an infarction resulting in hemorrhage in the (periventricular) brain tissue, often said to take place in the "watershed zones" between the end-arteries [46, 47].

Hypotension, hypertension, fluctuating blood pressures, poor autoregulation of cerebral blood flow, disturbances in coagulation, hyperosmolarity, and injury to the vascular endothelium by oxygen free radicals are the major contributors to the development of brain hemorrhages in the preterm infant. More severe brain hemorrhages can result in ventricular dilation and if the flow of cerebrospinal fluid is obstructed, posthemorragic hydrocephalus.

Cerebral hemorrhages with ventricular dilation, infarction of brain tissue or posthemorragic hydrocephalus have an increased risk of neurodevelopmental disability [48-50].

2.4.6.2 White matter injury and periventricular leukomalacies (PVL)

White matter injury labels an injury in the white matter which, above all, affects preterm infants. More and more, the concept of white matter injury is used instead of PVL since PVL originally meant cystic fluid filled spaces in the white matter. The concept of white

matter injury include focal cystic necrotic lesions (also called periventricular leukomalacies), ventricular dilatation with irregular ventricular edges, cerebral atrophy, extensive and bilateral white matter lesions. The preterm infants are vulnerable to white matter injuries due to circulation imbalance, ischemia, hypoxia, the sensitivity of the preoligodendrocytes to injury, and infection/inflammation [51]. In turn, a relationship between clinical chorioamnionitis, PVL and cerebral palsy has been found in preterms according to a meta-analysis [51].

Children with cystic PVL are at considerable risk for neurodevelopmental disabilities including cerebral palsy (CP). Holling and Leviton demonstrated that the risk is over 90 % with extensive bilateral cystic PVL [52]. The more focal unilateral PVL tend to lead to milder motor impairment [23]. Magnetic resonance imaging (MRI) studies have correlated thinner cortical regions at term (especially sensorimotor regions in both white and grey matter) to later cognitive and neuromotor impairments [53].

In fact, the brain injury which is the most dominant among VLBW-infants, has been suggested to be *encephalopathy of prematurity* (e.g. periventricular leukomalacies combined with axonal/neuronal damage). It has been described as a complex combination of primary destructive disease and deficits in the secondary maturational and trophic processes [45]. The mechanisms behind this combination of brain injuries are maturational dependent ischemia, inflammation, excitotoxicity and free radical attacks [54]. The main target cells in diffuse PVL are the preoligodendrocytes, resulting in incomplete myelinisation and slower axonal signal speed [47].

In MR-studies, there are correlations between typical radiological characteristics of encephalopathy of prematurity and clinical/cognitive outcomes which persisting into adolescence among very and extremely preterm/low birth weight infants [55, 56].

2.5 LONG-TERM OUTCOMES OF PRETERM BIRTH – WHAT DO WE KNOW?

A considerable number of cohorts of former patients from Neonatal Intensive Care Units (NICU's) have been created and followed prospectively over time [57]. At school age, 10–12 % have been described to have considerable impairment because of a neurological disability [39, 58], but a much larger group of children born very preterm or with very low birth weight show low cognitive test scores, poor school performance and an increased risk of behavior disturbances, including Attention-Deficit/Hyperactivity Disorder (ADHD) [59-62].

2.5.1 Motor disability

Among children with CP (*cerebral palsy*), 20–25 % are born preterm [63]. Preterm infants are at increased risk for all types of CP but spastic diplegia is the most frequent [64]. The rate of CP in a Swedish study of infants born after 23–27 weeks of gestation was in all 7 % (ranging from 14 % in those born after 23–24 gestational weeks, 10 % in those born after 25–27 gestational weeks and 3 % in those born after 27 gestational weeks) [65].

A quite recent analysis of CP in neonates with a very low birth weight in 16 different European cities demonstrates decreasing rates in 1996 compared to 1980, despite higher survival rates of infants with very low birth weight in 1996 [66]. The lower rate of CP was particularly noted among children born in week 29–32, while the rate remained quite similar over time in children with a gestation of 24–28 weeks. Swedish studies have demonstrated a similar pattern of improvement [67].

Even those preterm children without CP and with normal intelligence are at risk for mild neuromotor problems [68]. This often involves coordination difficulties and motor planning problems [69]. As subtle as these difficulties may be, they can, in a life-course perspective, influence the child's self-esteem and peer relationships, contributing to less favorable outcomes in the educational system and in social relationships. Supporting the development of these individuals may be a key in preventing adverse secondary consequences [70].

2.5.2 Cognitive difficulties and school situation

Even though preterm infants comprise a minor part of children with mental retardation, several studies note decreasing mean cognitive test scores and poor school performance with decreasing gestational age at birth [60-62, 71, 72]. Marlowe et al. demonstrated that 21 % of extremely preterm infants born at less than 26 weeks had an IQ of 2 or more standard deviations (SD's) below test mean, while 25 % had borderline intelligence (i.e. IQ 1–2 SD's below test mean) [73]. A follow-up at 20 years of age demonstrated a slightly lower IQ at 20 years of age and a persistent educational disadvantage in preterm with a birth weight below 1500 g [74], although a majority seem to have overcome earlier difficulties at the age of 22–25 years [75].

Notably, more mature preterms have also been shown to have an increased risk for mental retardation (infants born at 32–36 weeks of gestation had a 1.4 times increased risk of mental retardation in a Norwegian study compared with term infants [76].

As expected, the cognitive difficulties of the preterm infants reflect their school results. In a Dutch study from 2004 where 484 infants born before 32 gestational weeks were followed-up into adolescence, less than 50 % were claimed to perform normally in school [77], and a meta-analysis from 2002 demonstrates that preterms had more than a doubled risk of developing ADHD than full terms [60].

Preterm birth has been particularly associated with difficulties in the areas of arithmetic and reading [58, 60, 78]. Many studies have reported that school problems increase with decreasing gestational age at birth.

2.5.3 ADHD (Attention-Deficit-Hyperactivity Disorder)

Defining behavior and socio-emotional problems is challenging, and the majority of studies in this field rely on surveys of parents and teachers. ADHD is the most common neurodevelopmental disorder in Western countries [79], with a prevalence of 3–5 % in Swedish school children [17]. Several studies have indicated that attention problems are more common in children born preterm. In previous Swedish studies Farooqi et al. found that 11-year-old children born after 23–25 gestational weeks three to four times more often had attention problems compared with term infants [80], while Stjernqvist et al., in their study of Swedish 10-year-old children born after less than 29 weeks, found a more modest twofold increase [62]. A recent French study of 1102 5-year-old children, born after 22–32 gestational weeks, similarly demonstrated a twofold increase of risk for hyperactivity/inattention problems compared with term controls [81].

Follow-up studies of ADHD in children born preterm have, with very few exceptions, focused on children born extremely preterm and cared for in neonatal intensive units [60]. Studies including the moderately preterm have, however, indicated that this much larger

group of infants are also at risk for negative outcomes in school age and young adulthood [82-84] including ADHD [59].

2.5.4 Other psychiatric problems and alcohol and substance abuse

Some psychiatric symptoms, especially depression and anxiety, have been reported to occur more frequently among children with very low birth weight and children born very preterm than in children born at term [62, 85, 86]. However, there has previously been sparse evidence of a higher incidence of severe psychiatric disorders [87], although one exception seems to be schizophrenia, where preterm birth is one of several pregnancy/perinatal established risk factors [88].

A lower intellectual performance in general increases the risk of adult psychopathology like early-onset psychosis [89]. Low cognitive competence also predicts important future aspects of life, such as quality of peer relations and poor school performance, which in turn increase the risk of worse mental health outcome [90-92], illustrating the importance of applying a life course perspective when evaluating the consequences of an early event like premature birth.

However, an association between preterm birth and autism is not clearly established. There is evidence for a positive association [85, 93, 94] but also studies concluding a lack of association [95, 96].

Social skill deficits and shyness and withdrawn behavior have been described as more common in the preterm group [60, 97]. Nadeau et al. found that individuals born before 29 weeks were victims of bullying more often than their full term peers [98].

Most previous studies indicate less *risk-taking behavior* such as lower rates of alcohol drinking and illicit drug usage in ex-preterms as young adults [74, 99].

2.5.5 Long-term respiratory consequences

There is substantial evidence of an association between preterm birth and respiratory morbidity later in life [100]. Preterm children are born with underdeveloped lungs, decreased number of alveoli and an impaired respiratory function [101]. This contributes to an increased risk of asthma and bronchitis, especially during infancy [100]. Respiratory disease is particularly common among preterm children who develop bronchopulmonary dysplasia [102].

Some studies have demonstrated impaired airway function in general up to early adulthood. Only two previous studies have assessed the effects on asthma of moderately preterm (34–36 weeks) [103] or early term birth (36–38 weeks) [104] in children up to the age of six years. A recent Swedish national cohort study found a more than doubled risk for asthma medication in young adulthood for individuals born after 23–27 weeks of gestation, but no association between preterm birth and asthma medication in individuals with higher gestational age at birth [105].

2.5.6 Moderately preterm infants

Due to their large number, the moderately preterm infants imply a greater public health problem than the groups with lower gestational ages at birth. In research and development, there has been a strong focus on preterm infants with < 30 gestational weeks at birth.

Lately important evidence suggests that the perinatal complications, although less common than in extremely preterm infants, are a considerable problem also in the group with 30–36 gestational weeks at birth, although more research has been called for [106-108]. The neonatal morbidity risks in this group include poor feeding, hypoglycaemia, respiratory distress, jaundice and infection [7, 8, 10, 11]. The more mature group of preterm infants born after 30 gestational weeks has lately been the focus of interest for a number of perinatal epidemiologists around the world [5, 8, 10, 11, 109]. Altman et al. investigated the situation in Sweden for infants born after 30–34 weeks regarding short term morbidity.

Table 2. Neonatal morbidity in Swedish infants born at 30–34 gestational weeks, modified after Altman et al. [10].

Short term morbidity	Gestational age: 30–34 weeks
Acute lung disorder	28 %
Bacterial infection	15 %
Hypoglycemia	16 %
Hyperbilirubinemia	59 %

Even though the moderately/late preterm infants have lower morbidity rates than very and extremely preterm infants in childhood, they have early neurodevelopmental, school-related and other health problems which are considerable [12, 109-111]. Huddy et al. demonstrated that up to third of 7-year-olds born after 32 to 35 weeks of gestation had problems in school [112].

Hagberg et al. demonstrated that children born 1987–2000 between 32 and 36 weeks of gestation constitute less than 10 % of all births but account for 18 % of the children with CP [113]. Lately, indications of increased long-term vulnerability of early term (37–38 gestational weeks) infants have also been acknowledged [114].

2.6 METHODOLOGICAL CONCERNS

A number of methodological issues have to be taken into account when comparing different long-term follow-ups of preterm infants.

The study populations are often heterogeneous and many are embossed with high attrition rates, selection bias, self-report data versus register data, results reported by birth weight groups versus gestational age groups, different length of follow-up and varying methods of assessment [1]. The drop-outs are often afflicted with less favorable outcomes stressing the importance of documenting this group carefully to avoid falsely optimistic results in the follow-up studies [115].

Birth weight has often been used instead of gestational age in studies of preterm infants. This results in a heterogeneity problem since infants born Small for Gestational Age (SGA) and preterm infants will be pooled together. Since these groups differ in the pathological mechanisms resulting in the morbidity, it is important to keep this problem in mind in comparisons of follow-up studies [59, 116]. Furthermore, the SGA-group includes both the intrauterine growth restricted infants, which have a certain morbidity profile, but also the constitutionally small infants, a fact that is necessary to consider. Another concern is that SGA-infants and girls may get an ultrasound measured gestational age shorter than their actual gestational age (*Misclassification in the estimation of gestational age*, see also section 6.1.3) [117].

3 OBJECTIVES

In this thesis, the general objective was to investigate the long-term impact of all degrees of preterm birth on social adjustment and health.

Specific aims:

1. To determine how all degrees of preterm birth influence the health, social adjustment and level of education at 23–29 years of age (Paper I).

2. To determine how all degrees of preterm birth influence the risk for psychiatric and addictive hospital admissions at 8–29 years of age (Paper II).

3. To determine how all degrees of preterm birth influence the risk for ADHD medication, as a proxy for ADHD, at 6–19 years of age (Paper III).

4. To determine how all degrees of preterm birth influence the risk for inhaled corticosteroid medication, as a proxy for asthma, at 6–19 years of age (Paper IV).

5. To determine if socio-economic factors influence the effect of preterm birth on long-term outcomes (Papers I–IV).

4 MATERIAL AND METHODS

The studies in this thesis are based on national register information held by the *National Board of Health and Welfare* and *Statistics Sweden* (Swedish: *Socialstyrelsen* and *Statistiska centralbyrån*, respectively). The information about the study populations is linked through every individual's unique Personal Identification Number (PIN).

Setting
The four studies of this thesis were performed in Sweden where the conditions to do well-designed epidemiological investigations are favorable, particularly as a result of the national population-based registers, which can be linked through every individual's PIN [118]. The Swedish health care system is almost exclusively financed by taxes. The public medical service is divided into 20 administratively independent county councils (Swedish: "landsting") [119].

The study populations of the four cohort studies of this thesis were defined in the Swedish Medical Birth Register. The Swedish national registers provide prospectively collected information which is a major advantage since information bias, such as different kinds of recall bias, can be avoided. In fact, a great deal of the Swedish epidemiological research relies on the national registers held by the two national agencies The National Board of Health and Welfare and Statistics Sweden.

4.1 DATA SOURCES AND USAGE OF NATIONAL REGISTER INFORMATION IN SWEDEN

The National Board of Health and Welfare
The National Board of Health and welfare is a national agency under the Ministry of Health and Social Affairs. The agency administers several registers in order to analyze and follow the development in the health care and social service.

Statistics Sweden
Statistics Sweden is a national agency producing statistics for decision making, debate and research. They are also tasked to support and coordinate the Swedish system for official statistics as well as participating in international statistical co-operations.

THE NATIONAL REGISTERS

Regulations of the national registers
The use of health database registers is strictly regulated in Swedish law. When used in research, data are anonymised. Before start, each research project in Sweden based on register data needs approval from an ethical committee, one of whose tasks is to make sure that the personal integrity of the subjects under study will be sufficiently protected.

The Swedish Personal Identification Number (PIN)
The establishment of the kind of registers used in this thesis requires a possibility to uniquely identify each individual over time, independently of variable circumstances, such as home address. In Sweden, the Personal Identification Number (PIN), introduced in 1947, to serves as an identifier in the health care system and other areas of the Swedish society. The PIN contains ten digits. The first six indicate date of birth, and four following digits, one of which distinguishes males from females, make the number unique for each

individual. The possibility to link individual information from various data sources makes the PIN a key variable in all large register studies in Sweden [118].

Swedish Medical Birth Register (SMBR)
The SMBR started in 1973 and includes close to all pregnancies resulting in a delivery in Sweden [120]. The register includes all live born and stillborn infants after 22 complete gestational weeks. Note that the gestational age limit was changed on June 30th 2008. Before this date intrauterine fetal death was defined as delivery of a dead fetus with a gestational age of at least 28 complete weeks (see also page 2) [16]. The register includes information about maternal characteristics before and during pregnancy, delivery and the characteristics and care of the newborn infant. It is mandatory for all delivery clinics in Sweden to submit information to the register.

An evaluation of the SMBR, done by Cnattingius et al. in 1990, reported that, although there are problems of validity of diagnoses and in the information on uncommon medical events the quality of "hard" data such as perinatal survival and birth-weight distribution is fairly good [121]. The National Board of Health and Welfare summarized content and quality of the SMBR in a research report from 2003. The report states that only a small proportion (for most years, 1–2 %) of births is missing. The most serious loss of data is related to infant diagnoses [120]. The total attrition for maternity information was 2.6 % in 2008 [16].

Swedish Hospital Discharge Register
The Patient Discharge Register was established in 1964 and includes all hospital discharges in Sweden since 1987. The register includes up to six discharge diagnoses, surgery codes, and duration of hospital stays. The diagnoses are based on the Swedish version of the WHO's international classifications of diseases (ICD). The quality of The Patient Discharge Register was evaluated 2009 by the National Board of Health and Welfare and it was found that, although there are variations between counties and different years, the quality is generally good [122].

Register of Total Population
The Total Population Register is held by Statistics Sweden. It was established in 1968 and contains information about deaths, births, marital status, migration and country of birth for residents born outside Sweden [123].

Multi-generation Register
The Multi-generation Register is also held by Statistics Sweden since 2000 and uses available register data on the total Swedish population. All born 1932 and later and alive in January 1960 (so called index-persons), and their first-degree relatives are included. Through the register, parents, siblings and children to an index-person can be identified [124].

Swedish Prescribed Drug Register
Since July 1st 2005, the Swedish prescribed drug register contains information with unique patient identifiers for all pharmaceuticals and provisions prescribed and dispensed to the whole Swedish population. The register may be used for epidemiological investigations, research and statistical summaries [125].

Register of Societal Economical Assistance
The register of societal economical assistance was established in 1985. Since 1994, it is held by the National Board of Health and Welfare. The register contains information on

households having received economical assistance as well as refugee-households having received introductory support after arrival in Sweden. The register provides basic information for research and general societal information [126].

The register over interventions in accordance with the law about support and service for some disabled people (LSS)
The register exists since 2004 when statistics on LSS (Swedish: "Lagen om stöd och service till vissa funktionshindrade") became a part of the official statistics in Sweden. The purpose of the register is to inform about the extent of interventions to disabled people in accordance with the law on support and service for some disabled people (for example personal assistance) [127].

The National Cause-of-Death Register
Since 1749, cause-of-death statistics are collected in Sweden. The register is among the oldest of its kind in the world. The present Cause-of-Death-register, held by The National Swedish Board of Health and Welfare, started in1961, and contains all Swedish residents at time of death in Sweden regardless of citizenship. It is annually updated. According to the instructions by the WHO in the *International classifications of diseases* (ICD), the underlying cause of death is reported. The register provides the basis for the official mortality statistics in Sweden. The register includes the underlying cause of death, contributing cause of death, injury to the body/poisoning and the basis of the cause-of-death information [128].

A comparison of Swedish hospital discharge records and the death certificates showed that there is no apparent reason to question the death certificate if the main diagnosis and underlying cause agree, or if the main diagnosis is a probable complication of the stated underlying cause [129]. The quality of death certificates are challenged when multiple causes of death are common [130] but this seems to be a minor problem for the outcome suicide, relevant in this thesis.

Population and Housing Census
Using postal inquiries Statistics Sweden, in 1990, collected information on individuals and families. All residents aged 16, or older, were obliged to participate in the census, including characteristics about socio-economy (educational level, occupation, residency and housing) and with a response rate of 97.5 % [131].

In this thesis the socio-economic status (SES) of the household, housing situation, maternal country of birth and lone parent households were identified in the Swedish Population and Housing Census of 1985 and 1990. Socio-economic groups were defined according to a classification created by Statistics Sweden. The classification is based on occupation, but also takes the level of education, type of production and position at work of the head of the household into consideration [132].

Total Enumeration Survey
The total enumeration survey is held by Statistics Sweden. The income statistics contain information on income, taxes and social economical assistance. The register contains all registered residents in Sweden and includes information on income from employment, pension, sickness assistance and taxes paid [133].

Swedish Educational Register
The Swedish register of education is annually updated since its start in 1985. It is held by Statistics Sweden. It contains information on highest completed education for people

registered as living in Sweden and being 16–74 years of age per January 1st every year. The coverage is high, about 98 % in 2007 [134].

Table 3 (page 1 of 3). Register variables in the thesis.

Variables		National Register	Definitions
Outcome	Employment in November 2002	Total Enumeration Income survey of 2002	Indicating having an income from employment or own firm in November 2002.
	Education	Swedish Educational Register	As indicated by highest completed education as of December 2002. Education was categorised as < 9 years, Basic (9y), 10–11 y, 12–13 y and Postsecondary (≥ 14 y).
	Married	Total Enumeration Income Survey of 2002	Married November 2002.
	Lives with parents	Total Enumeration Income Survey of 2002	Residence in the household of the biological parents in 2002.
	Student in 2002	Total Enumeration Income Survey of 2002	As indicated by having received student support or loan.
	Social welfare in 2002 > 6 months	The Swedish Social Assistance Register	Indicating having received social assistance > 6 months during 2002.
	Sick allowance	Total Enumeration Income Survey of 2002	Indicating temporary economic support during at least 2 consecutive weeks because of illness from the national health insurance.
	Handicap allowance	Total Enumeration Income Survey of 2002	Indicating a permanent disability.
	Disability assistance	National Social Insurance Board	Indicating the need for a personal helper at least 4 hours daily during 2002.
	Sickness pension	Total Enumeration Income Survey of 2002	Indicating lifelong pension because of long-standing illness or disability.
	Net salary	Total Enumeration Income Survey of 2002	Indicating net income from employment and own firm.
	Disposable income	Total Enumeration Income Survey of 2002	Indicating the sum of all incomes including societal benefits, deducted by income tax.
	Net transfer to society	Total Enumeration Income Survey of 2002	As indicated by deducting disposable income from work income.
	Psychiatric Disorder	Swedish Hospital Discharge Register	As indicated by main or contributory discharge diagnosis found in the whole psychiatric chapter in International Classification of Diseases, Ninth Edition (ICD-9) with the exclusion of alcohol and drug-related diagnoses (a main or contributory diagnosis of 290–319 with the exclusion of 291,292, 202, 204, and 305A). The same principle was applied in the Tenth Edition of ICD (ICD-10) (a main or contributory diagnosis of F00 with the exclusion of 291, 292, 303, 304, 305A, and F10–F19).
	Psychotic disorders	Swedish Hospital Discharge Register	Main or contributory diagnosis of 295, 297, or 298 (ICD-9) in 1991–1996 and F20–F29 (ICD-10) in 1997–2002.
	Organic/ neuro-psychiatric disorders	Swedish Hospital Discharge Register	Main or contributory diagnosis of 290, 293, 294,299, 300C, 310, 314 to 315, or 317, to 319 (ICD-9) in 1991–1996 and F01 to F07, F09, F42, F70 to F89, F90 and F95 (ICD-10) in 1997–2002.
	Stress-related disorders	Swedish Hospital Discharge Register	Main or contributory diagnosis of 306, 308, or 309 (ICD-9) in 1991–1996 and F43 or F59 (ICD-10) in 1997–2002.
	Mood disorders	Swedish Hospital Discharge Register	Main or contributory diagnosis of 296, 300D, or 311 in 1991–1996 and F30 to F39 (ICD–10).
	Suicide death/suicide attempt	Swedish Hospital Discharge Register/Cause-of-death-register	An underlying cause of death (suicide death) or external cause diagnosis (suicide attempt) of E850 to E859 or E880 to E889 (ICD-9) in 1990–1996 and X60 to X84 and Y10 to Y34 (ICD-10) in 1997–2002.

Table 3, continued (page 2 out of 3).

Variables		National Register	Definitions
	Addictive Disorder	Swedish Hospital Discharge Register	Main or contributory diagnosis of 292, 304, 965.0, 968.5, 969.6, 969.7, 303,305.0, 357.5, 425.5, 535.3, 571.0–571.3, E860, E980 + 980 or 291 (ICD-9) during 1991–1996 and F11, F12, F14, F16, F19, F10, K70, G621, I426, or K294 (ICD-10) during 1997–2002.
	Addictive disorder with psychiatric disorder	Swedish Hospital Discharge Register	Main or contributory diagnosis of an addictive disorder as well as a psychiatric diagnosis according to the definitions above.
	Addictive disorder without psychiatric disorder	Swedish Hospital Discharge Register	Main or contributory diagnosis of an addictive disorder without a psychiatric disorder according to the definitions above.
	ADHD-medication 2006	Swedish Prescribed Drug Register	At least one purchase of prescription during 2006 of drugs with ATC-codes: NO6BA01–NO6BA04 or NO6BA01.
	Any asthma-medication 2006	Swedish Prescribed Drug Register	At least one purchase of a prescribed drug with an ATC-code starting with R03 in 2006.
	Inhaled corticosteroids (ICS) 2006	Swedish Prescribed Drug Register	At least one purchase of a prescribed drug with an ATC-code starting with ATC-codes of R03AK or R03BA in 2006.
Maternal/ paternal asthma	Asthma/inhaled corticosteroids (ICS)	Swedish Prescribed Drug Register	At least one purchase of a prescribed drug with an ATC-code starting with an ATC-code starting with R03 in 2006.
Perinatal Indicators	Gestational age	Swedish Medical Birth Register	Papers I and II: According to LMP in papers I and II or in some uncertain cases after estimation by attending pediatrician. Papers III and IV: According to ultrasound measures in early pregnancy (w 10–18) in 70.1 % and maternal report of LMP in the remaining.
	SGA (Small for gestational age)	Swedish Medical Birth Register	< –2 SD according to the scale created by Marsal et al. based on intrauterine ultrasound measures.[12]
	Caesarean delivery	Swedish Medical Birth Register	Categorised into yes/no.
	Multiple birth	Swedish Medical Birth Register	Categorised as no if singleton, all others as yes.
	Low Apgar	Swedish Medical Birth Register	Apgar < 7 at 5 min.
	Chorioamnionitis	Swedish Medical Birth Register	Maternal diagnosis at birth of O41.1 (ICD-10).
	Maternal smoking	Swedish Medical Birth Register	Information routinely collected by mid-wife at the first visit to the maternity health clinic after 8–12 weeks gestation. Categorised into No, 1+9 cig/day, 10+ cig/day and Missing.
	Birth weight (g)	Swedish Medical Birth Register	400–999, 1000–1999, 2000–2999, 3000–4999, > 5000.
	Gestation	Swedish Medical Birth Register	Single, Multiple.
	Parity	Swedish Medical Birth Register	Categorised as 1,2,3, ≥ 4 and missing.
	Significant malformation	Swedish Medical Birth Register	All (Q00-Q99 ICD-10) except undescended testicle, preauricular appendage, congenital nevus, and hip dislocation.
	Fetal distress	Swedish Medical Birth Register	Maternal diagnosis at birth of child: O68.3, O68.8 (ICD-10) 7753, 7764, 7765 (ICD8)
	Preeclampsia	Swedish Medical Birth Register	Maternal diagnosis at birth of child: 637.03, 637.04, 637.09, 637.10, 637.99, 762.00 (ICD 8) O14.0, O14.1, O14.1A, O14B, O141X, O14.9 (ICD-10).
Cerebral palsy		Swedish Hospital Discharge Register 1987–2005	At least one discharges with a diagnosis of G.80–G80.9 (ICD-10) after two years of age.

Table 3, continued (page 3 out of 3).

Variables		National Register	Definitions
Respiratory Syncytical Virus		Swedish Hospital Discharge Register 1987-2005	At least one discharge with a diagnosis of J12.1 or J20.5 (ICD-10) before 12 months of age.
Socio-demo-graphic indicators	Housing	Swedish Population and Housing Census 1990	Missing, Owned flat, One-family-house, Rented flat.
	Residence	Total Enumeration Income survey of 1990	Metropolitan area, Other urban area, Rural.
	County of residence	Register of Total Population	Paper III: A four-category county variable was created with different levels of retrieval of purchased ADHD-medication during 2006; high prescription rates (> 0.8 %), high average prescription rates (0.7–0.8 %), low average prescription rates (0.5–0.6 %) and low prescription rates (< 0.5 %). Paper IV: A four-category county variable with different levels of retrieval of purchased ICS medication during 2006 was created; 5.0–5.7 %, 4.6–4.9 %, 4.0–4.5 % and 3.5–3.9 %.
	Household Socioeconomic status (SES), 1990	Swedish Population and Housing Census 1990	Manual workers, Skilled workers, white collar 1–3, Unclassified (farmers self-employed, unemployed).
	Maternal education	Swedish National Education Register	Highest formal education attained by each individual up to 2005. If the mother was no longer a Swedish resident we replaced with paternal education if possible. Categorised by years of education into ≤ 9 years, 10–12 years, 13–14 years, 15+ and Missing.
	Age of mother at birth of first child	Swedish Medical Birth Register	Categorised in years into 12–24, 25–34, ≥ 35 and Missing.
	Teenage motherhood	Swedish Medical Birth Register	Mother aged < 20 at birth of first child.
	Maternal age	Swedish Medical Birth Register	Categorized in years into 12–19, 20–24, 25–29, 30–34, 35–39, 40+ and Missing.
	Maternal country of birth	Register of Total Population	Categorized as: Sweden, Eastern Europe, Western Europe, Outside Europe, Europe, Missing/unknown.
	Single parent household	Swedish Population and Housing Census 1990 (Papers I,II) and 2005 (Papers III, IV)	Household with only one adult.
	Social assistance	Social Assistance Register 1990 (Papers I, II) and 2005 (Papers III,IV)	Cash income allowance from local social authorities after a thorough means investigation with the purpose to guarantee the applicant a minimum standard of living.

4.2 GENERAL INTRODUCTORY COMMENTS ON THE METHODS

The variables used in this thesis and their register sources are specified in Table 3. An overview of the study design of the thesis is given in Figure 1 in this section.

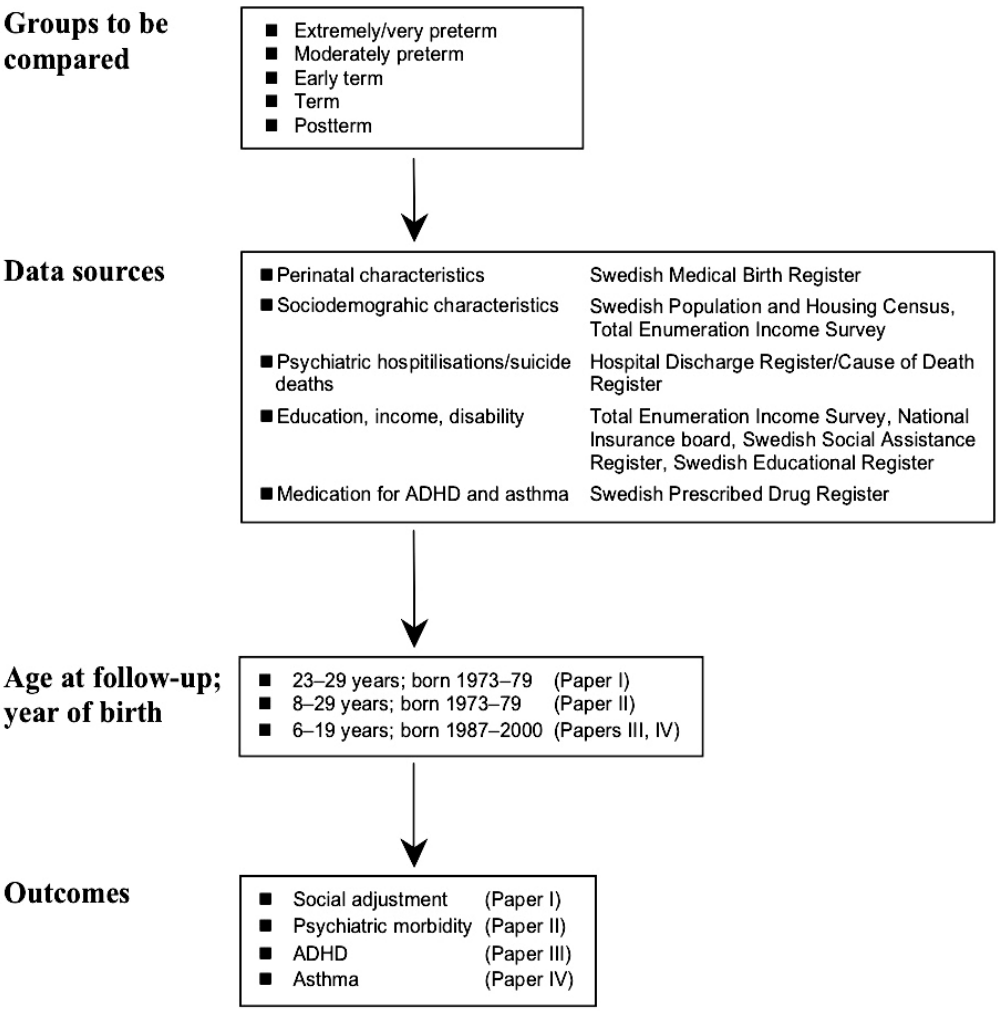
Ultrasound assessment of gestational age became widespread in Sweden around 1990 [135]. Accordingly, in papers I and II (infants born 1973–79) the gestational ages are in most cases estimated by using LMP, and in an unknown proportion, corrected by the pediatrician's estimation of maturity after delivery. During the first week of postnatal life, such a maturity assessment, was performed probably mostly in uncertain cases by the pediatrician. The generally recognized method for maturity assessments was brought about by Finnström 1977 (including examination and scoring of breast size, nipple formation, skin opacity, scalp hair, ear cartilage, finger nails, plantar skin creases). This assessment has a precision of ±2–3 weeks [136]. Earlier, the method by Dubowitz et al. was used to some extent [137].

In paper III and IV (infants born 1987–2000), the majority (70.1 %) of gestational ages was estimated by ultrasound assessment, which is a more reliable method. The reason for excluding postterm infants in paper I and II is that gestational age estimates by LMP have been demonstrated to be especially unreliable in the post term group of infants [138]. This is less of an issue in papers III and IV since gestational age was, in the majority of cases, estimated by ultrasound in the birth cohorts 1987–2000.

The study populations were all defined in the SMBR. Individuals with at least one reported malformation other than undescended testicle, preauricular appendage, congenital nevus or hip dislocation were excluded (see Table 3) since they were not the focus of this study, and their inclusion could have overestimated the negative outcomes associated with perinatal risk factors, such as preterm birth and SGA.

In paper III, only individuals with a Swedish born mother were included, and in paper IV, only those with two Swedish born parents were included in the study population. The reason for excluding offspring of immigrant mothers from the study population in paper III was that the circumstances in these families could possibly have biased a potential association between preterm birth and medication for ADHD [139]. Offspring of foreign born parents were excluded in paper IV because of the influence of ethnicity on asthma prevalence in Sweden [140].

Figure 1. Thesis study design



4.3 STATISTICAL ANALYSES, PAPERS I–IV

Logistic regression (paper I, III and IV)
Logistic regression is a form of regression which is used when the dependent variable is dichotomous. The associations between the outcome and the independent variables are presented as Odds Ratios (OR's). We used the OR's to approximate the relative risk (RR), which is a good estimate provided that the outcomes are rare (< 10 % in frequency). In Paper I however, where the outcomes were common (> 10 % in frequency), the OR would have overestimated the actual relative risk. For this reason OR's were converted to relative risks (*RR*) using the method of Zhang and Yu [141]:

$$RR = \frac{OR}{(1 - P_0) + (P_0 \cdot OR)}$$

P_0 = incidence of outcome in the non-exposed group

Linear regression (Paper I)
Linear regression describes the association between two variables assuming a linear relationship between the variables. The regression coefficient gives the change in value of the outcome (dependent) per unit change in the exposure (predictor).

Cox regression of proportional hazards (Paper II)
We used Cox regression to study the associations between independent variables and time-to-event outcomes. The associations were presented as Hazard Ratios (HR's).

Conditional logistic regression (Paper III)
Conditional logistic regression is used for dependent data. In the within-mother-interpregnancy sub-study of Paper II, this method was used to compare the effects between different pregnancies in the same mother.

4.4 METHODS, PAPER I

In the SMBR 1973–79, a total of 570 768 individuals with a gestational age of ≤ 41 weeks [120] and alive on December 31st of their year of birth, were identified. To exclude outliers with probable coding errors, only children with a birth weight less than +3 SD and greater than –6 SD, according to the growth chart developed by Marsal et al. [13], were included in the study population. Finally, only those without significant malformations as well as those who were still alive and residents in Sweden on December 31st 2002 were included in the study population (522 310 individuals).

Several social outcome variables were created with information about the situation in 2002 from the Total Enumeration Income Survey that year: (1) *sickness pension*, (2) *handicap allowance*, (3) *employment*, (4) *illness benefits*, (5) *residence in the household of the biological parents*, (7) *student*, (7) *net salary*, (8) *disposable income*, and (9) *net transfer* to society, were identified in the register kept at the National Social Insurance Board.

The number of months that social assistance was received during 2002 was identified in the Swedish Social Assistance Register. The highest completed education as of December 2002 was derived from the Swedish Educational Register. A summarized disability outcome variable was created that indicated the receipt of sickness pension, handicap allowance or disability assistance.

Statistical methods

The effects of very and moderately preterm as well as early term birth on social adjustment (education, employment, disability) were estimated by logistic regression. The effects of preterm/early term birth on income were estimated by linear regression.

Model 1 in the regression analyses was adjusted for sex and age only. Socioeconomic confounders were added as confounders in Model 2. Parental morbidity variables, SGA and multiple births were added to the variables of Model 2 as perinatal mediators/confounders in Model 3.

4.5 METHODS, PAPER II

A total of 573 869 individuals were identified in the SMBR 1973–1979, born after 41 gestational weeks or less. To exclude outliers with probable coding errors, only children with a birth weight less than +3 SD and more than – 6 SD according to the growth chart developed by Marsál et al. [13] were included in the study population. Finally, only those without significant malformations as well as those who were still alive and residents in Sweden on December 31st 1986 were included in the study population (545 628 individuals). The difference (n = 23 318) in study population between paper II and paper I consists of those who died or migrated from Sweden 1986–2002.

Psychiatric/addictive outcomes

Psychiatric and addictive outcome variables for the study population (psychiatric disorders in the children) and indicators of parental morbidity (maternal and paternal psychiatric disorders) were established by individual linkages to the Swedish Hospital Discharge Register 1987–2002 and the Swedish Cause of Death Register 1987–2001. The variables were defined according to the 9th revision of the WHO International Classification of Diagnoses (ICD-9) for 1987–96 and the 10th revision of WHO International Classification of diagnoses (ICD-10) for 1997–2002.

Statistical methods

Multivariate analyses were performed using Cox regression analyses of relative risk in HR's of time-to-event. Data on death, from the National Cause of Death Register, and the date of emigration from the Register of the Total Population, and the date of hospital admission from the Swedish Hospital Discharge Register were used calculating time to event. As the outcome variables tended to increase with age in a linear way, year of birth was entered as a continuous variable in the regression models. Missing data were entered as a separate category in the analysis.

The variables in the Cox regression models were entered in four steps. Models 1 to 3 include confounders, with sex and year of birth only in Model 1, adding socio-economic confounders in Model 2, and in Model 3 also variables representing parental psychiatric morbidity and addictive disorder. In the fourth model, we added perinatal variables (SGA and Apgar < 7 at 5 minutes) as possible mediating variables.

4.6 METHODS, PAPER III

The study population was created from the 1 242 459 children with a Swedish-born mother in the birth cohorts of 1987–2000 who survived infancy, according to the Swedish Medical Birth Register. Only children with a birth weight less than +3 SD and more than –6 SD according to the growth chart developed by Marsál et al. [13] were included in the study population. Also, only those who were Swedish residents in 2005, and born without significant malformations were included in the study population (1 180 616 individuals). They were followed up during the calendar year 2006 at the age 6–19 years.

Socio-demographic and parental morbidity variables were obtained through linkage via the Multi-generation register to the biological mother and father. Information on in-patient care in the Patient Discharge Register was used to create the parental morbidity variables and information on in- as well as out-patient care from the Patient Discharge Register was used to create the cerebral palsy (CP) variable.

ADHD

In this study we used the purchase of at least one prescription of a stimulant (The Swedish Prescribed Drug Register) during the calendar year 2006 as our outcome variable. There were considerable regional differences in the consumption of ADHD medication. Since these differences did not follow any obvious demographical or geographical pattern, we assumed that they mirrored varying prescription patterns in different counties rather than variations in the prevalence of ADHD. We categorized the counties by prescription levels and adjusted for this in the multivariate analysis (see table 3 for details).

Statistical methods

Logistic regression was used to calculate OR's with 95 % confidence intervals (CI's) as estimates of effects, with ADHD medication as the outcome variable.
We used three models to investigate the effects of preterm birth on ADHD medication, where variables were included step-wise, adding confounders in model 2 and perinatal mediators in model 3.

Model 1 included sex, a three-category variable for age (6–9, 10–15, 16–19) and county of residence in four categories according to level of ADHD medication. In Model 2, we added birth order, maternal age, maternal education, single parenthood, public welfare and maternal smoking and maternal and paternal psychiatric/addictive disorder (see Table 3 for definitions) as possible confounders. In the final model 3, we added low Apgar score and being Small for Gestational Age (SGA) as possible perinatal mediators/confounders of preterm birth.

To adjust the analysis influence for potential influence of genetic confounding, we analyzed the within-subjects variation in the subpopulation (N = 34 334) of offspring of mothers who had given birth to preterm as well as full term babies. A Generalized Linear Model with the binomial distribution was used to create a conditional logistic regression (dependent data), where the effects were compared between pregnancies in the same mother. This within-mother-between-pregnancy model, apart from maternal ID, was adjusted for sex and birth order of each child included, age of the mother at the birth of each child included, and age of each child included in 2006.

4.7 METHODS, PAPER IV

The study population was created from the 1 142 806 children born in Sweden 1987–2000 according to the Swedish Medical Birth Register (SMBR). Only individuals who were offspring of two Swedish parents and residents in Sweden on December 31st 2005 were included in the study population. In addition, they had to meet the criteria of having a birth weight less than +3 SD and more than – 6 SD according to the growth chart developed by Marsal et al. [13]. Finally, after including only those without significant malformations,
1 100 826 individuals were left to be included in the study population. Just like in paper III this population was followed up during the calendar year 2006 at the age of 6–19 years.

The two outcome variables were the purchase of at least one prescription of *inhaled corticosteroids* (ICS) and *any asthma medication* during the calendar year 2006 (see Table 3 for definitions).

There were considerable regional differences in the purchase of asthma medications, supposedly reflecting regional differences in prevalence of asthma as well as differences in access to, and prescription patterns, in care. A four-category *county* variable with different levels of retrieval of prescribed ICS was created to adjust the analysis to these regional differences (see table 3).

Statistical analysis
Logistic regression was used to calculate OR's with 95 % confidence intervals (CI's) as estimates of effects, with ICS as defined above as the outcome variable.

We used four models to investigate the effects of preterm birth on ICS. Age was entered as a continuous variable in all models according to the age profile of ICS use. Since this age profile differed between boys and girls, decreasing with higher age in boys and increasing with higher age in girls, we included an interaction term of age*sex in all models.

Model 1 was adjusted for age and sex only. In Model 2, we added county of residence, maternal education, social assistance, maternal and paternal asthma medication and maternal smoking during pregnancy as confounders. Thus, we considered Model 2 as the fully adjusted model. In Models 3 and 4, we investigated potential mediating variables by adding the potential perinatal mediators SGA, chorioamnionitis, multiple birth, asphyxia and caesarean delivery in Model 3 and hospital admission because of RSV-infection in Model 4.

5 RESULTS

5.1 SOCIAL ADJUSTMENT (PAPER I, BIRTH COHORTS 1973–79)

The rate of disability in the entire study population decreased by year of birth from 1.66 % in those born 1973 to 1.46 % in those born 1979, a risk ratio (RR) of 0.97 (95 % CI 0.96–0.98) per year.

Disability, social benefits and sickness allowance
Rates of disability allowance, sickness pension, and disability assistance increased gradually in steps with the degree of preterm birth. However, more than 85 % of even the extremely preterm children (week 24–28) had no such indication of a disability. After adjustment for age and sex in Model 1 in the multivariate analysis, the OR of children born very preterm (week 24–32) was 4.39 (3.79–5.07) for having at least one indication of a disability. Adding socio-economic and perinatal indicators decreased the OR's slightly, to 3.76 (3.14–4.49). Moderately preterm (week 33–36), and early term (week 37–38) had RR's of 1.51 (1.32–1.73) and 1.26 (1.17–1.35), respectively, in the final model. The total attributable risk for disability associated with preterm births was 7.0 %, of which 5.2 % were accounted for by moderately and early term births. Having received social welfare benefits and sickness allowance had a distribution by gestational age that was similar to the disability indicators.

Living with parents
Study subjects born preterm more often resided in the household of their parents than peers of the same sex and age born term: RR's 1.15 (1.05–1.25) , 1.05 (1.01–1.09) and 1.03 (1.01–1.05) for three preterm groups, respectively (not in tables). Adding confounders only marginally changed these estimates.

Income
Of the study population born at term, 74.1 % had an income from employment in November 2002 compared with 68.1 % of those born in week 24–28, 70.1 % in week 29–32 and 72.5 % of those born in week 33–36. When disabled individuals were excluded, however, preterm and term had very similar chances of having an employment.

Very preterm birth was associated with a lower net salary among the employed in a linear regression analysis of income, even after disabled had been excluded and socio-economic and perinatal mediators/confounders had been accounted for. Adults born preterm also had a lower disposable income than adults born term. When the disposable income was subtracted from the net salary a net mean individual transfer of 3 079 € to the society from the individuals born term in the study population was identified in 2002 (Table 5). In a linear regression it was demonstrated that this transfer was 715 € lower ($p = 0.02$) in those born very preterm, and 171 € lower ($P = 0.15$) in the moderately preterm, after socio-economic and perinatal confounders had been accounted for.

Effect modification
The effect of preterm birth on the chance of receiving a university education was greater in families with a low SES compared to high SES ($p = 0.005$). No statistically significant interaction effects for sex were seen.

5.2 PSYCHIATRIC HOSPITAL ADMISSIONS (PAPER II, BIRTH COHORTS 1973–79)

The rate of having been discharged from hospital at least once with a psychiatric (including suicide attempt or death) or an addictive diagnosis was 2.5 % and 1.6 %, respectively, in the entire study population.

Psychiatric diagnoses and addictive diagnoses
Rates of hospital admissions due to psychiatric disorders increased gradually with the degree of preterm birth. There was a considerable overlap between psychiatric and addictive diagnoses, with increased rates of addictive diagnoses in the preterm groups only in the presence of simultaneous psychiatric diagnoses. In a multivariate Cox regression analysis, the HR of children born in gestational week 24–32 was 1.80 (1.52–2.12) for having been hospitalized due to a psychiatric disorder, after adjustment of age and sex only. Adjusting for socioeconomic confounders and parental psychiatric disorders decreased the HR's to 1.66 (1.40–1.97) for psychiatric disorders. Moderately preterm (33–36 weeks' gestational age) and early term (37–38 weeks' gestational age) had HR's of 1.19 (1.10–1.29) and 1.07 (1.02–1.12), respectively, for psychiatric disorders in the corresponding model (model 3).

Diagnostic sub-groups
In an analysis of diagnostic sub-groups, organic/neuro-psychiatric disorders had the highest OR.

Socioeconomic status (SES)
HR's for psychiatric hospital admissions were higher for preterms from low-SES families than for preterms from high-SES families. For individuals with a gestational age of 24–32 weeks in low and high-SES families, the HR were 2.00 and 1.25, respectively, and for individuals with a gestation of 33–36 weeks the corresponding HR were 1.44 and 0.84.

Attributable risk
The attributable risk percentages for psychiatric disorders were 0.5 % for extremely preterm, 1.2 % for moderately preterm and 1.5 % for early term. Moderately preterm and early term birth accounted for 85 % of the risk attributed to preterm/early term birth.

Effect modification
In an interaction analysis, no statistically significant differences between the sexes were seen. However, in an interaction analysis there were statistically significant differences in psychiatric disorders between infants from high- and low-SES families, respectively, in all three groups of preterm/early term: gestational week 24–32 ($p < 0.001$), gestational week 33–36 ($p < 0.001$) and gestational week 37–38 ($p = 0.001$).

5.3 ADHD MEDICATION (PAPER III, BIRTH COHORTS 1987–2000)

In all, 1.1 % of the boys and 0.3 % of the girls had a record of ADHD medication in the register. ADHD medication was more common in the presence of the following variables: teenage mother, single parent, public welfare/social welfare benefits, low maternal education, maternal as well as paternal addictive/psychiatric disorder, low gestational age, SGA, low Apgar score, maternal smoking during pregnancy and CP.

ADHD medication in different gestational age groups

In logistic regression analysis of ADHD medication in Model 1, that was adjusted for age, sex and county of residence, the OR's for ADHD medication were 2.5 (1.8–3.5) for 23–28 weeks of gestation, 1.9 (1.5–2.3) for 29–32 weeks, 1.6 (1.3–1.9) for 33–34 weeks, 1.4 (1.2–1.5) for 35–36 weeks, and 1.2 (1.1–1.3) for 37–38 weeks, compared with birth at term (39–41 weeks) . The OR's decreased slightly to 2.2 (1.6–3.2), 1.7 (1.4–2.1), 1.4 (1.2–1.7), 1.3 (1.1–1.4), and 2.1 (1.1–1.3), after adjustment for socioeconomic confounders, maternal smoking during pregnancy and parental psychiatric disorders (model 2). Infants born postterm did not have any increased risk for ADHD.

Low Apgar, SGA and CP

A low Apgar score had a marginal effect on the risk of ADHD medication in preterms. Being SGA in children born term increased the OR for ADHD medication by 1.4 (1.2–1.6), after adjustment for socio-demographic variables. Having an indication of CP increased the OR of ADHD medication by 2.5 (1.8–3.3) in the whole study population. This effect was lower in all classes of preterm birth compared with term birth (OR's 0.3–0.4 in interaction analyses with $p < 0.05$ for a dichotomized variable of 22–36 weeks).

Within-mother-interpregnancy substudy

We performed two different regression analyses of 34 344 children who are offspring of mothers who had given birth both preterm (≤ w 34) and full term (w 39–41) in our study population. The first logistic analysis of the subgroup was adjusted for only age, sex and county of residence) with similar results as the corresponding analysis of the whole study population. In a second analysis we compared different offspring of the same mother in a within-mother between-pregnancy analysis, with OR's of 2.1 (0.9–3.2) for being born at 23–28 weeks of gestation, 1.7 (0.8–2.6) at 29–32 weeks and 1.4 (0.6–2.2) at 33–34 weeks, compared to term births (39–41 weeks), thus similar to those in the fully adjusted model of the whole study population, although the OR's did not reach significance in this analysis.

Effect modification

The effects of gestational age on ADHD medication were similar in boys and girls. In an interaction analysis, the effect of moderate preterm birth (week 33–36) on ADHD medication was higher ($p < 0.01$) in mothers with a low education. Neither a low Apgar score, nor being SGA did modify the effect of preterm birth on ADHD medication. However, the effect of having an indication of CP on ADHD medication was lower in all classes of preterm birth compared with term birth (OR's: 0.3–0.4 in interaction analyses with $p < 0.05$ for a dichotomized variable of 23–36 weeks).

5.4 ASTHMA MEDICATION (PAPER IV, BIRTH COHORTS 1987–2000)

In all, 7.39 % of the boys and 6.45 % of the girls-had purchased, at least once, any asthma medication in 2006. Corresponding rates for ICS were 4.89 % and 3.78 %, respectively.

The prevalence of ICS medication declined by increasing age in males, but in contrast, increased slightly by age in females born term. Increasing gestational age was related to a decreasing prevalence of ICS medication in both sexes (for trend, $p < 0.001$), with similar effect sizes for boys and girls of preterm birth on ICS in interaction analyses ($p = 0.21$–0.38).

Asthma medication in different gestational age groups

In logistic regression analysis the OR's for ICS medication were higher in all categories of gestational age less than 39 weeks than for term babies (week 39–41), and increased with degree of immaturity. The OR's for ICS medication, adjusted only for age, sex and county of residence, were 2.28 (1.96–2.64) for 23–28 weeks of gestation, 1.66 (1.53–1.81) for 29–32 weeks, 1.39 (1.29–1.50) for 33–34 weeks, 1.25 (1.20–1.31) for 35–36 weeks and 1.10 (1.08–1.13) for 37–38 weeks, compared with being born at term (39–41 weeks). Adjusting the analysis for confounding variables (county of residence, maternal education, parental asthma medication and maternal smoking during pregnancy) had only marginal effects on these estimates. The OR's were slightly attenuated in model 3 after addition of perinatal mediators (SGA, chorioamnionitis and caesarean delivery).

The increase in ICS use with decreasing gestational age at delivery was similar in boys and girls and declined with higher age.

Caesarean delivery, SGA and chorioamnionitis

The introduction of caesarean delivery contributed to the attenuation of the OR's for gestational age (in model 3). The OR for caesarean delivery was 1.13 (1.09–1.16) in model 3 and 1.20 (1.17–1.23) after removal of gestational age from the model. The addition of SGA and chorioamnionitis did not affect the OR's for gestational age. The OR's for SGA in models with and without gestational age were 1.06 (1.00–1.12) and 1.16 (1.10–1.22), respectively. Corresponding OR's for chorioamnionitis were 1.03 (0.83–1.26) and 1.32 (1.09–1.61), respectively.

Respiratory syncytical virus (RSV)

Children of all gestational ages who had been hospitalized for RSV-infection had an increased rate of ICS medication. The addition of RSV-hospitalization to the logistic regression analysis, however, did not affect the OR's for gestational age in the analysis, which indicates that hospital admissions for RSV did not affect the association between preterm birth and asthma.

Effect modification

The effects of the preterm birth categories on ICS were similar in boys and girls. The effect of extreme and very preterm birth (w 23–32) as well as moderately preterm birth (w 33–36) on ICS medication was attenuated by increasing age in boys as well as girls ($p < 0.001$ in interaction analyses for each sex separately). The effects were very similar in offspring of mothers with long (13+ years) compared to short education ($p = 0.27$–0.40).

6 GENERAL DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

Using a register based cohort design with prospectively collected information to achieve the aims of this thesis has strengths and limitations.

An important limitation in register-based studies is the researcher's inability to take part in the design of the background and outcome variables. She has to rely on the quality of the registers. For this reason, we have not been able to investigate the role of many important factors associated with preterm birth that might also affect the fetus directly, such as viral infections, maternal chronic diseases and maternal drug usage. Some of the major strengths are discussed below. The major strength of this thesis is the large study population made possible by the high quality and extensive coverage of the Swedish national registers, which enabled us to study a large number of infants with marginal attrition.

6.1.2 Selection bias

Beside information bias and confounding, selection bias is one of the main groups of biases (systematic errors). Many of the previous follow-up studies of preterm infants have suffered from a considerable attrition problem, often resulting in a selection bias, and a tendency to overestimate the outcomes for preterm individuals compared with term individuals. The register-based studies in this thesis have no such drop-out problem. The use of register data on income, disability, education, hospital admissions, ADHD medication and inhaled corticosteroid use excludes the possibility of self-reporting bias, which is otherwise a common problem in follow-up studies. Prospectively collected register information also eliminates any recall bias problem.

One source of selection bias in this thesis is that individuals born preterm, even during adolescence, may have easier access to psychiatric hospital care, and medication for ADHD or asthma, due to special attention from both parents and medical expertise. Especially, this may have been the case if the children were enrolled in specific programs aimed at following up neonatal intensive care. However, in the case of *moderately* preterm and *early term* neonates, this potential selection bias seems unlikely to have any major effect on the estimates, since these groups are rarely given special medical attention after the neonatal period.

6.1.3 Information bias

Categorization of gestational age groups
Differences between the results of this thesis and other long-term follow-up studies may very likely be a result of the differences in the categorization of gestational age groups. It is common to analyze infants born after 37–38 gestational weeks, as well as postterms born after 42 weeks or more, in the same category as infants born after 39–41 weeks [143-147]. A recent French neonatal morbidity follow-up study [148], as well as the studies included in this thesis, suggest that infants born after 37–38 weeks differ significantly from infants born after 39–41 weeks, and thus that they should be analysed separately. Similarly, since postterm birth may be associated with less favorable outcomes, it may be problematic not to distinguish between, on the one hand, individuals born after 42 weeks or more, and on the other hand, infants born after 39–41 weeks in the analysis [149, 150].

Misclassification in the estimation of gestational age

Skalkidou et al. have shown that ultrasound assessment in 1995–2007 compared to LMP-assessed births in 1973–78 may lead to a systematic misclassification of gestational age, with the result that proportionally fewer boys than girls are being considered premature. If the true gestational age is shorter in boys than in girls, this could lead to an overestimation of male-to-female differences in perinatal health in preterms [117]. Similarly, infants with early growth retardation may receive an estimated gestational age shorter than the actual one [151]. With our study design, there is no possibility to adjust for this kind of differential misclassification if it does not produce outliers that are excluded as improbable combinations of gestational age and birth weight. However, the kind of misclassification in ultrasound dated pregnancies, mentioned above, is not a problem in paper I and II, which are based on LMP-assessed births.

Coding errors

The cohort in papers I and II was born before ultrasound became a routine procedure to measure gestational age in early pregnancy. Coding errors of gestational age tend to create outliers that are falsely labeled preterm births [135]. To minimize this problem, we excluded individuals with very uncommon combinations of birth weight and gestational age. It seems likely that some miscoded individuals born at term remained in the study population coded as preterm, thus tending to attenuate the true associations of negative outcomes with preterm birth [135]. Probable coding errors are excluded in most register follow-up studies of preterm individuals [143, 145, 147, 152].

Due to unreliable/unknown gestational ages before ultrasound became a routine procedure, previous studies on preterm infants have dominantly used birth weight for inclusion. Such studies have some advantages, but they can rarely be used to analyze moderately preterm births.

Quality of outcome variables

In this thesis, register based outcome variables are used as proxies for disease. In paper II, investigating psychiatric morbidity, the quality of the diagnostic procedure is a potential bias. In a study from 2002 [153], the validity of schizophrenia diagnoses of young patients in the Patient Discharge Register proved to be quite high: 86 % fulfilled the DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders criteria) of schizophrenia syndrome. Broad categories including several diagnoses, as those primarily used in paper II of this thesis, are less likely to cause error in this sense.

The concept of ADHD is difficult to define in a reliable way in epidemiological studies because of the subjective and context-bound nature of the impairment criteria built into existing diagnostic classifications [154]. The ADHD medication variable in paper III should contain the more severe cases in this Swedish setting, since national guidelines issued by the National Board of Health and Welfare in 2002 stated that medication should be reserved for cases where other supportive interventions have failed. Also, the right to prescribe ADHD medication in Sweden is restricted to specialists with particular familiarity with treatment of this disorder.

The validity of the asthma-medication variable is supported by both a recent Danish study [155] (having notably included only those with more than one prescription of beta2-agonist or inhaled corticosteroids), indicating that register-based data on dispensed prescriptions can be used to identify asthmatic school children [155]. Furthermore, a

Norwegian study from 2011 concludes that mother-reported antiasthmatics in 7-year-old children well correspond to dispensed anti-asthmatics [156].

6.1.4 Confounders and intermediate links in the causal pathway

Since preterm birth is more common in socially disadvantaged groups in society, the issue of socioeconomic confounding is fundamental in follow-up studies in this field [20, 115]. By linking several national registers, we were able to include a wide range of socioeconomic characteristics as possible confounding factors in the analysis.

In order to further single out the impact of preterm birth versus other perinatal complications, we were able to adjust our analyses for possible mediators involved in the causal pathway between preterm birth and the outcomes in a separate model in the various studies (SGA, low Apgar score, cesarean delivery, multiple births).

Our parental morbidity-variables (parental psychiatric/addictive morbidity and parental asthma medication) were used to adjust for, and in one study single out, the impact of genetic confounding in the analyses. An advantage of our studies is the adjustment for parental psychiatric disorders. Such an adjustment was made in the Swedish national cohort study by Crump et al. [147], but not in some other Scandinavian register studies on long-term consequences of preterm birth [143-146].

6.1.5 Effect modification

Previous knowledge of how socioeconomic context modifies the effect of preterm birth on long-term outcomes is sparse. Regarding the psychiatric outcomes, including ADHD, for the moderately preterm group, SES and maternal education seems to be a modifier of particular importance.

We noted that the effect of preterm birth on psychiatric morbidity, including ADHD, was higher in infants from low-SES families/with low-educated mothers. A similar effect was not seen for inhaled corticosteroid use or disability, which underscores the importance of socioeconomic context for more subtle outcomes related to the central nervous system, while it has less importance for lung development/motor impairment.

According to our findings, neither boys nor girls were more vulnerable to preterm birth with regard to our outcomes. Thus, on our outcomes regarding social adjustment, psychiatric morbidity or asthma, sex did not seem to be an important modifier of the effects of preterm birth.

6.2 FINDINGS AND IMPLICATIONS

Controlling for a number of socioeconomic and perinatal indicators, this thesis investigates a wide range of long-term consequences of preterm birth. Decreasing gestational age at birth increases the risks for several less favorable long-term outcomes in a step-wise manner. Somewhat surprisingly, moderately preterm (w 33–36) and early term (w 37–38) infants are at significantly higher risks for less favorable outcomes than infants born after 39–41 weeks of gestation. Consequently, earlier beliefs that neurodevelopment is independent of gestation after 32 gestational weeks [157] may have to be re-evaluated.

Already in 2000, Kramer et al. convincingly demonstrated that moderately preterm birth carried substantial risks for neonatal as well as infant mortality in the US and Canada [2]. Recently, substantially increased risks for neonatal morbidity have also been demonstrated in the US [8, 109], France [148], and in Sweden [10]. These effects seem to persist into

infancy [158]. The French population-based study mentioned above notably demonstrated increased neonatal morbidity risks also for the group of infants born early term (w 37–38) [148], which is a finding in line with the significantly poorer long-term outcomes for the same group studied in this thesis.

Largely, the results obtained in this thesis are supported by Norwegian and Danish register study data on social adjustment in young adulthood [143-145], and Swedish register data on long-term psychiatric morbidity [147]. This thesis suggests that the associations of most negative outcomes with degree of prematurity did not differ significantly between boys and girls, which is in concordance with Norweigian results by Moster et al. [143].

Possibly, the pathways explaining our findings related to neurodevelopment, at least in the most immature group, have to do with the encephalopathy of prematurity (diffuse PVL and accompanying axonal/neuronal damage), which in imaging studies has been found in some 50 % of VLBW-infants. Severe brain hemorrhages/infarctions occurring in only some 5 % [45] of VLBW, probably are involved for a limited number of individuals.

That some mild type of encephalopathy of prematurity explains our findings in some of the infants born after 33–38 weeks' gestation [148], is possible but unclear. However, in similarity with the effect of preterm birth on the lung development by every gestational week [9], there is MRI-evidence that disruption of the intrauterine environment, resulting from preterm birth, leads to a dose-response dependent reduction in brain growth from gestational week 23 to 40. This indicates that every gestational week makes a difference [159]. In the preterm individuals, studied in paper III, we were unable to find a connection between ADHD and CP and SGA, which suggests mechanisms involving brain development rather than acute complications.

Early separation and psychosocially harmful consequences to infant-parent bonding [160, 161], as well as painful and stressful stimuli [162] in the NICU, may play considerable roles in the causal pathways. However, these factors are probably to a lesser extent responsible for the effects seen in the older gestational age groups, and so particularly in the early term group (w 37–38).

Factors related to the family environment during childhood are important mediators of the more subtle cognitive deficits that have repeatedly been described in school children and adolescents born preterm without major disabilities [62, 82]. The effect modifications seen for mental health outcomes in this thesis agree with previous work, which suggests that preterm infants of low-educated mothers are at particular risk for worse long-term consequences [163]. The brain develops in interaction with the environment, and before term, the norm for the development is the intrauterine milieu. At least for the moderately preterm group, an altered brain physiology due to the brain's early interplay with its extra uterine environment should be considered in attempts to explain our findings.

The effect modifications by socio-economy demonstrated for psychiatric morbidity were not seen for asthma and disability outcomes. This is in line with the brain being particularly vulnerable to the web of risk and protective factors that affect the interaction of the child with its environment and that are reflected in the markers parental SES and maternal education.

Generalilizations to younger cohorts

It is only with caution that the results of this thesis may be applied to the preterm/early term infants born today. The obstetric and perinatal care is getting more advanced, but on the other hand, a higher number of critically ill infants survive. These facts contribute to

the difficulties of making long-term prognoses for the group of preterm infants born today.

Nevertheless the inverse "dose-response pattern" of decreasing risks for less favorable outcomes with increasing gestational age at birth, which is consistent in infants born 1973–79 (papers I–II), as well as in infants born 1987–2000 (papers III–IV), suggests that the same pattern will be true also for the cohorts of today, but on a different level. The decreasing rates of CP in preterms, parallel to increased survival rates seen in the nineties, indicate generally improved outcomes of the preterm infants born today [66, 67].

Implications and future challenges

In the societal perspective, it is reasonable to believe that strategies to improve and develop the educational environment, in schools and pre-schools, of value for all children with cognitive difficulties would also be of great value for many children born preterm. [164, 165].

For obstetricians, it is important to know that the transition of risks for unfavorable outcomes in infants born after less than 39 complete weeks appears to be gradual, without a distinct threshold. In decisions on iatrogenic deliveries before 39 complete weeks, the advantages of earlier delivery should be weighed against the health costs of preterm/early term delivery [6].

The development of the care in the NICU is advancing fast, also in the field of improving the environmental care. Much attention has been directed towards diminishing pain and stress by individualizing the procedures in programs like "Newborn Individualized Developmental Care and Assessment Program" (NIDCAP), aiming at maintaining behavioral and motor system equilibria [166]. NIDCAP appears to have effect not only on brain function but also on brain structure [167], even though a meta-analysis from 2002 demonstrated insufficient evidence for NIDCAP on improving developmental outcomes at 2 years follow-up [168]. It seems to be of utmost importance to include the moderately preterm in further evaluations and follow-ups.

Improved methods for evaluations and follow-up studies of moderately preterm infants have been called for previously [106-108]. The findings, of this thesis, support suggestions to educate physicians, nurses, midwifes and parents that even healthy looking moderately preterm infants are physiologically immature [107]. It seems reasonable to give them early return appointments and consider them for long-term follow-up. High availability of the parents probably plays an important role in improvements of the care for the moderately preterm infants. A Cochrane review indicates that early developmental post-hospital discharge interventions, for preterms, focusing on parent-infant communication have favorable effects on cognitive outcome into pre-school age [169]. Domiciliary nursing care [170], family centered care [171], and promotion of Kangaroo mother care/skin-to-skin care [172] and breastfeeding should be further encouraged.

Studies investigating if any particular neonatal complications are especially associated with poor long-term outcomes would be beneficial in the development of targeted interventions for the moderately preterm infants. Also, we need to continue to increase the knowledge about the best way to monitor, evaluate and follow up the moderately preterm individuals. In all, our findings emphasise the value of current attempts to systematize and improve the care of these infants in Sweden [10, 171, 173] as well as internationally [107].

SUMMARY OF CONCLUSIONS

Disability
All levels of preterm birth were associated with an increased risk of disability at age 23–29 years in individuals born 1973–79. Moderately preterm and early term birth accounted for 74 % of the total disability associated with preterm/early term birth.

A total of 87 % of children born at 24 to 28 week's of gestation and 94 % born at 29 to 32 weeks' gestation received no economical assistance from society because of handicap or persistent illness.

Psychiatric morbidity
Preterm birth carried some increased risk for psychiatric hospital admissions in individuals born 1973–79 at 8–29 years. Moderately preterm and early term birth accounted for 85 % of the risk attributed to preterm/early term birth.

Hospital admissions related to alcohol/substance abuse did not seem to be a particular problem in the preterm individuals born 1973–79.

The association between preterm birth and ADHD medication in 6–19-year-olds was graded by immaturity in children born in 1987–2000.

The effect of preterm birth was greater on psychiatric morbidity and ADHD for individuals from families with low socioeconomic position.

Asthma
Degree of preterm birth was associated with inhaled corticosteroid use in 6–19-year-olds born 1987–2000, independent of socio-economic confounders, perinatal mediators and RSV infections in infancy. Even infants born early term (week 37–38) had an increased risk for inhaled corticosteroid use compared with term infants (week 39–41).

General conclusion
The risks for the unfavorable outcomes studied increased with decreasing gestational age at birth, in the follow-up studies of individuals born 1973–79 and 1987–2000. Even the most preterm group (< 33 weeks) born in the seventies contributed more economically to society than they received in societal assistance/benefits. Moderately preterm and early term individuals represented, due to their large number, most of the morbidity associated with preterm birth/early term birth. Hence, they deserve more attention in research and secondary prevention.

SUMMARY OF IMPLICATIONS

1. In decisions on iatrogenic deliveries before 39 complete weeks, the advantages of earlier delivery should be weighed against the health costs of preterm/early term delivery. This has been discussed in depth by other researchers with an interest for the groups of moderately preterm and early term infants [2, 6, 106, 108, 148].

2. Clinicians should consider the physiological immaturity and vulnerability also of the clinically "stable" moderately preterm/early term infants [106].

3. The fact that preterm birth had a higher effect on psychiatric outcomes including ADHD in socially disadvantaged families possibly imply that social and educational supportive interventions are particularly worthwhile in this group of individuals.

4. Researchers should consider including moderately preterm infants in investigations and in analyses, to separate infants born after 37–38 weeks of gestation from those born after 39–41weeks of gestation.

7 SVENSK SAMMANFATTNING

En normal graviditet varar 40 veckor; och födsel före 37 fulla veckor räknas som för tidig. Andelen *mycket* för tidigt födda barn med stora neurologiska skador har minskat. Många studier pekar ändå på kvarstående, mer subtila svårigheter under skolåren för en stor del av de mycket för tidigt födda. De flesta studier har undersökt situationen för just sådana barn, födda före fulla 33 graviditetsveckor, men *måttligt* för tidigt födda (födda efter 33–36 veckor) är mycket vanligare och är därför ur ett folkhälsoperspektiv betydelsefulla. I avhandlingens fyra delarbeten har långtidskonsekvenser av *alla* grader av för tidig födsel studerats. Som jämförelsepopulation har vi använt barn födda efter 39–41 veckor. Information i svenska nationella register har använts för att undersöka situationen i skolålder och ung vuxen ålder.

Betydelsen av för tidig födsel för social anpassning, mental hälsa och astma har undersökts. Dessutom har den för tidiga födselns samspel med sociala faktorer under uppväxten analyserats. Två födelsekohorter på drygt en halv miljon individer födda 1973–79 respektive drygt en miljon individer födda 1987–2000 har utgjort grunden för studiepopulationerna.

Jämfört med barn födda i vecka 39–41 löpte barn födda 1987-2000 i vecka 23–28, en drygt dubbelt så hög risk för att medicinera med inhalationssteroider (vår huvudindikator för astma) vid 6–19 års ålder. För dem som fötts omogna men efter en längre graviditet fanns en stegvis minskning av risken, ned till 10 procents ökad risk hos *tidiga fullgångna* (födda i vecka 37–38) jämfört med barn födda i vecka 39–41.

För individerna födda 1987–2000 märktes i skolåldern (6–19 års ålder) också ett samband mellan för tidig födsel och ADHD-medicinering, där risken för barn födda i graviditetsvecka 23–28 var drygt dubbelt så hög som för barn födda i vecka 39–41. Risken för ADHD-medicinering sjönk med ökande mognad vid födseln, men även tidiga fullgångna (graviditetsvecka 37–38) hade en riskökning på 20 procent jämfört med barn födda i graviditetsvecka 39–41 med liknande sociala bakgrundsförhållanden.

I en annan studie följdes individer födda 1973–79 upp med avseende på psykiatrisk slutenvård vid 8–29 års ålder. Riskökningen varierade med ökande mognad vid födseln från knappt 70 procent för dem som fötts i vecka 24–32 till knappt 10 procent för tidiga fullgångna (vecka 37–38) jämfört med gruppen individer som fötts efter 39–41 veckor.

Barn i socialt utsatta familjer var känsligare för effekten av för tidig födsel på psykiatrisk slutenvård. Den effekten är i samklang med att måttligt för tidigt födda (graviditetsvecka 33–36) till mödrar med låg utbildning var känsligare för effekten av för tidig födsel med avseende på risken för ADHD-medicinering.

En stor majoritet av de mest underburna barnen som fötts på 70-talet verkade leva produktiva och självförsörjande liv i ung vuxen ålder. Mycket för tidigt födda (vecka 24-32) hade dock en nästan fyra gånger så hög risk för funktionsnedsättningar efter att hänsyn tagits till socioekonomi och perinatala karakteristika. Riskökningen sjönk med ökande graviditetslängd men var signifikant högre även för gruppen födda i vecka 37–38 än i jämförelsegruppen födda i vecka 39–41.

Slutsatser
Riskerna för de studerade ofördelaktiga utfallen ökade med sjunkande graviditetslängd i uppföljningarna av barn födda 1973–79 och 1987–2000. Det ekonomiska bidraget till

samhället från gruppen med de mest för tidigt födda (< 33 fulla graviditetsveckor), som fötts på 70-talet, var avsevärt större än vad gruppen själv erhöll i bidrag. Måttligt för tidigt födda och tidiga fullgångna stod, på grund av sitt stora antal, för den största andelen av den totala sjukligheten förknippad med för tidig födsel/tidig fullgången födsel. Den gruppen behöver således uppmärksammas mer i klinisk utveckling och forskning.

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