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Birth-characteristics, hospitalisations, and childbearing

Epidemiological studies based on Swedish register data

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I wish we could open our eyes
to see in all directions at the same time
Oh, what a beautiful view
if you were never aware of
what was around you

~ Benjamin Gibbard ~

SUMMARY

In the past decades there has been an improvement in the medical treatment of children born preterm or with reduced foetal growth. This has resulted in a much higher survival rate of these children, but also in a higher number of surviving children with chronic conditions. These changes have, in turn, increased interest in investigating the connection between birth-characteristics and outcomes in later life. The overall aim of the present thesis was to study the relations between birth-characteristics, subsequent hospitalisations, and childbearing by means of data available in Swedish population-based registries.

The study population in this thesis consisted of women (and men in Paper III) born in 1973-75 according to the Medical Birth Register and the Total Population Register. Information available in other registries, such as the Hospital Discharge Register, was obtained by individual record linkage.

In Paper I, 148,281 women, alive and living in Sweden at 13 years of age, were included. Of the women, 4.1% were born preterm and 5.4% were born small for gestational age, and approximately 30% of all women had given birth between 13 and 27 years of age. We found that reduced foetal growth and possibly preterm birth were related to the likelihood of giving birth during the study period. The intergenerational effects of preterm birth and reduced foetal growth were investigated in Paper II and the study population consisted of 38,720 mother-offspring pairs. An intergenerational effect of reduced foetal growth was found, and reduced foetal growth in the mother also increased the risk for preterm birth in the child.

Paper III was concerned with 304,275 men and women living in Sweden at 13 years of age. Of these men and women, 30% were hospitalised during adolescence and early adulthood (i.e. between 12 and 23 years of age). We found that men and women born small for gestational age or preterm were more likely to be hospitalised, and that those born small for gestational age seemed to be more at risk compared to those born preterm. Finally, in Paper IV, the relation between hospitalisations during adolescence and the likelihood of giving birth was studied in 142,998 women living in Sweden at 20 years of age. We found that a majority of the causes of hospitalisation during adolescence were positively connected to the likelihood of giving birth between 20 and 27 years of age. The relations presented in Papers I-IV were evident although socio-economic characteristics were adjusted for.

Key words: Birth rate; Cohort studies; Epidemiology; Hospitalisation; Morbidity; Preterm infant; Reproduction; Small-for-gestational-age infant

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Ekholm K, Carstensen J, Finnström O**,** Sydsjö G.
The Probability of Giving Birth among Women Who Were Born Preterm or with Impaired Fetal Growth: A Swedish Population-based Registry Study.
Am J Epidemiol, 2005;16:725-33.

II. Ekholm Selling K, Carstensen J, Finnström O, Sydsjö G.
Intergenerational effects of preterm birth and impaired fetal growth: A population-based study of Swedish mother-offspring pairs.
BJOG, 2006;113:430-440.

III. Ekholm Selling K, Carstensen J, Finnström O, Josefsson A, Sydsjö G.
Hospitalizations in adolescence and early adulthood among Swedish men and women born preterm or small for gestational age.
Accepted in *Epidemiology*, April 2007.

IV. Ekholm Selling K, Carstensen J, Finnström O, Josefsson A, Sydsjö G.
Hospitalisations in adolescence increase the likelihood of giving birth between 20 and 27 years of age: A Swedish population-based register study.
Submitted.

CONTENTS

List of tables and figures in the order in which they appear in the text

ABBREVIATIONS

AGA	Appropriate for gestational age
BMI	Body mass index
CI	Confidence interval
HDR	Hospital Discharge Register
HR	Hazard ratio
ICD	International Classification of Diseases
MBR	Medical Birth Register
OR	Odds ratio
SD	Standard deviation
SGA	Small for gestational age
STI	Sexually transmitted infections
TPR	Total Population Register
WHO	World Health Organisation

EXPLANATIONS OF KEY TERMS

Birth-characteristics	Refers to preterm birth and 'reduced foetal growth' (see below) in this thesis.
Childbearing	The likelihood of giving birth (i.e. time, in years, to the first birth).
Hospitalisation	In this thesis hospitalisation is defined as a dichotomy (i.e. 'hospitalised'/'not hospitalised').
Pregnancy outcome	Preterm birth and reduced foetal growth in the child (see below).
Preterm birth	A gestational length shorter than 37 completed weeks (or shorter than 32 weeks).
Reduced foetal growth	In this thesis we have primarily used small for gestational age as a proxy for reduced foetal growth, and in some analyses very low birth weight was also used.
Small for gestational age	A birth weight < -2 SD of the mean weight for the gestational length according to the Swedish standard.
Socio-economic characteristics	Includes educational levels and marital status (measured on both the study population and their parents), as well as the age when giving birth, parity, and country of origin (parents).

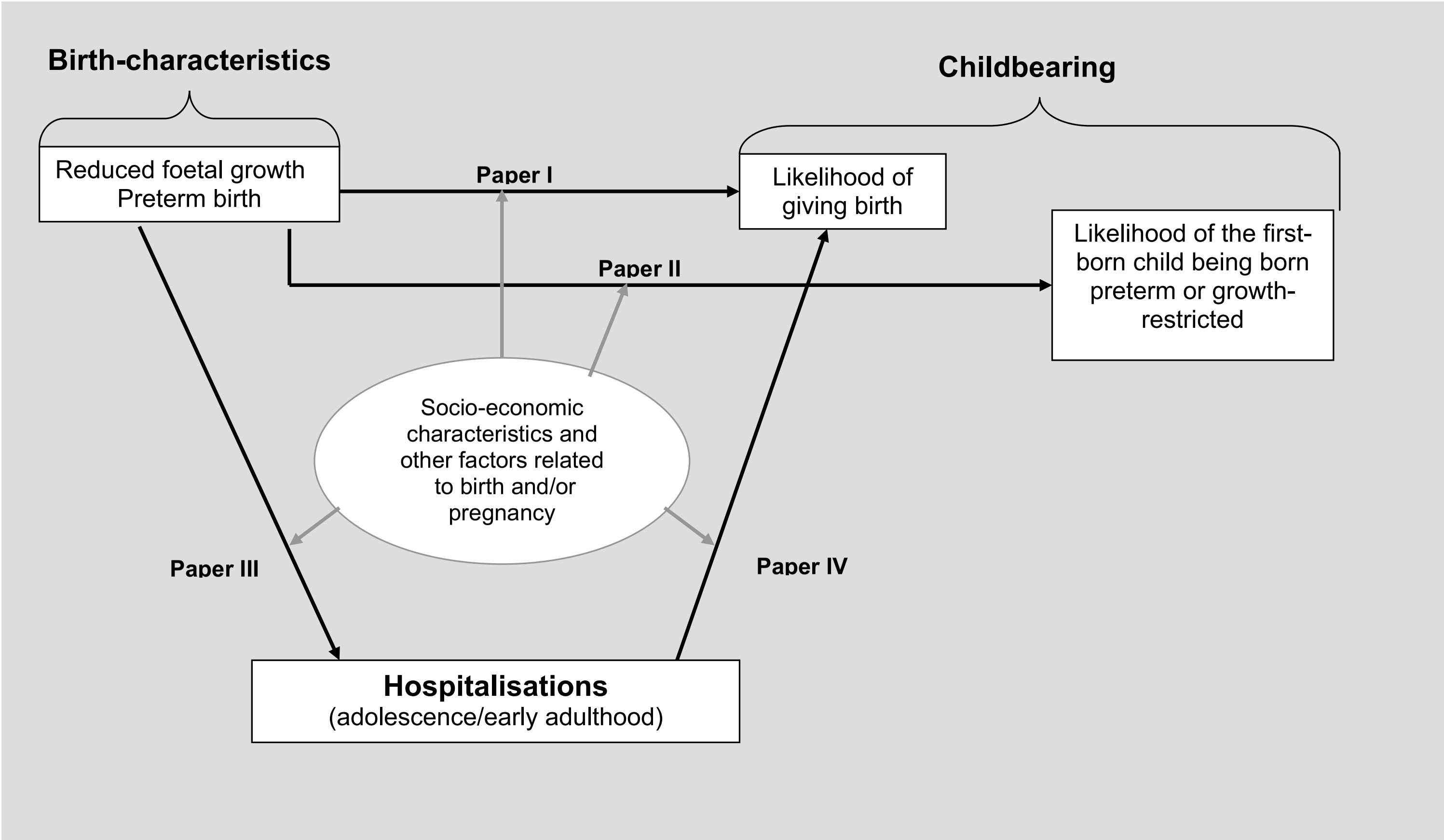
INTRODUCTION

In the past decades there has been a considerable improvement in the medical treatment of children born preterm or with reduced foetal growth. This has resulted in a much higher survival rate of these children, but also in a higher number of surviving children with chronic conditions. These changes have, in turn, increased interest in investigating the foetal origins of disease in later life. For example, there are plenty of studies proposing a connection between anthropometrical birth-data and an increased risk of the 'metabolic syndrome'. Preterm birth and reduced foetal growth have also been shown to be related to cerebral palsy and other neurodevelopment sequelae. However, we believe that there is still a need to evaluate the impact of birth-characteristics on the long-term consequences on health, especially in the more 'broad perspective'. In this thesis we have attempted to do so by investigating the effect of preterm birth and reduced foetal growth on all causes of hospitalisation during adolescence and early adulthood.

There is also some evidence of birth-characteristics being connected to reduced fertility and adverse pregnancy outcomes but these possible connections need further attention. In addition, the results of previous studies suggest a reduction in childbearing following several kinds of morbidity during growth. However, the relation between adolescent morbidity and future childbearing has not often been addressed, although adolescence, like the intrauterine period, is characterised as one of the most complex and interesting periods within human growth and development. Previous studies have further suggested a connection between non-optimal birth-characteristics and subsequent socio-economic status, as well as behavioural factors. Thus, the connections discussed might at least in part be due to other factors such as socio-economic or behavioural.

Swedish population-based registries offer an opportunity to study the effect of birth-characteristics on subsequent outcomes (such as hospitalisations and childbearing) in a large material. Through the registries, it is also possible to retrieve information on socio-economic characteristics. The overall aim of the present thesis was, thus, to study the relations between birth-characteristics, subsequent hospitalisations, and childbearing, and to see to what extent, if any, the connections found could be explained by socio-economic characteristics, see Figure 1.

Figure 1. Schematic overview of the present thesis.



BACKGROUND

The time period before, during, and after birth is a very important one for the infant and for the whole family. For the infant, the environment in which it develops and the gestational age in which it is born is critical for its long-term survival as well as physical and psychological development [1-4]. As the intrauterine developmental process is difficult to assess, most research in this area has focused on the infant's characteristics at birth. For example, anthropometrical birth-data such as birth weight as well as the gestational week in which the infant was born has been the subject of much research. Below, a brief overview of birth-characteristics in relation to outcomes in later life is presented, followed by a summary on some of the many factors related to childbearing and pregnancy outcome.

Birth-characteristics in relation to outcomes in later life

Long-term morbidity

It is well known that the short-term survival and morbidity among infants is highly dependent of their gestational lengths and birth weights [3, 5, 6]. The higher the birth weight and/or gestational length of the infant, the higher the survival rate. A Danish study has also found evidence of an inverse relationship between birth weight and all-cause mortality in early adult life among men [7].

A large number of studies in many parts of the world have proposed a connection between reduced foetal growth[1] and an increased risk for major diseases in later life such as the metabolic syndrome (including diabetes, high blood pressure, obesity, and cardiovascular disease) [1, 2, 4, 8]. During the past decades different theories aimed at exploring the mechanisms behind these associations have developed. Perhaps the most debated of these theories is the 'foetal origins of adult disease hypothesis'. The main concept of this theory is that "…an unfavourable environment, or insults during foetal life, might induce lifetime effects on the subsequent development of body systems and hence give rise to major disease processes…" [9] (see also [1, 2, 4] for a more detailed presentation of this theory as well as the mechanisms that are considered to underlie these connections). However, researchers have questioned the biologic basis and clinical importance of the 'foetal origins of adult disease hypothesis' [10], as well as the "selective emphasis on particular results" [11]. The statistical methodology used in many of the performed studies has also been debated [9, 10]. In any case, it is important to bear in mind that not only the size in early life but also the changes in size (i.e. speed of growth) across the whole time interval before the disease occurs may be important for subsequent health [10, 12]. Also, there are other 'critical periods' besides the intrauterine period, that are important in determining the later risk of disease, for example adolescence [12].

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[1] Most studies have used anthropometrical birth-data such as low birth weight (< 2,500 grams), very low birth weight (< 1,500 grams) or being born 'small for gestational age' as proxies for reduced foetal growth.

Previous research has found that especially preterm birth but also reduced foetal growth are related to diseases of the nervous system, such as cerebral palsy as well as visual and hearing impairments [13-17]. The mechanisms by which these connections occur may include both 'direct' and 'indirect' effects, such as intrauterine infections and reduced placental function, respectively, and the connections may also be due to complications during labour and the neonatal period [17]. Another possibility is that specific causes of restricted growth and preterm birth, such as central nervous system malformations, may cause a poor paediatric outcome independently of these birth-characteristics. Mental disorders also seem to be more common among those born preterm and/or growth restricted. Connections have been found for a range of mental disorders such as internalising symptoms (i.e. anxiety, depression, and withdrawal), attention problems, and relational problems [16, 18, 19]. Previous Swedish studies have also found that especially reduced foetal growth appears to be related to eating disorders, schizophrenia, and suicidal behaviour [20-22]. In addition, non-optimal birth-characteristics are connected to respiratory disease, especially asthma, and infectious disease [5, 16, 23-25], and some evidence exists of a connection to malignancy [26-28].

Socio-economic and behavioural characteristics

Non-optimal birth-characteristics appear to be associated with lower mean intelligence quotients as well as poorer school performances and lower educational levels [13, 14, 16, 29, 30]. Low birth weight has also been shown to be related to subsequent marital status in men but not in women [31, 32]. Women who themselves were born with reduced foetal growth seemed to be more likely to be smokers in adult life according to some studies [33]. However, other studies have shown that young adults who were born with very low birth weights report less risk-taking behaviour, including drug and alcohol use, compared to controls [16]. The personality of those born with reduced foetal growth has also gained some attention. Some studies report that men and women born with very low birth weights display less negative emotions and are more cautious in late adolescence and young adulthood, compared to controls [16, 34], while others report a higher risk of internalising symptoms, attention problems, and relational problems [16, 18, 19].

Childbearing and pregnancy outcome

As reduced foetal growth may alter organ structure and functioning [1, 2, 4], it is theoretically possible that reduced foetal growth is also connected to subsequent fertility. For example, women who were born with very low birth weights appear less likely, compared to controls, to have been pregnant or delivered a live born infant at the age of 20 years even after adjustments for socio-demographic factors [16]. Some researchers have investigated this connection in more detail and have found evidence of reduced foetal growth being connected to reduced ovulation rate and smaller internal genitalia [35]. There is also some evidence of reduced foetal growth affecting postnatal testis size and function into adulthood [36].

Previous research has shown an intergenerational effect of birth weight [37-42], and there appears to be an intergenerational effect of reduced foetal growth [33, 43-45]. Several studies have also suggested an intergenerational effect of preterm birth, although this effect has not always been statistically significant [41, 44-46]. It has been suggested that the intergenerational effects of birth weight and gestational length might be explained by a genetic mechanism [41, 42, 47]. In addition, pre-eclampsia has been shown to be enhanced among women who were themselves born small for gestational age [48], which could also be involved in explaining some of the intergenerational effects found. Also, a recent study found that women whose waiting-time to pregnancy was more than one year (which is a common definition of infertility [49]) seem to be at higher risk of adverse pregnancy outcomes such as preterm birth, even if they conceive without infertility treatment [50].

Factors related to childbearing

Morbidity

One of the most common causes of infertility among women in the western world is tubar and pelvic pathology, which is related to sexually transmitted infections (STI) [49, 51]. Adolescent girls have the highest rates of STI, not only due to more sexual risk-taking behaviour, but also due to physiological factors [52]. Premature ovarian failure and endometriosis, which are known to have a negative effect on fertility, have been shown to correlate with autoimmune diseases [53, 54]. Results of previous studies indicate that women with congenital anomalies are less likely to have children [55]. In addition, childhood cancer survivors have been reported to have an overall reduced fertility, as have women with epilepsy [56, 57]. On the other hand, women with adolescent onset psychiatric disorders have an increased probability of teenage pregnancy and early marriage [58]. Previous research also indicate that adolescents with chronic illness report similar or higher rates of sexual intercourse and unsafe sex, compared to healthy controls [59, 60]. However, other studies have shown that eating disorders, a majority of which reveal themselves in adolescence and early adulthood, appear to have a negative effect on the women's sexuality and fertility [52, 61].

Socio-economic and behavioural characteristics

The age of the woman is crucial in terms of both her biological ability of becoming pregnant and giving birth to a child, as well as the outcome of her pregnancy [49, 62-64]. According to Emanuel [65], studies indicate that both the conditions under which a mother is born and grows up, as well as the conditions under which her pregnancies occur are important for her reproductive success. Indicators of lower socio-economic status in both childhood and adulthood increases the likelihood of giving birth at an earlier age [66, 67]. Several studies also show that socio-economic characteristics such as educational levels and cohabitation status play a part in determining the risk of giving birth to a preterm or growth-restricted child [6, 62, 68, 69]. Alcohol and/or substance abuse, smoking, and high or low body mass index (BMI) are also risk factors for altered fertility and pregnancy outcome in women [6, 49, 62, 69-72]. In addition, it has been speculated that 'stress' might be involved in explaining 'unexplained infertility' and adverse pregnancy outcomes [69, 73].

AIMS OF THE PRESENT THESIS

The overall aim of the present thesis was to study the relations between birth-characteristics, subsequent hospitalisations, and childbearing by means of data available in Swedish population-based registries. More specifically, we wanted to investigate if

…there is a connection between being born preterm or with reduced foetal growth and the likelihood of giving birth between 13 and 27 years of age, and if this connection is evident after adjusting for the women's socio-economic characteristics (Paper I).

…women who themselves were born preterm or with reduced foetal growth are more likely to give birth to a child born preterm or with reduced foetal growth, even after accounting for socio-economic characteristics as well as smoking habits and body mass index during early pregnancy (Paper II).

… the risk of hospitalisation during adolescence and early adulthood differs between men and women who were born preterm or small for gestational age, respectively, as compared to those born at term and appropriate for gestational age, after adjustments are made for socio-economic characteristics (Paper III).

…hospitalisations during adolescence influence the likelihood of giving birth between 20 and 27 years of age, and if the connections are due to the woman being born preterm or small for gestational age or her socio-economic characteristics (Paper IV).

MATERIALS AND METHODS

Data sources

The papers included in this thesis were all based on data from Swedish population-based registries. All Swedish residents are assigned unique personal identification numbers and these numbers can be used to individually link the information present in the registries. On the following pages, the registries used in this thesis are presented along with the variables used.

The Swedish Medical Birth Register

Medical information on all births has been stored in the Medical Birth Register (MBR) since 1973 and the register was established after the introduction of standardised medical records used by all delivery units and antenatal care clinics in the country [74]. The MBR covers approximately 98-99% of all births in Sweden and the births not present in the registry constitute infants born abroad or infants with invalid or incomplete personal identification numbers. According to Swedish law, stillbirths born before 28 completed weeks of gestation are to be regarded as late abortions, not stillbirths, which may also explain some of the missing values in the MBR (as compared to the TPR). New variables have been introduced in the MBR, especially in 1994-95, at which point a new antenatal care record was established. The validity of the majority of the variables in the MBR is relatively good according to studies made in 1976, 1988, and 2001 and routine checks are performed by the registry holders (i.e. the Swedish National Board of Health and Welfare) to test the accuracy of some of the variables. From the MBR, information on birth weight and gestational length was retrieved. Although the overall information on gestational length and birth weight is reliable [74, 75], evaluations of the MBR have shown evidence of measurement errors in both extremes of the distributions of birth weight and gestational length [75, 76]. Other MBR-variables used were gender, year of birth, twin birth, parity, cohabitation status, smoking, and BMI.

The Hospital Discharge Register and the Causes of Death Register

The Hospital Discharge Register (HDR), also held by the Swedish National Board of Health and Welfare, was established in 1964 and has registered all public in-patient care in Sweden since 1987 [77]. From the register it is possible to retrieve the diagnoses for each hospitalisation. The diagnoses in the HDR are based on the Swedish version of the World Health Organisation's international classification of diseases (ICD). ICD-8 [78] was used until 1986, ICD-9 [79] between 1987 and 1996, and ICD-10 [80] is used from 1997 and onwards. In validation studies, the errors on the ICD-chapter level were estimated to be 6% in 1986 and 4% in 1990 and the highest relative frequency of errors was detected in diagnoses related to internal medicine and the lowest in gynaecologic diagnoses [81]. Furthermore, persons older than 64 or younger than 15 years had higher frequencies of diagnostic errors, and persons aged 15-44 years had the lowest. In this thesis, the HDR-variables used were the main diagnosis of hospitalisation, categorised into ICD-chapters and three-digit level diagnoses.

The Causes of Death Register was established in 1961 and records information on all deceased persons registered in the country at the time of death [82]. The cause of death is generally determined from the medical death certificates. In this thesis, the variable year of death was used.

The Total Population Register and the Multi-Generation Register

The Total Population Register (TPR), held by Statistics Sweden, was established in 1968 and contains information on births, deaths, and marital status, as well as on migration, and country of origin for Swedish residents born abroad [83]. The information in the register is based on information from the Swedish taxation authorities (Riksskatteverket) and is the foundation of all official population statistics. Validation studies have shown that the national registration includes a relatively large number of persons not living in Sweden, and this also reflects the information in the TPR. Other sources of error in the TPR are mainly that more than one biological mother and/or father are assigned to one child, or that the date of birth is incomplete. Estimations have shown that about 4,000 persons listed in the TPR have 'recycled' personal identification numbers (i.e. the same personal identification number as a deceased person). The TPR-variables used in this thesis were: year of birth, year of death, gender, parity, marital status, migration status, and country of birth.

The Multi-Generation Register which is founded on information from the TPR consists, at present, of persons that have been registered in Sweden during some period since 1961 and who were born in 1932 or later [84]. These 'index persons' and their parents constitute the Multi-Generation Register. In the Multi-Generation Register, personal identification numbers are available for 97% of the mothers to the index persons born in Sweden, and 95% of the fathers. If only index persons born in 1950 and onwards are studied, the corresponding percentages are 99 and 98, respectively. We used the Multi-Generation Register to identify the fathers of the studied men and women.

The Education Register and the 1970 Population and Housing Census

Since 1985, Statistics Sweden has continuously collected information on the educational level of the population in the Education Register [85]. In the register, the highest completed education for every Swedish resident is noted. A validation study made in 1991 showed that the proportion of persons with elementary school as the highest completed level of education was somewhat overestimated.

In Sweden, censuses were carried out every tenth year from 1860 to 1930, and after that every fifth year with 1955 and 1960 as exceptions [86]. In the 1970 Population and Housing Census the educational level was missing on approximately 4% [87]. The persons who did not state their educational levels in the census were women to a greater extent, and were also younger (20-30 years of age), compared to persons who did state their educational levels. In addition, the missing category consisted of a higher proportion of persons born abroad (11% missing values). A large proportion of the persons that did not answer the question on educational level did not send any completed form, and another group in the missing category constitutes of foreign citizens who were visiting Sweden for a short period of time.

In this thesis, the educational levels of the studied men and women were collected by means of The Education register and the educational levels of the parents to the study population were based on information from the 1970 Population and Housing Census.

The study population

Textbox 1. Definition of the study population.

All women (and men[1]) born in 1973-75, registered in the MBR and the TPR, who were alive and living in Sweden at 13 years of age[2].

Women (and men) with missing values on birth weight or gestational length were excluded, as were those with extremely high birth weights compared to their length of gestation[3], and those for whom information on the parents were missing.

[1] The men were included in Paper III.
[2] In Paper IV, the women who died, emigrated or gave birth before 20 years of age were excluded. In Paper II, only the women who had given birth before the end of year 2000 were included.
[3] The exclusion procedure is explained below.

All women (and men, in Paper III) born in 1973, 1974, and 1975 according to the MBR and the TPR, who were alive and still living in Sweden at 13 years of age, served as the study population (150,425 women and 158,362 men), see Textbox 1. Information available in the other registries was retrieved by use of the infant's or mother's unique personal identification number. Women and men with missing values on birth weight and/or gestational length were excluded (1,029 women and 1,161 men), as were those with extremely high birth weights compared to their length of gestation (126 women and 167 men). We excluded those who were born in the gestational week of $\leq$ 28 and who weighed > 2,000 g and those with a gestational length of 29 or 30 weeks who weighed > 2,500 g. Men and women born in gestational week 31 or 32 who weighed > 3,000 g were also excluded as were those born in week 33 or 34 who weighed > 3,500 g. In addition, 1,003 women and 1,161 men were excluded because it was not possible to identify their mothers and/or fathers in the registries. The final study population in the present thesis therefore consisted of 148,281 women and 155,994 men. However, only the women in the study population who had themselves become mothers before the end of 2000 were included in Paper II (see 'Design of the studies' for more details). In Paper IV, the women who died, emigrated, or gave birth before the age of 20 years were excluded.

When comparing the information in the MBR and TPR some inconsistencies were found (i.e. individuals who died and then gave birth some years later, different sex recorded in the registries, etc.). These individuals were excluded from the present study population. Moreover, the year of death, and the year of giving birth differed for some individuals in the study population. In case of a difference between the registries on these two variables, the earlier year was used. Some of the women (and men) migrated during the study period (some emigrated and were thus lost for follow-up, while some emigrated and then returned to Sweden). Due to certain characteristics of the outcomes studied we defined the study population as those were alive and living in the country at 13 years of age. Thus, individuals were defined as lost for follow-up when emigrating for the first time (after 13 years of age) or when deceased.

Exposures, outcomes, and covariates

In this paragraph, more details on the primary exposures, outcomes, and covariates are presented. Note that hospitalisation is defined both as an exposure (Paper IV) and an outcome (Paper III), as are preterm birth and SGA (Papers I and III, and Paper II, respectively). See also Figure 2 for a brief overview of the variables studied.

Primary exposures

Preterm birth and very preterm birth

In this thesis, preterm birth was defined as a gestational length < 37 completed weeks of gestation (Papers I-IV). Very preterm birth was defined as < 32 completed weeks of gestation (Papers I and III). We also split the gestational length into four categories: ≤ 31, 32-36, 37-41, and ≥ 42 weeks of gestation (Paper II). Since the middle of the 1980s, the gestational length has been measured by means of ultrasound examinations predominantly made at 16-18 weeks of gestation [74]. However, as the primary study population in this thesis was born in 1973-75 (see Textbox 1), their gestational length has been measured by using last normal menstrual period dating, which has been evaluated to produce, on average, 2-3 days longer gestational length estimates than the more precise ultrasound examination [88].

Reduced foetal growth

The proxy used for reduced foetal growth in this thesis was being born SGA according to the Swedish standard, presently used by the Swedish National Board of Health and Welfare [89]. The birth weight for gestational age was predominantly dichotomised into 'born SGA', and 'born AGA', respectively (Papers I-IV). However, in Paper II the birth weight for gestational length was also expressed in 'standardised SDs' and then split into six categories: <-2, -2 to -1.01, -1 to -0.01, 0 to +1, +1.01 to +2, and > +2 SDs by using the formula presented by Marsal *et al.* [89]. Contrary to most other growth curves, the growth curves used in the Swedish standard from 1996 are based on ultrasound estimations of foetal weight for gestational age [89]. This standard has been proven more sensitive in detecting SGA, especially among infants born preterm, compared to postnatal growth curves. We also used very low birth weight, defined as a birth weight < 1,500 g, as a proxy for reduced foetal growth in Paper I.

Figure 2. Schematic overview of the variables studied.

Parents

Socio-economic characteristics at the time of giving birth

Educational levels of the mothers and fathers in 1970
Parent's country of origin
Mother's marital status
Mother's age
Mother's parity

(Mother's marital status, age and parity: Measured at the time of giving birth)

Women (and men)

Birth-characteristics

Preterm birth (and very preterm birth)
SGA (and very low birth weight)
Year of birth
Twin birth

Hospitalisations (adolescence/early adulthood)[1]

All causes of hospitalisation (dichotomised), except for diagnoses related to 'complications of pregnancy, childbirth, and puerperium', and 'certain conditions originating in the perinatal period'

Socio-economic and related characteristics

Educational level
Marital status

(Educational level and marital status: Measured at 25 years of age)

BMI
Smoking habits
Age when giving birth
Cohabitation status

(BMI, smoking habits, age when giving birth and cohabitation status: Available for the women who had become mothers during the study period)

Outcomes related to the children

Likelihood of giving birth

Time (in years) to the first birth

Birth-characteristics

Preterm birth and SGA

[1] In Paper III, hospitalisations between 12-23 years of age were included, and in Paper IV, hospitalisations between 13-19 years of age.

Hospitalisations during adolescence

Hospitalisation during adolescence (i.e. between 13 and 19 years of age) was treated as a dichotomy; 'hospitalised one or more times during adolescence' and 'not hospitalised during adolescence' (Paper IV). For women born in 1973 the hospitalisation period studied was 14 to 19 years of age, since the HDR did not have complete coverage in 1986 when these women were 13 years old. All causes of hospitalisation except for those listed in the ICD-9 chapters: 'complications of pregnancy, childbirth, and puerperium' and 'certain conditions originating in the perinatal period' were included as exposures in the analyses. However, we only included the information on main diagnosis of each hospitalisation.

Primary outcomes

Likelihood of giving birth

In Paper I, the primary outcome was the likelihood of giving birth between 13 and 27 years of age, and in Paper IV the outcome studied was the likelihood of giving birth between 20 and 27 years. The likelihood of giving birth was estimated as 'time (in years) to the first birth'. The time-variable was defined as the women's age and the women contributed to the time of follow-up until they were deceased, emigrated for the first time, gave birth, or reached the end of follow-up, whichever took place first. As the main focus was the likelihood of giving birth, we did not include information on possible successive births. There were two possible information sources regarding the endpoint; the MBR and the TPR. For some women, the information in the two registries differed. In case of discrepancy, the earlier year was included as the endpoint in the analyses.

Probability of the child being born preterm or SGA

As we were interested in the intergenerational effects of preterm birth and SGA, the outcome variable in Paper II was defined as the probability of the first-born child being born preterm or SGA. Thus, possible successive births were not studied. The first-born child's birth weight for gestational length was also expressed in 'standardised SDs' and then split into six categories: <-2, -2 to -1.01, -1 to -0.01, 0 to +1, +1.01 to +2, and > +2 SDs by using the formula presented by Marsal *et al.* [89].

Hospitalisation during adolescence and early adulthood

Hospitalisations in adolescence and early adulthood (i.e. between the years 1987-96, when the men and women were between 12 and 23 years of age) according to each ICD-chapter, respectively, was treated as dichotomies, i.e. 'hospitalised one or more times during the study period' and 'not hospitalised during the study period' (Paper III). Like in Paper IV, we only studied the main diagnosis of hospitalisation, and hospitalisations according to the chapters 'complications of pregnancy, childbirth, and puerperium' and 'certain conditions originating in the perinatal period' were not included as outcomes in the analyses.

Covariates

Childhood socio-economic characteristics

In Papers I-IV, adjustments were made for the educational levels of the women's mothers and fathers in 1970, the parents' country of origin, as well as the mother's marital status, age, and parity in 1973-75 (i.e. when the studied women (and men) were born). These characteristics are referred to parental or childhood socio-economic characteristics in the text. The educational levels of the parents were coded according to the Swedish educational system: 'elementary school' (9 or 10 years of education), 'high school' (11-13 years), and 'graduate and postgraduate education' (14 years or more). Information on the parents' country of origin was coded as: 'both Nordic', and 'one or both non-Nordic'. The marital status of the mother was coded as 'married', 'unmarried', and 'divorced or widowed', and her parity was split into two categories: 'no previous children' and 'one or more previous children'. Finally, the mother's age when giving birth was coded as '13-19', '20-26', '27-33', and '≥ 34' years.

There were a relatively large number of missing values on the mothers' and fathers' educational levels. For example in Paper I, values were missing on 10.9% of the mothers and 6.9% of the fathers. The parents for whom data on the educational level were missing were younger and born outside the Nordic countries to a greater extent. Therefore, we decided to treat these missing values as separate categories in the analyses throughout this thesis. Missing values on other childhood socio-economic characteristics (< 2% on each variable) were assigned to the most commonly occurring category on each variable (usually the reference category). However, in Paper II, all mother-offspring pairs for which information on childhood socio-economic characteristics were missing were excluded from the analyses in which these characteristics were adjusted for.

Socio-economic characteristics of the study population

Data on the study population's socio-economic characteristics were collected when they were aged 25 (Papers I, II, and IV). The educational levels were coded in the same way as the parent's educational levels: 'elementary school' (9 or 10 years of education), 'high school' (11-13 years), and 'graduate and postgraduate education' (14 years or more). However, in some of the analyses, this variable was dichotomised into: 'completed graduate and postgraduate education' and 'not completed graduate and postgraduate education'. The marital status was dichotomised into 'unmarried' or 'married', respectively. We chose to retrieve information on these variables at the age of 25 years, as the women (and men) of study had theoretically been able to reach the highest category of educational attainment at that point. Missing values on socio-economic characteristics at the age of 25 were assigned to the most commonly occurring category on each variable, except for Paper II, in which mother-offspring pairs with missing values were excluded from the adjusted analyses.

Other background characteristics of the study population

The MBR-variables 'twin birth', classified as 'twin birth' and 'singleton birth', and year of birth of the study population (i.e. 1973, 1974, or 1975) were adjusted for in Papers I, III, and IV. Furthermore, data on age when giving birth, as well as smoking habits, BMI, and cohabitation status during early pregnancy on the women in the study population who had become mothers were retrieved from the MBR (Paper II). The women's age was split into three categories: '≤ 19', '20-24', and '≥ 25' years. Smoking was coded as 'yes' or 'no', as was cohabitation status (i.e. if the women were living with the infant's father or not). The weight and height of the mothers were used to calculate the BMI, which was then divided into four categories: '< 20', '20-26', 27-33', and '≥ 34'. Information on the women's smoking habits, cohabitation status, and BMI was missing in 5.4, 6.0, and 16.1% of the 38,720 women included in Paper II. As data on maternal weight were not available in the MBR during the years 1990-91 [74], missing values on BMI were more common among teenage mothers. The same held true for the cohabitation variable, even though information was recorded in the MBR during the whole study period. Missing values on smoking habits were more common among mothers aged 25 years or more when giving birth to their first child. In Paper II, all mother-offspring pairs for which information on these variables were missing, were excluded from the adjusted analyses.

Design of the studies

Paper I

In order to investigate whether preterm birth or reduced foetal growth was connected to the likelihood of giving birth, all 148,281 women in the study population were analysed (see Textbox 1). The birth-characteristics studied were preterm birth, very preterm birth, very low birth weight, and SGA. The primary outcome measured was the hazard ratios for giving birth before 2001 (i.e. when the oldest women in the cohort were aged 27 years). Adjustments were made for childhood socio-economic characteristics, see Figure 2 for more details. The year of birth of the women and the classification of the birth as twin birth or singleton birth were also adjusted for. In addition, we stratified the women into three strata by their age: '13-19 years', '20-24' years, and '≥ 25 years'. In the last stratum, additional adjustments were made for the studied women's own educational levels and marital status at the age of 25 years. In Table 1, an overview of the papers is displayed.

Paper II

To evaluate the intergenerational effects of preterm birth and SGA, 40,152 women in the study population who had themselves become mothers before or at 27 years of age were identified through the registries. Of these women-first-born offspring pairs, 262 were excluded due to missing values on the child's birth weight and/or gestational length, and 5 due to extreme birth weights compared with the length of their gestation. In addition, mother-offspring pairs where either the mother or the child was the result of a twin birth (n = 548 and 356, respectively) were excluded, as were pairs for whom the grandparents (i.e. the studied women's parents) could not be identified in the registries (n=273), leaving 38,720 mother-offspring pairs available for analysis. The effect of the studied woman's gestational length and her birth weight for gestational length (expressed in 'standardised SDs') on the occurrence of preterm birth and SGA in the first-born child was evaluated in more detail by categorising the woman's gestational length into four categories and her birth weight for gestational length into six categories (see 'Exposures, outcomes, and covariates' for more details). In addition, the effect of the women's birth weight for gestational age on reduced foetal growth in the children was also evaluated in more detail.

Table 1. Overview of the papers included in the present thesis.

Paper	Subjects	Exposures	Primary outcomes	Covariates[2]
I	All women in the study population (*n* = 148,281)[1]	Preterm birth, very preterm birth, SGA, and very low birth weight	Hazard ratio for giving birth between 13 and 27 years of age	Socio-economic characteristics of the parents and the women, the women's year of birth, and twin birth.
II	All singleton women in the study population[1] who had become mothers (*n* = 38,720)	Preterm birth and SGA	The probability of the first-born child being born preterm or SGA	Socio-economic characteristics of the parents and the women, the women's smoking habits, BMI, and cohabitation status during early pregnancy.
III	All men and women in the study population[1] (*n* = 304,275)	Preterm birth and SGA	Hospitalisations during adolescence and early adulthood (i.e. 1987-96)	Parental socio-economic characteristics, the men and women's year of birth, and twin birth.
IV	All women in the study population[1], living in Sweden at 20 years of age (*n* = 142,998)	Hospitalisations during adolescence	Hazard ratio for giving birth between 20 and 27 years of age	Socio-economic characteristics of the parents and the women, the women's year of birth, preterm birth, SGA, and twin birth.

1 See Textbox 1 for the definition of the study population.
2 'Parents' refers to the study population's parents, while 'men' and 'women' refers to members of the study population.

Adjustments were made for childhood and adult socio-economic characteristics of the women (i.e. mothers), like in Paper I. Additional adjustments were made for the women's smoking habits, BMI, and cohabitation status in early pregnancy, as well as their age when giving birth.

Paper III

In Paper III, we wanted to study if the risk of all-cause hospitalisation in adolescence and early adulthood differed between men and women who were born preterm or SGA, as compared to those born at term and AGA. The study population consisted of 155,994 men and 148,281 women (see Textbox 1). Hospitalisation during adolescence and early adulthood (i.e. between the years 1987-96, when the men and women were between 12 and 23 years of age) according to each ICD-chapter, respectively, was treated as a dichotomy. In order to evaluate the relations in more detail, hospitalisations due to the three most common main diagnoses on the three-digit level in each ICD-chapter for the men and the women, respectively, were also used as outcomes. Adjustments were made for childhood socio-economic characteristics. The year of birth of the men and women and the classification of the birth as twin birth or singleton birth were also adjusted for.

Paper VI

The aim of Paper IV was to examine the effect of hospitalisation during adolescence on the likelihood of giving birth. As the main exposure studied was hospitalisation during adolescence (dichotomised as in Paper III), we excluded women who emigrated, died, or gave birth before 20 years of age. Thus, the study population consisted of 142,988 women, who were followed up to evaluate the likelihood of their giving birth between 20 and 27 years of age. In order to evaluate the associations in more detail, hospitalisations due to the five most common main diagnoses on the three-digit level in each of the studied ICD-chapters, respectively, were also used as independent variables. Adjustments were made for childhood socio-economic characteristics. The year of birth of the women and if the women were born as a result of twin birth, or born preterm or SGA, were also adjusted for. As in Paper I, some analyses were stratified by the women's age: '20-24' years and '≥ 25 years'. In the last stratum, additional adjustments were made for the studied women's own educational levels and marital status at the age of 25 years.

Statistical methods

Logistic regression

The primary results in Papers II and III were retrieved by use of logistic regression analysis and SPSS was used to compute the odds ratios (OR) and 95% confidence intervals (CI). In Paper II, analyses were performed both on the original study population and on the mother-offspring pairs for which information on neither of the included variables was missing (n = 24,520). Odds ratios and 95% confidence intervals were adjusted for covariates (see Table 1). When estimating the effect of the women's birth weight for gestational age on reduced foetal growth in the children, a series of three logistic regression analyses was used. In the first analysis, all mother-offspring pairs were included; in the next analysis, we excluded children who were SGA and examined the children whose birth weights for gestational length were between -2 SD and -1.01 SD. Finally, we excluded all children below -1 SD and investigated the children whose birth weights for gestational length were between -1 to -0.01 SD. The final models were then evaluated by creating two-way interaction terms between the women's birth characteristics and the other independent variables studied. The interaction terms were determined by forward stepwise regression, and the significance level of the interactions were set to $p \leq 0.01$ (due to the relatively large number of tests).

In Paper III, the dependent variables were hospitalisations (dichotomised into 'hospitalised one or more times' and 'not hospitalised') during the study period according to each ICD-chapter category, and odds ratios (OR) and 95% confidence intervals (CI) were computed. Due to the large number of analyses in screening on the most common main diagnoses among the men and women, respectively, the significance level in the screening was set to $p \leq 0.01$. All diagnoses included in the screening are presented in Electronic appendix 1 in Paper III.

Cox's proportional hazards model

The primary results in Papers I and IV were retrieved by modelling the data through Cox's proportional hazards model and SPSS was used to compute the hazard ratios (HR) and 95% confidence intervals (CI). The time-dimension in the models was defined as age, and subjects exited from risk when they gave birth to the first child, emigrated for the first time, died, or reached the end of follow-up. In Paper I, the primary independent variables investigated were the women's birth-characteristics (i.e. preterm birth, very preterm birth, very low birth weight, and SGA). In Paper IV, the primary independent variables were hospitalisations during adolescence (dichotomised) according to each ICD-chapter category. The significance level in screening on the most common main diagnoses was set to $p \leq 0.01$.

The Cox's proportional hazards models were checked for proportionality by creating interaction terms between the time-variable and each of the four birth-characteristics (Paper I) as well as hospitalisations during adolescence (ICD-chapters) (Paper IV), respectively. As these model validations revealed some violations of the proportional hazards assumption, additional analyses were performed in which the time-variable (i.e. the women's age) was stratified for. Two-way interaction terms between the primary exposures and each covariate included were also created to evaluate the models. The interaction terms were determined by the forward stepwise method and the significance level of the interactions were set to $p \leq 0.01$.

RESULTS

Birth-characteristics in relation to childbearing (Paper I)

Of the 148,281 women born in 1973-75, alive and still living in Sweden at 13 years of age (see Textbox 1), 4.1% were born preterm, 0.3% were born very preterm, 0.3% were born with very low birth weights, and 5.4% were SGA (Paper I). Among the women, 30.2% had given birth to one child or more at ≤ 27 years of age. Table 4 in Paper I shows that the hazard ratio of giving birth during the study period was 25% lower among women who themselves were born with very low birth weights, compared to women who weighed ≥ 1,500 g at birth, and adjusting for childhood socio-economic characteristics did not markedly change the results. Also, women who were the result of a twin birth were less likely to have given birth during the study period (Table 3 in Paper I). On the other hand, women who were born SGA were 9% more likely to have given birth during the study period (Table 4 in Paper I). This increase in 'risk' was evident after accounting for the increase in birth weight between 1973-75 and 1996, when the Swedish SGA-standard was calculated (Appendix 1). As the growth curves used are based on singleton births we also evaluated the effect of using a SGA-standard specially designed for twins on the results [90]. However, using this standard produced similar results compared to the ones presented in Table 4 in Paper I (Appendix 1).

Table 2. Birth-characteristics in relation to the likelihood of giving birth, stratified by the women's age.

Birth-characteristics	Age of the women (time-strata)					
	13-19 years[1]		20-24 years[1, 2]		25-27 years[3]	
	HR	95% CI	HR	95% CI	HR	95% CI
Preterm births (all)	1.04	0.90-1.20	1.01	0.95-1.08	0.92	0.84-1.01
Very preterm birth	1.38	0.90-2.12	0.89	0.70-1.13	0.71	0.50-1.01
Very low birth weight	0.97	0.56-1.67	0.84	0.65-1.10	0.51	0.33-0.78
SGA	1.17	1.04-1.32	1.06	1.00-1.12	1.07	1.00-1.16

[1] Cox's proportional hazards model adjusted for childhood socio-economic characteristics, as well as for the year of birth of the studied women and if the women were born as a result of twin birth.

[2] Excluded in the analyses were 5,293 women who gave birth, died, or emigrated before the age of 20 years.

[3] The models were adjusted for the variables presented in [1] as well as the women's own marital status and educational level at the age of 25. Excluded in the analyses were 31,646 women who gave birth, died, or emigrated before the age of 25 years.

Table 2 (which is similar to Table 5 in Paper I) shows the relation between the birth-characteristics studied and the likelihood of giving birth, when stratified by time (i.e. the age of the women). The reduced likelihood of giving birth among very low birth weight women was most marked among women aged ≥ 25 years. In this stratum, there were also tendencies of reduced hazard ratios for giving birth among women who were born preterm and very preterm. However, women who were born SGA were more likely to have given birth irrespective of age, but when a more extreme group (< -3 SD) was analysed, the results showed a similar pattern to that of the other birth-characteristics presented in Table 2 (Table 6 in Paper I).

Birth-characteristics and pregnancy outcome (Paper II)

Of the women born in 1973-75, 38,720 had given birth to a (singleton) child at ≤ 27 years of age (Paper II). Of these mothers, 3.7% were born preterm and 5.5% were SGA. The corresponding percentages among the first-born children were 6.4 and 2.8, respectively. Preterm birth appeared to be more common in children whose mothers were born preterm or SGA, compared to mothers born at term or AGA (Table 3, Table 3 in Paper II). However, when the analyses were restricted to include only the mothers with no missing data on covariates, no significant intergenerational effect of preterm birth was found.

Table 3 further shows an intergenerational effect of SGA, while preterm birth in the mothers did not significantly influence the occurrence of SGA in the child. In addition, Figures 1 and 2 in Paper II demonstrate that mothers whose foetal growth was moderately reduced but who did not meet the criterion of being born SGA were also at higher risk of giving birth to both preterm and SGA children, respectively. The results presented in Table 3 remained substantially the same even though we restricted the analyses to include only mother-offspring pairs in which the mother also was first-born, if both preterm birth and SGA in the mothers were simultaneously adjusted for, and if accounting for the mean increase in birth weight between 1973-75, when the studied women were born, and 1996, when the Swedish SGA-standard was calculated (Appendix 2).

Table 3. Intergenerational effects of preterm birth and SGA.

	Crude OR[1]	**Adjusted OR**[2]	**95% CI**	***p***
Child born preterm				
Mother born preterm	1.31	1.24	0.95-1.62	0.12
Mother born SGA	1.23	1.30	1.05-1.61	0.017
Child born SGA				
Mother born preterm	1.29	1.08	0.70-1.64	0.74
Mother born SGA	2.79	2.68	2.11-3.41	< 0.001

1 Analyses performed on all eligible mother-offspring pairs (*n* = 38,720).

2 Analyses performed on all mother-offspring pairs with complete data on all background variables (*n* = 24,520). The logistic regression analyses were adjusted for the mother's smoking habits, cohabitation status, BMI, and age at the time of pregnancy. Adjustments were also made for childhood socio-economic characteristics.

Effect of socio-economic characteristics as well as BMI and smoking on childbearing and pregnancy outcome

Socio-economic characteristics in relation to childbearing (arrows 1-2, Figure 3)

Childhood socio-economic characteristics influenced the likelihood of giving birth among women aged ≤ 27 years and the general trend was that higher socio-economic status yielded in a lower likelihood of the outcome (Table 3 in Paper I). Lower educational levels and being married at the age of 25 were indicative of increased likelihood of giving birth between 25 and 27 years of age among the women studied (Appendix 3).

Socio-economic characteristics, BMI, and smoking in relation to pregnancy outcome (arrows 3-6, Figure 3)

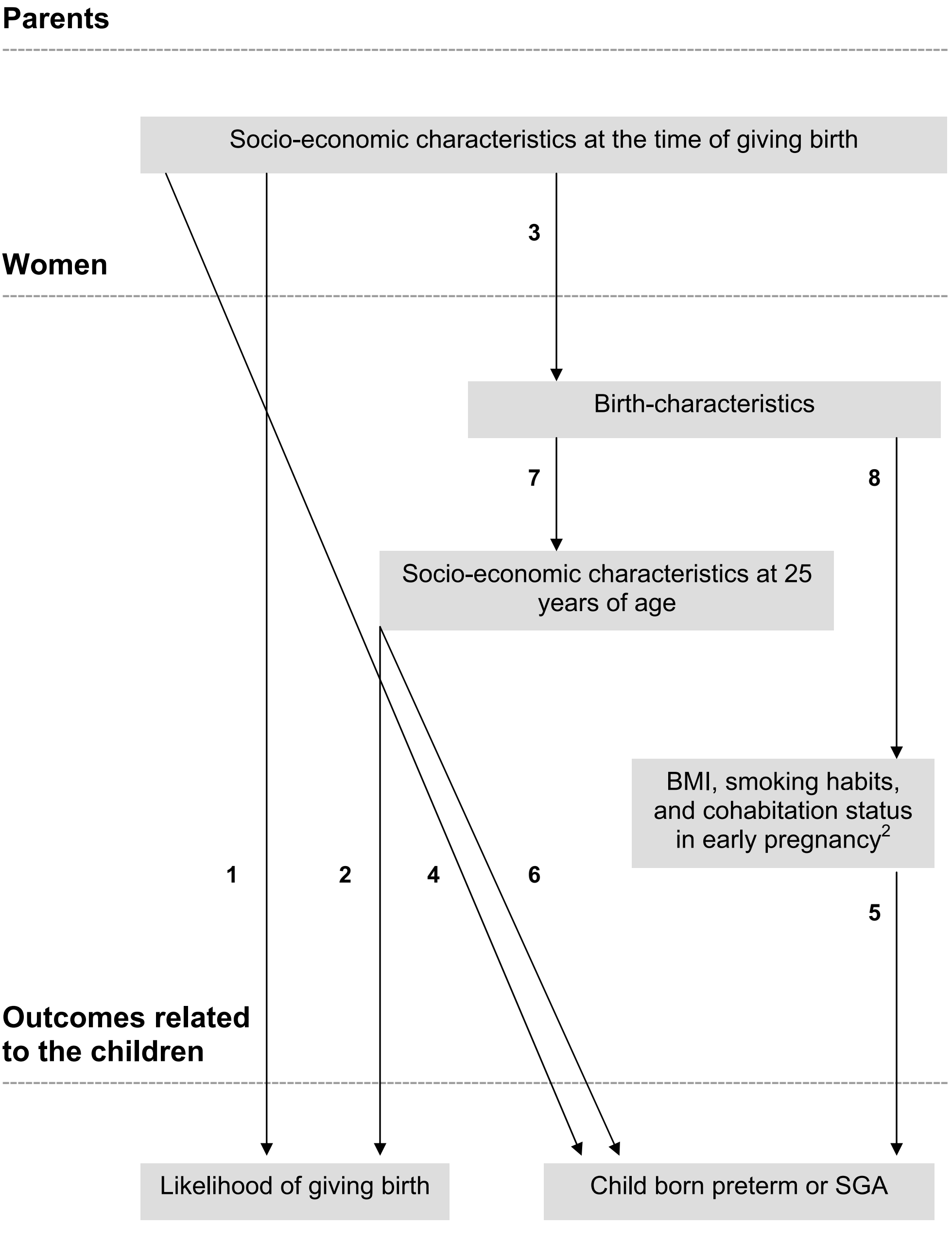
Analyses made in Paper I showed that parental socio-economic characteristics were related to the studied women's probability of being born preterm, very preterm, SGA or with a very low birth weight (Table 1 in Paper I, Appendix 4A-D). The general trend was that the presence of markers of lower socio-economic status in the parents increased the probability of giving birth to a child with non-optimal birth-characteristics. The educational level of the mother in 1970 was also connected to the probability of the studied women's children being born preterm (Table 2 in Paper II).

When analysing the women who had become mothers at ≤ 27 years of age (n = 24,520, see Paper II), there was evidence of a higher risk for giving birth to a SGA child among women who smoked at the time of their pregnancy, compared to non-smokers (Table 2 in Paper II). There was also some evidence that underweight women (i.e. BMI < 20) were more likely to give birth to SGA children, while preterm birth in the child was positively associated with BMI ≥ 25. In addition, women who had higher educational levels at the age of 25 were less likely to give birth to SGA children, whereas the women's marital status at 25 did not affect the outcome of her pregnancy (Appendix 5).

Birth characteristics in relation to subsequent socio-economic characteristics, BMI, and smoking habits (arrows 7-8, Figure 3)

Table 2 in Paper I indicates that among the women born in 1973-75, those born preterm, very preterm, SGA, or with very low birth weights were less likely to have reached the highest level of education at the age of 25, compared to women born at term or whose foetal growth was not affected. However, there was no evidence of birth-characteristics influencing the likelihood of being married at the age of 25. Women born SGA who had become mothers at ≤ 27 years of age were more likely to be smoking at the time of their own pregnancy and had lower pre-pregnancy BMI, compared to women born AGA (Table 1 in Paper II, Appendix 6). In addition, women who were born preterm and who had given birth to one child or more appeared to be less likely to be living with the child's father at the time of pregnancy.

Figure 3. Schematic overview of the relations studied regarding birth characteristics, socio-economic characteristics, BMI, and smoking (Papers I and II)[1].



[1] For more details on the variables included, see Figure 2.
[2] These variables are available for the women who became mothers at ≤ 27 years of age only.

Birth-characteristics and hospitalisations (Paper III)

Of the 304,275 men and women born in 1973-75, studied in Paper III, 4.0% were born preterm (and AGA), 4.6% were SGA (and at term), and 0.4% were both born preterm and SGA. Of the men and women studied, 30.0% were hospitalised one or more times in adolescence and early adulthood (i.e. between 12 and 23 years of age) according to the 15 ICD-chapters studied. The most common causes of hospitalisation during the study period are listed in Electronic appendix 1 in Paper III. Men and women born preterm had higher overall risks of hospitalisation by 6% during adolescence and early adulthood, while the risks among those born SGA and both preterm and SGA were 16 and 42%, respectively, compared to those born AGA and at term (Figures 1-3 and Electronic appendix 2 in Paper III, see also Appendix 7 for the risk estimates among those born very and moderately preterm, respectively). Adjusting for childhood socio-economic characteristics had relatively little effect on the relations found. However, twins were of lower risk of being hospitalised during the study period (Table 1 in Paper III). Although the women were somewhat more likely to be hospitalised than were the men, there was little evidence of interaction by sex (Electronic appendix 3 in Paper III).

All birth-characteristics studied were indicative of increased risks for hospitalisations according to diagnoses listed in the ICD-chapters: 'mental disorders', 'diseases of the nervous system, 'congenital anomalies', and 'symptoms, signs, and ill-defined conditions' (Table 4, as well as Figures 1-3 and Electronic appendix 2 in Paper III). Men and women who were born preterm (and AGA), and both preterm and SGA, respectively, seemed to be of higher risks of, for example, 'endocrine, nutritional, and metabolic diseases'. Being born SGA was positively connected to hospitalisations according to 'diseases of the genitourinary system' even after stratifying the women into those who had given birth and those who did not give birth during the study period and after excluding men and women with congenital malformations of genital organs (Appendix 8). Higher risks for 'injury, poisoning, and other external causes' were also found among those born SGA. A screening was performed on the three most common three-digit level diagnoses listed in each ICD-chapter for the men and women, respectively, and the results are presented in Tables 2-4 in Paper III.

Socio-economic characteristics and hospitalisation

All childhood socio-economic characteristics measured, except for the parent's country of origin, were connected to the overall risk of hospitalisation during adolescence and early adulthood among the men and women studied (Table 1 in Paper III). The general trend was that lower socio-economic status yielded a higher risk for hospitalisation. Also, men and women who were born in 1973 were more likely to have been hospitalised during adolescence and early adulthood, compared to those born 1974 and 1975.

Table 4. Birth-characteristics in relation to hospitalisations in adolescence and early adulthood. Selected output[1].

	Preterm (only)		SGA (only)		Preterm and SGA	
ICD-9 chapter	OR[2]	95% CI	OR[2]	95% CI	OR[2]	95% CI
Infections and parasitic diseases	0.97	0.85-1.11	1.12	1.00-1.26	1.43	1.01-2.02
Endocrine, nutritional, and metabolic diseases	1.30	1.08-1.56	1.14	0.95-1.37	1.61	0.98-2.66
Mental disorders	1.22	1.09-1.37	1.45	1.32-1.60	1.71	1.27-2.29
Diseases of the nervous system	1.57	1.39-1.77	1.60	1.43-1.79	3.04	2.32-3.98
Diseases of the circulatory system	1.15	0.93-1.43	1.24	1.02-1.51	1.71	0.98-2.98
Diseases of the respiratory system	1.02	0.93-1.11	1.08	0.99-1.17	1.28	1.00-1.63
Diseases of the genitourinary system	1.06	0.94-1.18	1.36	1.24-1.49	1.31	0.96-1.79
Diseases of the skin and subcutaneous tissue	1.21	0.99-1.48	0.92	0.74-1.14	1.72	1.01-2.94
Congenital anomalies	1.36	1.15-1.61	1.72	1.49-1.98	1.84	1.20-2.85
Symptoms, signs, and ill-defined conditions	1.11	1.03-1.20	1.29	1.20-1.37	1.23	0.99-1.53
Injury, poisoning, and other external causes	1.01	0.95-1.07	1.10	1.04-1.16	1.10	0.92-1.32

1 Only relations with $p \leq 0.05$ in at least one analysis (i.e. among those born 'preterm', 'SGA', or 'preterm and SGA') are displayed in the table.

2 Logistic regression analysis adjusted for childhood socio-economic characteristics, as well as for sex and year of birth of the studied men and women and if the men and women were born as a result of twin birth.

Table 5. Hospitalisations during adolescence in relation to the likelihood of giving birth. Selected output[1].

ICD-9 chapter	**HR[2]**	**95% CI**
Infections and parasitic diseases	1.26	1.16-1.36
Blood diseases and immunity disorders	1.60	1.42-1.80
Mental disorders	1.35	1.25-1.45
Diseases of the respiratory system	1.32	1.26-1.38
Diseases of the digestive system	1.24	1.18-1.31
Diseases of the genitourinary system	1.66	1.57-1.76
Diseases of the skin and subcutaneous tissue	1.26	1.10-1.45
Diseases of the musculoskeletal system and connective tissue	1.21	1.12-1.30
Symptoms, signs, and ill-defined conditions	1.54	1.48-1.60
Injury, poisoning, and other external causes	1.24	1.19-1.29

1 Only relations with $p \leq 0.05$ are displayed in the table.

2 Cox proportional hazards model adjusted for childhood socio-economic characteristics, as well as for the year of birth of the studied women and if the women were born as a result of twin birth or born preterm or SGA.

Hospitalisations in relation to childbearing (Paper IV)

Of the 142,998 women born in 1973-75, alive and living in Sweden at 20 years of age, the overall risk of being hospitalised one or more times during adolescence was 22.1% and 28.8% had given birth between 20 and 27 years of age (Paper IV). Women hospitalised according to a main diagnosis in at least one of the 15 studied ICD-chapters were 32% more likely to have given birth between ages 20-27, compared to those not hospitalised during adolescence. Evidence of positive relations were found for diagnoses listed in 11 out of 15 ICD-chapters (Table 1 in Paper IV). Women who were hospitalised due to diagnoses listed in ICD-chapters 'diseases of the genitourinary system', 'symptoms, signs, and ill-defined conditions', and 'blood diseases and immunity disorders', respectively, one or more times during adolescence seemed to be the most likely to have given birth (Table 5 and Table 1 in Paper IV). However, there was some indication of a reduced likelihood of giving birth between ages 20-27 among women who were hospitalised due to diagnoses related to the ICD-chapter 'congenital anomalies' and the three-digit level diagnosis 'infantile cerebral palsy' (Tables 1 and 2 in Paper IV). A screening was performed on the five most common three-digit level diagnoses listed in each ICD-chapter and the results are presented in Table 2 in Paper IV.

For diagnoses related to some of the ICD-chapters there was evidence of the hazard ratios decreasing by time (i.e. the women's age), and the most marked negative time-trend was found for the ICD-chapter 'mental disorders' (Table 3 in Paper IV). Women hospitalised according to this ICD-chapter during adolescence had an increased likelihood of giving birth between 20 and 24 years of age, but a reduced likelihood of giving birth between ages 25-27. The results in the last stratum in Table 3 (in Paper IV) remained substantially the same even if the women's own educational levels and marital status at 25 years of age were not adjusted for (Appendix 9).

Hospitalisation and subsequent socio-economic characteristics

Additional analyses made in Paper IV revealed that women who had been hospitalised during adolescence were more likely to be married at the age of 25. They were also less likely to have completed a graduate or postgraduate education at that time. These associations were evident after stratifying the women into those who had given birth and those who had not given birth between 20-27 years (Appendix 10).

Effect of hospitalisation on the relation between birth-characteristics and childbearing

The results in Paper I indicate a connection between birth-characteristics and the likelihood of giving birth. As hospitalisation is connected to both the birth-characteristics studied as well as to the likelihood of giving birth among the women studied (Electronic appendix 3 in Paper III and Table 1 in Paper IV), we performed additional analyses in which hospitalisations during adolescence were also accounted for, see Table 6. However, these additional adjustments had little effect on the relation between birth-characteristics and the likelihood of giving birth.

Table 6. Birth-characteristics in relation to the likelihood of giving birth.

	Crude HR[1]	**Adjusted HR**[1, 2]	**95% CI**	***p***
Preterm birth	0.99	0.98	0.93-1.03	0.38
Very preterm birth	0.91	0.91	0.76-1.09	0.30
Very low birth weight	0.75	0.75	0.61-0.92	0.005
SGA	1.13	1.07	1.02-1.12	0.003

1 Cox's proportional hazards model. Excluded in the analyses were 5,293 women who gave birth, died, or emigrated before the age of 20 years.

2 Adjusted for childhood socio-economic characteristics, as well as for the year of birth of the studied women and if the women were born as a result of twin birth. Adjustments were also made for hospitalisation during adolescence (i.e. the 15 ICD-chapters studied in Papers III and IV).

DISCUSSION

Summary of principal findings

In summary, the following results were found (see Figure 4 for a schematic overview):

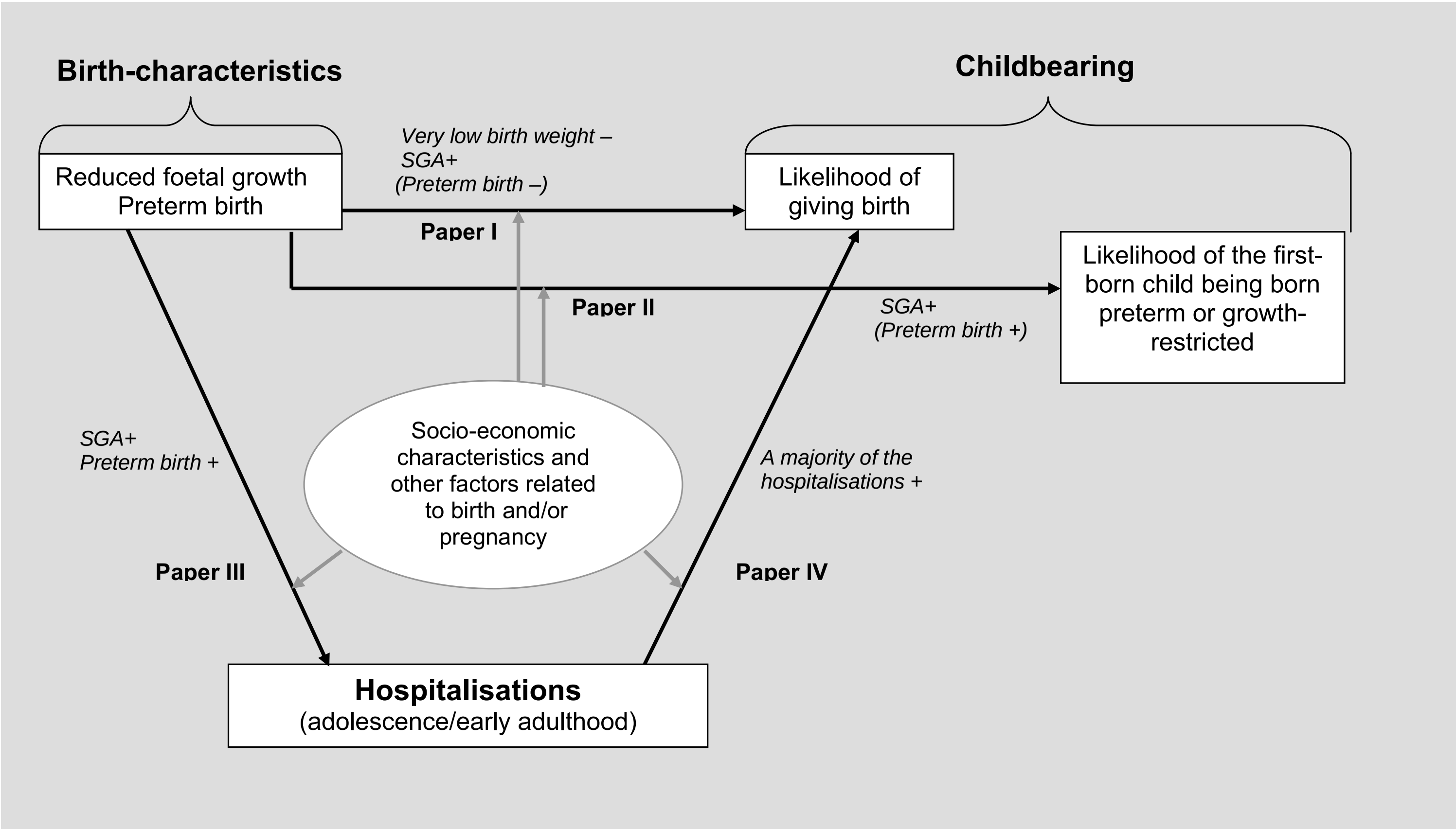
… Reduced foetal growth and, possibly, preterm birth was connected to the likelihood of giving birth between 13 and 27 years of age (Paper I). The results presented suggest that very low birth weight women were less likely to have given birth between 13 and 27 years of age compared to women with higher birth weights, and this was most apparent among women aged 25 or more years. In this age group there was also some indication of reduced likelihood for giving birth among women who were born preterm. On the other hand, women born SGA, which is a 'broader' proxy for reduced foetal growth than is very low birth weight, seemed more likely to have given birth between 13 and 27 years of age, compared to women born AGA. However, when a more extreme group of SGA was defined the relation was less evident.

… We found an intergenerational effect of reduced foetal growth, but no consistent intergenerational effect of preterm birth (Paper II). Women who themselves had been born SGA were more likely to have given birth to SGA and preterm children, respectively, between 13 and 27 years of age, compared to women born AGA. Women whose foetal growth was moderately reduced but who did not meet the criterion of being born SGA were also at higher risk for these outcomes. However, women who were born preterm were not significantly more likely to deliver their own children preterm or SGA, compared to women born at term.

… Men and women born SGA or preterm were at higher risk for hospitalisations during adolescence and early adulthood (i.e. between 12 and 23 years of age), compared to those born AGA and at term (Paper III). Men and women born SGA appeared to be more at risk compared to those born preterm. More specifically, these birth-characteristics were connected to higher risks for outcomes such as congenital anomalies, neurodevelopment sequelae, and 'unspecified symptoms'. Preterm birth was also connected to diabetes mellitus, while being born SGA was related to short stature, and genitourinary diseases. In addition, drug use appeared to be more common among men and women born SGA.

… A majority of the causes of hospitalisation during adolescence increased the likelihood of giving birth between 20 and 27 years of age (Paper IV). Evidence of positive relations were found for diagnoses listed in 11 out of 15 ICD-chapters, and, for example, women who were hospitalised due to genitourinary diseases, abdominal problems, and abuse of alcohol and drugs were more likely to have given birth during the study period. However, hospitalisations according to cerebral palsy and congenital malformations tended to decrease the likelihood of giving birth. For diagnoses related

Figure 4. Schematic summary of the present thesis[1].



[1] + indicates a positive connection and - a negative connection between the exposures and the outcomes studied.

to some of the ICD-chapters there was evidence of a negative time-trend. For example, women hospitalised due to mental disorders had an increased likelihood of giving birth between 20 and 24 years of age, but a reduced likelihood of giving birth between ages 25-27.

… Although socio-economic characteristics were connected to both the exposures and outcomes studied in Papers I-IV, they had little effect on the relations found. The same held true for smoking habits and BMI during early pregnancy (Paper II), and for birth-related variables such as year of birth and twin birth (Papers I, III, and IV).

Methodological considerations

One of the major strengths of the studies included in the present thesis is that they are based on a large population-based cohort with prospectively collected register data. However, the epidemiological nature of the studies that constitute this thesis prevent us from drawing straightforward conclusions about causality or the mechanisms underlying the relations found.

Birth-characteristics

Although the overall information on gestational length and birth weight is reliable, evaluations of the MBR have shown evidence of measurement errors in both extremes of the distributions of birth weight and gestational length [75, 76]. We have tried to reduce these errors by excluding men and women whose birth weights were 'extremely high' compared to the estimated length of their gestation. As the study population in this thesis was born in 1973-75, their gestational length has been measured by using last normal menstrual period dating, which has been evaluated to produce longer gestational length estimates than the more precise ultrasound estimation [88]. Thus, the study population may include some persons who ought to have been classified as preterm but were wrongly classified as full-term (i.e. 'false negatives'). However, this ought to have a conservative influence on the relations found. Moreover, the growth curves used to calculate SGA may not be representative for infants born in 1973-75 as the birth weights were lower compared to 1996 (when the SGA standard was calculated) [91]. However, additional analyses in which the mean increases in birth weight were accounted for did produce similar results to those presented in Papers I and II. It is important to bear in mind that SGA and very low birth weight are only proxies for 'true' reduced foetal growth [2, 92], but also that specific causes of restricted growth and preterm birth may cause a poor paediatric outcome independently of these birth-characteristics.

Hospitalisations

It is also important to recognise that we studied hospitalisations, not morbidity. Hospitalisations only cover more serious conditions and the likelihood of being hospitalised may be influenced by social and behavioural factors. However, hospitalisations could be regarded as a proxy for a substantial part of the morbidity. A consequence of studying hospitalisation in a 'broad perspective' is an increased risk of ‘false significances’ due to the many analyses that were performed. The value of so called risk-factor epidemiology (or ‘Black-box epidemiology’) has been debated and the main criticism has been that it is an empty research for associations with little theoretical relevance [93]. However, Greenland *et al.* [93] defend risk-factor epidemiology “…as a valuable source of seemingly unrelated facts that await coherent explanation by novel theories and that provide empiric tests of theories.”, but he also point out that one should be cautious in drawing any conclusions on causality. In Papers III and IV, we only considered $p \leq 0.01$ to be significant in the performed screenings and also focused the discussions on the more general and/or consistent relationships found. The HDR includes errors that may have consequences for the results [77, 81]. In addition, we only studied the main diagnoses of hospitalisation. Thus, some caution should be observed in (over)interpreting the results.

Childbearing

In Papers I and IV the outcome studied was the likelihood of giving birth. We had no information on abortions, or if the women studied actually tried to become pregnant, which, naturally, is highly associated with a woman’s likelihood of giving birth during any given period of time. The follow-up period was also relatively short in terms of estimating this outcome, but as the MBR started in 1973 a longer time of follow-up was not possible at the time when the studies were performed. In Sweden, the mean age of giving birth to the first child was 27.7 years in 2000 [91] at which point the women in the present study were 25-27 years of age. In Paper IV, teenage pregnancies were excluded. However, teenage deliveries are relatively uncommon in Sweden (about 2% in the year 2000 [91]) and excluding them ought to have little impact on the results presented. The relatively short follow up time regarding the likelihood of giving birth in Papers I and IV, together with the fact that the hazard ratios seemed to be decreasing with time (i.e. age), raise questions about the effect of a longer follow-up period on the relations found.

Socio-economic characteristics

Through the registries, we were able to get information on several socio-economic characteristics in childhood and adulthood, which are important to account for, as they were related to both the exposures and outcomes studied. However, we only retrieved information on socio-economic characteristics at two points in time: parental socio-economic characteristics were measured at the time of birth of the population studied and socio-economic characteristics of the men and women in the study population were retrieved when they were 25 years of age. As many of the socio-economic characteristics measured may change over time, it is important to note that the variables retrieved provide only a ‘snapshot’. Moreover, it should be noted that the included socio-economic characteristics taken together are to be regarded as a crude proxy for the arbitrary variable ‘socio-economic status’ (see for example the discussion in Plant *et al.* [94]).

We had information on the study population’s educational levels at the age of 25 at which point they were all theoretically able to have reached the highest category of educational attainment. The disadvantage in retrieving this information relatively late during the study period is that it is more difficult to adjust for these variables in the analyses because of the possible bias due to reversed causality (for example the educational level could affect the likelihood of giving birth, but giving birth before age 25 could also affect the educational level at 25 years). As a consequence, not all analyses were adjusted for adult socio-economic characteristics. On the other hand, assessing the educational level at a younger age would have led to less informative and accurate data. Thus, there may still be residual confounding by socio-economic position.

Principal findings in relation to other research

Birth-characteristics in relation to childbearing and pregnancy outcome

There are not many studies reporting on the connection between birth-characteristics and the likelihood of giving birth (as reported in Paper I). However, previous studies have shown that women whose waiting time to pregnancy was more than one year (a common definition of infertility [49]), seem to be at higher risk of adverse pregnancy outcomes such as preterm birth [50]. In Paper II, we found that reduced foetal growth in the mother increases the risk of her giving birth to a growth restricted or preterm child. We also found some evidence of preterm birth in the mother increasing the risk of the child being born preterm. These connections seem to be in keeping with several other studies [37-46]. Thus, non-optimal birth-characteristics may be related to a longer waiting time to pregnancy/infertility. It has also been suggested that the intergenerational effects of birth-characteristics could be explained by genetic mechanisms [41, 42, 47], and the connection between SGA in the mother and preterm birth in the child, found in Paper II, could be explained by women born SGA having an increased risk for pre-eclampsia [48].

One Norwegian study has found that women with congenital anomalies, which are more common among those born preterm or with reduced foetal growth (Paper III), are less likely to have children [55]. Also, a recent review showed that fewer very-low-birth-weight women than controls had had intercourse, been pregnant, or delivered a live born infant at the age of 20 years, even when controlling for socio-demographic status [16]. This appears to be in line with the results of Paper I. Studies on adolescent girls have also shown that there seems to be a connection between being born SGA and subsequent risk of reduced fertility [35]. However, the findings in Paper I do not seem to support such an association as women born SGA were more likely to have given birth between 13 and 27 years of age, compared to those born AGA. On the other hand, the results of Paper III reveal an association between SGA and subsequent risk for genitourinary diseases in adolescence and early adulthood, which could be regarded as to be in line with the findings of Ibanez *et al.* [35]. As hospitalisations due to genitourinary diseases also seem to increase the likelihood of giving birth at ≤ 27 years (Paper IV), one might speculate that the higher risk of genitourinary diseases (or other morbidity) is involved in explaining the positive relation between being born SGA and subsequent likelihood of giving birth. However, preliminary analyses do not support that theory (see Table 6).

Birth-characteristics in relation to hospitalisations in adolescence and early adulthood

Not many studies have been performed in order to investigate the connection between birth-characteristics and subsequent risk of hospitalisation in a 'broad perspective' (i.e. by studying all causes of hospitalisation). However, a Danish study found evidence of an inverse relationship between birth weight and all-cause mortality in early adult life among men [7]. In line with previous research, we found that men and women born preterm or with reduced foetal growth were at higher risk for neurodevelopment sequelae and mental disorders [13, 16-18, 95], as well as respiratory disease [16, 23, 24]. We found that preterm birth was connected to hospitalisations due to diabetes mellitus, and SGA to short stature. These relations have also been shown in previous research [8, 13, 96, 97]. In addition, we found that being born SGA was connected to subsequent hospitalisation due to genitourinary diseases which could be regarded as to be in line with the findings of Ibanez *et al.* [35], as mentioned previously.

Paper III shows men and women who were born SGA were more likely to be hospitalised due to use of drugs and to injury and poisoning. The latter connection seems to be in keeping with two Nordic studies [7, 21], but the relation to drug use appears to be contradictory to the results of a recent review [16]. In Paper III we used SGA as a proxy for reduced foetal growth while Hack reviewed the long-term effects of very low birth weight [16]. Thus, the discrepancy might be due to the proxy used. The connection to drug use could also be an effect of residual confounding by social position, as the social environment is a marker of substance abuse in adult life [98]. Men and women born SGA or preterm also seemed to be at higher risk of hospitalisation according to 'symptoms, signs, and ill-defined conditions'. Diagnoses related to this ICD-chapter have not previously been reported on although hospitalisations according to this chapter are among the most common causes of hospitalisation during adolescence and early adulthood at least in Sweden. Although it is difficult to theorise on the cause of these associations, it is possible that those born SGA or preterm are more prone to seek medical advice for less severe conditions, as previously hypothesised by Källén *et al.* [99].

Hospitalisations in adolescence and childbearing

As mentioned in the introduction, the relation between adolescent morbidity and future childbearing has not often been addressed. In Paper IV, we found that a majority of the causes of hospitalisation during adolescence increased the likelihood of giving birth at ages 20 to 27, although the results of other studies suggest a reduction in fertility following certain kinds of morbidity [51, 52, 54-57]. However, there is some evidence to suggest that chronic illness is positively connected to sexual risk-taking behaviour [59, 60]. Previous research implies that morbidity related to neurodevelopment sequelae and congenital anomalies may have a negative effect on future fertility [55, 56], which is in line with results of Paper IV.

We found that women hospitalised due to genitourinary diseases during adolescence had a higher likelihood of giving birth. Diagnoses connected to abdominal problems were also positively connected to the outcome studied. Abdominal and pelvic pain is a common symptom in the adolescent female, and might be related to ectopic pregnancy and pelvic inflammatory disease [100]. An explanation to these positive connections could be that these women display a sexual risk-taking behaviour to a higher extent than women not hospitalised due to genitourinary diseases and/or abdominal problems, which increases the risk of STI [52]. STI, in turn, has been shown to increase the risk of pelvic inflammatory disease and related sequelae [49, 51, 52]. Another explanation could be that some of these women, after investigation and treatment, were advised to try to become pregnant as soon as possible in case they were planning to have children.

In Paper IV, we found that women hospitalised according to 'mental disorders' during adolescence had an increased likelihood of giving birth between 20 and 24 years of age, but a reduced likelihood of giving birth between 25 and 27 years of age. Previous research indicate that people with adolescent-onset psychiatric disorders have increased chances of teenage pregnancy and early marriage, which is strongly associated with adverse consequences such as financial insecurity and lack of social support [58]. Thus, the increased likelihood of giving birth among women aged 20-24 years may be explained in terms of residual confounding by social and/or behavioural factors whereas the decrease in likelihood of childbearing in women aged 25-27 years could be a 'real' adverse effect of mental illness.

GENERAL CONCLUSIONS

- We found that reduced foetal growth, and possibly preterm birth, was connected to the likelihood of giving birth between 13 and 27 years of age, and adjusting for socio-economic characteristics and other birth-related variables, as well as hospitalisations during adolescence did not substantially affect the relations found. However, the effect of reduced foetal growth on the outcome appears to be dependent of the proxy used.

- There was an intergenerational effect of reduced foetal growth, and reduced foetal growth in the mother also increased the risk for preterm birth in the first-born child. These relations were evident although socio-economic characteristics as well as smoking habits and body mass index during pregnancy were adjusted for.

- Men and women who were born small for gestational age or preterm were more likely to be hospitalised during adolescence and early adulthood (i.e. between 12 and 23 years of age), compared to those born at term and appropriate for gestational age. Men and women born small for gestational age seemed to be more at risk compared to those born preterm, and adjusting for socio-economic characteristics as well as other birth-related variables did not substantially affect the relations found.

- A majority of the causes of hospitalisation during adolescence increased the likelihood of giving birth between 20 and 27 years of age, even after adjustments were made for socio-economic characteristics as well as birth-related variables. However, the positive relations found were most marked for women aged 20-24 years.

FUTURE PERSPECTIVES

- The follow-up period was relatively short in terms of estimating the likelihood of giving birth, but as the Medical Birth Register started in 1973 a longer time of follow-up was not possible at the time when the studies included in this thesis were performed. Nevertheless, we found that birth-characteristics such as reduced foetal growth, as well as hospitalisations during adolescence affect the likelihood of giving birth. In the future, it would be of interest to see if the relations are evident in a material with a longer follow-up period.

- It would also be interesting to see if birth-characteristics are connected to the likelihood of having a child among the men, but as men tend to be older than women when they plan parenthood it was not possible to study this research question in the present cohort. However, our intention is to explore this in a material with a longer follow-up period.

- In this thesis, the relation between birth-characteristics and hospitalisations in adolescence and early adulthood was studied. As the Hospital Discharge Register did not cover all hospitalisations before 1987 we did not study hospitalisations in childhood, although this would also have been interesting. However, it is possible to do that with younger birth-cohorts born 1987 and later.

- In addition, more detailed studies concerning the relations presented in this thesis, especially regarding the influence of birth-characteristics and hospitalisations on the likelihood of giving birth, are needed in order to evaluate the mechanisms behind the relations found. For example, some of the results presented raise questions about the influence of other factors, such as behavioural.

The truth is out there

~ The X-files ~

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Who wouldn't be the one you love?
Who wouldn't stand inside your love?

~ Billy Corgan ~

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APPENDICES

The results presented in the following appendices are equivalent to the data presented as 'data not shown' in Papers I-IV.

Appendix 1. SGA in relation to the likelihood of giving birth (Paper I).

Small for gestational age	HR[1]	95% CI
'Adjusted' for weight gain between 1973-75 and 1996	1.09	1.04-1.14
Defined as birth weight < 10th percentile	1.10	1.06-1.15
Different standard for twins [90]	1.08	1.04-1.13

[1] Analyses were performed on all women in the study population (*n* = 148,281). Cox's proportional hazards models were adjusted for parental socio-economic characteristics as well as for the year of birth of the studied women and if the women were born as a result of twin birth.

Appendix 2. Intergenerational effects of preterm birth and SGA (Paper II).

	OR[1]	95% CI
Only mothers who were first-born were included in analyses (*n* = 9,233)		
Child born preterm		
Mother born preterm	1.00	0.62-1.60
Mother born SGA	1.44	1.06-1.95
Child born SGA		
Mother born preterm	1.05	0.51-2.15
Mother born SGA	1.79	1.18-2.73
SGA and preterm birth (in the mother) included in the same model (*n* = 24,520)		
Child born preterm		
Mother born preterm	1.22	0.94-1.60
Mother born SGA	1.28	1.04-1.59
Child born SGA		
Mother born preterm	1.00	0.66-1.53
Mother born SGA	2.65	2.08-3.38
SGA in the mother 'adjusted' for weight gain (*n* = 24,520)		
Child born preterm		
Mother born SGA	1.30	1.02-1.65
Child born SGA		
Mother born SGA	2.54	1.93-3.33

[1] The logistic regression analyses were adjusted for the mother's smoking habits, cohabitation status, BMI, and age at the time of pregnancy. Adjustments were also made for socio-economic characteristics of the mothers' parents.

Appendix 3. The women's educational levels and marital status at the age of 25 in relation to their likelihood of giving birth at 25-27 years of age (Paper I).

	HR[1]	95% CI
Educational level at 25 years of age		
9-10 years	1.00	0.94-1.06
11-13 years	ref.	
≥ 14 years	0.48	0.46-0.50
Marital status at 25 years of age		
Not married (including divorced etc.)	ref.	
Married	4.57	4.38-4.77

[1] Cox's proportional hazards model. Excluded in the analyses were 31,646 (out of 148,281) women who gave birth, died, or emigrated before the age of 25 years.

Appendix 4A. Parental socio-economic characteristics in relation to preterm birth (Paper I).

	OR[1]	95% CI
Father's educational level		
Missing	1.03	0.93-1.14
9-10 years	ref.	
11-13 years	0.94	0.89-1.00
≥ 14 years	0.97	0.87-1.08
Mother's educational level		
Missing	1.19	1.08-1.32
9-10 years	ref.	
11-13 years	0.92	0.86-0.98
≥ 14 years	0.74	0.66-0.83
Mother's marital status		
Married	ref.	
Divorced/widowed	1.29	1.13-1.49
Unmarried	1.12	1.04-1.19
Mother's age		
13-19 years	1.17	1.04-1.33
20-26 years	ref.	
27-33 years	1.19	1.12-1.27
≥ 34 years	1.73	1.58-1.90
Mother's parity		
No previous children	ref.	
≥ 1 previous children	0.79	0.75-0.84
Parent's country of origin		
Both Nordic	ref.	
≥ 1 non-Nordic	1.22	1.11-1.35

[1] Analysis was performed on all women in the study population (*n* = 148,281). The multiple logistic regression analysis was adjusted for all variables in the table. All parental characteristics were measured at the time of birth of the studied women.

Appendix 4B. Parental socio-economic characteristics in relation to very preterm birth (Paper I).

	OR[1]	95% CI
Father's educational level		
Missing	1.15	0.82-1.62
9-10 years	ref.	
11-13 years	1.05	0.85-1.28
≥ 14 years	1.04	0.69-1.56
Mother's educational level		
Missing	1.31	0.95-1.82
9-10 years	ref.	
11-13 years	0.81	0.65-1.00
≥ 14 years	0.68	0.44-1.03
Mother's marital status		
Married	ref.	
Divorced/widowed	1.37	0.84-2.22
Unmarried	1.38	1.10-1.73
Mother's age		
13-19 years	0.88	0.58-1.35
20-26 years	ref.	
27-33 years	1.21	0.97-1.51
≥ 34 years	1.58	1.13-2.21
Mother's parity		
No previous children	ref.	
≥ 1 previous children	0.78	0.64-0.96
Parent's country of origin		
Both Nordic	ref.	
≥ 1 non-Nordic	1.41	1.02-1.95

[1] Analysis was performed on all women in the study population (*n* = 148,281). The multiple logistic regression analysis was adjusted for all variables in the table. All parental characteristics were measured at the time of birth of the studied women.

Appendix 4C. Parental socio-economic characteristics in relation to very low birth weight (Paper I).

	OR[1]	95% CI
Father's educational level		
Missing	1.23	0.86-1.76
9-10 years	ref.	
11-13 years	1.01	0.81-1.25
≥ 14 years	0.99	0.65-1.49
Mother's educational level		
Missing	0.99	0.69-1.42
9-10 years	ref.	
11-13 years	0.81	0.64-1.01
≥ 14 years	0.92	0.62-1.36
Mother's marital status		
Married	ref.	
Divorced/widowed	1.83	1.17-2.85
Unmarried	1.03	0.81-1.31
Mother's age		
13-19 years	1.20	0.76-1.88
20-26 years	ref.	
27-33 years	1.10	0.87-1.39
≥ 34 years	1.58	1.13-2.22
Mother's parity		
No previous children	ref.	
≥ 1 previous children	0.63	0.51-0.79
Parent's country of origin		
Both Nordic	ref.	
≥ 1 non-Nordic	1.32	0.93-1.87

[1] Analysis was performed on all women in the study population (*n* = 148,281). The multiple logistic regression analysis was adjusted for all variables in the table. All parental characteristics were measured at the time of birth of the studied women.

Appendix 4D. Parental socio-economic characteristics in relation to SGA (Paper I).

	OR[1]	95% CI
Father's educational level		
Missing	1.13	1.04-1.24
9-10 years	ref.	
11-13 years	0.91	0.86-0.96
≥ 14 years	0.77	0.69-0.86
Mother's educational level		
Missing	0.94	0.86-1.03
9-10 years	ref.	
11-13 years	0.83	0.79-0.87
≥ 14 years	0.70	0.63-0.78
Mother's marital status		
Married	ref.	
Divorced/widowed	1.61	1.42-1.81
Unmarried	1.18	1.12-1.25
Mother's age		
13-19 years	0.88	0.78-0.98
20-26 years	ref.	
27-33 years	1.03	0.97-1.09
≥ 34 years	1.06	0.96-1.16
Mother's parity		
No previous children	ref.	
≥ 1 previous children	0.64	0.61-0.68
Parent's country of origin		
Both Nordic	ref.	
≥ 1 non-Nordic	1.13	1.03-1.24

[1] Analysis was performed on all women in the study population (*n* = 148,281). The multiple logistic regression analysis was adjusted for all variables in the table. All parental characteristics were measured at the time of birth of the studied women.

Appendix 5. Educational levels and marital status at age 25 in relation to the likelihood of giving birth to a child born preterm or SGA (Paper II).

	OR[1]	95% CI
Child born preterm		
Educational level at 25 years of age		
9-10 years	1.15	0.86-1.56
11-13 years	ref.	
≥ 14 years	0.88	0.73-1.07
Marital status at 25 years of age		
Not married (including divorced etc.)	ref.	
Married	0.91	0.74-1.12
Child born SGA		
Educational level at 25 years of age		
9-10 years	0.97	0.60-1.56
11-13 years	ref.	
≥ 14 years	0.62	0.45-0.86
Marital status at 25 years of age		
Not married (including divorced etc.)	ref.	
Married	0.83	0.60-1.15

[1] Multiple logistic regression analysis including the 9,201 (out of 24,520) women who had not given birth before 25 years of age.

Appendix 6. Preterm birth and SGA in relation to subsequent socio-economic characteristics as well as BMI and smoking habits (Paper II).

	Woman born preterm		**Woman born SGA**	
	OR[1]	95% CI	OR[1]	95% CI
Age ≥ 25 years				
No	ref.		ref.	
Yes	0.88	0.77-1.00	1.04	0.94-1.16
Smoker				
No	ref.		ref.	
Yes	1.17	1.02-1.35	1.24	1.11-1.40
Cohabiting				
No	1.22	1.01-1.48	1.11	0.95-1.31
Yes	ref.		ref.	
BMI < 20				
No	ref.		ref.	
Yes	1.05	0.89-1.25	1.37	1.21-1.56
Education ≥ 14 years				
No	ref.		ref.	
Yes	0.76	0.63-0.92	0.71	0.61-0.83
Married				
Yes	ref.		ref.	
No	0.97	0.84-1.12	1.11	0.98-1.26

[1] Multiple logistic regression analysis including 24,520 mother-offspring pairs with complete data on all background variables, adjusted for parental socio-economic characteristics.

Appendix 7. Very preterm birth and moderately preterm birth in relation to hospitalisations in adolescence and early adulthood (Paper III).

	Very preterm birth		Moderately preterm birth	
	OR[1]	95% CI	OR[1]	95% CI
Endocrine, nutritional, and metabolic diseases	1.45	0.78-2.72	1.30	1.08-1.58
Mental disorders	1.78	1.26-2.50	1.18	1.05-1.33
Diseases of the nervous system	3.55	2.65-4.77	1.42	1.25-1.62
Congenital anomalies	2.46	1.57-3.84	1.26	1.05-1.51
Symptoms, signs, and ill-defined conditions	1.21	0.93-1.57	1.10	1.02-1.19
Total risk	1.18	1.03-1.36	1.05	1.01-1.09

1 Analyses were performed on all men and women in the study population (*n* = 304,275). The multiple logistic regression analyses were adjusted for parental socio-economic characteristics as well as for sex and year of birth of the studied men and women and if the men and women were born as a result of twin birth.

Appendix 8. SGA in relation to hospitalisations due to genitourinary diseases in adolescence and early adulthood (Paper III).

SGA	**OR[1]**	**95% CI**
Stratified for the women giving birth during the study period or not, respectively[2]		
Gave birth	1.34	1.15-1.57
Did not give birth	1.26	1.08-1.46
Excluding men and women with congenital anomalies of genital organs[3]	1.38	1.26-1.51

1 The multiple logistic regression analyses were adjusted for parental socio-economic characteristics as well as for sex and year of birth of the studied men and women and if the men and women were born as a result of twin birth.
2 Analyses perfomed on the 148,281 women in the study population.
3 Excluded in analysis: 397 men and women (out of 304,275).

Appendix 9. Hospitalisation during adolescence in relation to the likelihood of giving birth between 25 and 27 years of age. Analyses not adjusted for the women's educational levels and marital status at age 25 (Paper IV).

ICD-9 chapter	HR[1]	95% CI
Blood diseases and immunity disorders	1.37	1.10-1.72
Mental disorders	0.82	0.70-0.95
Diseases of the nervous system	0.87	0.74-1.03
Diseases of the respiratory system	1.15	1.06-1.26
Diseases of the digestive system	1.08	0.98-1.19
Diseases of the genitourinary system	1.40	1.26-1.55
Diseases of the musculoskeletal system and connective tissue	1.09	0.96-1.23
Symptoms, signs, and ill-defined conditions	1.22	1.13-1.32
Injury, poisoning, and other external causes	1.07	0.99-1.15

[1] Cox proportional hazards model adjusted for parental socio-economic characteristics as well as for the year of birth of the women and if the women were born as a result of twin birth or born preterm or SGA. Excluded in the analyses were 26,353 women (out of 142,998) who gave birth, died, or emigrated before the age of 25 years.

Appendix 10. Hospitalisation during adolescence in relation to educational level and marital status at the age of 25 (Paper IV).

	OR[1]	95% CI
Gave birth during the study period		
Educational level at 25 years of age		
< 14 years	ref.	
≥ 14 years	0.72	0.67-0.77
Marital status at 25 years of age		
Not married (including divorced etc.)	ref.	
Married	1.05	0.99-1.11
Did not give birth during the study period		
Educational level at 25 years of age		
< 14 years	ref.	
≥ 14 years	0.74	0.72-0.76
Marital status at 25 years of age		
Not married (including divorced etc.)	ref.	
Married	1.12	1.04-1.21

[1] The multiple logistic regression analyses were adjusted for parental socio-economic characteristics as well as for the year of birth of the women and if the women were born as a result of twin birth or born preterm or SGA. Analyses performed on the 142,998 women did not give birth, die, or emigrate before the age of 20 years.