Birth Characteristics’ Impact on Future Reproduction and Morbidity Among Twins and Singletons

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We must welcome the future, remembering that soon it will be the past; and we must respect the past, remembering that it was once all that was humanly possible.

George Santayana
ABSTRACT
Globally, in both developed and developing countries, the twinning rates have increased since the early 70’s. A large proportion of twins are born preterm and/or small-for-gestational-age (SGA) and/or with a low birth weight. Several studies have been performed on the long-term effect of these non-optimal birth characteristics on future reproductive performance and morbidity. Yet, most studies exclude twins or higher order pregnancies and thus the findings are based on singleton pregnancies only.

The aim of the present thesis was therefore to investigate the impact of non-optimal birth characteristics in terms of preterm birth, small-for-gestational age, and low birth weight, on the reproductive pattern and morbidity among twins and singletons. Furthermore, the present thesis attempted to establish whether twins and singletons were affected in the same manner.

The studies included in this thesis are prospective population-based register studies, including all men and women, alive and living in Sweden at age 13, who were born between 1973 and 1983 (1,000,037 singletons and 16,561 twins) for the first three studies with follow-up till the end of 2006 and 2009. The last study included all men and women, alive and living in Sweden at age 13, who were born between 1973 and 1993 (2,051,479 singletons and 39,726 twins) with follow-up till the end of 2012.

In general, twins were found less likely to reproduce between 13 and 33 years of age compared with singletons. Stratifying data by different birth characteristics, it was found that twins had a lower likelihood of reproducing on several different birth characteristics (appropriate-for-gestational-age, normal birth weight, low birth weight, term birth, preterm birth). However, twins born very preterm had an increased likelihood of reproducing compared with singletons born very preterm.
Not taking birth characteristics into account, twinning was associated with a higher degree of hospitalization. However, accounting for the diverging birth characteristics this difference diminished and for some diagnoses the relationship was reversed such that twins were actually less likely to be hospitalized compared with singletons.

In terms of the heritability of non-optimal birth characteristics singleton mothers born preterm were more predisposed to give birth to a child that was preterm while singleton mothers born SGA more often gave birth to a child either born preterm or SGA. Among twins this heritability was not as evident. The only difference observed was among twin mothers born SGA who were more likely to give birth to a child born SGA.

In the extended cohort comprising those born between 1973 and 1993, male and female twins were found to be less likely to become parents compared with singletons. No difference was found among women in terms of having a second child, while male twins were more likely to have a second child compared with male singletons. It was also found that the likelihood of becoming a first-time parent and second-time parent was positively associated with the number of siblings.

**Keywords:** Twin, singleton, preterm birth, SGA, reproduction, hospitalization, siblings
## CONTENTS

**ABSTRACT** .......................................................................................................................... 3  
**LIST OF PUBLICATIONS** .................................................................................................... 7  
**LIST OF TABLES AND FIGURES** ........................................................................................ 9  
**ABBREVIATIONS** ................................................................................................................ 11  
**EXPLANATIONS OF KEY TERMS** ....................................................................................... 13  
**INTRODUCTION** .................................................................................................................. 17  
**BACKGROUND** ..................................................................................................................... 19  
Birth-characteristics in relation to outcomes in later stages of life ...................................... 21  
  *Twinning* ............................................................................................................................... 21  
  *Mortality* ............................................................................................................................... 21  
  *Long-term morbidity* ........................................................................................................... 22  
  *Socio-economic and lifestyle factors’ effect on future pregnancy outcome* ......................... 24  
  *Childbearing and pregnancy outcome* .................................................................................. 24  
  *Heritability and Epigenetics* .................................................................................................. 25  
**AIMS OF THE PRESENT THESIS** .................................................................................... 27  
**MATERIAL AND METHODS** .............................................................................................. 29  
Retrieval of data ....................................................................................................................... 29  
International Classification of Diseases .................................................................................. 30  
Data sources .............................................................................................................................. 31  
  *The Swedish Medical Birth Register* ..................................................................................... 31  
  *The National Patient Register* ............................................................................................. 31  
  *The Cause of Death Register* .............................................................................................. 32  
  *The Total Population Register* ........................................................................................... 32  
  *The Multi-Generation Register* .......................................................................................... 32  
  *The Education Register and the 1970 Population and Housing Census* ............................ 32  
The study population studies I-III ............................................................................................. 33  
The study population study IV .................................................................................................. 36  
Design of the studies ................................................................................................................ 38  
  *Study I* .................................................................................................................................. 38  
  *Study II* .................................................................................................................................. 39  
  *Study III* ................................................................................................................................ 40  
  *Study IV* ................................................................................................................................ 41  
Statistical methods .................................................................................................................... 42  
  *Logistic Regression* .............................................................................................................. 42  
  *Cox’s proportional hazards model* ......................................................................................... 44  
  *Intra-pair correlation due to twinning* .................................................................................... 45  
  *Analysis with respect to familial factors* ............................................................................... 45  
Exposure, outcomes and covariates ......................................................................................... 45  
  *Primary exposures* ............................................................................................................... 45  
  *Primary outcomes* ................................................................................................................ 47  
  *Covariates/confounders* ......................................................................................................... 48  
**ETHICAL CONSIDERATIONS** ............................................................................................ 51  
**RESULTS** ............................................................................................................................. 53  
Study I. Likelihood of giving birth among twins and singletons with respect to birth characteristics 53  
Study II Hospitalization in adolescence and young adulthood among twins and singletons .......... 54
LIST OF PUBLICATIONS

Study I  
Bladh M, Josefsson A, Carstensen J, Finnström O, Sydsjö G.

Study II  
Bladh M, Carstensen J, Josefsson A, Finnström O, Sydsjö G.
Hospitalization in adolescence and young adulthood among twins and singletons: a Swedish cohort study of subjects born between 1973 and 1983
doi: 10.1017/thg.2013.27. Epub 2013 May 10. PMID: 23659898

Study III  
Bladh M, Josefsson A, Carstensen J, Finnström O, Sydsjö G.
Intergenerational cohort study of non-optimal birth characteristics in twins and singletons
Accepted for publication in Twin Research and Human Genetics

Study IV  
Bladh M, Josefsson A, Carstensen J, Finnström O, Sydsjö G.
Reproductive pattern among twins and singletons in relation to number of siblings – a Swedish cohort study of individuals born between 1973 and 1993
Submitted
LIST OF TABLES AND FIGURES

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

**Figure 1.** Different types of twinning.

**Figure 2.** Areas with long-term effect of preterm birth.

**Figure 3.** Consequences of non-optimal birth characteristics and future reproductive performance in young ages.

**Table 1.** Conversion of ICD-9 to ICD-10.

**Figure 4.** Flowchart of the exclusion of study participants in studies I-III.

**Figure 5.** Flowchart of the exclusion of study participants in study IV.

**Figure 6.** Design of study I.

**Figure 7.** Design of study II.

**Figure 8.** Design of study III.

**Figure 9.** Design of study IV.

**Figure 10.** Calculation of odds ratio.

**Figure 11.** Alternatives on when to enter and exit the Cox proportional hazards model.

**Table 2.** Study population and its distribution of twinning and sex, study I-III.

**Table 3.** Hazard ratio of becoming a parent among females and males in sub-groups defined by birth characteristics, comparing twins vs. singletons.

**Table 4.** Likelihood of being hospitalized stratified by optimality at birth.

**Table 5.** Likelihood of giving birth to a child born preterm or SGA, stratified by twinning status.

**Table 6.** Hazard ratio for becoming a parent in relation to number of siblings, stratified by twinning and sex.

**Table 7.** Hazard ratio of giving birth by number of siblings for twins and singletons.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>AGA</td>
<td>Appropriate-for-Gestational-Age</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>FOAD</td>
<td>Fetal Origins of Adult Disease</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IVF</td>
<td>In-Vitro Fertilization</td>
</tr>
<tr>
<td>LBW</td>
<td>Low Birth Weight</td>
</tr>
<tr>
<td>LGA</td>
<td>Large-for-Gestational-Age</td>
</tr>
<tr>
<td>MBR</td>
<td>Medical Birth Register</td>
</tr>
<tr>
<td>NPR</td>
<td>National Patient Register</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>PT</td>
<td>Preterm Birth</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small-for-Gestational-Age</td>
</tr>
<tr>
<td>TPR</td>
<td>Total Population Register</td>
</tr>
<tr>
<td>VLBW</td>
<td>Very Low Birth Weight</td>
</tr>
<tr>
<td>VPT</td>
<td>Very Preterm Birth</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
EXPLANATIONS OF KEY TERMS

Twinning

Twinning can be separated into dizygotic and monozygotic, fraternal or identical, twins. This is further complicated by whether the twins share the placenta or not, or as is only possible among monozygotic twins, also share the amniotic sac. See Figure 1 for detailed description of different types of twinning.

http://twinpossible.com/twin-moms-to-be-want-to-know-are-my-twins-identical-or-fraternal

Figure 1. Different types of twinning.

Birth characteristics

In this thesis birth characteristics refer to information regarding birth weight, gestational age at birth, and size for gestational age.

Non-optimal birth characteristics

Includes the following birth characteristics: small-for-gestational age (SGA), large-for-gestational-age (LGA), low birth weight, or preterm birth.
Optimal birth characteristics
Includes birth characteristics born at term, and appropriate-for-gestational-age.

Hospitalization
In study II hospitalization was studied, as a proxy for morbidity. A registered in- or outpatient visit in The Swedish National Patient Register served as the base for this variable. Two different variants of hospitalization were used a) any hospitalization vs. no hospitalization registered and b) 0-6 hospitalizations vs. more than 6 hospitalizations.

Preterm birth
Children born before gestational week 37.

Very preterm birth
Children born before gestational week 32.

Intra-uterine growth restriction/retardation
The fetus has not been able to achieve its potential size.

Body Mass Index (BMI)
BMI was defined according to the “standard” definition, i.e. as weight (in kilograms) divided by the squared height (in meters). The BMI was further divided into 4 categories:
1) Underweight <18.5
2) Normal weight 18.5-24.99
3) Overweight 25.00 – 29.99
4) Obese >= 30

Nicotine use
Indicator variable of whether the mother either smoked or used “snuff” 3 months prior to pregnancy or during pregnancy.
Socio-economic characteristics

Factors included were: maternal and paternal level of education, maternal and paternal country of origin, mother’s civil status and mother’s age when giving birth, parity, BMI, and nicotine use.

Large-for-gestational-age (LGA)

Born with a high birth weight given sex and the gestational age at birth. Defined as a birth weight above 2SDs of the mean birth weight according to the Swedish standard.

Small-for-gestational-age (SGA)

Born with a low birth weight given sex and the gestational age at birth. Defined as a birth weight below 2SDs of the mean birth weight according to the Swedish standard.

Appropriate-for-gestational-age (AGA)

Born with an appropriate birth weight given sex and the gestational age at birth, i.e. those not born SGA or LGA.

Low birth weight

Defined as a birth weight below 2,500 grams.

Very low birth weight

Defined as a birth weight below 1,500 grams.

Sibling

Children born to the same mother.
INTRODUCTION

In the past decades the number of twins has increased globally. In Sweden alone it rose from 8.2 births/1000 women in 1973 to 16.3 births/1000 women in 2003. From 2004 onward the twin birth rate has stabilized around 14 births/1000 women. During the same time period the proportion of preterm births has remained around 6% in Sweden, though the absolute number has increased. According to the World Health Organization (WHO) it is estimated that approximately 13 million children are born preterm and approximately 20 million children are born with a low birth weight each year around the world. The increasing number of children born preterm and/or with low birth weight in combination with the improved medical care of these children have led to an increasing number of surviving children with non-optimal birth characteristics.

Several studies have established a relationship between non-optimal birth characteristics and long-term sequelae such as mental disorders, neurological disorders (including cerebral palsy), reduced reproduction, and metabolic syndrome, the latter being a known risk factor for type 2 diabetes, high blood pressure and cardiovascular disease. However, the majority of these studies have only included singleton births in their study populations. As twins are often born preterm and with a low birth weight it is reasonable to consider them a sub-group of all children born preterm, SGA and/or with a low birth weight.

In this thesis the aim was to investigate whether twins and singletons, born with non-optimal birth characteristics, exhibited different patterns with respect to reproductive pattern and general morbidity. For this purpose we had access to the unique Swedish population registers that provided an excellent opportunity to investigate these outcomes. Using the personal identification number assigned to each person residing in Sweden it was possible to link data on birth, hospitalizations and socio-demographics.
BACKGROUND

In 2005 it was estimated that approximately 9.6% of all births around the world were preterm births. Europe had the lowest rate of preterm births, 6.2% and Africa had the highest rate of preterm births 11.9% closely followed by North America with a 10.6% preterm birth rate\(^1\). Another study estimated the worldwide incidence of preterm birth to be 11.1% in 2010\(^2\).

It is well known that both short- and long-term survival among humans is highly dependent on the gestational week in which they were born, but also on their birth weight and birth weight in relation to gestational age\(^3\)-\(^5\). In addition, restricted fetal growth is related to an elevated level of morbidity in general but also due to specific diagnoses. More specifically, children who are born preterm have an increased risk for hospitalizations due to physical conditions (e.g. type 2 diabetes, cardiovascular diseases, metabolic syndrome), mental conditions/diseases (e.g. psychiatric morbidity and drug abuse), and neurological disorders in adolescence and early adulthood\(^6\)-\(^8\) (Figure 2).

**Figure 2. Areas with long-term effect of preterm birth.**
Prior research has shown that restricted fetal growth in general is related to increased likelihood of early childbearing (between the age of 13 and 27 years) in girls, whereas more prominent growth restriction is related to reduced likelihood\(^9\) (Figure 3).

![Diagram showing the relationship between low birth weight, small-for-gestational-age, preterm, reduced fertility, reduced ovulation rate, reduced ovarian and uterus size, and increased fertility.]

**Figure 3.** Consequences of non-optimal birth characteristics and future reproductive performance in young ages.

It is possible that the short- and long-term effects of non-optimal birth characteristics are different for twins compared with singletons due to the difference in the etiology of preterm birth. Generally, the cause of preterm birth among twins is different than the cause of preterm birth among singletons. It has been quantified that, overall, somewhere between 30-40% of all preterm births are caused by maternal infections, while mechanical reasons such as increased uterine pressure and overdistention of the uterus, i.e. lack of space, are major causes of preterm birth among twins\(^{10-11}\). In many cases twins are born preterm and with a low birth weight\(^{12}\). Despite this most epidemiological studies on morbidity and reproductive patterns exclude twins and higher order pregnancies from their studies\(^{13-16}\). The reality today is that very few studies have focused on the potential effect twinning may have on reproductive pattern and general future health outcomes. Thus, there is a lack of knowledge on the risk for long-term morbidity associated with twin pregnancy and delivery when comparing twins with singletons.
Birth-characteristics in relation to outcomes in later stages of life

Twinning

Around the world the incidence of twin birth has increased since the mid 70’s\textsuperscript{17-18}. In Sweden alone the rate rose to 16.3 births/1000 women in 2003. However, since then the twin birth rate has stabilized around 14 births/1000 women\textsuperscript{19}. Important factors explaining some of the increase in twin birth rates are IVF-treatment and hormone stimulation as is the increasing maternal age when giving birth\textsuperscript{18,20}.

The elevated risk associated with twin pregnancies is mainly due to the high number of preterm births and the increased proportion of children born growth restricted. Another important factor affecting the risk in twin pregnancies is delivery complications, although with the improved medical care of newborns born with non-optimal birth characteristics over the years this risk has declined some\textsuperscript{21-22}.

Mortality

Both short- and long-term health and survival among children are highly dependent on the gestational week in which they were born, but also on size and weight in relation to gestational age\textsuperscript{3-5}. Preterm birth and complications associated with preterm birth, such as respiratory distress, seizures, and infections are substantial contributors to neonatal and infant mortality. Close to 30\% of all neonatal deaths can be attributed to preterm birth while 60-80\% of all neonatal deaths are due to the infants being born with a low birth weight\textsuperscript{23-25}. In a longer perspective, studies have reported slightly discrepant results. A study by Swamy et al reported that preterm birth was associated with a higher risk of mortality reaching into late childhood among both boys and girls\textsuperscript{13}. This was not confirmed in a later study by Crump et al; they did however find that preterm birth was associated with an increased likelihood for mortality in early adulthood\textsuperscript{26}. 


**Long-term morbidity**

In the past decades there has been an improvement in the medical treatment of children that are born preterm or with restricted fetal growth. This improvement has resulted not only in a much higher survival rate of these children, but also in a higher number of surviving children with both mental and physical chronic conditions. Restricted fetal growth and prematurity are related to an increased risk of morbidity in general but also due to several specific diagnoses. In particular, children born preterm have an increased risk for hospitalizations due to neurological sequelae, physical (congenital malformations, type 2 diabetes, cardiovascular diseases, metabolic syndrome), and mental conditions/diseases (psychiatric morbidity and drug abuse) in adolescence and early adulthood\(^6\)-\(^8\). In a review by Räikkönen et al several long-term effects due to prematurity and SGA were listed on a number of areas including cognitive functioning, temperament and personality, mental disorders and increased sensitivity to stress\(^27\) (Figure 2).

**Physical morbidity**

A large number of studies have proposed a connection between restricted fetal growth and an increased risk for major diseases later in life, e.g. the metabolic syndrome, which includes diabetes, high blood pressure, obesity, but also increases the risk for cardiovascular disease\(^28\)-\(^30\). Different theories aimed at explaining the mechanisms behind these associations have been developed and perhaps the most debated of these is ‘the fetal origins of adult disease hypothesis’ (FOAD). The main concept of this theory is that “...an unfavorable development, or insults during fetal life, might induce lifetime effects on the subsequent development of body systems and hence give rise to major disease processes...”\(^28,31\). This theory has received some criticism over the years both regarding its theory (too widely and vaguely formulated) and the methodology used i.e. missing important confounders, over-adjustment resulting in the “reversal paradox”. This criticism has resulted in the
theory being slightly revised and in the development of an analytical scheme recommended when analyzing the FOAD related hypothesis\textsuperscript{32-38}.

Previous research has also established that non-optimal birth characteristics, in addition to the well-established risks associated with pregnancy complications, are related to diseases of the nervous system, such as cerebral palsy as well as visual and hearing impairments\textsuperscript{39-40}. The mechanisms by which these complications occur include intrauterine infections, central nervous system malformations, and reduced placental function\textsuperscript{40}. In addition, preterm birth and restricted fetal growth have been discovered to be related to respiratory disease and infectious diseases, and some evidence also exist of a relationship with malignancy\textsuperscript{41-43}.

\textit{Psychiatric morbidity and personality}

Preterm birth and restricted fetal growth have recently been subject for research concerning mental illness. Low birth weight has been related to both psychiatric symptoms and psychiatric disorders, such as eating disorders, schizophrenia, and suicidal behavior\textsuperscript{44-46}. Some evidence exist that high psychiatric morbidity increases between adolescence and young adulthood among children born SGA or with a low birth weight\textsuperscript{47}. An increased risk for attention deficit and hyperactivity disorder (ADHD) has also been noted among children born SGA and with a low birth weight\textsuperscript{48}. Similarly, an increased likelihood for autism spectrum disorders among children born preterm has been observed\textsuperscript{49}. This was partly validated in a within-twin study where it was concluded that low birth weight is associated with all forms of ADHD symptoms\textsuperscript{50}. The personality of those born with restricted fetal 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 with controls\textsuperscript{41,51}, while others report an increased risk of delinquent, aggressive and externalizing problems\textsuperscript{52}. Others on the other hand report a higher risk of internalizing symptoms, attention problems, and relational problems\textsuperscript{41,53}. In addition, preterm birth and low birth weight have
been studied with respect to future cognitive outcomes. Several studies provide
evidence that future cognitive functioning is related to both prematurity\textsuperscript{54} and low
birth weight\textsuperscript{53,56}. It has also been suggested that these effects can extend all the way
in to old age by causing “...a more rapid cognitive decline...” as the person becomes
old\textsuperscript{27}.

\textbf{Socio-economic and lifestyle factors’ effect on future pregnancy outcome}
Several socio-economic factors have been identified to influence the outcome of
future pregnancies. Increasing maternal age when giving birth is a major factor
influencing not only the likelihood of twinning (and higher order pregnancies) but is
also a known predictor of children being born preterm as well as children born SGA.
Other established factors related to having a child born preterm and/or a child born
SGA include maternal educational level, unemployment, lack of social support and
the mother’s marital status\textsuperscript{56-58}. Moreover, the mother’s BMI and her smoking habits
during pregnancy have been identified as risk factors for preterm birth and having a
child with low birth weight\textsuperscript{59-60} as do the familial socio-economic position, during
both childhood and adulthood, income, and childhood health and environment \textsuperscript{59-60}.

\textbf{Childbearing and pregnancy outcome}
Hack et al\textsuperscript{41} have proposed that differences in personality and/or behavior may be
involved in explaining the reduced childbearing among women born with restricted
fetal growth. One of these potential factors influencing the future likelihood of
becoming a parent is the onset of romantic relationships. Studies have indicated that
children born preterm were less likely to be in a romantic relationship in early
adulthood\textsuperscript{63,64}, or ever having been married or in a registered relationships\textsuperscript{65}, while
children with a low/very low birth weight had a decreased likelihood of having
experienced sexual relationships\textsuperscript{66}. This may in turn be caused by the reduced
likelihood of very low birth weight children to leave the parental home\textsuperscript{66}. 
It is also well known that restricted fetal growth, including low birth weight and SGA, may have an impact on organ structure and functioning, including the reproductive organs,\textsuperscript{8,28-29}, and therefore may be connected to future fertility and reproductive pattern. Studies have indicated that women born SGA may have a reduced ovarian and uterus size but also a reduced ovulation rate\textsuperscript{67}. Meanwhile, intra-uterine growth restricted men are at an increased risk for hypospadias, cryptorchidism\textsuperscript{x68} and men born preterm have an increased risk for testicular cancer\textsuperscript{68-69}. Previous research on Swedish population data have found that preterm birth and low/very low birth weight were associated with a decreased likelihood of becoming a parent while being SGA did not decrease the likelihood of becoming a parent\textsuperscript{70}. The latter finding was in disagreement with a previous study on partly the same data (smaller cohort with a shorter follow-up time) where it appeared as if women born SGA had an increased likelihood of becoming a mother\textsuperscript{9}.

**Heritability and Epigenetics**

The heritability of non-optimal birth characteristics has been widely studied previously, though focusing on singletons only. In a previous study, on partly the same data as this thesis, on the heritability of preterm birth and intrauterine growth restriction among singletons, it was found that women born SGA were more likely to themselves give birth to a child born SGA or preterm\textsuperscript{71}. A more recent study added knowledge on the heritability by showing that women born in a spontaneous preterm delivery were more likely to repeat this in their own pregnancies\textsuperscript{72}. Studies have also indicated that mothers giving birth to preterm twins are, in subsequent deliveries, more likely to give birth to preterm singletons\textsuperscript{73-74}.

It has further been shown that genetic and environmental factors are equally important factors affecting birth characteristics of the newborn in terms of birth weight, prematurity and size for gestational age\textsuperscript{75-76}. Several studies have also focused on explaining the mechanisms that have been hypothesized and shown to
cause the alteration of how certain genes are expressed and thereby affecting the risk for preterm birth\textsuperscript{77-83}. 
AIMS OF THE PRESENT THESIS

As most studies on reproductive pattern and its outcomes, morbidity and heritability of non-optimal birth characteristics are limited to the inclusion of only singleton births it is of importance to elucidate whether twins and singletons differ on these outcomes.

Hence, the principal aim of this research was to investigate the impact of non-optimal birth characteristics, i.e. preterm birth and SGA, on somatic health and reproductive pattern among adolescent and young adult men and women born as either twins or singletons. To this end, four separate sets of questions were formulated, investigated, and answered in the course of research leading up to the present thesis:

Firstly, if twins and singletons exhibit different reproductive patterns and if potential differences can be explained by their non-optimal birth characteristics? (Study I)

Secondly, having survived till the age of 13, is the future morbidity among twins and singletons different and is the morbidity affected differently due to non-optimal birth characteristics? (Study II)

Thirdly, does an intergenerational effect of non-optimal birth characteristics, as measured by preterm birth and SGA exist among twins and singletons and are twins and singletons affected differently? (Study III)

Fourthly and lastly, how does family size affect future reproductive pattern among twins and singletons? Do twins and singletons differ in the likelihood of becoming 1st and 2nd time parents? (Study IV)
MATERIAL AND METHODS

Retrieval of data

In Sweden it is possible to obtain unique data on a personal level due to the long tradition of registrations but also due to the unique personal identification number assigned to every person residing in Sweden, enabling linking information from different registers. Prior to retrieving any data several steps have to be taken. First, to be able to request data from any of the population-based registers an ethical approval has to be obtained from the Human Research Ethics Committee. After approval from the Human Research Ethics Committee a request to each agency responsible for the registers from which data are to be retrieved. One should bear in mind that an ethical approval does not imply that the agencies will be able to deliver the requested data, the legal expertise at each agency has first to approve of the data request making sure that delivery of the data are in line with current ethical principles and Swedish legislation. However, once data have been delivered, usually in the form of several data files, the data have to be set up into a manageable database. In setting up a database, comprising three generations, where data have been retrieved from several population-based registers, the data files have to be carefully merged. In addition, upon receiving the data a careful investigation must be undertaken to ensure that delivered data are indeed the desired data. Delivered data have further to be scrutinized meticulously for inconsistencies. This includes, e.g. crosschecking the different variables that could be used to identify twinning, birth weight and gestational age as well as birth weight with respect to gestational age. This also entails making sure that predefined variables in the data define what is to be investigated. If not, re-coding of these variables has to be performed. An example of this is that the Swedish Board of Health and Welfare changed the definition of parity. Previously it was defined as number of deliveries, where the delivery of multiples counted as one. This was later changed in to number of children delivered (i.e. if a primiparous woman delivered a pair of twins the first child had parity=1 and second child had parity=2).
International Classification of Diseases

The first version of the International Classification of Diseases (ICD) was published in 1949. Over the years the ICD has been through a couple of revisions and for the purpose of this thesis the three latest versions have been used. ICD-10 was released in 1994 and the use of this release in Sweden started in 1996, replacing the previous version, ICD-9, which had been in use since 1987 when ICD-8 was replaced (in use since 1969). In order to obtain definitions of diseases that were comparable over the years the classifications of ICD-10 had to be converted to the classifications in ICD-9. ICD-9 was chosen as baseline since the individuals in study I-III were born in 1973 and 1983 but also since the aim was to study morbidity in late childhood and early adolescence. The conversion of ICD-10 to ICD-9 is presented in Table 1.

<table>
<thead>
<tr>
<th>Diagnosis codes for each of the different ICD version used in this thesis</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and parasitic diseases (1)</td>
<td>001-139</td>
<td>A00-B99</td>
</tr>
<tr>
<td>Neoplasm (2)</td>
<td>140-239</td>
<td>C00-D48</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases and immunity disorders (3)</td>
<td>240-279</td>
<td>E00-E90</td>
</tr>
<tr>
<td>Blood diseases (4)</td>
<td>280-289</td>
<td>D80-D99</td>
</tr>
<tr>
<td>Mental disorders (5)</td>
<td>290-319</td>
<td>D50-D77</td>
</tr>
<tr>
<td>Diseases of the nervous system and sense organs (6)</td>
<td>320-389</td>
<td>F00-F99</td>
</tr>
<tr>
<td>Diseases of the circulatory system (7)</td>
<td>390-459</td>
<td>G00-H95</td>
</tr>
<tr>
<td>Diseases of the respiratory system (8)</td>
<td>460-519</td>
<td>I00-I99</td>
</tr>
<tr>
<td>Diseases of the digestive system (9)</td>
<td>520-579</td>
<td>J00-J99</td>
</tr>
<tr>
<td>Diseases of the genitourinary system (10)</td>
<td>580-589</td>
<td>K00-K93</td>
</tr>
<tr>
<td>Diseases of the skin and subcutaneous tissue (12)</td>
<td>680-686</td>
<td>L00-L99</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue (13)</td>
<td>710-739</td>
<td>M00-M99</td>
</tr>
<tr>
<td>Congenital anomalies (14)</td>
<td>740-759</td>
<td>Q00-Q99</td>
</tr>
<tr>
<td>Symptoms, signs and ill-defined conditions (16)</td>
<td>780-789</td>
<td>R00-R99</td>
</tr>
<tr>
<td>External causes of morbidity and mortality (17,18)</td>
<td>800-999</td>
<td>S00-T98</td>
</tr>
<tr>
<td></td>
<td>E807-E999</td>
<td>V01-X59</td>
</tr>
</tbody>
</table>

Table 1. Conversion of ICD-9 to ICD-10.
**Data sources**

**The Swedish Medical Birth Register**

The Swedish Medical Birth Register (MBR) was introduced in 1973. From the start information regarding prenatal, obstetrical, delivery and neonatal factors was based on “Medical Birth Reports” (Medicinska Födelsemeddelande, MFM). However, some inconsistencies in reporting were present and after an evaluation in 1976 a revised procedure for data collection was implemented in 1982 to minimize reporting errors. At the same time, it was decided to include information pertaining to diseases during pregnancy. Since then the information collected has been through additional changes in 1990, 1994 and 1998. Today MBR contains information on prenatal care (age, maternal height and weight, nicotine use, previous pregnancies and diagnoses prior and during pregnancy), delivery (mode of delivery, fetal presentation, pain relief used during labor and delivery) and neonatal care (birth weight, body length, gestational age and newborns’ diagnoses) as well as maternal chronic diseases. The Swedish Medical Birth Register has a high coverage rate with only 0.5-3.0% missing records.

**The National Patient Register**

The National Patient Register, previously known as Hospital Discharge Register, was established in 1964. From the start it mainly included information on psychiatric care. In 1984 it was decided that all inpatient care should be reported to the register and this was implemented in 1987. The register was further revised in 2001, when all outpatient visits (including outpatient surgery and psychiatric care from both private and public caregivers) were included in the mandatory reporting to the register. As of today the register contains information on e.g. sex, age, date of admission and discharge, main and secondary diagnoses. The register has a high total coverage rate of about 99%, and in a recent validation of the register it was concluded that for the most part the diagnoses in the register are of a high quality with an the overall positive predictive value (PPV) in the range 85-95%.
The Cause of Death Register
The Cause of Death Register, in its current form, was established in 1961 and contains information regarding the cause of death for all persons residing in Sweden. This means that cases where the death occurred abroad are also included in the register. The register does not include infants who died at birth. Starting from 2012 all deaths occurring in Sweden are registered in the Cause of Death register, implying that those, at time of death, who currently does not reside in Sweden but who dies while in Sweden are also included. The coverage rate is close to 100% but approximately 2.5% of the entries are incomplete.

The Total Population Register
The Total Population Register (TPR) was established in 1968 and contains information regarding a person’s citizenship, country of birth, marital status, migration (both immigration and emigration) and deaths and births. The register is of good quality, though some over-coverage exists due to missing reports of deaths and emigrations (i.e. people are registered though they should not be).

The Multi-Generation Register
The Multi-Generation Register, which is based on the TPR, includes all persons who were born in Sweden from 1932 and onward, but also include persons who, at some point, have been registered in Sweden since 1961. The register is used to identify the biological parents or adoptive parents of these “indexpersons”.

The Education Register and the 1970 Population and Housing Census
Prior to 1985 when the Swedish Register of Education was established, data on level of education were retrieved from the Population and Housing Census that took place in 1970. Today the register is updated regularly and contains information on highest level of education, year of completion and some basic demographic data such as age and sex. The register is limited to individuals between 16 and 74 years of age.
The study population studies I-III

The study population in studies I-III was defined as all men and women born in Sweden between 1973 and 1983 who were alive and living in Sweden at the age of 13.

The starting population, consisting of all men and women born between 1973 and 1983, endpoints included, included a total of 1,070,380 individuals. However, individuals who were deceased before their 13th birthday, individuals who did not reside in Sweden at the age of 13, individuals with missing values on birth weight and/or gestational length and individuals who had an unlikely birth weight with respect to the gestational age (Figure 4) were removed from the study population.

The limits for removal due to extremely high birth weight with respect to gestational age were defined as:

- \( > = 2000 \) grams for gestational weeks, \(< = 28,\)
- \( > = 2500 \) grams for gestational weeks 29 and 30,
- \( > = 3000 \) grams for gestational weeks 31 and 32,
- \( > = 3500 \) grams for gestational weeks 33 and 34,
- Birth weights for other gestational weeks were within limit.

Limits for removal due to extremely low birth-weights with respect to gestational age were defined as:

- \( \leq 400 \) grams in gestational week 29,
- \( \leq 800 \) grams in gestational week 30,
- \( \leq 1000 \) grams in gestational week 31,
- \( \leq 1150 \) grams in gestational week 32,
- \( \leq 1250 \) grams in gestational week 33,
- \( \leq 1450 \) grams in gestational week 34,
- \( \leq 1600 \) grams in gestational week 35,
- \( \leq 1700 \) grams in gestational week 36,
- \( \leq 1800 \) grams in gestational week 37,
- \( \leq 1950 \) grams in gestational week 39,
<= 2000 grams in gestational weeks 40, 41 and 42,
<= 2500 grams in gestational weeks 43 and 44.

After removal of individuals due to these events, the final study population consisted of 1,016,908 individual of which 16,561 were identified as twins.
Figure 4. Flowchart of the exclusion of study participants in studies I-III.
The study population study IV

The study population in study IV was defined as all men and women born in Sweden between 1973 and 1993 who were alive and living in Sweden at the age of 13. The starting population, consisting of all men and women born between 1973 and 1993, endpoints included, encompassed a total of 2,148,960 individuals. However, after removal of individuals who had deceased before their 13th birthday, individuals who did not reside in Sweden at the age of 13, individuals with missing values on birth weight and/or gestational length and finally removal of individuals who had an unlikely birth weight with respect to the gestational age (Figure 5), the final study population consisted of 2,091,205 individual of which 39,726 were identified as twins.

The limits for removal due to an extremely high birth weight or extremely low birthweights were defined as for studies I-III.
Figure 5. Flowchart of the exclusion of study participants in study IV.
Design of the studies

Study I

In this study the primary focus was to investigate the effect of twinning on future reproductive performance and to investigate if the reproductive performance among both twins and singletons were affected by non-optimal birth characteristics in the same way. For this purpose all twins and singletons born between 1973 and 1983 in Sweden and who were alive and residing in Sweden at age 13 were included and followed until the end of 2006, for more detailed description see Figure 4. Data on each study subject’s own birth as well as the birth of their first offspring, and the study object’s parental socio-demographic factors were collected from Swedish population based registers, Figure 6. Stratified analysis on gender where hazard ratios of the likelihood of becoming a parent and corresponding 95% CI were calculated using Cox proportional hazards model. Two sets of models were considered, in the first model estimates were adjusted for socio-demographic factors and in the second model estimates were further adjusted for the men’s and women’s own birth characteristics.

Figure 6. Design of study I.
Study II

In this national population-based register study, all individuals born between 1973 and 1983 who were alive and living in Sweden at 13 years of age constituted the sample. The purpose of this study was to examine the morbidity, where hospitalization was used as a proxy for morbidity, among both twins and singletons and to evaluate if the outcome differed depending on twinning status and to what extent non-optimal birth characteristics affected the morbidity. Data on each study subject’s own birth, parental socio-demographic factors as well as data on hospitalizations were collected from Swedish population based registers, Figure 7. Odds ratios of the likelihood of being hospitalized and corresponding 95% CI were calculated using logistic regression. Several different outcomes were evaluated, general hospitalization due to any cause but also due to each the groups of diagnosis present in each of the main chapters in ICD-9. Moreover, due to an intra-class correlation among twins all confidence intervals were adjusted accordingly.

**Figure 7. Design of study II.**
Study III
This is a population-based register study of mother-firstborn offspring pairs recorded in the Swedish Medical Birth Register. The study included 268,867 mothers born in 1973-1983 and their firstborns born in 1986-2009. The main focus of this study was to investigate the intergenerational effect of preterm birth and SGA among both twins and singletons and try to elucidate if any differences in the intergenerational effect between twins and singletons were present. Socio-demographic data on grandmothers as well as mothers, birth characteristics of the mothers and their offspring were collected from validated Swedish registers, Figure 8. Multiple logistic regression models were performed to estimate the likelihood of giving birth to a child born preterm or SGA. In these models adjustment were made for both grandmothers’ and mothers’ socio-economic background but also for the mothers’ own birth characteristics.

Participants in study III:
All women who had given birth during the study period

Exposure:
Low birth weight
Preterm birth
SGA
Twinning

Outcome:
Odds ratio of giving birth to a preterm child or a child born SGA

Covariates:
Grandmother’s and mother’s education
Parental origin
Grandmother’s and mother’s age when giving birth
Grandmother’s and mother’s marital status
Mother’s nicotine use
Mother’s BMI

Figure 8. Design of study III.
Study IV
This is a register-based study where the study population consisted of all men and women born in Sweden between 1973 and 1993 who were alive and living in Sweden at 13 years of age. Data on the study objects’ own births as well as their offspring, parental socio-demographic factors were collected from Swedish population based registers, Figure 9. Hazard ratios for the likelihood of becoming a parent were estimated using Cox’s proportion hazard models. All models were adjusted for socio-demographic factors as well as birth characteristics and a categorized indicator on the number of siblings, approximated by the number of biological brothers and sisters with the same mother.

**Participants in study IV:**
All men and women born as twins and singletons in the study population

**Exposure:**
- Low/very low birth weight
- Preterm/very preterm birth
- Size for gestational age
- Twinning

**Outcome:**
- Hazard ratio of becoming 1st time parent
- Hazard ratio of becoming 2nd time parent

**Covariates:**
- Maternal education
- Paternal education
- Parental origin
- Maternal age when giving birth
- Maternal marital status
- Number of siblings

*Figure 9. Design of study IV.*
**Statistical methods**

**Logistic Regression**

Binary logistic regression can, if simplified, be separated into two model types - "single logistic regression" and "multiple logistic regression". The first model type is limited to one nominal (e.g. yes/no) dependent variable and one independent variable that can be either categorical or continuous and is used when one wants to predict the probability of the outcome. The second model type pertains to models with two or more independent variables. When performing logistic regression it is assumed that the observations are independent and that the relationship between the natural log of odds ratio and the independent variable is linear. The logistic regression model predicts the odds ratio of the studied event happening and is relevant when studying the cumulative incidence of an event (i.e. proportion of new events occurring within a pre-specified time period). A short description of how the odds ratio is calculated is provided in Figure 10.

In studies II and study III this was the chosen method of analysis in order to test each studies hypothesis. In study II multiple logistic regression was used to calculate the odds ratio for hospitalization due to the main chapters in ICD-9 and total hospitalization, comparing twins with singletons. Each main chapter was modeled separately. We also considered models where data were stratified by twinning status but also according to optimality at birth (non-optimal vs. optimal birth characteristics).
In study III multiple logistic regression was used to estimate the odds ratio of giving birth to a child that was either born preterm or SGA. The analyses were stratified upon whether the mother was born preterm or SGA.

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>EVENT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

\[
\text{OR} = \frac{A}{C} = \text{proportion of events among those exposed compared with those not exposed}
\]

\[
\text{B/D} = \text{proportion of non-events among those exposed compared with those not exposed}
\]

Figure 10. Calculation of odds ratio.
**Cox’s proportional hazards model**

In short, Cox proportional hazards model is a time-to-event model strategy in which the relative risk for an event happening at a specific time is estimated (hazard ratio). As in logistic regression models it is possible to have more than one independent variable in the model. Moreover, when analyzing data through Cox proportional hazards models it is possible to allow censoring of the study subjects. This means that study subject can exit from the model prior to the studied event happening, or enter the study at different time-points and estimates of the hazard will take this into account as displayed in Figure 11.

*Figure 11. Alternatives on when to enter and exit the Cox proportional hazards model.*

In Cox proportional hazards model, it is assumed that the hazard ratio (e.g. between twins and singletons) remains constant over time. If this is substantially violated it is possible to model data with time dependency or to use separate models in different time periods of follow-up.

In study I and study IV, Cox proportional hazards model was used to estimate the likelihood of becoming a parent. The time variable was defined as age, and
individuals exited from the models when they became parents, emigrated, died or reached the end of follow-up, depending on which of these events was the first event to occur.

**Intra-pair correlation due to twinning**
Due to a correlation of the incidence of hospitalization and 1<sup>st</sup> and 2<sup>nd</sup> twin, the confidence intervals for the OR’s in study II were adjusted using cluster design effect formulas<sup>97</sup>.

**Analysis with respect to familial factors**
In analyzing the effect birth characteristics have on future reproduction, pregnancy outcome and morbidity it is important to also acknowledge familial factors affecting the outcome. Examples of such factors include family size, social position (employment, income, education, social support network, place of residence), dietary intake, and the general environment into which the child is born. Due to the nature of the registers we were not able to obtain data on all of these factors. In study IV, we used number of maternal full-siblings as a proxy for family size and in all studies information on maternal and paternal level of education were included in all studies as were parental region of origin. Also, in studying the pregnancy outcome of the index persons’ own pregnancies BMI and maternal nicotine use were included.

**Exposure, outcomes and covariates**
**Primary exposures**
**Gestational age at birth**
Gestational age at birth was separated into four categories: < 32 completed gestational weeks (very preterm), 32-36 completed gestational weeks (moderately preterm), 37-42 completed gestational weeks and lastly >42 completed gestational weeks (post-term), this definition of gestational age was used in all studies. The persons in this study were born between 1973 and 1983 in studies I-III and 1973 and 1993 in study IV. During this time period the gestational length has mainly been
measured by the last menstrual period but also with the assistance of ultrasound. These two ways to determine the gestational age may yield slightly different estimates since estimates using the menstrual period usually are 2-3 days higher than the estimates from an ultrasound\(^8\,^9\).

**Birth weight**
Birth weight were split in to three categories: very low birth weight was defined as a birth weight < 1500 grams, low birth weight between 1500 grams and 2499 grams, and normal birth weight ≥2500 grams (used in all studies).

**Small for gestational age**
For the purpose of this thesis small for gestational age was defined as a birth weight < -2 SD of the mean weight for the gestational length\(^9\) according to the Swedish standard and currently used by the National Board of Health and Welfare.

**Non-optimal birth characteristics**
Non-optimal birth characteristics, used in study II, was defined as being either SGA or born preterm while optimal birth characteristics were defined as being born at term and appropriate for gestational age (AGA).
**Twinning**

Twinning is a key exposure in this thesis and was used in all studies. Twinning was dichotomized into two levels; singletons and twins. All higher order pregnancies were excluded from the studies due to a very limited number (n=220 in studies I-III and n=346 in study IV).

**Primary outcomes**

**Likelihood of giving birth**

In studies I and IV the outcomes studied were the likelihood of giving birth, estimated using Cox proportional hazards model. In study I the individuals were followed till the end of 2006 thus among those that we could follow through all years the endpoint was anywhere between 23 and 33 years of age. In study IV the endpoints were 29 and 39 years of age. This implies that most of the participants only had begun reproducing; mean age in Sweden when women had their first child was 28.5 years in 2013\textsuperscript{100}. Only a limited number of participants were approaching the end of their reproductive years.

**Likelihood of being hospitalized**

In study II we wanted to investigate the morbidity in adolescence and young adulthood. As a proxy for morbidity we analyzed the likelihood of being hospitalized according to the main chapters in ICD-9 and total (all-cause) hospitalization. Total number of hospitalizations was dichotomized into two levels, <6 and ≥6 hospitalizations.

**Likelihood of giving birth to a child born preterm or SGA**

The primary aim in study III was to study the intergenerational effect of preterm birth and SGA, subsequently the outcomes studied were the likelihood of giving birth to a child born preterm or SGA.
Covariates/confounders

Several different covariates were considered in this thesis and can be divided into two main groups. The first group consists of socio-demographic factors related to the childhood of the study population and included parental level of education divided into “elementary school” (9 to 10 years of schooling), “high school” (11-13 years of schooling) and “graduate/postgraduate education” (≥14 years of schooling) and since there was a great number of missing values on this variable a separate category labeled “unknown” was included. The parents’ origin was categorized into “both parents from Nordic countries” and “one or both parents from non-Nordic countries”. Finally, factors only related to the mothers of the study population were included; mother’s marital status when giving birth was divided into “married”, “unmarried” and “divorced or widowed” while mother’s age when giving birth were divided into four categories “13-19 years of age”, “20-26 years of age”, “27-33 years of age” and “34 years of age or older”. Mother’s parity was divided into “primiparous” and “multiparous”.

The second group of variables relates to the study population when they themselves became parents and included, age when giving birth, level of education, and marital status. All of these variables were coded as for the mothers of the study objects except age when giving birth which was divided into “≤ 19 years of age”, “20-24 years of age” and “≥ 25 years of age”. In addition, for the study population we had access to information on the women’s BMI in early pregnancy and nicotine use prior and during pregnancy. Women’s BMI was divided into four categories “<18.5”, “18.5-24.9”, “25.0-29.9” and “≥30.0” according to WHO classification of BMI. Nicotine use was defined as using either cigarettes or snuff, both before and during pregnancy, and was categorized into “yes” and “no”.

48
In study IV we also used a family size variable. As a proxy for family size we used the number of siblings with the same mother, and this was further categorized into, “0-2” and “≥ 3” number of siblings.
**ETHICAL CONSIDERATIONS**

Population-based registers are widely used in medical research today. In Sweden Statistics Sweden and the National Board of Health and Welfare frequently supply researchers with data, either from just one agency or, which is often the case, merged information on individuals from both agencies. For the agencies to consider releasing data to the researcher an ethical approval has to be obtained from the Human Research Ethics Committee. However, an approval does not guarantee that the researcher will obtain any data. It is up to each agency to establish that current ethical principles and Swedish legislation will not be violated prior to delivering any data to the researcher, thus it is possible to be denied access to data. According to current legislation in Sweden the Regional Ethical Review Committee has the right to make a judgment based on balancing the individual’s right to have his/her integrity inviolate, against the societal benefits from a specific research project. This means that the individuals in the registers have no possibility to either approve or disprove of the usage of their information.

The registers of today provide the researchers with invaluable research opportunities, and if consents were to be collected from each and every person in the registers much research would not be performed, and hence important knowledge would be missed. However, is it ethically viable to include persons in a research project, based on population-based registers, without their consent? In most cases it may be assumed that the public benefits outweigh the integrity problem. In most cases this does not cause a problem since data are anonymized and the results are reported on a group level, not on an individual level. However, in some cases when the focus is on rare outcomes the risk for identifying individuals increases. It is the researcher’s responsibility to assure that the personal integrity is not violated, and one way of accomplishing this is to publish data on group levels only.
Another ethical consideration when working with large population-based studies is the very large sample size. Having a large sample size will often yield a statistical significance even when the differences are very small which may be without clinical importance. This requires the researcher to be aware of the implication of extremely large sample sizes and interpret the findings with caution. A statistical significance does not always equal clinical significance.

The studies included in this thesis were approved by the Regional Ethical Review Board in Linköping 03-556, 07-M66 08 – 08-M 233-8.
RESULTS

Study I. Likelihood of giving birth among twins and singletons with respect to birth characteristics

A total of 1,016,688 men and women were included in this study of which 16,561 (1.6%) were born as twins, Table 1. Among both twins and singletons the proportion of males and females was equal (50.1% were men and 49.9% were women among twins and 51.4% were men and 48.6% were women among singletons). During the follow-up, which ended in 2006, 40% of the twin females and 24% of the twin males had become parents. Corresponding percentages for singletons were 44% among females and 26% among males.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton</td>
<td>513,801 (98.4%)</td>
<td>486,326 (98.3%)</td>
<td>1,000,037 (98.4%)</td>
</tr>
<tr>
<td>Twin</td>
<td>8,313 (1.6%)</td>
<td>8,248 (1.7%)</td>
<td>16,561 (1.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>522,114 (51.4%)</td>
<td>494,574 (48.6%)</td>
<td>1,016,688 (100.0%)</td>
</tr>
</tbody>
</table>

Table 1. Study population and its distribution of twinning and sex.

The primary finding in this study was that twins in general had a reduced likelihood of reproducing compared with singletons, HR=0.87 (95% CI=0.84-0.90) among females and HR=0.89 (95% CI=0.85-0.94) among males. Moreover comparisons on the likelihood of reproducing among twins vs. singletons were further elaborated using sub-group analyses were the sub-groups were defined by birth characteristics. It was found that for a number of birth characteristics twins had a reduced likelihood of reproducing compared with singletons. Among females, twins born AGA, had a normal to low birth weight, born at term or moderately preterm had a lower likelihood of reproducing compared with singletons. Among males, twins born AGA, with a lower birth weight, born moderately preterm had a decreased likelihood of reproducing, Table 2.
Table 2. Hazard ratio of becoming a parent among females and males in sub-groups defined by birth characteristics, comparing twins vs. singletons.

Study II Hospitalization in adolescence and young adulthood among twins and singletons

The study population in this study was the same as for study I, see Table I for distribution of twinning and gender.

The main aim of this study was to study the morbidity, where hospitalization was used as proxy variable, among twins and singletons. For this purpose we studied the main chapters of the Swedish version of ICD-9 in order to capture general morbidity. Twinning was, in general, associated with a slightly increased likelihood of being hospitalized, (Total hospitalization, OR=1.04 95% CI=1.00-1.07; Hospitalized ≥ 6 times, OR=1.17 95% CI=1.09-1.25) compared with singletons. They were also at an
increased risk for hospitalization due to Infections and parasitic diseases, Diseases of the nervous system and sense organs, Diseases of the digestive system, Congenital anomalies and External causes of morbidity and mortality (see Study II for details). When stratifying data by optimality at birth, many of the relationships were reversed indicating that twins seem to fare somewhat better when accounting for birth characteristics (Table 3).

<table>
<thead>
<tr>
<th>Hospitalization diagnosis according to ICD-9</th>
<th>Optimal twin vs. optimal singletons</th>
<th>Non-optimal twin vs. non-optimal singleton</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine, nutritional and metabolic diseases and immune disorders</td>
<td>1.03 (0.86-1.23)</td>
<td>0.82 (0.69-0.97)</td>
</tr>
<tr>
<td>Blood diseases</td>
<td>0.99 (0.80-1.23)</td>
<td>0.70 (0.55-0.89)</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>0.83 (0.74-0.94)</td>
<td>0.88 (0.79-0.98)</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>0.87 (0.82-0.93)</td>
<td>0.87 (0.82-0.93)</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>0.92 (0.83-1.02)</td>
<td>0.82 (0.74-0.91)</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td>0.97 (0.87-1.09)</td>
<td>0.88 (0.79-0.99)</td>
</tr>
<tr>
<td>Symptoms, signs and ill defined conditions</td>
<td>0.87 (0.81-0.93)</td>
<td>0.81 (0.76-0.87)</td>
</tr>
<tr>
<td>External causes of morbidity and mortality</td>
<td>1.07 (1.02-1.13)</td>
<td>1.02 (0.97-1.07)</td>
</tr>
<tr>
<td>Total (any hospitalization)</td>
<td>0.96 (0.92-1.01)</td>
<td>0.90 (0.86-0.95)</td>
</tr>
</tbody>
</table>

Table 3. Likelihood of being hospitalized stratified by optimality at birth.

However, also adjusting for birth characteristics non-optimal twins had a reduced likelihood of being hospitalized due to congenital anomalies (OR=0.86 95% CI=0.77-0.96) but also exhibited a lower likelihood of being hospitalized more than 5 times (OR=0.86 95% CI=0.78-0.94) compared with non-optimal singletons.

**Study III Intergenerational effect of preterm birth and small-for-gestational-age**

In study III 268,867 women born between 1973 and 1983 and their firstborn offspring, born between 1986 and 2009, were included. Among these women 4,073
(1.5%) were born as twins while 264,794 (98.5%) were born as singletons. Analyzing the intergenerational effect of SGA it was found that women born SGA were more likely to give birth to a SGA child among both twins and singletons while an increased likelihood of giving birth to a preterm child was only present among mothers born as singletons. If the mother herself was born preterm singleton she was more likely to give birth to preterm child. However, no statistical differences were present in the difference between twins and singletons even though the parameter estimates, for most estimates, were lower among twins compared with singletons. As this could be caused by a low power of the study, due to a relatively low number of twins included, linear regression models were also considered. In these models, a statistically significant interaction term between twinning and mothers’ size for gestational age was present, indicating that singleton mothers born SGA had a higher likelihood of having a child with low birth weight compared with twin mothers born SGA, Table 4.
<table>
<thead>
<tr>
<th>Logistic regression</th>
<th>Mother Singleton OR (95% CI)</th>
<th>Mother Twin OR (95% CI)</th>
<th>Twin vs. Singleton</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child preterm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother preterm</td>
<td>1.40 (1.28-1.52)</td>
<td>1.11 (0.80-1.55)</td>
<td>0.191</td>
</tr>
<tr>
<td>Mother SGA</td>
<td>1.35 (1.25-1.46)</td>
<td>1.13 (0.80-1.60)</td>
<td>0.380</td>
</tr>
<tr>
<td><strong>Child SGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother preterm</td>
<td>1.11 (0.97-1.28)</td>
<td>1.39 (0.90-2.14)</td>
<td>0.265</td>
</tr>
<tr>
<td>Mother SGA</td>
<td>2.96 (2.71-3.24)</td>
<td>2.15 (1.40-3.31)</td>
<td>0.232</td>
</tr>
<tr>
<td><strong>Linear regression</strong></td>
<td>β (95% CI)</td>
<td>β (95% CI)</td>
<td>Twin vs. Singleton</td>
</tr>
<tr>
<td><strong>Child birth weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother preterm</td>
<td>-53.88 (-65.72 - -42.04)</td>
<td>-58.56 (-96.77 - -20.34)</td>
<td>0.296</td>
</tr>
<tr>
<td>Mother SGA</td>
<td>-255.79 (-237.10 - -214.47)</td>
<td>-116.41 (-157.18 - -75.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Child gestational age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother preterm</td>
<td>-0.28 (-0.32 - -0.24)</td>
<td>-0.22 (-0.35 - -0.09)</td>
<td>0.068</td>
</tr>
<tr>
<td>Mother SGA</td>
<td>-0.20 (-0.24 - -0.16)</td>
<td>-0.06 (-0.19 - -0.08)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Table 4. Likelihood of giving birth to a child born preterm or SGA, stratified by twinning status.
Study IV Reproductive pattern among twins and singletons in relation to number of siblings

The study population for study IV was an extended cohort compared with studies I-III and with a longer follow-up. The study population for this study was all men and women born between 1973 and 1993 and they were followed till the end of 2012. In total 2,091,205 men and women were included of which 39,726 were born as twins. In Table 5 the distribution of twinning and sex is presented.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,053,819 (98.1%)</td>
<td>997,660 (98.1%)</td>
<td>2,051,479 (98.1%)</td>
</tr>
<tr>
<td>Twin</td>
<td>20,014 (1.9%)</td>
<td>19,712 (1.9%)</td>
<td>39,726 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,073,833 (100.0%)</td>
<td>1,017,372 (100.0%)</td>
<td>2,091,205 (100.0%)</td>
</tr>
</tbody>
</table>

Table 5. Study population and its distribution of twinning and sex.

In this study it was found that twins had a lower likelihood of reproducing (men, HR=0.96 95% CI=0.93-0.99; women, HR=0.90 95% CI=0.88-0.93) compared with singletons. No difference was detected in the likelihood of having a second child among women, however among men the likelihood of having a second child was larger among twins compared with singletons (HR=1.07, 95% CI=1.02-1.11). Including the dichotomous variable on the number of siblings, 0-2 siblings and >2 siblings the likelihood of reproducing was higher, among both male and female twins and singletons, if the person had more than two siblings. This effect remained when analyzing the likelihood of having a second child.
<table>
<thead>
<tr>
<th>Number of siblings</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twins HR (95% CI)</td>
<td>Singletons HR (95% CI)</td>
</tr>
<tr>
<td>0-2</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;2</td>
<td>1.17 (1.08-1.27)</td>
<td>1.16 (1.15-1.18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of siblings</th>
<th>HR for becoming a first-time parent</th>
<th>HR for becoming parent to a second child</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>1.17 (1.08-1.27)</td>
<td>1.13 (1.01-1.26)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>1.16 (1.15-1.18)</td>
<td>1.13 (1.12-1.15)</td>
</tr>
</tbody>
</table>

Table 6. Hazard ratio for becoming a parent in relation to number of siblings, stratified by twinning and sex.
DISCUSSION

Summary of principal findings

• It was found that twins, both males and females, in general have a lower likelihood of reproducing in ages 13-33 compared with singletons. The diverging birth characteristics among twins and singletons fail to fully explain this difference.

• Overall, twins had a higher likelihood of being hospitalized in adolescence and early adulthood compared with singletons. However, even though twin pregnancies increases the risk for the newborn to be born with a low birth weight, preterm or SGA it appears as twins actually had a lower risk for being hospitalized due to several diagnoses when taking their diverging birth characteristic into account.

• An intergenerational effect of preterm birth and SGA births was present among both twins and singletons. Mothers born as singletons and preterm or SGA had an increased likelihood of giving birth to a child that was either preterm or SGA. The intergenerational effect was most pronounced among women born a singleton SGA who had a 3 times higher hazard rate of giving birth to a child SGA compared with singleton women not born SGA, which also was the only risk present among twins.

• Twin males and females have a lower likelihood of becoming a first-time parent compared with singletons. These differences vanished or were reversed when studying the chance of becoming a parent again. The likelihood of male twins becoming a second-time parent was higher compared with singletons while there was no difference between female twins and singletons.
• The number of siblings was found to be an important factor when studying future reproductive performance among both twins and singletons. Having three or more siblings was associated with an increased likelihood of becoming parents among male and female twins and singletons alike.

**Methodological considerations**

As with all research, the designs of these studies have their advantages and disadvantages. A major strength of all studies in this thesis is that data are prospectively collected from large population-based registers yielding a large study population. This may also impose a problem, as even very small differences will become statistically significant.

In using population-based register data it is important to be aware of the quality of the data and the possible effects it could have on the research. Even though all registers used have been validated and are of good quality some flaws still exist that may affect the results despite our efforts to minimize these risks. The first consideration pertains to the birth characteristics of the study population. In the first three studies the study population comprised men and women born between 1973 and 1983, and in the last study the cohort was extended to include men and women born between 1973 and 1993. It is possible that intrauterine growth curves provided by Marsal et al in 1996\(^99\) to calculate SGA and LGA are inappropriate for those born prior to 1996 as the mean birth weight of children has increased over time. Other possible problems involve the estimation of gestational age. From 1973 to the mid 80’s, when ultrasonogram was introduced in the estimation of gestational age, the last menstrual period was the method used. These two methods yield slightly different estimates on gestational age, as estimates using the last menstrual period are usually two to three days higher\(^84,98\). Moreover, validation of the birth weights registered in MBR has shown that some measurement errors exist at both endpoints, i.e. among those with extremely low or extremely high birth weights. The majority of
these errors are simply due to errors when transferring data from paper to computer. In an attempt to alleviate this problem we excluded individuals with an extremely high or extremely low birth weight with respect to the gestational length.

The second consideration pertains to the reproductive performance of the study population. As of today it is not possible to obtain any information on whether the women had undergone an induced abortion or had experienced a spontaneous abortion. This could cause an underestimation of the general reproductive rate as our estimates are based on live born infants. However, there is no obvious reason to expect that either twins or singletons are more prone to have had induced abortions. Thus, this is not expected to cause any bias regarding the comparisons of reproductive pattern of twins and singletons. There was also a lack of information on whether the men and women had tried to conceive. Moreover, in the studies of reproductive pattern the follow-up time was limited with follow-up ending in 2009 in study I and 2012 in study IV. Hence, the oldest persons were 33 years old at the end of follow-up in study I, and 36 years old in study IV. In 2013 women were, on average, 28.5 years old when they gave birth to their first child and usually men are on average somewhat older than women when starting a family. Thus, many of the participants have just started their reproduction and have many reproductive years left.

The third consideration is related to twinning. Nationally and internationally the twinning rates are at a much higher today compared with some 20 years ago\textsuperscript{17-18}. A possible explanation to this is the increasing maternal age at childbirth, but the introduction of IVF-treatment of couples having problems conceiving “naturally” could also be a contributing factor\textsuperscript{18}. As all individuals in study I were born prior to the introduction of IVF-treatment this cannot affect the twinning rate, nor should hormonal treatment have a major effect on the twinning rate. It is likely, however, that some of their offspring is the result of a successful IVF-treatment. Moreover, we
did not have information on whether the twins were monozygotic or dizygotic. This was not considered to be a major problem as the research focused on reproductive pattern, hospitalization, and the intergenerational effect of non-optimality at birth indifferent of zygoticity.

The fourth consideration is focused on the estimation of morbidity. For this work the presence of hospitalization according to any of the main chapters in ICD-9 was used. Since primary care is not part of the NPR we only managed to study the most severe cases were studied, i.e. those requiring treatment as an inpatient or outpatient at a hospital, of each main chapter.

The last consideration pertains to population-based register studies in general. Selecting a large cohort of individuals, potentially, a large number of statistically significant differences will be found. This means that even small differences, which are negligible or not have clinical relevance, will become statistically significant. It is thus very important to also consider the estimates (and confidence limits) of the associations when interpreting the findings.

**Principal findings in relation to other research**

In comparing the findings in this thesis with previous research presently available it is important to be aware of how the researches have defined their variables as e.g. SGA. Depending on study design and different standards the definition of SGA varies from study to study. In our studies we have used <2SD of the mean birth weight depending on sex and gestational age. In one study analyzing the risk for thrombocytopenia among SGA infants SGA was defined as below the 10\(^{th}\) percentile\(^{102-103}\) while in a study by Diaz et al in 2015 SGA was defined as <2SD for gestational age\(^{104}\) and in yet another study <2.5SD for gestational age was used\(^{105}\). Even minor differences in the definition of SGA birth are likely to affect the results and thus the comparability across studies.
In addition to the different definitions of SGA differences in the definition of study population are likely to be present – all depending on the availability of register data. In comparing studies and their findings it is important to take these differences into account, as is the design of the study. One should ask oneself several questions such as: Which study design was used? How was the data collected? How were the controls selected? Any matching, and if so which variables were used? How is migration and deaths accounted for in the follow-up? All of these factors will inevitably affect the comparability across studies.

Reproductive pattern
Several studies have provided evidence that birth characteristics is related to the future likelihood of giving birth\(^9\,70-71\), although the findings have not been conclusive. The studies in the present thesis found that women born SGA, or with a low/very low birth weight or preterm/very preterm had a decreased likelihood of giving birth but also very preterm males had a decreased likelihood of becoming a parent. These findings are in agreement with previous research on Swedish register data\(^9\,70-71\). Performed studies were also able to verify the findings of women born SGA being less likely in having a child, which is the conclusion drawn from a previous study on partly the same data but with a smaller cohort and where the follow-up time was shorter\(^9\).

In the present work it was further found that twins had a lower likelihood of reproducing compared with singletons. This could be due to a variety of causes. Twins often form relationships at a later stage in life\(^106-107\) and more often have a university degree\(^108\). The first explanation may very well cause twins postponement in entering parenthood, while the latter explanation could be either way – twins more often pursue an academic education due to not being able to have children or the postponement is caused by their educational focus. Also, though the models have been adjusted for several socio-demographic factors, there is always the
possibility of additional important confounding factors not adjusted for that influence the estimates\textsuperscript{109}.

**Hospitalization according to the main chapters in ICD-9**

Twinning per se has been found to be associated with morbidity and mortality in several studies, especially during the neonatal period. In the present work it was found that twins had an increased risk for being hospitalized due to several diagnoses, defined by the main chapters in ICD-9, including congenital malformations, which is in accordance with a previous study by Cooke et al\textsuperscript{110}. It was also found that being born a twin increased the risk for hospitalization due to mental disorders; this is also in alignment with previous research\textsuperscript{110-111}. However, stratifying data by optimality at birth and adjusting for socio-demographic factors and birth characteristics, it was found that in the non-optimal group twins appeared to fare somewhat better compared with singletons. A possible explanation to this is the etiology of preterm birth among twins and singletons. Twins are more likely to be delivered preterm due to mechanical reasons as lack of space, while among singletons the major cause for preterm birth are maternal complications during pregnancy such as infections\textsuperscript{10-11,18}.

**Intergenerational effect of non-optimal birth characteristics**

As several previous studies\textsuperscript{71-74}, the studies included in this thesis were able to establish an intergenerational effect of non-optimal birth characteristics. A slightly different intergenerational effect of preterm birth among mothers who themselves were born preterm was detected. Mothers who were born as singletons and born preterm had an increased risk for delivering a preterm child as well as a SGA child while there was no effect of preterm birth among mothers born as twins. In addition, we established a relationship among mothers born as twins and singletons with respect to SGA, mothers born as singletons and SGA had an increased risk to deliver
a child either preterm or SGA, twin mothers born SGA also had an increased risk to deliver a child who was SGA.
These findings are in accordance with several previous studies on singletons in which being born preterm or having a sibling born preterm, increases the risk for having a preterm child\textsuperscript{72}. These findings are also in accordance with a previous study by Selling et al\textsuperscript{71}, which found an intergenerational effect of mothers born SGA having a greater risk for delivering a SGA child. However, unlike this study we were able to establish that singleton women born preterm were more likely to deliver their own children both preterm or SGA.

**Reproductive pattern in relation to number of siblings**

Having 3 or more siblings was found to increase the chances of becoming a first-time parent among both twins and singletons as well as becoming parent a second time. This is in part in agreement with a previous study by Murphy and Knudsen who found that one of the most important intergenerational factors with respect to future reproductive pattern was the total number of siblings\textsuperscript{112}. Nevertheless, the number of siblings fail to fully explain the difference in reproductive pattern among twins and singletons after adjustment for socio-demographic and birth characteristics.
We also found an indication of male twins being more likely to have a second child compared with singletons, while this difference was not present among females. There are several potential explanations to this phenomenon. First, men are usually older when becoming parents for the first time, and evidence has been presented that male twins have a reduced likelihood of reproducing as well. Thus, it is plausible to assume that male twins are older than female twins when they become parents and therefore have a higher reproductive rate once the firstborn has arrived. This finding is in alignment with the results from a Norwegian study where male reproduction increased with the number of siblings, this effect was not present among females\textsuperscript{113}. Another study has also claimed that future reproduction and at
what age one decides to start a family is highly dependent on family values and may be of greater importance than “traditional” socio-demographic factors114.
GENERAL CONCLUSIONS

Up till now, most epidemiological studies on reproductive pattern and morbidity exclude twins (and higher order pregnancies), without explaining why. This thesis provides an addition to the current knowledge, mainly derived from intra-twin studies, on twin morbidity and reproductive pattern.

• Twins aged 13-33 years of age had a lower likelihood of reproducing compared with singletons after adjustment for both socio-demographic factors and birth characteristics (Study I).

• Having survived till the age of 13, and thereby surviving the most vulnerable time among newborn twins, twins still had an increased risk for being hospitalized in adolescence and young adulthood compared with singletons. Adjusting for both socio-demographic factors and optimality at birth this effect was diminished and even reversed, as twins with non-optimal birth characteristics seemed to fare better than non-optimal singletons (Study II).

• The intergenerational effect of preterm birth and SGA was present among both twins and singletons, though the effect seems to be greater among singletons compared with twins (Study III).

• Both male and female twins had a lower likelihood of becoming a first time parent. This decreased likelihood vanished in studying the likelihood of becoming a second-time parent and among males twins exhibited an increased likelihood of becoming a second-time parent compared with singletons. In terms of familial factors, the number of siblings affects future reproductive pattern among both twins and singletons (Study IV).
FUTURE PERSPECTIVES

This thesis provides indications that twins have a lower likelihood of reproducing compared with singletons. Since the studies had a limited follow-up, with respect to reproductive age, it is of importance to continue these studies but with a follow-up until the end of their reproductive years. This would further elucidate the importance of twining on future reproductive performance as well as provide a measure of “total” fertility.

As the study population in this thesis mainly were born prior to IVF-treatment it is also important to study if there are any differences on optimality at birth and subsequent fertility between twins conceived by IVF and “natural” twins.

In study IV we found that the number of siblings a person has affects the future likelihood of becoming a parent. In the future it is of importance to compare if the reproductive pattern among twins and their singleton siblings are different. This could provide further knowledge on the importance of the epigenetic effect (due to the intrauterine environment) on reproductive performance and outcomes.

In study II twins showed an increased likelihood of being hospitalized due to external causes of morbidity and mortality, after adjusting for both socio-demographic background factors as well as birth characteristics. In the future it would be of interest to investigate how the personality of the child is affected by different birth characteristics and how this in turn affects the likelihood of being hospitalized due to e.g. external causes of morbidity and mortality.

In the future it would be interesting to perform a clinical study including both twins and singletons where hormonal data, uterus size, ovulation rate, sperm quality etc. are collected in addition to asking the participants questions regarding chronic conditions, medications, infertility treatment, induced and spontaneous abortions.
Adding population-based register data on parental level of education, country of birth, employment, their own birth characteristics, mother’s pregnancy induced conditions, pregnancy outcome etc. would allow us to gain valuable knowledge on the reproductive pattern and morbidity among both twins and singletons.
POPULÄRVETENSKAPLIG SAMMANFATTNING


Syftet med denna studie var således att undersöka hur både tvillingars och enlingars reproduktion och sjuklighet påverkas av att vara född antingen för tidigt, med låg födelsevikt eller liten-för-tiden. För att besvara dessa frågor inhämtades anonymiserade persondata från Statistiska Centralbyrån och Socialstyrelsen.

I denna avhandling visade studierna att mellan åldrarna 13 och 33 år har tvillingar, generellt sett, en lägre sannolikhet att få barn även när man tar hänsyn till sociodemografiska faktorer såsom föräldrarnas utbildningsnivå, moderns ålder då personen själv föddes, om modern var förstföderska eller omföderska och föräldrars födelseland.

Dessutom har tvillingar överlag en högre risk för att ha kontakt med specialiserad sjukvård (öppenvård eller slutenvård) under tonåren och som unga vuxna. Men, när hänsyn tas till de olika födelsekarakteristika som tvillingar och enlingar har så försvinner många av skillnaderna och tvillingar med icke-optimala födelsekarakteristika tycks till och med ha ett lägre antal vårdbesök vid sjukhus jämfört med ”icke-optimala” enlingar för ett flertal diagnoser.

Dessutom fanns ärförlighet av icke-optimala födelsekarakteristika hos både tvillingar och enlingar, men mest uttalat hos enlingar då mödrar födda lätt-för-tiden hade en

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