

**Psychological and psychophysiological  
functioning of young adults born preterm:  
The Helsinki Study of  
Very Low Birth Weight Adults**

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## ABSTRACT

Improvements in neonatal intensive care during the last few decades have led to a remarkable improvement in the survival rates of preterm infants born with very low birth weight (< 1500 g; VLBW). However, VLBW may have a cost for the physical, psychosocial and cognitive development of the survivors. Nevertheless, there has been little research into the long-term consequences of VLBW that last till or emerge in adulthood. In addition, there have been relatively few studies on whether the adult outcomes of VLBW depend on sex or fetal growth.

Within the Helsinki Study of Very Low Birth Weight Adults, we studied whether young adults with VLBW differ from term-born adults in psychological and psychophysiological functioning as well as in recollections of parenting, and whether potential group differences are modified by sex or intrauterine growth. The original cohort comprised 335 VLBW infants born between 1978 and 1985, treated at the Children's Hospital of Helsinki University Central Hospital, and discharged alive. A total of 373 infants born at term at the same birth hospitals were identified to form a control group. At the first follow-up visit in young adulthood (mean age 22.5 years), 166 VLBW (42.8% men) and 172 term-born control adults (40.1% men) participated. Of the VLBW participants, 33.1% were born small for gestational age (SGA; birth weight for gestational age < -2 SD), which was used as a crude indicator of poorer intrauterine growth. In conjunction with the first visit, the participants filled in questionnaires on personality, romantic attachment and the parenting behavior of their parents. In addition, blood pressure reactivity to psychosocial stress was measured in a subsample of 44 VLBW and 37 control adults. At the second follow-up visit, three years later (mean age 25.0 years), 113 VLBW (44.2% men; 37.2% SGA) and 105 control adults (42.9% men) participated, and their academic achievement was self-reported and neurocognitive abilities were tested. In addition, the parents of the participants filled in questionnaires on their own parenting behaviors.

In comparison to the term-born adults, the VLBW adults scored lower in all the neurocognitive tests, and they had more often received remedial education, although they did not differ in years of education or in their grade point averages (Study I). The VLBW adults also showed a higher diastolic blood pressure reactivity to psychosocial

stress (Study II). Sex and being born SGA modified the results concerning personality, romantic attachment and parenting. In the personality assessment, all the VLBW adults reported less fun seeking indicating less spontaneous eagerness for new, potentially rewarding actions, but only the VLBW-SGA women reported more behavioral inhibition than the term-born women (Study III). In relation to their romantic attachment style, the VLBW adults, with the exception of the VLBW-SGA women, reported less anxiety than the controls, indicating less concerns over being rejected by their partner. In contrast, the VLBW-SGA women reported increased attachment-related avoidance behavior (Study IV). In relation to parenting, the VLBW women reported that their mothers had been more protective and authoritarian than did women in the term-born group, but there were no group differences in parental care. The parents of the VLBW adults reported more supportive parenting than the parents of the term-born adults (Study V).

In conclusion, we found that the VLBW adults differed from those born at term in all the areas of functioning included in the thesis. Of the VLBW adults, more alterations were found in women and in those with poor intrauterine growth. Overall, according to the results in young adulthood, VLBW may be related to vulnerabilities such as lower neurocognitive abilities and increased blood pressure reactivity; however, it may also give rise to potentially protective factors, such as higher parental involvement. Knowledge of the different vulnerabilities and protective factors could be utilized in planning interventions and optimal measures of support among preterm children and their families.



## TIIVISTELMÄ

Keskosten tehohoito on kehittynyt merkittävästi viime vuosikymmenien aikana. Tämän ansiosta pikkukeskosten (syntymäpaino < 1500 g) selviytymisennuste on parantunut huomattavasti. Pikkukeskosuus voi kuitenkin vaikuttaa yksilön fyysiseen, psykososiaaliseen ja kognitiiviseen kehitykseen. Silti pikkukeskosuuden aikuisuuteen ulottuvia tai aikuisuudessa ilmaantuvia pitkäaikaisseurauksia ei vielä riittävästi tunneta. Lisäksi harvassa tutkimuksessa on arvioitu, miten sukupuoli ja hidas sikiöaikainen kasvu voivat muokata keskosuuden ja myöhemmän kehityksen yhteyttä.

Osana kohorttitutkimusta 'Pikkukeskosten terveys aikuisiässä' (The Helsinki Study of Very Low Birth Weight Adults) tutkimme, ovatko pikkukeskosina syntyneet nuoret aikuiset erilaisia kuin täysiaikaisina syntyneet verrokki aikuiset psykologisessa ja psykofysiologisessa toiminnassaan sekä muistikuvissaan vanhempinsa vanhemmuuskäyttäytymisestä. Tutkimme myös, vaikuttavatko sukupuoli tai sikiöaikainen kasvu eroihin pikkukeskosina ja täysiaikaisina syntyneiden aikuisten välillä. Alkuperäinen kohortti koostui 335 vuosina 1978 – 1985 syntyneestä pikkukeskosesta, joita hoidettiin Helsingin yliopistollisen keskussairaalan Lastenkliniikalla ja jotka kotiutuivat sieltä elossa. Yhteensä 373 samassa sairaalassa täysiaikaisena syntynyttä lasta identifioitiin verrokkiryhmään. Ensimmäiselle tutkimuskäynnille varhaisaikaisuudessa (keski-ikä 22.5 vuotta) osallistui 166 pikkukeskosena (42.8% miehiä) ja 172 täysiaikaisena (40.1% miehiä) syntynyttä tutkittavaa. Pikkukeskostutkittavista 33.1% oli syntynyt raskauden keston nähden pienipainoisina (SGA; syntymäpaino suhteessa raskauden keston < -2SD), mitä käytettiin tutkimuksessa hitaan sikiöaikaisen kasvun karkeana merkkinä. Ensimmäisen tutkimuskäynnin yhteydessä tutkittavat täyttivät persoonallisuutta, parisuhdekiintymystä ja vanhemmuutta koskevat kyselylomakkeet. Lisäksi mitattiin psykososiaalisen stressikokeen aikaista verenpainereaktiivisuutta 44 pikkukeskosena ja 37 täysiaikaisena syntyneen tutkittavan osajoukossa. Toiselle tutkimuskäynnille kolme vuotta myöhemmin (keski-ikä 25.0 vuotta) osallistui 113 pikkukeskosena (44.2% miehiä; 37.2% SGA) ja 105 täysiaikaisena (42.9% miehiä) syntynyttä tutkittavaa. Tutkittavien koulusuoriutumista kartoitettiin kyselylomakkeella ja neurokognitiivisia taitoja testeillä.

Lisäksi tutkittavien vanhemmat täyttivät heidän omaa vanhemmuuskäyttäytymistään koskevat kyselylomakkeet.

Verrattuna täysiaikaisiin verrokkeihinsa, pikkukeskosena syntyneet aikuiset suoriutuivat heikommin kaikissa neurokognitiivisissa testeissä. He olivat myös saaneet enemmän tukiopetusta, vaikka eivät eronneet verrokeistaan opiskeluvuosien tai päättötodistuksen keskiarvon suhteen (osajulkaisu I). Lisäksi pikkukeskosina syntyneiden aikuisten diastolinen verenpainereaktiivisuus psykososiaaliseen stressiin oli suurempi kuin verrokeilla (osajulkaisu II). Sukupuoli ja raskauden kestoon suhteutettu pienipainoisuus vaikuttivat persoonallisuutta, parisuhdekiintymystä ja vanhemmuutta koskeviin tuloksiin. Persoonallisuuden osalta pikkukeskosena syntyneet aikuiset raportoivat vähemmän hauskuuden tavoittelua, jolla viitataan spontaaniin tapaan innostua ja ryhtyä uusiin mahdollisesti palkitseviin toimintoihin. Pikkukeskosena syntyneet SGA-naiset raportoivat lisäksi verrokkinaisia voimakkaampaa välttämiskäyttäytymistä (osajulkaisu III). Parisuhdekiintymyskyselyssä pikkukeskosena syntyneet raportoivat, SGA-naisia lukuun ottamatta, vähäisempää ahdistusta, jolla viitataan huoleen torjutuksi tulemisesta. SGA-naiset sen sijaan raportoivat voimakkaampaa välttämiskäyttäytymistä parisuhteessa kuin verrokkinaiset (osajulkaisu IV). Vanhemmuuskyselyssä pikkukeskosnaiset raportoivat äitiensä olleen suojelevampia ja autoritaarisempia kuin mitä verrokkinaiset raportoivat, mutta keskos- ja verrokkiryhmät eivät eronneet vanhempien hoivan suhteen. Lisäksi pikkukeskosena syntyneiden vanhemmat itse raportoivat enemmän lasta tukevaa vanhemmuutta kuin verrokkien vanhemmat (osajulkaisu V).

Väitöstutkimuksessa pikkukeskosina syntyneet aikuiset erosivat täysiaikaisina syntyneistä aikuisista kaikilla tutkituilla osa-alueilla. Eniten eroja havaittiin pikkukeskosnaisilla sekä niillä, joiden sikiöaikainen kasvu oli hitaampaa. Tulosten mukaan pikkukeskosena syntyminen on yhteydessä riskitekijöihin kuten kohonneeseen stressiverenpaineeseen ja heikompiin neurokognitiivisiin taitoihin, mutta myös mahdollisiin suojaaviin tekijöihin kuten vanhempien osallistuvaan vanhemmuuteen. Tietoa keskosten riskitekijöistä ja vahvuuksista voidaan hyödyntää keskoslasten ja heidän perheidensä parissa tehtävien interventioiden ja tukitoimien suunnittelussa.

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- III Pyhälä, R., Räikkönen, K., Pesonen, A.-K., Heinonen, K., Hovi, P., Eriksson, J.G., Järvenpää, A.-L., Andersson, S., & Kajantie, E. (2009). Behavioral inhibition and behavioral approach in young adults with very low birth weight – The Helsinki study of very low birth weight adults. *Personality and Individual Differences*, *46*, 106–110.
- IV Pyhälä, R., Räikkönen, K., Pesonen, A.-K., Heinonen, K., Hovi, P., Järvenpää, A.-L., Eriksson, J.G., Andersson, S., & Kajantie, E. (2010). Romantic attachment in young adults with very low birth weight – The Helsinki Study of Very Low Birth Weight Adults. *Journal of Developmental Origins of Health and Disease*, *1*, 271–278.
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## ABBREVIATIONS

11 $\beta$ -HSD2	11 $\beta$ -hydroxysteroid dehydrogenase-2 enzyme
ADHD	Attention-deficit hyperactivity disorder
AGA	Appropriate for gestational age
BAS	Behavioral approach/activation system
BIS	Behavioral inhibition system
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CP	Cerebral palsy
CPT II	Conners' Continuous Performance Test II
DOHaD	Developmental origins of health and disease
ECR-R	Experiences in Close Relationships – Revised
ELBW	Extremely low birth weight (< 1000 g)
FFS	Fight/flight system
FFFS	Fight-flight-freeze system
HeSVA	Helsinki Study of Very Low Birth Weight Adults
HPAA	Hypothalamic-pituitary-adrenal axis
ICD-10	International Classification of Diseases 10 <sup>th</sup> revision
IQ	Intelligence quotient
IUGR	Intrauterine growth restriction
LBW	Low birth weight (< 2500 g)
LGA	Large for gestational age
NICU	Neonatal intensive care unit
PBI	Parental Bonding Instrument
ROCF	Rey-Osterrieth Complex Figure Test
ROP	Retinopathy of prematurity
RST	Reinforcement sensitivity theory
SD	Standard deviation
SES	Socioeconomic status
SGA	Small for gestational age
TMT	Trail Making Test

TSST	Trier Social Stress Test
VLGA	Very low gestational age (< 32 gestational weeks)
VLBW	Very low birth weight (< 1500 g)
WAIS III	Wechsler Adult Intelligence Scale III
WHO	World Health Organization



# 1 INTRODUCTION

Improvement in neonatal intensive care in 1960's led to remarkable improvement of the survival rate of preterm infants (Euro-peristat project, 2008; K. S. Lee et al., 1995; Stewart et al., 1981). Despite this, preterm birth is still one of the leading causes of infant mortality (Blencowe et al., 2012; Lawn et al., 2010; Liu et al., 2012). In addition, prematurity and survival after preterm birth have their costs not only economically to the society (Lindström et al., 2007; Petrou, 2003; S. Saigal & Doyle, 2008) but also in terms of long-term health and wellbeing to the survivors and their families.

Physical immaturity predisposes severely preterm infants to both short and long-term morbidity. Physical immaturity and exceptionally early beginning of their extrauterine life also make early social environment to be different for preterm infants in comparison to those born at term. With regard to psychological outcomes, a growing body of evidence shows that former preterm infants have pronounced vulnerability to cognitive, emotional, behavioral and social problems in comparison to those born at term (for reviews or meta-analyses, see Aylward, 2002; Bhutta et al., 2002; Burnett et al., 2011; Hack, 2009; Hayes & Sharif, 2009). Survival after severely preterm birth have, however, become increasingly possible due to modern neonatal intensive care only during the last few decades and the long-term consequences lasting till or emerging in adulthood still lack sound understanding.

Physical, social and psychological aspects of development have reciprocal effects on each other and, importantly, on both physical and psychological well-being, which in turn have major effects on individuals everyday functioning. Increased rates of preterm birth and its consequences on mortality, morbidity and long-term costs for society make preterm birth an important public health issue. To build a coherent understanding on development of preterm infants and finally develop interventions and optimal measures of support, it is crucial to gain information on long-term outcomes among former preterm infants, including both physiological and psychological perspective.

## **1.1 Preterm birth: definitions, epidemiology and short-term morbidity**

### **1.1.1 Definitions related to preterm birth, birth weight and gestational age**

Full-term human pregnancy takes approximately 40 weeks and, for example in Finland, mean birth weight has been approximately 3500 g during the last decade (Vuori & Gissler, 2011a). Both gestational age and birth weight are commonly used to determine subcategories for preterm birth (see Table 1).

In terms of gestational age, World Health Organization (WHO) defines all births between 37 and 42 completed gestational weeks as full-term, births before 37 completed gestational weeks as preterm and births after 42 completed gestational weeks as postterm. At the earlier stages of medical history when estimations for gestational age were more inexact, prematurity was more often defined by birth weight. Finnish pioneering pediatrician Arvo Ylppö (1920) defined premature infant as an infant whose birth weight is less than or equal to 2500 g. To this day, birth weight is a practicable, exact and commonly used birth measure. Birth weight in relation to gestational age has traditionally been used as a crude indicator of intrauterine growth and being small for gestational age (SGA) as a crude indicator of intrauterine growth restriction (IUGR), although they are not equivalent (see 1.1.2.2).

Definitions have also been given to different time periods of the pre- and early postnatal life of an infant. Perinatal period pertains to time before, during and shortly after delivery, but there is variation in the exact time limits used. For example, in official statistics of Finland, perinatal mortality includes stillbirths after 22 weeks of gestation and deaths during the first six days after birth (Vuori & Gissler, 2011b). Regarding stillbirths, the International Classification of Diseases, 10<sup>th</sup> revision (ICD-10) relates late fetal deaths to those with weight over 1000 g or gestational age over 28 weeks, and early fetal deaths to those with weight between 500 and 1000 g or gestational age between 22 and 28 weeks. The range of gestational age cut-offs used for stillbirths vary across countries between 16 and 28 weeks (Blencowe et al., 2012; Lawn et al., 2010).

**Table 1.** Definitions for commonly used categories of birth weight, gestational age and time periods regarding the pre- and early postnatal life of an infant.

Category	Abbreviation	Definition
<b>Gestational age in postmenstrual weeks at birth<sup>1</sup></b>		
Term		37 to 42 weeks
Postterm		> 42 weeks
Preterm		< 37 weeks
Late preterm		34 to 36 + 6/7 weeks
Moderate preterm		32 to 33 + 6/7 weeks
Very preterm		28 to 31 + 6/7 weeks or < 32 weeks
Extremely preterm		< 28 weeks
Very low gestational age	VLGA	< 32 weeks
<b>Birth weight</b>		
Low birth weight	LBW	< 2500 g
Very low birth weight	VLBW	< 1500 g
Extremely low birth weight	ELBW	< 1000 g
<b>Birth weight for gestational age<sup>2</sup></b>		
Small for gestational age	SGA	a) < -2 SD units b) < 10 <sup>th</sup> percentile
Appropriate for gestational age	AGA	a) within $\pm 2$ SD units b) within the 10 <sup>th</sup> and 90 <sup>th</sup> percentile
Large for gestational age	LGA	a) > +2 SD units b) > 90 <sup>th</sup> percentile
<b>Early periods of postnatal life</b>		
Early neonatal		the first 6 days after birth
Late neonatal		days between the 7 <sup>th</sup> and 28 <sup>th</sup> day after birth
Neonatal		the first 28 days after birth
Infancy		the first year after birth

<sup>1</sup>For example, Euro-peristat project, 2008; Lumley, 2003; March of Dimes, PMNCH, Save the Children, WHO, 2012; Shapiro-Mendoza & Lackritz, 2012

<sup>2</sup>For example, P. A. Lee et al., 2003

## **1.1.2 Etiology of preterm birth and low birth weight**

### **1.1.2.1 Preterm birth**

Preterm birth is considered as a syndrome with multiple origins. Preterm delivery can be medically indicated or spontaneous. Spontaneous preterm delivery can follow prelabor premature rupture of the membranes or intact membranes. While the etiology of preterm birth is not fully understood and the cause is not always known, several risk factors have been identified. They may act through physiological mechanisms, psychosocial effects, or both. Many of them are interrelated and can interact to influence preterm birth. These factors include genetic and epigenetic mechanisms as well as inflammations, infections and other immunological processes, which are also suggested to mediate the association between preterm birth and many other risk factors (Goldenberg et al., 2008; Menon, 2008; Menon et al., 2012; Muglia & Katz, 2010).

Medical indications for preterm elective delivery include conditions that threaten health or life of the mother or fetus, such as maternal pre-eclampsia which is frequently accompanied by placental dysfunction leading to IUGR. These fetal and maternal conditions also increase the risk of spontaneous preterm birth (Goldenberg et al., 2008; Moutquin, 2003). Other risk factors include prior preterm birth or pregnancy losses (both spontaneous and induced abortion), birth defect, short interval between pregnancies, assisted conception, multiple birth, young or high maternal age, low pregnancy body mass index (BMI), maternal smoking or substance use during pregnancy, social disadvantages such as low education and low family income, psychological and social stress, hard physical work, and factors related to ethnicity (Goldenberg et al., 2008; Lumley, 2003; Moutquin, 2003; Muglia & Katz, 2010; Slattery & Morrison, 2002). For example in the USA, rates of preterm birth are highest among non-Hispanic black and lowest among non-Hispanic white (Lawn et al., 2010; Martin et al., 2011).

### **1.1.2.2 Intrauterine growth**

One example of a fetal condition related to either spontaneous or induced preterm birth is IUGR. Prenatal adversity (relating to maternal, fetal or placental issues) that may have led to preterm birth may also have led to IUGR (Bernstein & Divon, 1997;

Nardozza et al., 2012; Ott, 1993). Severe IUGR may threaten the life of the fetus and necessitate medically indicated preterm delivery. Fetal malnutrition and fetal overexposure to glucocorticoids are commonly known examples of such prenatal adversities. Excess of glucocorticoids may derive from maternal stress, antenatal corticosteroid treatment and/or inactivity of the placental 11 $\beta$ -hydroxysteroid dehydrogenase-2 (11 $\beta$ -HSD2) enzyme. Normally 11 $\beta$ -HSD2 converts majority of maternal cortisol passing through placenta to the fetus into inactive cortisone. Inactivity of 11 $\beta$ -HSD2 may thus lead to increased concentration of fetal cortisol, which in turn can lead to restricted intrauterine growth (Benediktsson et al., 1993; Kajantie et al., 2003). Also pregnancy disorders such as maternal pre-eclampsia are frequently accompanied by IUGR.

Accordingly, low birth weight of a preterm infant may have resulted from low gestational age, poor intrauterine growth or both. Being born SGA is generally used as a crude proxy of IUGR, although they are not equivalents. While the term IUGR is recommended to be used only if intrauterine growth has been documented at least by two intrauterine growth assessments, the term SGA refers to size at birth (P. A. Lee et al., 2003). Birth weight is strongly genetically driven (Lunde et al., 2007), and consequently, infants born SGA also include many of those, who have not suffered from IUGR but have genetic disposition to small birth size, while infants born AGA may also include those who would be genetically disposed to higher birth weight but who have not reached their genetic growth potential due to IUGR. In addition, infants with IUGR may vary in their timing of the growth restriction during pregnancy. Growth restriction during early or mid-pregnancy is suggested to result in symmetric IUGR apparent in both weight and head growth while growth restriction during later pregnancy is suggested to result in asymmetric IUGR with spared head growth (Rosenberg, 2008). It is also of note that during their early extrauterine life, many severely preterm infants suffer from undernutrition leading to neonatal growth restriction resembling IUGR (Euser et al., 2008).

In preterm groups determined by a birth weight cut-off, e.g. VLBW infants, those born SGA are overrepresented in comparison to all births. Prevalences between 19 and 53% have been reported for infants born SGA among VLBW study samples (Gäddlin et al., 2009; Hack et al., 2004; Horbar et al., 2002; Lemons et al., 2001; Lund et al., 2011;

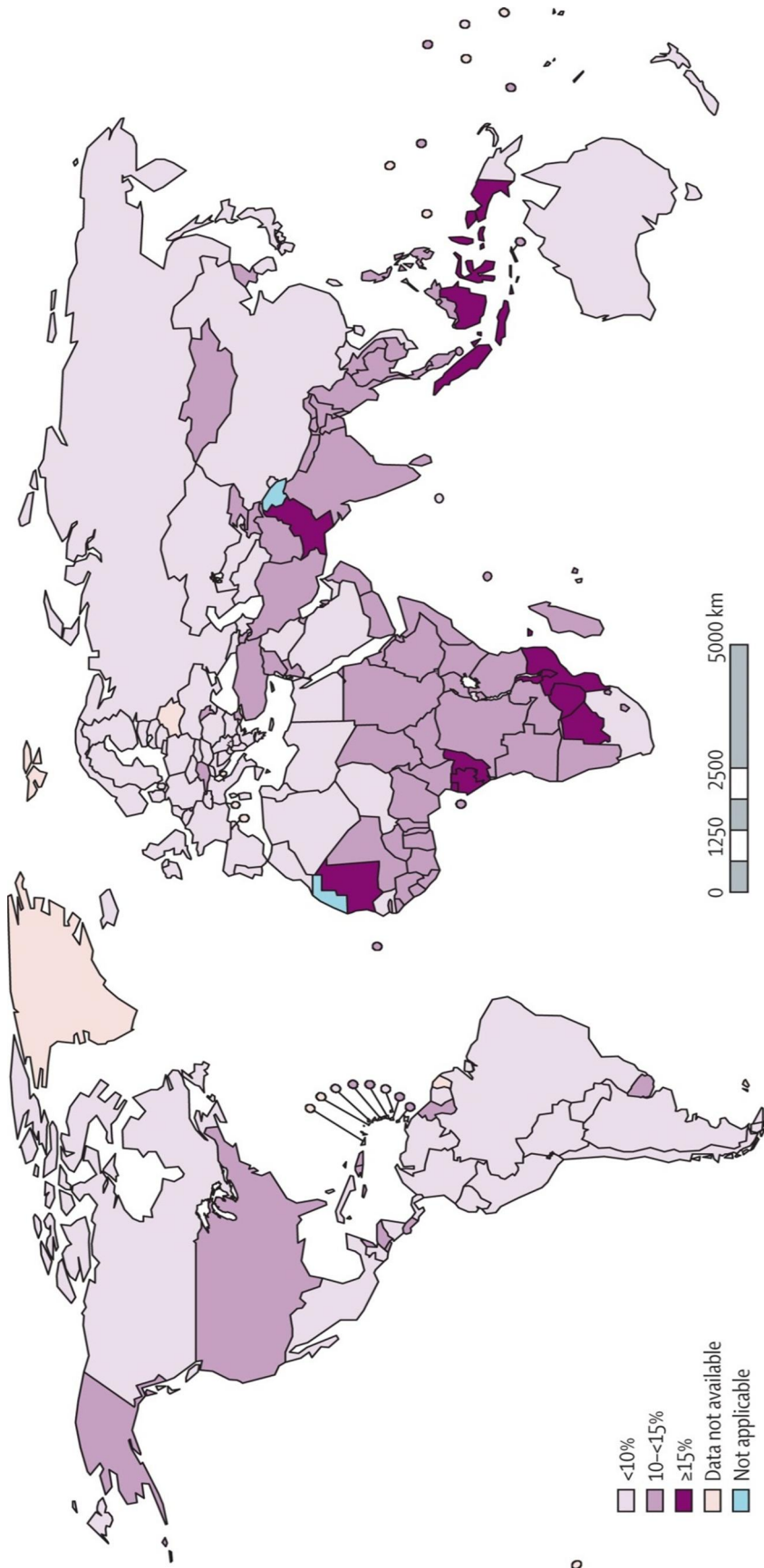
Lund et al., 2012). This range of SGA prevalences is compatible also with the Helsinki Study of Very Low Birth Weight Adults (HeSVA), the VLBW study sample of this thesis.

### **1.1.3 Prevalence of preterm birth**

#### **1.1.3.1 Worldwide prevalence of preterm birth**

The worldwide prevalence of preterm birth is now estimated to be approximately 11.1% of all live births, converting into 14.9 million births in a year (Blencowe et al., 2012). Compatible estimates were suggested two years earlier with worldwide prevalence of 9.6% of all births, translating into 12.9 million preterm births per year (Beck et al., 2010). Rates vary across countries (Figure 1), the heaviest burden of preterm births being in developing regions such as Africa and parts of Asia, where preterm birth is estimated to account for 11 – 13% of all births (Beck et al., 2010; Blencowe et al., 2012; Lawn et al., 2010), and even over 15% in some countries (Blencowe et al., 2012). Preterm births in Africa and Asia are estimated to cover 85% of all preterm births in the world (Beck et al., 2010), reflecting also a high total number of births in these regions. However, also in the USA the prevalence of preterm birth is approximately 12% (Martin et al., 2011). In Europe, the rates vary between 6 and 11% across countries, the lowest being in Finland, the Baltic countries and Ireland, and the highest in Austria, Germany and Hungary (Euro-peristat project, 2008). In Finland, in 2010, the prevalence of preterm birth was 5.8% of all births (Vuori & Gissler, 2011a).

Those classified as very preterm (< 32 gestational weeks, VLGA) or born with VLBW (< 1500 g) comprise about 1.5 – 2% of all births in the USA (Martin et al., 2011) and 1% in Europe (Euro-peristat project, 2008). Of all births in 2010 in Finland, 499 infants (0.8%) were born with VLBW and 560 (0.9%) with VLGA (Vuori & Gissler, 2011a). Comparison between rates from different countries is, however, complicated by varying classifications and definitions, particularly concerning the lower cutoff for stillbirth or livebirth registrations (Blencowe et al., 2012).



**Figure 1.** Estimated preterm birth rates by country for the year 2010. Reprinted from The Lancet, 379, Blencowe et al. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications, 2162 – 2172. Copyright (2012), with permission from Elsevier.

### 1.1.3.2 Trends across time in prevalence of preterm birth

Rates of preterm birth seem to have risen over the last few decades in most countries, for example in the USA, Australia and several European countries (Beck et al., 2010; Blencowe et al., 2012; Lawn et al., 2010; Martin et al., 2011). However, in some countries the trend is the opposite or the prevalence has been stable over the years (Lawn et al., 2010; Lumley, 2003). Even in the USA, the rates have declined slightly during the last few years (Hamilton et al., 2011). In Finland, the rate of preterm birth decreased from 1960's till 1980's (Olsén et al., 1995), but has remained essentially the same since then (Vuori & Gissler, 2011a).

The observed increase in preterm rates is primarily attributable to infants born late preterm (Davidoff et al., 2006; Martin et al., 2011; Shapiro-Mendoza & Lackritz, 2012) and may be associated with several etiological factors also depending on the geographical region. At least in middle- and high-income countries one such etiological factor may be increased use of elective delivery in cases of fetal or maternal complications (Goldenberg et al., 2008; Lumley, 2003). Another factor may be rise in fertility treatments, as it increases the risk of prematurity directly (Helmerhorst et al., 2004) and through increased rates of multiple births (Goldenberg et al., 2008; Lumley, 2003; Martin et al., 2011). Increase in preterm birth rates may also partly reflect changes in perceptions of viability and practices in reporting births of those with borderline viability. In addition, the methodological change in estimating gestational age may play a small role. Estimation by ultrasound assessment of fetal size gives in general younger gestational ages than the traditional estimation based on last menstrual period (Lumley, 2003). Poverty and infections may partly be responsible for the increase of preterm delivery in low-income countries, while decrease of preterm rates in some other countries may at least partly be explained by improvement in socio-economic factors and prevention programs (Lumley, 2003).

### 1.1.4 Survival after preterm birth

Preterm birth is closely related to increased mortality. It has been estimated that complications related to preterm birth cause more than a million neonatal deaths



worldwide in a year (Lawn et al., 2010; Liu et al., 2012) and are now listed as the most important cause of neonatal deaths (Liu et al., 2012). In the USA, VLBW births comprise about 1.5% of all births, but they comprise more than half of all infant deaths (Mathews et al., 2006). Similarly in Finland, nearly 45% of infant deaths are attributable to those with VLBW (Euro-peristat, 2008).

The current neonatal mortality rate for VLBW infants is approximately 20% in USA (Mathews et al., 2012). In Europe, it was 12.2% in 2006 (Euro-peristat, 2008), and, in Finland it was 12.3% in 2007 – 2008 and 10.7% in 2009 – 2010 (Vuori & Gissler, 2011a). Trends across time in survival after preterm birth are introduced in chapter 1.1.5.3.

Survival of the VLBW/VLGA infant is dependent on the degree of prematurity, fetal growth and neonatal morbidity, but also on the level of available neonatal care (Saigal & Doyle, 2008; Vuori & Gissler, 2011a). Thus mortality is high particularly in developing regions including Africa and Southeast Asia (Liu et al., 2012). If facilities for neonatal intensive care are accessible, the limit for viability appears to lie around 23 to 24 gestational weeks and survival increases after every additional week (MacDorman & Mathews, 2010; S. Saigal & Doyle, 2008; Vuori & Gissler, 2011a; R. M. Ward & Beachy, 2003). In Europe, in 2006 neonatal mortality was 63.9% for those born earlier than at 24 gestational weeks, 16.9% for those born at 26 – 27 weeks and no more than 2.6% for those born at 30 – 31 weeks (Euro-peristat project, 2008). In terms of birth weight, neonatal mortality was 37% within the birth weight category of 501 – 750 g, but only 2.7% among those with birth weight 1251 – 1500 g (Euro-peristat project, 2008).

### **1.1.5 Neonatal morbidity and intensive care of preterm infants**

#### **1.1.5.1 Neonatal morbidity of preterm infants**

Although technical developments in intensive care have improved survival of preterm infants, the preterm survivors are still susceptible to high rates of morbidity. Some of the factors, such as genetic predisposition (Hallman, 2012) and being SGA (Qiu et al., 2012), that may contribute to the preterm birth may contribute to the morbidity of preterm infants. However, prematurity by itself is considered to be the major cause of

morbidity in preterm infants (R. M. Ward & Beachy, 2003). It constitutes adversity for development and maturation, as it leads to early conditions and growth environment that are very different from the normal intrauterine growth environment in late pregnancy. Furthermore, although treatment methods have improved over the few decades of neonatal intensive care, some of them may cause injury in fragile organs of a preterm infant. The risk of complications increases with decreasing gestational age at birth (R. M. Ward & Beachy, 2003).

The most frequent and significant complications of the central nervous system include intraventricular hemorrhage, periventricular hemorrhagic infarction and periventricular leucomalasia (R. M. Ward & Beachy, 2003). Part of the infants with intraventricular hemorrhage develops hydrocephalus (Robinson, 2012). Gastrointestinal problems include feeding intolerance, which, when prolonged, may lead to intravenous nutrition with all its complications. Due to nutritional problems the preterm infant may suffer from hypoglycemia, malnutrition and postnatal growth failure. Necrotising enterocolitis is a relatively rare but potentially fatal inflammatory disorder of the gastrointestinal tract (Lin & Stoll, 2006; Neu & Walker, 2011). Pulmonary complications among preterm infants is commonly manifested in respiratory distress syndrome, which may develop into a chronic lung disease, bronchopulmonary dysplasia (BPD), which is now commonly defined as oxygen requirement at 36 weeks postmenstrual age (Philip, 2012; R. M. Ward & Beachy, 2003). Patent ductus arteriosus refers to condition in which ductus arteriosus, the blood vessel connecting pulmonary artery and aortic arch, does not close after birth. Severe prematurity is also related to retinopathy of prematurity (ROP), which refers to disorder of the blood vessels in the retina. ROP can finally lead to retinal detachment and blindness (Chen & Smith, 2007). Additionally, very preterm neonates often suffer from temperature instability, sepsis, seizures, and jaundice/ hyperbilirubinemia (Lemons et al., 2001).

#### 1.1.5.2 Trends across time in intensive care after preterm birth

Interventions and preventions targeted to improve neonatal outcomes include both pre- and postnatal treatments and they have improved tremendously since the 1960's. Important landmarks of neonatal intensive care include introductions of assisted

ventilation in the late 1960's, antenatal and postnatal glucocorticoids in the 1970's and postnatal surfactant therapy in the 1980's (Philip, 2012). These treatments were primarily targeted to improve the outcome related to pulmonary problems (Lemons et al., 2001; Philip, 2012; Rügger et al., 2012; R. M. Ward & Beachy, 2003). Use of supplemental oxygen since 1950's was associated with increase in hyperoxia and ROP diagnoses (Chen & Smith, 2007), but although decrease in oxygen use lead to decrease in ROP, it also lead to increase in mortality (Philip, 2012). Consequently, oxygen levels are now monitored and controlled more carefully than at the early stages (Philip, 2012). In addition, ROP is currently treated with cryotherapy, laser photocoagulation and laser ablation (Chen & Smith, 2007; R. M. Ward & Beachy, 2003). Apart from special technology, also breastfeeding and kangaroo care, first introduced by Edgar Rey in the 1970's, are shown to be beneficial in reducing neonatal mortality and morbidity (Lawn et al., 2011). In kangaroo care the infant is in continuous skin-to-skin contact usually with the mother, positioned against her chest, wearing just a diaper and a hat. This is suggested to provide a variety of benefits including optimal thermal environment and sensory stimulus, facilitation of breastfeeding, early discharge to home and promotion of parent-infant attachment (Charpak et al., 2005; Conde-Agudelo et al., 2011). These milestones have been accompanied by continuous improvements in neonatal nutrition, nursing and other aspects of care.

#### 1.1.5.3 Trends across time in survival and morbidity after preterm birth

Gradually increasing use and development of prenatal and neonatal treatments have contributed to improving survival and neonatal health of preterm infants. Mortality among VLBW infants in developed countries was approximately 60% before the 1960's, but around 40 – 50% in the 1970's (K. S. Lee et al., 1995; Stewart et al., 1981), 35% in the 1980's (Järvenpää & Granström, 1987; K. S. Lee et al., 1995) and 10 – 20% in the 2000's (Euro-peristat project, 2008; Mathews et al., 2010; Vuori & Gissler, 2011a). Improvement and then stabilization of survival have concerned first late and moderate preterm infants and then gradually the more premature ones. While survival rates for more mature VLBW infants had stabilized, survival of the most premature infants with ELBW (Horbar et al., 2002; Meadow et al., 2004; Platt et al., 2007) or

gestational age below 27 weeks (Rüegger et al., 2012) continued to improve still during the 1990's.

An overall trend seems to be that increasing survival of the most preterm infants has first been accompanied by increased morbidity (K. S. Lee et al., 1995; Lemons et al., 2001) and lengthened stay in neonatal intensive care unit (NICU) (Meadow et al., 2004; Rüegger et al., 2012). However, the following trend may be a decrease in morbidity and NICU days, as have happened among more mature preterm infants (Rüegger et al., 2012). Overall, despite increased survival among all VLBW infants, rates for severe neonatal morbidity and neurosensory impairments have not increased, but rather decreased (Horbar et al., 2002; K. S. Lee et al., 1995; Platt et al., 2007; Rüegger et al., 2012; R. M. Ward & Beachy, 2003) or remained stable (Lemons et al., 2001; Stewart et al., 1981) as a result of increased use of pre- and postnatal treatment.

## **1.2 Physical health of former preterm infants**

Former preterm infants are more prone to long-term morbidity in their later life than their term-born peers. This susceptibility applies to major disabilities as well as to some non-communicable diseases and their risk factors. Prematurely born individuals have more rehospitalizations after their discharge from NICU than those born at term (E. M. Boyle et al., 2012). Higher rate of disabilities is also reflected in their increased likelihood of receiving sickness pension, disability allowance and assistance (Lindström et al., 2007; Moster et al., 2008). Further, prematurity is shown to be related to increased mortality not only in infancy, but also in early childhood and in young adulthood (Crump et al., 2011). In young adulthood, the increased mortality among those born preterm was mostly connected to congenital anomalies, respiratory disorders, endocrine disorders and cardiovascular mortality (Crump et al., 2011).

### **1.2.1 Neurosensory impairments and major disabilities**

Prematurity (Hack et al., 2002; Moster et al., 2008; Saigal & Doyle, 2008; R. M. Ward & Beachy, 2003) and neonatal complications (Chen & Smith, 2007; Hintz et al., 2005; Lin & Stoll, 2006; Neu & Walker, 2011; Robinson, 2012) are related to higher rates of

major neurosensory impairments including cerebral palsy (CP), developmental deficit, visual impairment and hearing impairment (Ancel et al., 2006; Marlow et al., 2005; Platt et al., 2007). Neurosensory impairments are most common among the survivors with shortest gestations. Within extremely preterm cohorts, rates of 21 – 35% have been reported (Saigal & Doyle, 2008).

### **1.2.2 Cardiovascular and metabolic health**

Concerning cardiovascular risk factors in terms of blood pressure, reports from the HeSVA study have shown higher office blood pressure (Hovi et al., 2007), higher ambulatory blood pressure and increased risk of hypertension (Hovi et al., 2010) in adults born with VLBW in contrast to controls born at term. These findings are supported by other research. Preterm birth is associated with elevated office systolic blood pressure at least in adolescence (Edstedt Bonamy et al., 2008; Rossi et al., 2011) and young adulthood (Dalziel, Parag et al., 2007; Hack et al., 2005; Irving et al., 2000; Johansson et al., 2005; Rotteveel et al., 2008). In some studies, minor effects on diastolic blood pressure have also been found in adolescence (Edstedt Bonamy et al., 2008) and adulthood (Johansson et al., 2005; Rotteveel et al., 2008). Apart from the HeSVA study (Hovi et al., 2010), data on ambulatory blood pressure (Keijzer-Veen et al., 2010; Kistner et al., 2005) is limited, but suggests a similar trend (for a systematic review and meta-analysis see F. de Jong et al., 2012). Ambulatory recordings overcome the effect of ‘white coat hypertension’ that may be present in office measurements, but they do include responses to everyday stress (Kamarck et al., 2002). Very little is known about the association between preterm birth and blood pressure reactivity to psychosocial stress.

In childhood, the associations between prematurity and higher blood pressure are not as strong as in adulthood (Cheung et al., 2004; Willemsen et al., 2008). In some childhood studies the associations do not exist at all (Cheung et al., 2004; Menezes et al., 2007) and in some studies prematurity may even be associated with lower blood pressure (Bracewell et al., 2008). In line with this, two recent reviews on preterm birth and blood pressure (F. de Jong et al., 2012; Norman, 2010) have demonstrated that the

effect of preterm birth on elevated systolic blood pressure increases from prepubertal age to adolescence and young adulthood.

Also data on other cardiovascular risk factors among individuals born preterm are scarce, but suggest no increased risk regarding endothelial functioning or intima-media thickness, but potential alterations, for example, in capillary density and microvascularization among those born preterm (Norman, 2008). Partly in line, the VLBW adults in the HeSVA study had increased carotid artery intima-media thickness in relation to lumen size but not in absolute size (Hovi et al., 2011). Data on arterial stiffness is controversial (Norman, 2008), some studies showing increased stiffness in subgroups of preterm participants (Cheung et al., 2004; Rossi et al., 2011) and some showing no differences (Hovi et al., 2011).

According to most studies, being born SGA does not increase cardiovascular risks within preterm groups with varying severity of prematurity (Dalziel, Parag et al., 2007; Hack et al., 2005; Hovi et al., 2007; Hovi et al., 2010; Hovi et al., 2011; Irving et al., 2000; Johansson et al., 2005; Keijzer-Veen et al., 2010), although it is shown to do so at least in one study among preterm children (Cheung et al., 2004), in another study among late preterm men (Johansson et al., 2005) and in population-based studies covering the whole range of birth weights and gestational ages (Järvelin et al., 2004). However, among term-born children at the age of 12 years, those born SGA had higher ambulatory blood pressure than those born AGA, but only after adjusting for current BMI, which was lower in the SGA group (Rahiala et al., 2002).

With regard to metabolic problems that are identified as key defining features and risk factors for type 2 diabetes and also for cardiovascular disease, higher indices of insulin resistance and glucose intolerance were found in the VLBW adults in comparison to the term-born adults of the HeSVA study (Hovi et al., 2007). In a similar vein, other studies have found that children (Hofman et al., 2004) and adults (Dalziel, Parag et al., 2007; Pilgaard et al., 2010; Rotteveel et al., 2008) born preterm have higher insulin resistance than those born at term, and that the effect is similar among those born SGA and those born AGA.

Of actual diseases, in few studies self-reported diagnoses of hypertension (Dalziel, Parag et al., 2007) or blood pressure values indicating hypertension (Hovi et al., 2010; Johansson et al., 2005) have been found more frequently in young adults born preterm

than in those born at term. However, studies concerning diseases have mostly been conducted among middle-aged adults. In such studies, preterm birth has been related to higher rate of type 2 diabetes (Kaijser et al., 2009; Kajantie et al., 2010; Pilgaard et al., 2010), while hypertension (Bonamy et al., 2008; Kaijser et al., 2008) and ischemic heart disease (Kaijser et al., 2008; Koupil et al., 2005) has been related to poorer fetal growth but not to preterm birth. Stroke has been related to preterm birth in some (Koupil et al., 2005) but not all studies (Osmond et al., 2007). Thus, results concerning relations between prematurity and cardiovascular problems in middle-aged and older people are so far contradictory. In addition, they are not necessarily easy to apply to preterm infants born during the latest decades due to changes in neonatal intensive care, consequent survival and estimation of gestational age (Norman, 2010).

### **1.2.3 Other non-communicable diseases and health problems**

Apart from cardio-metabolic diseases and major disabilities, former preterm infants are shown to be at increased risk of various other somatic health problems in later life (E. M. Boyle et al., 2012; Tideman et al., 2001). They report poorer physical abilities along with more neurosensory impairments (Hack et al., 2007), but also individuals without neurosensory impairments report poorer physical abilities (Cooke, 2004; Ericson & Källén, 1998; Hille et al., 2007; Saigal et al., 2007). Former preterm infants may have more respiratory symptoms and pulmonary problems in childhood (E. M. Boyle et al., 2012; Hack et al., 2011) and adulthood (Doyle et al., 2006; Vrijlandt et al., 2006), particularly if they have suffered from BPD in infancy (Doyle, 2008; Gough et al., 2012; Greenough, 2012). Accordingly, it was shown in the HeSVA study that they undertake much less leisure-time physical activity, promotion of which may be an important target for prevention of chronic disease (Kaseva et al., 2012). They also reported more sleep-disordered breathing in young adulthood (Paavonen et al., 2007). In addition, altered skeletal development has been found to characterize individuals born preterm (Chan et al., 2008; Fewtrell, 2011; Hovi et al., 2009).

## **1.3 Psychological development of former preterm infants**

In addition to posing a challenge to physical health, preterm birth may pose a challenge to psychological development and mental health. Psychological outcomes after preterm birth are mostly studied in childhood and the body of adulthood studies is growing, although many aspects still lack understanding. In addition, the risk of adverse psychological development in preterm infants may be modified or pronounced by several confounders, including sex, fetal problems such as IUGR, and later vulnerability factors, although knowledge of these associations is restricted. These latter associations may shed light into the mechanisms underlying preterm birth and later developmental outcomes.

### **1.3.1 Cognitive and academic abilities after preterm birth**

#### **1.3.1.1 Outcomes in childhood**

Prematurity and low birth weight are related to deficits in cognitive functioning in childhood (for reviews see Anderson & Doyle, 2008; Aylward, 2002; Bhutta et al., 2002; Mulder et al., 2009; Shenkin et al., 2004). These deficits are reported to be visible already in infancy and toddlerhood (Magill-Evans & Harrison, 1999; Rose et al., 2002; Sansavini et al., 1996). When compared to term-born children, preterm infants (Lundqvist-Persson et al., 2012) and toddlers (Voigt et al., 2012) have also shown lower self-regulation or effortful control, which may contribute to their poorer early cognitive (Voigt et al., 2012), attentional, motor and emotional development (Lundqvist-Persson et al., 2012), including their poorer ability to joint attention (Olafsen et al., 2006).

In comparison to children born at term, pre-school- and school-aged children born preterm or with LBW, VLBW or ELBW are reported to have poorer cognitive test scores (for reviews see Anderson & Doyle, 2008; Aylward, 2002; Bhutta et al., 2002; Shenkin et al., 2004). This poorer functioning is reflected in lower intelligence quotient (IQ) and other overall scores indicating lower general intelligence (Aarnoudse-Moens et al., 2011; Elgen et al., 2002; Hack et al., 1992; Hack et al., 2011; Horwood et al., 1998; Jaekel et al., 2012; Lind et al., 2011; Marlow et al., 2005; Peng et al., 2005; Sansavini et



al., 1996; Sommerfelt et al., 1993), but lower scores are evidenced also in tests pertaining to specific cognitive domains including both visual-motor and verbal tasks (Anderson & Doyle, 2008; Aylward, 2002; Hack et al., 1992; Lind et al., 2011). Their mean performance, however, often falls within the normal range indicating only minor cognitive deficits in comparison to term-born peers.

According to multiple studies, including two meta-analyses (Aarnoudse-Moens et al., 2009; Mulder et al., 2009), preterm children have problems also in different subdomains of attention and executive functioning, which refers to cognitive processes that direct behavior towards intended goals. Executive processes that have been reported to be poorer in preterm children include working memory, response inhibition, shifting mental sets (or cognitive flexibility), planning and verbal fluency (Anderson & Doyle, 2008; Lind et al., 2011; Mulder et al., 2009; Rose et al., 2011). Attentional processes are closely related to executive functioning and can be divided into selective and sustained attention, which both appear to be weaker among preterm children than among term-born children (Anderson & Doyle, 2008; Mulder et al., 2009; Rose et al., 2011). Also processing speed is reported to be slower among those born preterm (Rose & J. F. Feldman, 1996; Rose et al., 2002; Rose et al., 2011). Memory processes apart from working memory are little studied among preterm groups, but in one study, long-term memory appeared to be intact in preterm children (Lind et al., 2011), while in few other studies poorer performance was found at least in some tests (Hack et al., 1992; Rose et al., 2011). In addition, cognitive performance of preterm children seems to deteriorate more by increasing difficulty of a task (Rose & J. F. Feldman, 1996).

Poorer “core cognitive abilities” such as processing speed, working memory, attention and representational competence (a prerequisite for abstract thinking), are shown to account for the lower IQ scores (Rose et al., 2011), and further, for less successful school performance in preterm children (Anderson & Doyle, 2008; Mulder et al., 2010). On the other hand, at least in extremely preterm children, lower general cognitive ability explained some of their specific language problems, but it did not explain all of their educational difficulties (Wolke et al., 2008). In comparison to term-born peers, children with varying severity of prematurity present poorer learning skills (Aylward, 2002; Rose & J. F. Feldman, 1996), they repeat a class more frequently (Aarnoudse-Moens et al., 2011; Hack et al., 2002), they have lower school grades and

teacher-rated academic attainment (Mulder et al., 2010; Wolke et al., 2008), more problems in reading, writing and mathematics (Aarnoudse-Moens et al., 2011; Horwood et al., 1998; Johnson et al., 2011; Mulder et al., 2010) and they need more often remedial education (Mulder et al., 2010) or special education (Aarnoudse-Moens et al., 2011; Horwood et al., 1998; Johnson et al., 2011; MacKay et al., 2010).

Prematurity thus seems to affect neurocognitive development adversely, including different domains of it. At least extremely preterm children have demonstrated significant continuation in poorer educational outcomes from six to 11 years of age (Johnson et al., 2011), although another study has implied that some cognitive deficits seen in earlier childhood may attenuate by developmental catch-up (H. G. Taylor, Minich, Klein et al., 2004). Yet another possibility is that certain deficits that are not yet apparent in childhood emerge at later age when cognitive demands from the environment increase and subtle neural insults restrict brain plasticity and normative development of higher skills (Aylward, 2002; Luciana, 2003).

#### 1.3.1.2 Outcomes in adolescence and adulthood

Regardless of the possible catch-up development in some cognitive skills, deficits in cognitive abilities seem to be present still in adolescence and young adulthood. Similar to children, prematurely born adolescents (Allin et al., 2008; Kulseng et al., 2006; Levy-Shiff et al., 1994; Lund et al., 2012; Narberhaus et al., 2007; Rickards et al., 2001; Saigal, 2000; Saigal et al., 2000) and young adults (Allin et al., 2008; Hack et al., 2002; Hallin et al., 2010; Lohaugen et al., 2010; Nosarti et al., 2007) earn lower IQ estimates than term-born controls. As in childhood, their poorer performance applies to both visual-motor and verbal tasks (Allin et al., 2008; Grunau et al., 2004; Hallin et al., 2010; Lohaugen et al., 2010; Lundgren et al., 2003; Narberhaus et al., 2007; Rickards et al., 2001).

With regard to executive functioning, very or extremely preterm adolescents and adults have shown to have impairments in working memory (Hallin et al., 2010), shifting mental sets (Hallin et al., 2010; Kulseng et al., 2006; Narberhaus et al., 2008; Nosarti et al., 2007), response inhibition (Nosarti et al., 2007) and verbal fluency (Allin et al., 2008; Gimenez et al., 2006; Narberhaus et al., 2008; Nosarti et al., 2007; Rushe et

al., 2001). They have also performed poorer on tasks of attention (Kulseng et al., 2006; Nosarti et al., 2007) and demonstrated slower processing speed (Hallin et al., 2010; Kulseng et al., 2006; Strang-Karlsson et al., 2010). However, not all studies confirm the findings on poorer response inhibition (Kulseng et al., 2006), ability to shift mental sets (Rushe et al., 2001) or attention (Grunau et al., 2004).

Concerning studies of memory processes, results in preterm adolescents are very scarce and partly inconsistent, and, to my knowledge, no previous study has focused on preterm adults. There are two separate studies implying poorer short-term visual memory (Rickards et al., 2001) or problems in global everyday memory (Caldú et al., 2006; Narberhaus et al., 2007) among preterm adolescents, but a third study does not confirm these memory problems (Rushe et al., 2001). Long-term visual memory appears to be unimpaired among preterm adolescents (Caldú et al., 2006; Narberhaus et al., 2007; Rickards et al., 2001; Rushe et al., 2001).

In accordance with altered neurocognitive performance, preterm adolescents (Indredavik, Vik, Heyerdahl, Kulseng et al., 2005) and adults (Hallin et al., 2010; Hille et al., 2007) report lower academic achievement if compared to term-born controls or general populations. Preterm adolescents are reported to have poorer arithmetic skills in particular (Grunau et al., 2004; Rickards et al., 2001; Saigal, 2000; Saigal et al., 2000), and sometimes also poorer reading (Grunau et al., 2004; Saigal, 2000; Saigal et al., 2000) and spelling skills (Saigal, 2000; Saigal et al., 2000). They have received more remedial education according to some (Saigal, 2000; Saigal et al., 2000), but not all studies (Rickards et al., 2001), and they repeat grades more often (Rickards et al., 2001). Preterm birth and low birth weight have also been related to later school enrollment (Reuner et al., 2009), less frequent graduation from high school (Ericson & Källén, 1998; Hack et al., 2002; Reuner et al., 2009), less frequent graduation from postsecondary education and lower net salary among the employed, indicating vocational impairment, although no difference in employment between preterm and term groups has been found (Lindström et al., 2007; Moster et al., 2008; Nosarti et al., 2007; Saigal, Stoskopf, Steiner et al., 2006). Lower education has also been found in Cooke's (2004) study, where the preterm participants were more often at paid work, but the term-born participants were more often students.

The above-described neurocognitive and academic outcomes in adulthood are based on restricted number of studies (Allin et al., 2008; Hack et al., 2002; Hallin et al., 2010; Hille et al., 2007; Lohaugen et al., 2010; Nosarti et al., 2007; Strang-Karlsson et al., 2010), of which few have included one or more individual tests assessing any domain of executive functioning (Allin et al., 2008; Hallin et al., 2010; Nosarti et al., 2007). Moreover, knowledge of the role of possibly essential contributing factors such as IUGR or small head circumference at birth is still vague in relation to adulthood neurocognitive outcomes. While IUGR and small head circumference have been related to lower general intelligence within severely prematurely born adults (Weisglas-Kuperus et al., 2009) and within general population (Lundgren et al., 2003; Räikkönen et al., 2009), it is unclear whether IUGR explains the differences in neurocognitive functioning between severely preterm and term-born adults. To clarify the long-term cognitive risks after preterm birth, more detailed studies on different neurocognitive skills and their development into adulthood among preterm individuals are needed.

### **1.3.2 Personality development after preterm birth**

#### 1.3.2.1 Outcomes in childhood

Personality and temperament have been approached in research through varying theoretical frameworks and therefore also findings related to preterm birth and personality development vary in terms of conceptual framework used. However, it is commonly accepted that temperament refers to innate, relatively stable and biologically based individual traits that build a basis for personality development, which is influenced by accumulating life experiences and reciprocal interactions with psychosocial environment. Temperament and personality have a regulating effect on behavior and emotion and thus affect vulnerability to psychopathology. However, how prematurity affects long-term personality development and how it affects wellbeing, is surprisingly little studied.

When compared to term-born controls or norms for full-term children, preterm infants and toddlers are reported by their parents to exhibit more temperament characteristics that may be perceived as difficult to manage. Following the theoretical

framework by Thomas and Chess (1977), these characteristics include lower predictability, higher fuzziness (Gennaro et al., 1990), lesser rhythmicity (Goldstein & Bracey, 1988; Hughes et al., 2002; Langkamp et al., 1998; Weiss et al., 2004), higher distractibility (Hughes et al., 2002; Weiss et al., 2004), lower sensory threshold (Langkamp & Pascoe, 2001; Sajaniemi et al., 1998), lower adaptability (Gennaro et al., 1990; Langkamp et al., 1998; Langkamp & Pascoe, 2001; Medoff-Cooper, 1986; Weiss et al., 2004), more intense emotional expressiveness (Langkamp & Pascoe, 2001; Medoff-Cooper, 1986), more negative mood (Langkamp et al., 1998; Langkamp & Pascoe, 2001), weaker persistence (Hughes et al., 2002; Medoff-Cooper, 1986), and lesser approaching (Hughes et al., 2002). Moreover, very preterm birth has been associated in toddlerhood to poorer effortful control (Voigt et al., 2012) and in preschoolers to lesser attentional focusing (Nygaard et al., 2002), which are essential aspects of self-regulation, a characteristic domain of temperament (e.g. Rothbart & Ahadi, 1994).

However, differing findings exist. In some studies preterm children did not differ from term-born children in their temperament (Halpern et al., 2001; Oberklaid et al., 1991; Ross, 1987), or differed only in one characteristic, for example being less socially responsive (Larroque et al., 2005), more withdrawing (Honjo et al., 2002) or displaying more motor activity (Keresteš, 2005). Further, some studies have found preterm children to have also traits related to easy temperament, for example being less intense in emotional expressions (Hughes et al., 2002; Oberklaid et al., 1991; Sajaniemi et al., 1998), less active, more adaptive and more positive in mood (Sajaniemi et al., 1998).

### 1.3.2.2 Outcomes in adulthood

Results of adulthood personality in former preterm infants are scarce, but demonstrate a cautious, controlled and conscientious phenotype. Allin and others (2006) reported that adults born preterm scored lower on extraversion and higher on neuroticism than controls born at term. The VLBW adults in our HeSVA cohort differed from their term-born peers by showing higher conscientiousness, lower openness to experience, and also lower scores in excitement seeking, assertiveness, hostility and impulsivity, although no difference in overall scale of neuroticism was found (Pesonen et al., 2008). In addition,

another cohort of ELBW adults displayed more shyness, lower sociability and higher socialization indicating more prosocial and cautious behavior in comparison with their term-born peers (Schmidt et al., 2008). They also showed a tendency towards more behavioral inhibition, although groups did not differ in behavioral approach (Schmidt et al., 2008).

It has been suggested that the difficult temperament of preterm infants observed in earlier studies might have resulted from the prematurity-related immature neural organization (Gennaro et al., 1992) and in part from neonatal morbidity and neural irritability (Langkamp & Pascoe, 2001; Larroque et al., 2005), while explanations to differences in adulthood may also relate to other developmental factors.

### **1.3.3 Mental health after preterm birth**

Higher incidence of psychopathology has been reported in preterm populations in comparison to controls born at term. However, there is particular discrepancy between self-reports and reports from parents and teachers.

#### **1.3.3.1 Outcomes in childhood**

According to parent- and teacher-reports, children born preterm with LBW, VLBW or ELBW have both higher rate of externalizing and internalizing symptoms than their full-term peers (Reijneveld et al., 2006; for reviews see Aylward, 2002; Hack, 2009; Hayes & Sharif, 2009; for a meta-analysis see Bhutta et al., 2002). Externalization in preterm groups often relates to clinician-diagnosed attention-deficit hyperactivity disorder (ADHD) (Elgen et al., 2002) or related attentional symptoms (Elgen et al., 2002; Hille et al., 2001; Horwood et al., 1998; Reijneveld et al., 2006) and sometimes to hyperactivity (Hoff, Hansen et al., 2004; Horwood et al., 1998; Pharoah et al., 1994). In some reports also higher rates of delinquent or aggressive behavior have been described (Elgen et al., 2002; Reijneveld et al., 2006; Sommerfelt et al., 1993), although not all studies have found increased externalizing behavior in LBW (Tessier et al., 1997) or in ELBW children (Hille et al., 2001).

Parent- and teacher-reported internalization among preterm children often manifests in anxiousness and in depressive (Elgen et al., 2002; Hall & Wolke, 2012; Hille et al., 2001; Horwood et al., 1998) and withdrawing behavior (Hall & Wolke, 2012; Reijneveld et al., 2006; Tessier et al., 1997). In addition, according to parents, ELBW children have lower satisfaction with health, lower comfort and achievement and less risk avoidance than term-born children (Hack et al., 2011). In late childhood, preterm birth is also shown to increase the risk of anxiety and depressive disorder diagnoses (Burnett et al., 2011).

Self-reports are more rare in studies focusing on mental health in childhood, but at least in one study preterm children themselves reported more problems in school performance and attention, more aggressive behavior and lower self-esteem than their term-born peers (Elgen et al., 2002), while in another the preterm and term groups did not differ (Hack et al., 2011).

### 1.3.3.2 Outcomes in adolescence and adulthood

Problems related to psychological wellbeing seem to continue beyond childhood. For example, M. H. Boyle and others (2011) found that internalizing and externalizing problems in ELBW adolescents predicted similar problems in young adulthood. Similarly, Lund and others (2012) found that psychiatric morbidity was persistent in VLBW participants from adolescence to young adulthood, and further, that clinician-rated psychosocial functioning in adolescence predicted significantly psychiatric morbidity in adulthood.

However, adulthood data on some aspects of mental wellbeing are sparse and inconsistent and not all findings indicate worse outcome in adults born preterm. In addition, clear inconsistencies between parent and self-reports have been reported in childhood (Hack et al., 2011), and still in adolescence and adulthood (Dahl et al., 2006; Hack et al., 2004; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Saigal et al., 2003; Zwicker & Harris, 2008), parents reporting problems but preterm participants themselves not as much.

According to parent and teacher reports, adolescents and young adults born preterm have more emotional, behavioral (Grunau et al., 2004; Hack et al., 2004; Indredavik,

Vik, Heyerdahl, Kulseng et al., 2005; Indredavik et al., 2010; Levy-Shiff et al., 1994; Stevenson et al., 1999), and attention problems (Dahl et al., 2006; Grunau et al., 2004; M. Hack et al., 2004; Indredavik et al., 2004; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Indredavik et al., 2010; Lund et al., 2011). They also have more symptoms of hyperactivity according to some (Indredavik et al., 2010; Levy-Shiff et al., 1994), but not all reports (Hack et al., 2004; Indredavik et al., 2004; Lund et al., 2011; Stevenson et al., 1999).

Also according to some self-reports prematurely born adolescents and adults have experienced lower emotional wellbeing (Schmidt et al., 2008), more anxiety, depression and withdrawal (M. H. Boyle et al., 2011; Levy-Shiff et al., 1994), and less resilience (Hack et al., 2007) in comparison with their controls born at term, but more often they do not report differences in psychosocial wellbeing (Cooke, 2004; Hack et al., 2007; Hallin & Stjernqvist, 2011; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Indredavik, Vik, Heyerdahl, Romundstad et al., 2005; Tideman et al., 2001). In the HeSVA study, only those VLBW adults who were born SGA reported more often than the term-born controls a depression diagnose, depressive symptoms (Räikkönen et al., 2008) and symptoms of ADHD (Strang-Karlsson et al., 2008). Results on self-esteem vary, some indicating lower self-esteem in adolescents and adults born preterm (M. H. Boyle et al., 2011; Levy-Shiff et al., 1994; Rickards et al., 2001) and others not (Grunau et al., 2004; Hack et al., 2007; Indredavik, Vik, Heyerdahl, Romunstad et al., 2005; Saigal et al., 2002).

In line with the higher rates of psychiatric symptoms, preterm groups have more psychiatric disorders. This is well demonstrated in Scandinavian register-based studies. A Swedish register study found unadjusted odds ratios between 1.56 and 1.85 for VLBW in any psychiatric disorder, schizophrenia, alcohol/drug disorders, affective disorder or neurotic, stress-related and somatoform disorders (Abel et al., 2010). According to another Swedish register study with partially overlapping sample, moderate and very preterm birth was related to an increased risk of psychiatric hospitalization due to a range of disorders, including nonaffective psychosis, depressive disorder and bipolar affective disorder (Nosarti et al., 2012). In addition, preterm birth has been related to severe personality disorders based on structured clinical examination (Fazel et al., 2012), very preterm birth to a higher risk of eating disorders and moderate



preterm birth to drug and alcohol dependency based on diagnoses in hospital registers (Nosarti et al., 2012). National registers from Norway revealed an association between preterm birth and behavioral or emotional disorders (Moster et al., 2008), and finally, a register study from Denmark found an association between low birth weight or preterm birth and comorbid affective disorder and schizophrenia (Larsen et al., 2010). Similarly, based on psychiatric diagnostic interviews, prematurely born adolescents and adults have poorer clinician-rated functioning (Indredavik et al., 2004; Indredavik et al., 2010; Lund et al., 2011), more often psychiatric disorders including depression (Patton et al., 2004), anxiety disorder (Indredavik et al., 2004; Indredavik et al., 2010; Lund et al., 2011) and ADHD (Lund et al., 2011), and more often comorbid disorders (Indredavik et al., 2004; Lund et al., 2011). In psychiatric interviews, they also express more subthreshold symptoms of anxiety and inattention (Indredavik et al., 2004). Interestingly, however, preterm adolescents and adults do not differ in their self-rated quality of life or satisfaction (Cooke, 2004; Dinesen & Greisen, 2001; Hack et al., 2007; Hallin & Stjernqvist, 2011; Saigal, Stoskopf, Pinelli et al., 2006; Tideman et al., 2001), which may imply at least partial adaptation to their possible functional limitations.

#### **1.3.4 Social functioning after preterm birth**

##### **1.3.4.1 Social competence**

Preterm birth has been related to higher degrees of social withdrawing already at age one year in clinical observations (Guedeney et al., 2012). Parents and teachers have reported more problems in social skills among children (Elgen et al., 2002; Hille et al., 2001; B. Hoff, Hansen et al., 2004; Reijneveld et al., 2006) and adolescents (Grunau et al., 2004; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005) born preterm than among their term-born peers. Although VLBW adolescents themselves did not report more social problems than the controls, they reported lower social competence in some (Indredavik, Vik, Heyerdahl, Kulseng et al., 2005), but not all studies (Grunau et al., 2004). They also reported lower romantic confidence (Grunau et al., 2004). In comparison to term-born peers, VLBW adolescents are also more frequently being bullied (Grindvik et al., 2009) or rated by their teacher as socially rejected (Rickards et

al., 2001). Also adults born with ELBW reported more shyness and less sociability as well as higher rates of socialization referring to prosocial behavior, cautiousness, risk aversion and adherence to social norms (Schmidt et al., 2008). Furthermore, adults born very preterm reported less social interactions, but not reduced satisfaction with that condition (Hallin & Stjernqvist, 2011).

#### 1.3.4.2 Risk-taking behavior

Related to social behavior, adolescents and adults born preterm have consistently reported less risk-taking behaviors such as alcohol (Cooke, 2004; Hack et al., 2002; Hack et al., 2007; Saigal et al., 2003) and illicit drug use (Cooke, 2004; Dalziel, Lim et al., 2007; Hack et al., 2002; Hack et al., 2007), sexual activity (Hack et al., 2002; Hack et al., 2007; Kajantie et al., 2008) and delinquent behavior (Hack et al., 2002; Hack et al., 2004; Hack et al., 2007), and they reported less visits to pub or disco (Cooke, 2004). In a study by Hack's group (2007), the VLBW adults also reported more risk-avoidance related to peer influences, such as peers abusing drugs or alcohol. Similarly in the HeSVA study, the VLBW adults reported less substance use than those born at term (Strang-Karlsson et al., 2008).

#### **1.3.5 Parenting, attachment development and starting a family after preterm birth**

##### 1.3.5.1 Parenting a preterm child

Preterm birth of an infant and subsequent periods of intensive neonatal care brings for parents worry, anxiety, helplessness, disappointment, grief, even guilt and number of other emotions related to distress, which may continue even after discharge from the NICU (Eisengart et al., 2003; Miles & Holditch-Davis, 1997; Moore et al., 2006; Singer et al., 1999). Preterm birth and parental distress may evoke parents' perception of vulnerability in their infant (Allen et al., 2004; Green & Solnit, 1964). This perception may be aggravated by immaturity-related behaviors that characterize preterm infants (Langkamp & Pascoe, 2001; Medoff-Cooper, 1986; Weiss et al., 2004). Behavior of a

preterm infant, continuing parental distress and sense of vulnerability may add also to the later parent-reported behavioral and emotional problems in their children (Estroff et al., 1994; Huhtala et al., 2012; Miceli et al., 2000; Perrin et al., 1989). In addition, they may promote interaction style or parenting behavior that differs from parenting a term-born infant (R. Feldman, 2007; Stern et al., 2006; Zelkowitz et al., 2009).

For instance in infancy, if contrasted with parents of term-born infants, mothers and/or fathers of preterm infants have been reported to be less sensitive (R. Feldman, 2007; Forcada-Guex et al., 2011), less optimal in their interaction style, less responsive (Harrison & Magill-Evans, 1996), less reciprocal (R. Feldman, 2007) and more controlling (Forcada-Guex et al., 2006; Forcada-Guex et al., 2011). Further, within a preterm group, maternal perception of vulnerability was related to lesser positive expressions and more intrusiveness and hostility in interaction with their infant (Stern et al., 2006). The infants, in turn, show more negative emotionality (R. Feldman, 2007) and lesser activity in interaction (Stern et al., 2006) with their less sensitive and more intrusive parent.

Altered parenting may contribute to the later psychological development of a preterm child or parent-reports concerning it. For example, controlling parenting style has been related to higher rates of later mother-rated behavioral problems in children (Forcada-Guex et al., 2006). Sensitive and positive interaction style in parenting has been associated to more favorable cognitive (Hoff, Munck et al., 2004; Magill-Evans & Harrison, 1999; Treyvaud et al., 2009) and emotional development (Treyvaud et al., 2009), at least in preterm children who were rated as prone to distress (Poehlmann et al., 2011; Poehlmann et al., 2012).

However, not all studies show altered parenting or interaction style in parents of preterm infants (Harrison, 1990). Further, it has been suggested that even if parents of preterm infants were less sensitive and more controlling, their parenting would normalize after the first few years (Hoff, Hansen et al., 2004; Hoff, Munck et al., 2004; Muller-Nix et al., 2004). Yet, in comparison with parents of term-born children, Jaekel and others (2012) reported that mothers were less sensitive and more controlling among very preterm children at six and eight years of age, Wightman and others (2007) found that overprotective style was more prevalent among parents of eight-year-old preterm

children and Elgen and others (2002) reported that child rearing was less nurturing among mothers of 11-year-old LBW children.

Data on associations between preterm birth and parenting behavior are extremely scanty beyond childhood. In addition, father's role is usually neglected and studies including the perspective of the preterm child on parenting are missing. There is, to my best knowledge, only one previous study meeting these requirements in adolescence. Indredavik, Vik, Heyerdahl, Romundstad et al. (2005) found that VLBW adolescents perceived their parents as more protective than those born at term, although this was not confirmed in parent-reports. The VLBW and term-born groups did not differ in parental care in reports from parents or adolescents (Indredavik, Vik, Heyerdahl, Romundstad et al., 2005). Patton and others (2004) reported that low maternal care and high control were associated to depression in a sample of adolescents born preterm and at term, but they did not report whether the groups differed in terms of perceived parenting. No corresponding studies have been reported in adulthood.

#### 1.3.5.2 Attachment style after preterm birth

According to Bowlby's (1969) theory, an infant builds mental representations of the self and other in interactions with their caregivers. Parenting behavior is a key factor in this early attachment development. Sensitive, responsive and warm parenting is expected to lead to positive representations of both the self and the other as well as to a sense of security, as the infant learns that the caregiver is available when needed. These representations and patterns of the early attachment relationship are expected to be internalized into a general 'working model' of the self and others, which is then reflected in the attachment pattern manifesting in later relationships.

In studies of normal birth weight populations, a connection between early and later attachment patterns has been demonstrated (Roisman et al., 2001; Waters & Merrick, 2000). The attachment pattern is also shown to associate with later psychological wellbeing. Insecurity and attachment-related avoidance or anxiety correlate with psychopathology and social problems (Dykas et al., 2008; Fortuna & Roisman, 2008; Raikes & Thompson, 2008). In addition, an insecure attachment pattern is suggested to

increase vulnerability to physical illness for example through susceptibility to stress (Maunder & Hunter, 2001).

Given its potential effects on later health, attachment patterns are surprisingly little studied in preterm populations, and even if studied, term-born control groups are often missing (Brisch et al., 2003; Brisch et al., 2005; Goldberg et al., 1986; Rode et al., 1981; Sajaniemi et al., 2001). According to few studies, preterm birth does not increase the risk of a less secure attachment during infancy (Brisch et al., 2003; Brisch et al., 2005; Frodi & Thompson, 1985; Rode et al., 1981). Compatibly, distributions of maternal attachment representations of their preterm infants have been reported to be similar to those in term-born groups (Korja et al., 2009; Korja et al., 2010; Meijssen et al., 2011). According to these few studies, non-balanced maternal representations indicating an insecure attachment were associated to maternal depressive symptoms or negative feelings (Korja et al., 2009; Meijssen et al., 2011) as well as to poorer quality of dyadic interaction (Korja et al., 2010) in both preterm and term groups. However, whether the preterm and term groups are similarly vulnerable to possible long-term effects of poor dyadic interaction on attachment development is left unanswered in these articles.

According to contrasting reports, higher percentage of preterm children than term-born children exhibit an insecure (Mangelsdorf et al., 1996; Wille, 1991), atypical/disorganized (Sajaniemi et al., 2001) or marginally secure (Goldberg et al., 1986) attachment pattern and higher percentage of mothers of preterm infants than mothers of term-born infants demonstrated non-balanced attachment representations, regardless of the mother's posttraumatic stress level (Forcada-Guex et al., 2011). In addition, adolescents born preterm demonstrated less secure attachment than their term-born peers (Lubetzky & Gilat, 2002) and adults born very preterm expressed more often a preoccupied attachment style than their controls born at term, although no differences were found in the attachment style, if a categorization of secure versus nonsecure attachment was used (Hallin & Stjernqvist, 2011). To my knowledge, how attachment patterns appear in romantic relationships of adults born preterm has not been studied.

### 1.3.5.3 Leaving parental home and starting a family

Prematurely born young adults are more likely than their peers born at term to still live with their parents (Cooke, 2004; Kajantie et al., 2008; Lindström et al., 2007). They are also less likely to have experienced a sexual relationship (Hack et al., 2002; Kajantie et al., 2008), to cohabit with an intimate partner (Kajantie et al., 2008; Moster et al., 2008) or a friend (Cooke, 2004), to be married (Lindström et al., 2007; Moster et al., 2008) and to be parents (Hack et al., 2002; Moster et al., 2008; Swamy et al., 2008).

Also some differing results have been reported. For example, ELBW was not related to differences in proportion living independently, being married or cohabiting or being a parent among young adults (Saigal, Stoskopf, Streiner et al., 2006), LBW was not related to being in an intimate relationship or to pregnancy rates (Cooke, 2004), and moderately or late preterm birth was not related to marital status (Dalziel, Lim et al., 2007).

### 1.3.6 Factors affecting psychological outcomes after preterm birth

Psychological and psychophysiological functioning after preterm birth may result from cumulative effect of multiple factors and mechanisms related to etiology of preterm birth, fetal conditions, pre- and postnatal health and social environment. Some of these factors are summarized in Figure 2. In addition, some important factors that affect the research outcomes after preterm birth are reviewed in this chapter.

#### 1.3.6.1 Severity of prematurity

With regard to most psychological outcomes, the risk of adverse development appears to increase with decreasing gestational age at birth. According to increasing number of studies, also moderate and late preterm infants have poorer long-term cognitive (M. de Jong et al., 2012; Lundgren et al., 2003) and psychiatric (Nosarti et al., 2012) outcome, although this is not confirmed in all studies (Dalziel, Lim et al., 2007). Indeed, for example, the risk of psychiatric disorders is demonstrated to increase after more severe preterm birth (Nosarti et al., 2012). The severity of prematurity is particularly strong

determinant of later cognitive development. The lower the gestational age at birth is the higher the risk is for brain tissue alterations (Keunen et al., 2012) and for later cognitive problems (Anderson & Doyle, 2008; Aylward, 2002; Bhutta et al., 2002; Lundgren et al., 2003). Depending on the cognitive domain, also catch-up may be less probable with younger gestational ages at birth, but more research is needed to confirm this in different areas of cognitive functioning (Mulder et al., 2009).

### 1.3.6.2 Neonatal complications and neural abnormalities

Neurologic abnormalities related to neonatal complications and treatments are more common in preterm infants (Hack et al., 1992; Keunen et al., 2012) and may cause major neurosensory impairments and cognitive deficits. However, less severe cognitive alterations are often present even if there are no apparent neurological handicaps (Aylward, 2002; Hack et al., 1992; Horwood et al., 1998). In this kind of situation preterm infants may have suffered from minor neurological insults and subsequent interruptions in the neural development (Luciana, 2003; Mulder et al., 2009). These interruptions may underlie the found alterations in cognitive performance and academic achievement. Indeed, cognitive outcomes after preterm birth have been predicted by perinatal medical complications (Lorenz et al., 2009; H. G. Taylor et al., 2004), subnormal head size development (Hack et al., 1991) and abnormal cerebral structure (Caldú et al., 2006; Iwata et al., 2012; Martinussen et al., 2009; Skranes et al., 2008).

In addition, neonatal complications, neurosensory impairments and functional limitations following preterm birth may add to parental distress (Eisengart et al., 2003; Halpern et al., 2001; Singer et al., 1999), family burden (Moore et al., 2006; H. G. Taylor et al., 2001) as well as to less sensitive and more protective (Wightman et al., 2007) or controlling parenting (Muller-Nix et al., 2004). They and cognitive problems also increase the risk of altered psychological wellbeing (Aylward, 2002; Hack, 2009; Indredavik et al., 2010; Whitaker et al., 2011).

### 1.3.6.3 Intrauterine growth

Many preterm infants have encountered adverse conditions in utero, often manifesting in poorer intrauterine growth, of which being SGA at birth is used as a crude indicator (see 1.1.2.2). Thus being SGA could contribute to the differences found between term and preterm groups. Studies examining this contribution are, however, relatively scarce. Being SGA is associated to lower general intelligence among term-born children, adolescents and adults (Lundgren et al., 2003; Lundgren & Tuvemo, 2008; Peng et al., 2005). Scarce data within preterm groups indicate similarly that children born AGA perform better than those born SGA (Lorenz et al., 2009; Sansavini et al., 1996; Sommerfelt et al., 1993), at least if SGA children have also suffered from postnatal growth problems (Casey et al., 2006). Also in adulthood, IUGR, particularly symmetric IUGR (determined as being SGA in terms of weight and head circumference at birth), has been related to lower general intelligence within severely prematurely born individuals (Weisglas-Kuperus et al., 2009), but it is unclear whether IUGR explains the differences between preterm and term-born adults. It is also of note that during their neonatal period many of preterm infants have suffered from nutritional problems and subsequent neonatal growth restriction, which may also affect further development. Neonatal growth restriction after preterm birth has been related at least to lower general intelligence (Weisglas-Kuperus et al., 2009).

In regard to mental health, poor intrauterine growth is suggested to compromise it in general populations (for a review see Schlotz & Phillips, 2009). Further, some studies have shown that being born preterm and SGA at the same time may increase the risk of psychiatric disorder and poorer psychosocial functioning (Lund et al., 2011; Lund et al., 2012), increase the likelihood of behavioral problems (Dahl et al., 2006), internalizing problems (M. H. Boyle et al., 2011), depression (Räikkönen et al., 2008) and symptoms of ADHD (Strang-Karlsson et al., 2008) and lower the likelihood of cohabiting with a partner (Kajantie et al., 2008). Being born SGA may also add to the parental intrusiveness with their preterm infants (R. Feldman, 2007).

Being SGA at birth may be a result of a number of medical conditions. Whether the consequences of being SGA depend on the cause of SGA has been little studied.



#### 1.3.6.4 Sex

Some associations between prematurity and cognitive outcome may be different among men and women, but reports concerning it are inconsistent. In childhood and adolescence, most reports do not examine sex interactions, some show that the risk is similar for both sexes (Grunau et al., 2004; Horwood et al., 1998), some indicate that boys are more vulnerable than girls to the effects of severely preterm birth on neurocognitive development (Aylward, 2002; Hack et al., 2002; Marlow et al., 2005; Saigal et al., 2000; Wolke et al., 2008) and very few report increased vulnerability in girls in any cognitive domain (Grunau et al., 2004). Greater vulnerability of boys is in line with a report showing higher rates of neonatal mortality and morbidity and functional disability in male infants born extremely preterm (Kent et al., 2012).

Externalizing and hyperactivity seem to be more often a problem for preterm boys than for girls (Pharoah et al., 1994; Potijk et al., 2012) and internalizing for preterm girls than for boys (Dahl et al., 2006; Potijk et al., 2012), although majority of the studies do not report essential sex interactions in emotional or behavioral problems. Similarly in adolescence and adulthood, a few reports have shown that higher rates of internalizing problems or depressive diagnoses pertain to women but not to men born preterm (Dahl et al., 2006; Hack et al., 2004; Patton et al., 2004). However, reports from adolescence or adulthood do not point to higher rates of externalizing even among men born preterm (M. H. Boyle et al., 2011; Dahl et al., 2006). Instead, in a study by Hack et al. (2002), VLBW was related to lower alcohol and drug use only among women and to lesser delinquent behavior only among men. Further, lesser likelihood of cohabiting with a partner (Cooke, 2004; Kajantie et al., 2008) and lesser sexual activity (Hack et al., 2002) has been shown particularly among preterm women and not men.

With regard to personality development, Allin and others (2006) reported results for men and women separately and found higher neuroticism and lower extraversion among preterm women but not in men. In other studies, the sexes did not differ in terms of the effects of prematurity on personality (Pesonen et al., 2008; Schmidt et al., 2008).

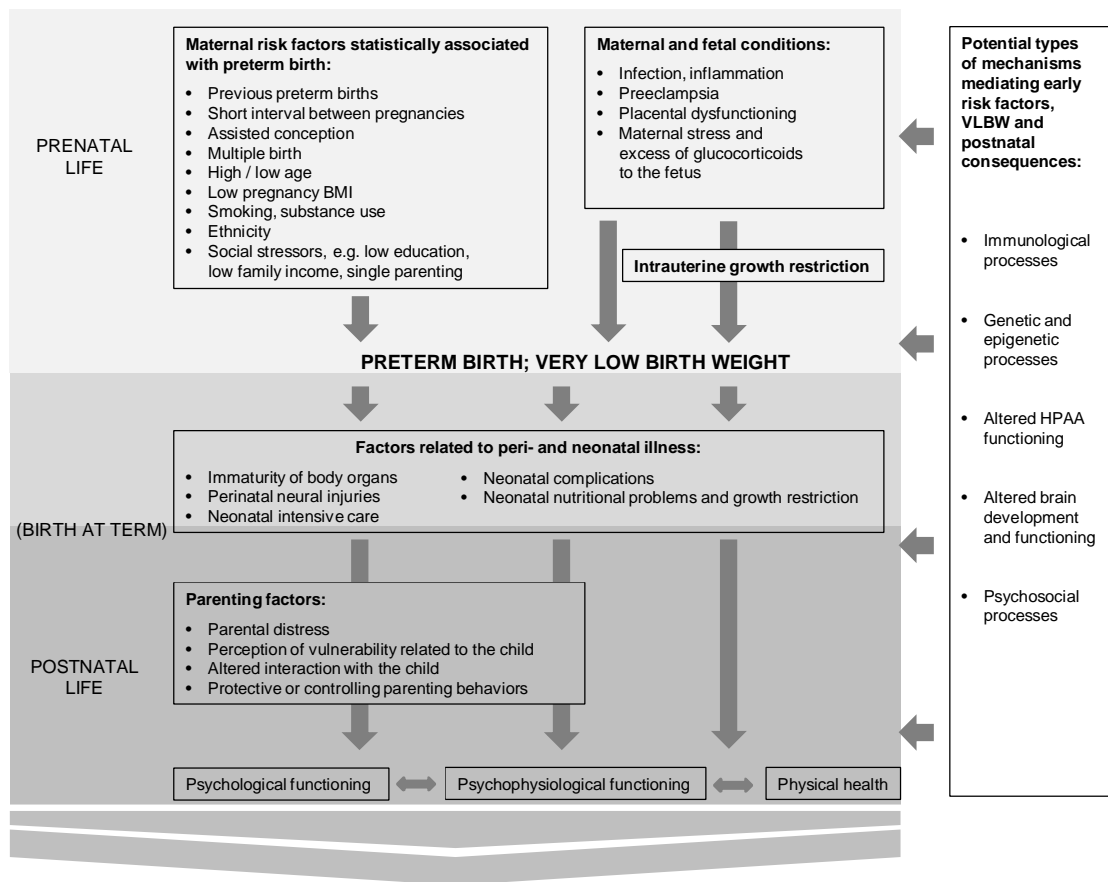
#### 1.3.6.5 Socioeconomic status

Preterm birth has been related to a lower socioeconomic status (SES) (L. K. Smith et al., 2007). For example, parental education, which is commonly used as a proxy of SES, is often lower in preterm groups than in term-born groups (Aarnoudse-Moens et al., 2011; Petersen et al., 2009; Shenkin et al., 2004). It has been suggested that social environment may have more influence on intelligence than intrauterine growth (Hack, 1998) or prematurity (Hack et al., 1992; Ornstein et al., 1991), at least in healthy samples. Accordingly, a low SES or parental education is shown to be a significant predictor of cognitive outcome among people born preterm (Hutton et al., 1997; Ornstein et al., 1991; Rickards et al., 2001; Sansavini et al., 1996; Shenkin et al., 2004; Sommerfelt et al., 1993; Weisglas-Kuperus et al., 2009). The risk of altered psychological development in preterm infants may also be raised by parental sociodemographic vulnerabilities (Hack et al., 2007; Hall & Wolke, 2012), although they do not explain them entirely.

#### 1.3.6.6 Age

Age at assessment is essential when evaluating the implications of a study concerning effects of preterm birth. Developmental pathways among preterm infants may differ from those born at term and all long-term prospects cannot be predicted by early outcomes. For example, there are indications that in some areas of cognitive functioning there may be catch-up development after early developmental delays (Mulder et al., 2009). However, at least some cognitive deficiencies among preterm children may only become apparent and worsen over time as demands from environment increase and subtle neonatal neural injuries may restrict the normative development of higher skills (Aylward, 2002; Luciana, 2003).

Thus, to clarify the long-term risks after preterm birth, more detailed studies on different psychological outcomes and their development into adulthood among preterm individuals are needed. We also need more studies on developmental pathways and factors possibly directing, modifying and altering the effects of preterm birth on health and wellbeing.



**Figure 2.** Potential factors and mechanisms that may contribute to the psychological, psychophysiological and physical functioning of individuals born preterm. Some factors and mechanisms may act concurrently, interact or be interrelated, while some may be caused or affected by preceding factors.

## 2 AIMS OF THE STUDY

Although the survival rate of preterm infants with VLBW has improved during the past few decades, accumulating evidence suggests that these former preterm infants may be at an increased risk for compromised development as they grow up. However, existing data on psychological well-being among individuals born severely preterm are not consistent, and are mainly focused on childhood. Moreover, the mechanisms underlying the possible psychopathology or otherwise compromised development after preterm birth are not fully understood, and further, there is a gap of knowledge concerning the factors that link psychological outcomes with physiological health. One such factor may be physiological reactivity to psychological stress.

- 1) The first aim of this thesis was to study whether young adults with VLBW differ from adults born at term in different psychological outcomes or in physiological responses to psychosocial stress, all being factors that contribute to well-being.
- 2) The second aim of the thesis was to examine whether the group differences in the outcome measures were modified by being born SGA, which is used as a proxy of IUGR. Many of the VLBW infants have suffered from IUGR, which may contribute to the found differences between the VLBW and term-born groups. Thus we tested the effect of being SGA to gain information of the potential etiological factors underlying the outcomes related to VLBW.
- 3) In addition, several studies show differing outcomes related to a preterm birth among men and women, but the findings are inconsistent. To clarify this inconsistency, the third aim of the thesis was to examine whether the group differences in the outcome measures were modified by sex.

These three aims were targeted in five separate studies covering the following outcomes:

**Study I:** Neurocognitive performance including general intelligence, executive functioning, attention, visual memory and academic performance

**Study II:** Blood pressure responses to psychosocial stress

**Study III:** Personality defined as sensitivities of the behavioral inhibition system (BIS) and the behavioral approach system (BAS)

**Study IV:** Patterns of attachment in romantic relationships

**Study V:** Recollections of parenting reported by  
a) VLBW adults and term-born control adults  
b) Parents of the VLBW adults and term-born control adults

## **3 METHODS**

### **3.1 Outline of the study**

The thesis was conducted as a part of the HeSVA study, which aims at examining the long-term health consequences of severely preterm birth and VLBW. Another aim of this cohort study is to collect data to reveal potential mechanisms mediating the associations between VLBW and later health. The HeSVA study is carried out as collaboration between the Hospital for Children and Adolescents at the Helsinki University Central Hospital, the National Institute for Health and Welfare, and the Institute of Behavioural Sciences in the University of Helsinki.

Health-related adulthood outcomes are studied with multiple methods on a large scale, including register data, questionnaires, physiological measurements and several psychological measures. As young adults, participants have been invited to two clinical visits. With regard to individual studies of this thesis, their personality (Study III), romantic attachment (Study IV) and their own perception of the parenting behavior of their parents (Study V) were assessed in conjunction with the first clinical visit in 2004 – 2005, and their neurocognitive abilities (Study I) and parent perspective of parental behavior (Study V) were assessed in conjunction with the second clinical visit in 2007 – 2008. A subsample participated in an additional stress reactivity assessment (Study II) after the first clinical visit.

### **3.2 Participants**

#### **3.2.1 VLBW group**

The original study cohort of the HeSVA comprised 474 VLBW infants who were born between 1978 and 1985 in one of the five birth hospitals in the province of Uusimaa in Finland, and treated in the NICU of the Children's Hospital at the Helsinki University Central Hospital (Järvenpää & Granström, 1987). This NICU serves the whole population living in the province of Uusimaa. A total of 335 of the original VLBW cohort survived until discharge (survival rate 70.7%). When these former VLBW

infants were young adults, those 255 who we were able to trace and who were still living within 110 km from Helsinki were invited to the first clinical visit and 166 (65.1%; 49.6% of those discharged alive from NICU) of them participated. A total of 55 (33.1%) of the participants were born SGA (birth weight for gestational age < -2 SD according to the Finnish birth weight charts (Pihkala et al., 1989)) while the rest were born AGA (birth weight for gestational age -2 to +2 SD). Of the participants who attended the first clinical visit, 159 (95.8%) were invited to the second clinical visit and 113 (71.1%) of the invited participated. A total of 42 (37.2%) of the participants were born SGA.

### **3.2.2 Control group**

To collect a control group, we selected for each VLBW infant in the original study cohort the next consecutive and available singleton infant with the same birth hospital, same sex, gestational age of 37 weeks or above and who was not SGA. Those 314 who were still traceable and living in the greater Helsinki area in their young adulthood were invited to the first clinical visit and 172 (54.8%) of them participated. To the second clinical visit we invited 154 (89.5%) of the participants of the first visit and 105 (68.2%) of the invited participated. Descriptive characteristics for all participants of the clinical visits 1 and 2 are presented in Table 2. Exact sample sizes in each study of the thesis and attrition of the study sample are presented in Figure 3.

**Table 2.** Descriptive characteristics for the VLBW and control participants of the clinical visits 1 and 2. Mean (SD) or n (% of the total N participating) are given unless otherwise indicated.

	Clinical visit 1		Clinical visit 2	
	VLBW	Control	VLBW	Control
N	166	172	113	105
Men, n (%)	71 (42.8)	69 (40.1)	50 (44.2)	45 (42.9)
<i>Perinatal</i>				
Birth weight, g	1120 (221) ***	3593 (471)	1128 (219) ***	3609 (489)
Gestational age at birth, wk	29.2 (2.2) ***	40.1 (1.1)	29.3 (2.4) ***	40.1 (1.1)
Birth weight for gestational age, SD units	-1.29 (1.52) ***	0.04 (1.02)	-1.32 (1.54) ***	0.07 (1.06)
Small for gestational age				
(birth weight < -2 SD), n (%)	55 (33.1) ***	0 (0)	42 (37.2) ***	0 (0)
Multiple births, n (%)	28 (16.9) ***	0 (0)	18 (15.9) ***	0 (0)
Head circumference at birth, cm <sup>a</sup>	26.2 (1.9) ***	35.1 (1.3)	26.2 (2.1) ***	35.0 (1.2)
Head circumference at birth for gestational age, SD units <sup>a</sup>	-1.1 (1.3) ***	-0.1 (0.9)	-1.1 (1.2) ***	-0.1 (0.8)
Age at discharge from hospital, median days (25 <sup>th</sup> – 75 <sup>th</sup> percentile) <sup>b</sup>	70 (53 - 90)	N/A	70 (51 - 90)	N/A
<i>Neonatal complications and treatments</i>				
Duration of ventilation treatment, median days (25 <sup>th</sup> – 75 <sup>th</sup> percentile) <sup>c</sup>	5 (0 - 14)	N/A	4 (0 - 14)	N/A
Duration of supplementary oxygen, median days (25 <sup>th</sup> – 75 <sup>th</sup> percentile) <sup>d</sup>	13 (4 - 34)	N/A	9 (2 - 35)	N/A
Sepsis verified by blood culture, n (%) <sup>c</sup>	12 (7.2)	N/A	10 (8.8)	N/A
Bronchopulmonary dysplasia, n (%) <sup>e</sup>	30 (18.1)	N/A	26 (23.0)	N/A
Received indomethasin, n (%) <sup>f</sup>	47 (28.3)	N/A	36 (31.9)	N/A
Surgery due to patent ductus arteriosus, n (%) <sup>f</sup>	9 (5.4)	N/A	8 (7.1)	N/A
Blood exchange transfusion due to hyperbilirubinemia, n (%) <sup>c</sup>	28 (16.9)	N/A	16 (14.2)	N/A
<i>Parental</i>				
Maternal pre-eclampsia, n (%)	35 (21.1) ***	13 (7.6)	27 (23.9) **	9 (8.6)
Maternal smoking during pregnancy, n (%) <sup>g</sup>	31 (18.7)	28 (16.3)	19 (16.8)	16 (15.2)
Maternal age at childbirth, y	29.8 (4.9)	29.8 (4.9)	30.3 (4.9)	29.7 (5.1)



Highest education of either parent, n (%) <sup>h</sup>				
Elementary	17 (10.2)	11 (6.4)	11 (9.7)	6 (5.7)
High school	35 (21.1)	30 (17.4)	22 (19.5)	18 (17.1)
Intermediate	66 (39.8)	57 (33.1)	43 (38.1)	35 (33.3)
University	45 (27.1) **	73 (42.4)	35 (31.0)	46 (43.8)
<i>At the clinical visit</i>				
Age, y	22.4 (2.1)	22.5 (2.2)	25.0 (2.1)	25.0 (2.2)
Height, cm				
Women <sup>i</sup>	162.0 (7.7) ***	167.3 (6.8)	162.0 (7.7)**	166.1 (6.1)
Men	174.6 (7.7) ***	180.6 (6.4)	174.7 (7.7) ***	180.4 (6.1)
Body mass index, kg/m <sup>2</sup>				
Women <sup>i</sup>	22.3 (4.0)	22.8 (3.7)	22.8 (4.5)	23.3 (5.0)
Men	22.0 (3.6) *	23.3 (3.2)	23.0 (3.6)	24.4 (3.4)
Head circumference, cm <sup>j</sup>	55.2 (1.9) ***	56.3 (1.6)	55.3 (1.9) ***	56.3 (1.6)
Neurosensory impairments, n (%) <sup>k</sup>	19 (11.4) ***	2 (1.2)	10 (8.8) **	1 (1.0)

\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001 against the control group of the same clinical visit

<sup>a</sup> Information missing from 3 VLBW and 1 control participants of the clinical visit 1 and from 3 VLBW participants of the clinical visit 2.

<sup>b</sup> Information missing from 72 VLBW participants of the clinical visit 1 and from 53 VLBW participants of the clinical visit 2.

<sup>c</sup> Information missing from 3 VLBW participants of the clinical visits 1 and 2.

<sup>d</sup> Information missing from 8 VLBW participants of the clinical visits 1 and 2.

<sup>e</sup> Information missing from 6 VLBW participants of the clinical visit 1 and from 4 VLBW participants of the clinical visit 2.

<sup>f</sup> Information missing from 2 VLBW participants of the clinical visits 1 and 2.

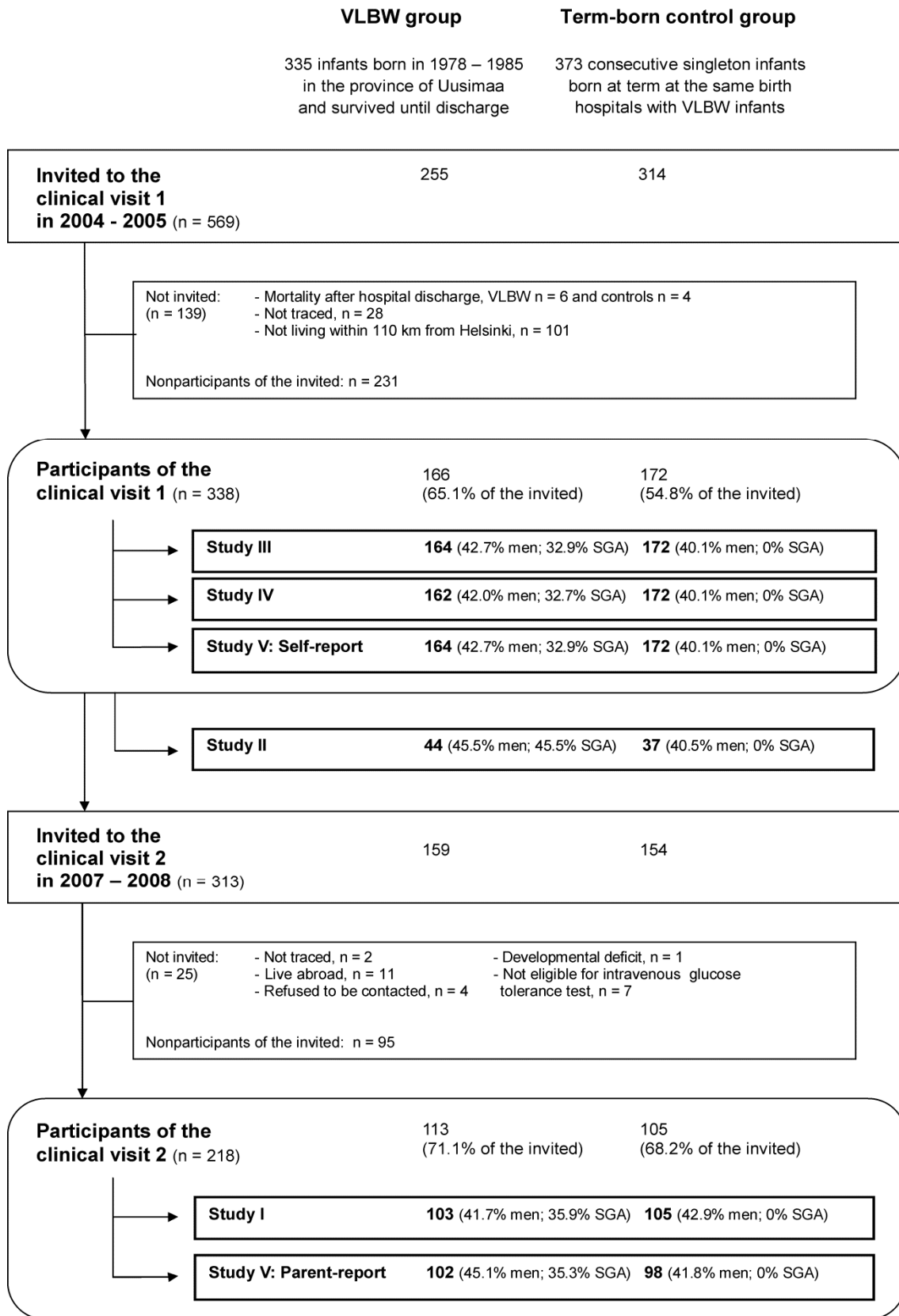
<sup>g</sup> Information missing from 10 VLBW and 4 control participants of the clinical visit 1 and from 8 VLBW and 3 control participants of the clinical visit 2.

<sup>h</sup> Information missing from 3 VLBW and 1 control participants of the clinical visit 1 and from 2 VLBW participants of the clinical visit 2.

<sup>i</sup> Information missing from 1 VLBW participant of the clinical visit 2.

<sup>j</sup> Information missing from 12 VLBW and 7 control participants of the clinical visit 1 and from 5 VLBW and 5 control participants of the clinical visit 2.

<sup>k</sup> Including cerebral palsy, developmental deficit, blindness and severe hearing impairment.



**Figure 3.** Attrition of the study sample in the Helsinki Study of Very Low Birth Weight Adults and final sample sizes in the original studies of the thesis (I - V).

## **3.3 Measures**

### **3.3.1 Neurocognitive abilities and academic performance**

#### **3.3.1.1 General cognitive ability**

General neurocognitive ability was tested using four subtests of the Wechsler Adult Intelligence Scale (WAIS) -III: Vocabulary measures verbal comprehension, Digit span measures verbal attention and working memory, Similarities measures concept forming and Block design measures visuo-spatial processing. Verbal IQ was estimated from Similarities, Vocabulary, and Digit span. Performance IQ was estimated from Block design. Full IQ was estimated from the verbal and performance IQ's according to the Finnish norms (Wechsler/Psykologien kustannus, 2005). These subtests were chosen to cover both verbal and visuo-spatial cognitive ability as well as more crystallized and fluid intelligence.

#### **3.3.1.2 Executive functioning and related abilities**

Executive functioning, attention and visual memory were assessed using altogether five tests. These tests were chosen to cover effectively a range of different executive and attentive functions:

- Trail Making Test (TMT) comprises parts A and B and their difference (Reitan, 1958). While the part A tests visual-motor speed and tracking as well as attention in general, the part B requires ability to shift mental sets (cognitive flexibility).
- The Bohnen modification of the Stroop Test (Bohnen et al., 1992) comprises baseline and interference tasks and the difference between them. The baseline task mainly relates to speech-motor function and the interference task measures response inhibition and working memory.

- Verbal fluency, number of words in 60 seconds, comprises phonetic (words beginning with letters S and P) and category (vegetables/fruits and animals) subtests.
- Conners' Continuous Performance Test II (CPT II) measures sustained attention and ability to inhibit automatic responses (Conners, 2004).
- Rey-Osterrieth Complex Figure Test (ROCF) measures visual-motor processing, organizing and visual memory process including encoding, storage and retrieval phases of the visual memory (Rey, 1941). The test comprises three conditions (copy, immediate recall and delayed recall) and differences between them.

### 3.3.1.3 Academic performance

Remedial education at school, average school grades at the end of comprehensive school and years of full-time education were self-reported.

## 3.3.2 Blood pressure responses to psychosocial stress

### 3.3.2.1 Psychosocial stress test

In order to measure blood pressure responses to psychosocial stress we administered The Trier Social Stress Test (TSST), a standardized psychosocial stressor, in a laboratory setting (Feldt et al., 2007; Kirschbaum et al., 1993). Members of our team were trained at the University of Trier where the test has been developed. The TSST protocol includes several components that elicit stress (e.g., uncontrollableness, social-evaluative threat related to audience, ego involvement and anticipation of negative consequences), and as such is shown to be effective in inducing consistent physiological responses (Dickerson & Kemeny, 2004). Prior to the TSST, every participant had a 45 minute resting period during which they filled in questionnaires and intravenous catheter was inserted to obtain blood samples during the protocol. The participant was then led to the TSST laboratory, blood pressure recording devices were connected, and

the participant stood still for a five minute baseline recording period. After that the participant was asked to accomplish two stress inducing tasks, each taking five minutes, in front of two experimenters introduced as ‘evaluation committee members’ (Figure 4). First, in a public speaking task, participant was instructed to imagine (s)he was applying for a job and (s)he now was supposed to give a speech to convince the committee why (s)he was the best candidate for that job. If the speech took less than five minutes, additional questions were asked by the evaluation committee. Second, in a mental arithmetic task, the participant was instructed to perform serial subtractions, starting from 2023 and subtracting 17 at a time. The subtractions were asked to be performed as fast as possible, but if a mistake occurred, the committee stopped the participant and asked her/him to start again from 2023. If the task appeared to be too difficult for the participant, after one minute the subtraction task was changed to an easier one. Apart from necessary instructions for conducting the tasks, the committee minimized all verbal and non-verbal communication with the participant. After completion of both tasks, all recording devices were removed and the participant was led to another room for the recovery period and a brief debriefing session where the purpose of the study was explained and all questions from the participant were answered.



**Figure 4.** The evaluation committee members of the Trier Social Stress Test.

### 3.3.2.2 Blood pressure measurement

Continuous blood pressure measurement was conducted using Finometer® (FMS, Amsterdam, The Netherlands), a non-invasive beat-to-beat finger photoplethysmograph, which has been validated against mercury sphygmomanometer (Guelen et al., 2003; Schutte et al., 2004). The blood pressure readings were averaged to two mean values, one for the baseline and the other for the TSST tasks. Using averaged values improves reliability of the measurements (Kamarck et al., 2000) and allows comparability with number of previous studies using aggregated values (Feldt et al., 2007; Jennings et al., 2004; K. A. Matthews et al., 2006; A. M. Ward et al., 2004).

### 3.3.3 Personality

Personality was assessed by applying the Reinforcement Sensitivity Theory (RST) by J. A. Gray (1991; 1994), who originally differentiated three emotion systems forming the biological basis for behavior. Of these systems, the behavioral inhibition system (BIS) refers to sensitivity to conditioned aversive stimuli indicating punishment or the end of reward, and activation of the system leads to inhibition of behavior (Gray, 1991). The original fight/flight system (FFS) refers to sensitivity to unconditioned aversive stimuli and activates defensive aggression or escape (Gray, 1991). The behavioral approach system (BAS; also referred as behavioral activation system) refers to sensitivity to signals of reward or signals indicating the end of punishment, and it activates behavior to approach the stimuli (Gray, 1991). In a later modification of the RST, the names and roles of the systems were slightly changed: the new fight-flight-freeze system (FFFS) refers to sensitivity to both conditioned and unconditioned aversive stimuli (combines the tasks of previous BIS and FFS) and activates avoidance and escape behavior while the new BIS only gets activated by halting behavior in a goal conflict situation between approach (BAS) and avoidance (FFFS) (Gray & McNaughton, 2000; for a review see Corr, 2004). Assessment methods applying the RST, however, at the moment usually aim to measure personality with two dimensions: sensitivity to punishment (BIS/FFFS; behavioral inhibition and avoidance) and sensitivity to reward (BAS; behavioral approach and activation) (Bijttebier et al., 2009; Corr, 2004).

Accordingly, to assess personality, we used the BIS/BAS Scales (Carver & White, 1994), which is a self-assessment questionnaire pertaining to sensitivities of BIS/FFFS and BAS. It consists of 20 items rated on a four point scale ranging from strongly disagree (1) to strongly agree (4). The items fall into four subscales, one for BIS (from now on the scale is referred as BIS although it also includes items of FFFS) and three for BAS. The BIS subscale measures *Sensitivity to cues for punishment* and is named accordingly (seven items, e.g. “I worry about making mistakes”). *Drive* subscale measures BAS-related tendency to persistently strive for appetitive goals (four items, e.g. “When I want something I usually go all-out to get it”), *Fun seeking* measures BAS-related attraction for new potentially rewarding events and spontaneous eagerness to approach them (four items, e.g. “I’m always willing to try something new if I think it will be fun”), and *Reward responsiveness* measures the extent of BAS-related positive responses to occurred rewards or anticipation of such reward (five items, e.g. “When I’m doing well at something I love to keep at it”).

### **3.3.4 Romantic attachment**

Attachment was assessed with the 36-item Experiences in Close Relationships Questionnaire – Revised (ECR-R) (Fraley et al., 2000). It measures adult attachment in romantic relationships with two dimensions, both compounding of 18 items. The dimension of *Attachment-related anxiety* measures concerns about being rejected or abandoned by the partner (e.g. “I’m afraid that I will lose my partner’s love”), and is suggested to reflect a negative working model of the self. The dimension of *Attachment-related avoidance* measures discomfort being close to others and avoidance of intimacy (e.g. “I don’t feel comfortable opening up to romantic partners”). It is proposed to reflect a negative model of others. Individual sumscores were calculated for both dimensions. Positive models of both the self and others (i.e., low levels of attachment-related anxiety and avoidance) are suggested to be related to secure attachment whereas negative models of the self and/or others (i.e., high levels of attachment-related anxiety and/or avoidance) are suggested to be related to insecure attachment. Each item of the ECR-R is rated by a respondent on a scale from 1 (strongly disagree) to 7 (strongly agree).

### **3.3.5 Child and parent perspectives on parenting**

#### **3.3.5.1 Child reports**

We used the Parental Bonding Instrument (PBI) (G. Parker et al., 1979), which is a 25-item questionnaire for adults to assess the parenting behavior of their parent during the first 16 years of their life. Participants assessed their mothers and fathers separately. We used three subscales labeled as *Care* (assessing parental warmth and affection; 12 items), *Protectiveness* (assessing denial of psychological autonomy; seven items), and *Authoritarianism* (assessing discouragement of behavioral freedom; six items).

#### **3.3.5.2 Parent reports**

For parental self-reports we used the Parent Behavior Inventory, which is a 20-item questionnaire measuring parenting as perceived by the parents themselves (Lovejoy et al., 1999). Similar to the child reports of PBI, the questionnaire was applied to assess the parental recollections of their parenting behaviors during the first 16 years of their child's life. Items were divided into subscales labeled as *Supportive/engaged parenting* (assessing affectionate acceptance and emotional and behavioral support; ten items) and *Hostile/coercive parenting* (assessing negative affect and use of coercion, threat and physical punishment; ten items).

### **3.3.6 Neonatal characteristics and other information**

The information concerning neonatal characteristics was gathered from hospital records. Parental and adult characteristics were collected from questionnaires filled in by the participants and data gathered in conjunction with the clinical visits. Height, weight and head circumference at adulthood were measured during the clinical visits.

All the studies of this thesis were included to the HeSVA study protocol, which was approved by the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at the Helsinki University Central Hospital. Every participant gave a written informed consent.



## **3.4 Statistical analyses**

### **3.4.1 Differences between the study groups**

Between group differences were examined using multiple linear regression analyses for continuous outcome variables. Due to skewness of some distributions of the outcome variables, we used logarithmic, square or square root conversions in the analyses when needed (neurocognitive abilities (Study I) and romantic attachment (Study IV)). Logistic regression analysis was used to test group differences in dichotomous outcome variables and multinomial regression analysis in outcome variables composed of more than two categories. The main outcome variables served, one at a time, as dependent variables and the VLBW versus control grouping together with major confounders as independent variables. Similarly, we compared the VLBW participants born AGA and the VLBW participants born SGA against the control group and against each other adjusting for the major confounders.

### **3.4.2 Moderation by sex**

Moderation by sex was tested by entering sex by grouping –interaction term into the regression equation with the main effects. If a statistically significant sex interaction was found, we analyzed men and women separately.

### **3.4.3 Adjustment for covariates and confounders**

In statistical analyses, we used several different adjustment models to test the effect of potential confounding variables on the group differences in outcome variables. All outcomes were adjusted for sex, age at testing and the highest education of either parent as a proxy of SES. In addition, the analyses related to neurocognitive abilities were adjusted for head circumference at adulthood, head circumference SD score at birth and estimated full IQ. In the analyses of blood pressure responses to stress, adjustments were made for height, BMI, maternal pre-eclampsia and history of parental hypertension. The personality outcomes were adjusted for BMI, maternal smoking

during pregnancy and maternal pre-eclampsia. The analyses for romantic attachment were adjusted for whether the participant was currently in a romantic relationship. In the analyses of parenting outcomes, adjustments were made for maternal/paternal age, parental divorce/death and number of siblings in the family.

Finally, effect of neurosensory impairments (cerebral palsy, developmental delay, blindness and deafness) was also considered. In regard to neurocognitive abilities, all participants with neurosensory impairments were excluded from all analyses. In regard to other outcome variables, final analyses were run to test whether the results remained similar after adjustment for neurosensory impairments (outcomes related to personality) or after exclusion of participants with neurosensory impairments (outcomes related to blood pressure stress response, attachment and parenting).

## 4 RESULTS

### 4.1 Representativeness of the study samples

Survival rate until discharge from the NICU was 70.7% for our original VLBW cohort. This rate is comparable to survival rates reported for cohorts born in industrialized countries at or close to the same time period (Doyle et al., 2000; Gould et al., 2000; Hack et al., 2002; K. S. Lee et al., 1995).

Of the 255 VLBW and 314 control adults who were invited to the first clinical visit, 166 VLBW (65.1%) and 172 (54.8%) control adults participated. The participants and nonparticipants did not differ in perinatal characteristics, except for the rate of CP at 15 months of age, which was lower in the VLBW participants compared to VLBW nonparticipants (Hovi et al., 2007). Similarly, the 113 VLBW and 105 control participants of the second clinical visit (44.3% and 33.4% of those invited to the first clinical visit, respectively) differed from the others who were invited to the first clinical visit only in the lower rate of CP at 15 months of age among the VLBW participants (4.4 vs. 15.5%,  $p < 0.01$ ). We then examined representativeness of the exact subsamples that participated in the individual studies of this thesis by comparing them with all others who were invited to the first clinical visit but did not participate or were excluded due to insufficient data. The lower rate of CP at 15 months of age among the VLBW participants in comparison to the VLBW non-participants was found in all subsamples except for the subsample in measurements of blood pressure reactivity (other  $p$ -values  $\leq 0.01$ ).

We further compared the subsamples of participants with non-participants in other perinatal characteristics (birth weight, gestational age, birth weight for gestational age, percentage of SGA, birth length, head circumference at birth and age at discharge from the neonatal hospital), maternal characteristics (pre-eclampsia, hypertension and smoking during pregnancy, maternal age at birth) and neonatal complications and treatments (duration of ventilator treatment and supplementary oxygen, sepsis verified by blood culture, BPD, having received indomethacin, and surgery due to patent ductus arteriosus). Information on neonatal complications and treatments and the age at

discharge from the neonatal hospital was available only for those born with VLBW. Few differences were found between the participants and non-participants.

In measurements of blood pressure reactivity (Study II), the percentage of those born SGA was higher in the VLBW participants than in the VLBW non-participants (45.5 vs. 28.9%,  $p = 0.03$ ), and, within the control group, maternal pre-eclampsia was more frequent among the participants (13.5 vs. 4.3%,  $p = 0.03$ ). In assessments of personality (Study III), romantic attachment style (Study IV) and child perspective on parenting (Study V), there were more women among the control participants than among the control non-participants (59.9 vs. 47.2%,  $p = 0.02$ ). No other differences were found in comparisons between the subsamples of participants and all others invited to the first clinical visit.

To control for the potential effect of the factors that we found to differentiate participants and nonparticipants, we adjusted the analyses concerning the outcome measures for the potentially confounding factors. In addition, the effect of CP or other neurosensory impairments was tested by reanalyzing all of the results with adjustment for neurosensory impairments (Study III) or after exclusion of participants with neurosensory impairments (Studies I, II, IV and V).

## **4.2 Study I: Neurocognitive abilities**

### **4.2.1 Comparisons of the VLBW and control groups**

When the VLBW and control groups were compared with adjustments for sex and age, the VLBW group scored lower on several indices of the neurocognitive tests. In regard to general intelligence assessed by the WAIS-III, the VLBW group had lower full, verbal and performance IQ estimates (Table 3). Of the subtests, the VLBW group scored lower on Similarities (mean difference 0.40 SD units,  $p < 0.01$ ) and Block design (mean difference 0.69 SD units,  $p < 0.001$ ), indicating poorer verbal and visual-motor functioning. Further adjustments for parental education, head circumference at adulthood and head circumference SD at birth had marginal effects on the associations.

**Table 3.** IQ estimates and academic performance in the VLBW and control groups.

Data are presented as group means (SD) unless otherwise indicated.

	VLBW			Control
	All n = 103	AGA n = 66	SGA n = 37	n = 105
Grade point average at the end of comprehensive school <sup>a</sup>	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.2 (0.8)
Years of education, yr <sup>b</sup>	13.4 (2.1)	13.6 (2.3)	13.2 (1.6)	13.5 (1.9)
Remedial education, n (%) <sup>c</sup>	46 (46.5)***	27 (42.2)**	19 (54.3)***	20 (19.2)
Full IQ estimate	102.2 (15.3)***	103.2 (15.4)**	100.4 (15.2)***	110.6 (12.0)
Verbal IQ estimate	104.1 (14.4)*	104.9 (14.9)	102.8 (13.5)*	108.0 (11.6)
Performance IQ estimate	99.8 (19.0)***	101.0 (19.2)***	97.8 (18.7)***	112.3 (15.3)

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  against the control group if adjusted for sex and age (in academic outcomes) or for sex alone (in IQ estimates determined by age specific norms)

<sup>a</sup> Information available for 63 VLBW-AGA, 32 VLBW-SGA, and 103 control participants

<sup>b</sup> Information available for 65 VLBW-AGA, 35 VLBW-SGA, and 104 control participants

<sup>c</sup> Information available for 64 VLBW-AGA, 35 VLBW-SGA, and 104 control participants.

In regard to executive functioning and related abilities, the VLBW group scored lower on some indices of all the five tests, again indicating restrictions in both verbal and visual-motor functioning (Figure 5). In detail, they scored lower on verbal fluency (both category and phonetic) indicating slower speed and poorer flexibility of verbal thought processes, but they also scored lower on the TMT indicating slower speed, poorer tracking and poorer cognitive flexibility in visual-motor processes. The VLBW group also performed slower in the Stroop baseline and made more Stroop errors (odds ratio for  $\geq 3$  vs. 0 errors 12.25,  $p = 0.001$ ) indicating slower processing speed, poorer response inhibition and more restricted working memory. Further, they made more omission errors in the CPT II (odds ratio for  $\geq 5$  vs. 0 errors 3.37,  $p = 0.03$ ), indicating more difficulty in sustaining attention, although they did not differ in other indices of the CPT II. Finally, the VLBW group scored lower on the ROCF copy, immediate recall and delayed recall tasks, and showed more deterioration of the performance between the copy and immediate recall as well as between the copy and delayed recall, but not

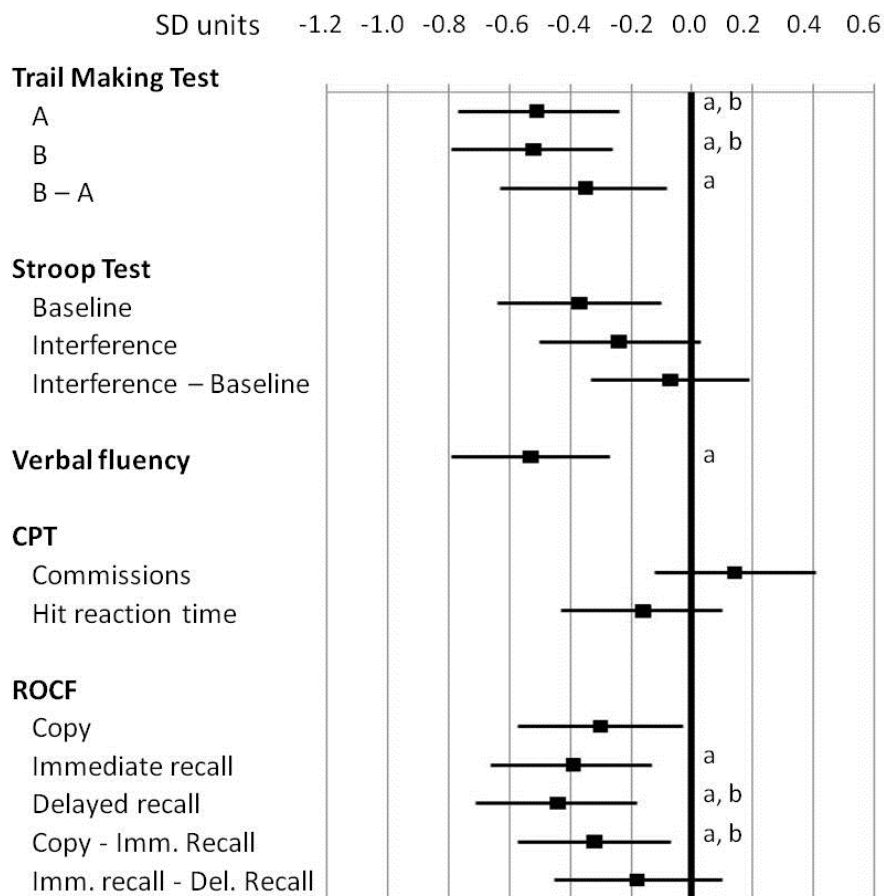
between the immediate and delayed recall. This indicates poorer visual encoding hampering working memory processes, but more intact long-term storage and retrieval. Few of these statistically significant group differences (the Stroop baseline, the CPT omissions and the ROCF copy) were attenuated by further adjustments for parental education, head circumference at adulthood and head circumference SD at birth and few more differences were attenuated by even further adjustment for full IQ estimate (the TMT difference between the A and B conditions, verbal fluency and the ROCF immediate recall).

In regard to academic performance, the VLBW and control groups did not differ in self-reported years of education or in grade point average at the end of comprehensive school, but the VLBW participants had received more often remedial education than those in the control group (Table 3). The difference remained significant after adjustments for confounders.

#### **4.2.2 Modifying effects of SGA status and sex**

Overall, in comparison to the term-born controls, the lower scores in neurocognitive tests and higher percentage of those having received remedial education pertained to both the VLBW-AGA and VLBW-SGA participants (Table 3; Figure 6), although not all of the group differences in the VLBW vs. control comparisons reached statistical significance in these subgroup analyses. The VLBW-AGA and VLBW-SGA groups had little or no differences between them.

The lower scores in neurocognitive tests and higher rate of remedial education pertained to both the VLBW men and women. Sex had a minor modifying effect only on two indices of the ROCF. In comparison to the control women, the VLBW women as a whole and the VLBW-AGA women separately showed greater deterioration in their performance between the copy and delayed recall. In addition, the VLBW-AGA women showed greater deterioration in their performance between the copy and immediate recall. No such differences were found among men.



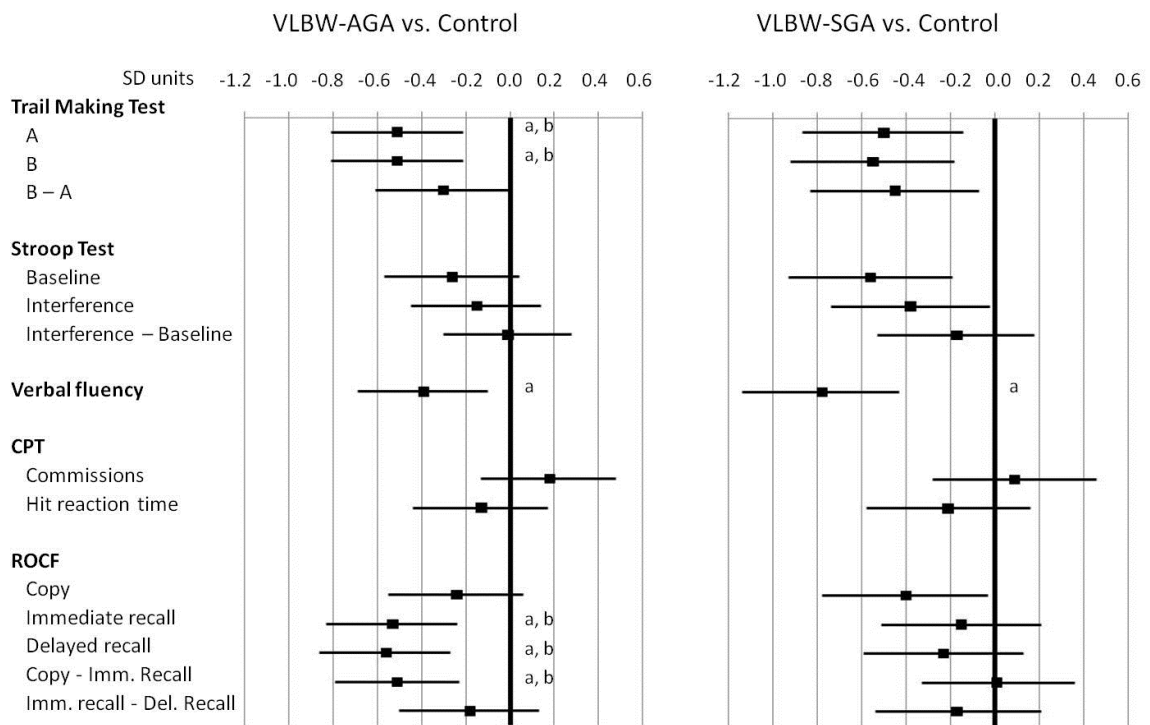
**Figure 5.** Executive functioning of the VLBW vs. control participants.

Forest plot displays the differences between the VLBW (error bars) and term-born control (zero line) groups in continuous outcome variables of executive functioning. The mean differences in SD units and their 95% confidence intervals are presented. A mean difference below zero indicates weaker performance in the VLBW group. Sex and age at assessment are adjusted for.

<sup>a</sup> Statistically significant group difference after further adjustment for parental education, current head circumference, and head circumference SD score at birth.

<sup>b</sup> Statistically significant group difference after previous adjustment model and further adjustment for IQ estimate.

(Pyhälä et al., 2011. Neurocognitive abilities in young adults with very low birth weight, *Neurology*, 77, 2052–2060, reprinted with permission.)



**Figure 6.** Executive functioning of the VLBW-AGA and VLBW-SGA vs. control participants.

Forest plots display the differences between the VLBW subgroups (error bars) and term-born controls (zero line) in continuous outcome variables of executive functioning. The mean differences in SD units and their 95% confidence intervals are presented. A mean difference below zero indicates weaker performance in the VLBW subgroup. Sex and age at assessment are adjusted for.

<sup>a</sup> Statistically significant group difference after further adjustment for parental education, current head circumference, and head circumference SD score at birth.

<sup>b</sup> Statistically significant group difference after previous adjustment model and further adjustment for IQ estimate.

(Pyhälä et al., 2011. Neurocognitive abilities in young adults with very low birth weight, *Neurology*, 77, 2052–2060, reprinted with permission.)



## **4.3 Study II: Blood pressure responses to psychosocial stress**

### **4.3.1 Comparisons of the VLBW and control groups**

The VLBW and control groups had a similar diastolic blood pressure at the baseline, but the VLBW group had a higher diastolic blood pressure during the psychosocial stress task (97.8 vs. 92.5 mmHg,  $p = 0.01$ ) and accordingly, a higher diastolic blood pressure reactivity (20.7 vs. 17.2 mmHg,  $p = 0.05$ ). Although the mean systolic blood pressure was higher in the VLBW group than in the controls at the baseline (129.7 vs. 117.2 mmHg,  $p = 0.28$ ) and during the task (150.7 vs. 147.3 mmHg,  $p = 0.38$ ), the differences were not statistically significant.

### **4.3.2 Modifying effects of SGA status and sex**

The effects of VLBW on diastolic blood pressure response was similar for both the AGA and SGA groups, although the differences between the VLBW-SGA and control groups did not reach statistical significance ( $p = 0.07$  for difference during the task and  $p = 0.50$  for difference in reactivity) due to the small number of participants. Sex did not modify any of the outcomes.

## **4.4 Study III: Personality**

### **4.4.1 Comparisons of the VLBW and control groups**

Of the four subscales measuring personality, the VLBW and control groups differed in one. When adjusted for sex, the VLBW group scored lower on Fun seeking (scores 11.42 vs. 12.24,  $p < 0.001$ ), which is one of the three subscales of behavioral approach. Lesser fun seeking indicates lesser spontaneous eagerness to approach new potentially rewarding events and actions among the VLBW adults in comparison to the term-born adults. The group difference remained essentially the same after further adjustments for age, BMI, parental education, maternal smoking during pregnancy, maternal pre-eclampsia and neurosensory impairments.

#### **4.4.2 Modifying effects of SGA status and sex**

Lesser fun seeking in comparison to term-born controls concerned both the VLBW-AGA and VLBW-SGA adults ( $p$ -values  $< 0.01$ ), indicating no modification by SGA status. However, the SGA status and sex modified two other outcomes. An association between the VLBW-SGA vs. control status and behavioral inhibition was modified by sex ( $p$  for interaction = 0.02). The VLBW-SGA women ( $p = 0.03$ ) but not men ( $p = 0.32$ ) scored higher than their same-sex controls. In addition, when the VLBW-AGA and VLBW-SGA groups were contrasted against each other, sex modified the group difference in Drive, one of three subscales of behavioral approach ( $p$  for interaction = 0.03): the VLBW-SGA men ( $p = 0.03$ ), but not women ( $p = 0.81$ ), scored higher than their same-sex VLBW-AGA counterparts. Again, adjustments for confounders did not considerably affect the associations.

### **4.5 Study IV: Romantic attachment**

#### **4.5.1 Comparisons of the VLBW and control groups**

The VLBW group reported less attachment-related anxiety than the term-born controls, but the difference became statistically significant only after adjusting for the current romantic relationship in addition to adjusting for sex, age and parental education (scores 51.5 vs. 55.0,  $p = 0.01$ ; Figure 7). The current romantic relationship was marginally less frequent in the VLBW group than in the controls (41.6 vs. 51.7%,  $p = 0.06$ ) and it correlated with lesser attachment-related anxiety (Pearson's correlation coefficient - 0.39,  $p < 0.001$ ). Excluding those with neurosensory impairments did not change the result. The groups did not differ in attachment-related avoidance.

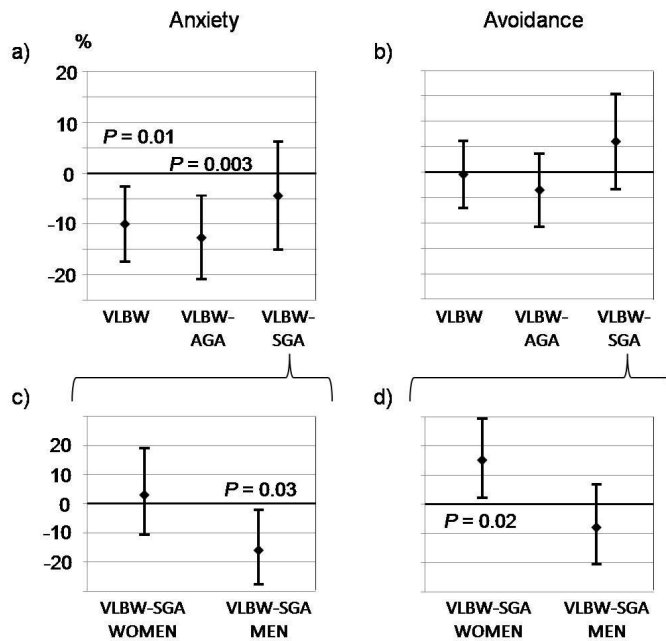
#### **4.5.2 Modifying effects of SGA status and sex**

When the VLBW-AGA and VLBW-SGA groups were separately contrasted against the controls, only the VLBW-AGA group scored lower in attachment-related anxiety (Figure 7). The unadjusted difference between the VLBW-AGA and control groups was

marginal ( $p = 0.06$ ), but the statistical significance increased by further adjustments for sex, age and parental education ( $p = 0.04$ ) and further for current relationship ( $p < 0.01$ ). The VLBW-AGA and VLBW-SGA groups did not differ statistically significantly from each other.

Sex affected the outcomes of the comparisons between the VLBW-SGA and control groups in attachment-related anxiety ( $p$  for interaction = 0.03) and in avoidance ( $p$  for interaction = 0.01). In regard to attachment-related anxiety, only among men the VLBW-SGA group scored lower than the controls (Figure 7). Again, the unadjusted difference was marginal ( $p = 0.06$ ), but became statistically significant after adjustments for age, parental education and current relationship ( $p = 0.03$ ). In regard to attachment-related avoidance, only among women the VLBW-SGA group scored higher than the controls ( $p < 0.01$ ) and the difference remained similar after adjustments for covariates (Figure 7). All results remained similar after exclusion of the participants with neurosensory impairments.

Thus all other VLBW adults except for the SGA women reported lower attachment-related anxiety than their term-born controls. The SGA women, instead, reported more attachment-related avoidance than the control women.



**Figure 7.** Attachment-related anxiety and avoidance in the VLBW and control groups.

Error bars represent the mean differences in percent and their 95% confidence intervals between the controls (zero line) and the VLBW group as a whole or the VLBW-AGA and VLBW-SGA groups separately in attachment-related anxiety (a) and avoidance (b). Due to statistically significant sex interactions ( $P < 0.05$ ), the VLBW-SGA vs. controls comparison was carried out separately for women and men in anxiety (c) and avoidance (d). Adjustments were made for age at assessment, parental education and whether the participant was currently in a relationship, and in a) and b) also for sex.

(Pyhälä et al., 2010. Romantic attachment in young adults with very low birth weight – The Helsinki Study of Very Low Birth Weight Adults, *Journal of Developmental Origins of Health and Disease*, 1, 4, 271 – 278, reproduced with permission.)

## 4.6 Study V: Child and parent perspectives on parenting

### 4.6.1 Comparisons of the VLBW and control groups

In regard to child perspective reported by the VLBW and term-born control adults, the VLBW group rated their mothers as more protective, when adjusted for sex and age of the participant, parental age and parental education ( $p = 0.03$ ). In regard to parent perspective reported by parents of the VLBW and control adults, both the mothers ( $p =$

0.04) and fathers ( $p = 0.04$ ) reported more supporting parenting in the VLBW than in the control group. However, if non-singletons and participants with neurosensory impairments were excluded, the group differences in parental support rendered nonsignificant ( $p > 0.07$ ).

#### **4.6.2 Modifying effects of SGA status and sex**

Both the SGA status and sex of the participant moderated the results. In the child perspective, the VLBW and control men did not differ from each other. Instead, among women the VLBW group rated their mothers as more protective ( $p = 0.001$ ) and more authoritarian ( $p = 0.03$ ), when adjusted for age of the participant, maternal age and parental education. The higher maternal protectiveness was reported by both the VLBW-AGA ( $p = 0.01$ ) and VLBW-SGA women ( $p = 0.01$ ), but the higher maternal authoritarianism was only reported by the VLBW-AGA women ( $p = 0.01$ ). In addition, the VLBW-AGA adults rated their fathers higher on care ( $p = 0.04$ ) and marginally higher on protectiveness ( $p = 0.08$ ) and authoritarianism ( $p = 0.09$ ) than the controls did, when adjusted for sex and age of the participant, paternal age and parental education.

Also the parent perspective was moderated by the SGA status and sex. Fathers of the VLBW-AGA group differed from fathers of the control ( $p < 0.01$ ) and VLBW-SGA ( $p = 0.04$ ) groups by reporting more support in parenting when adjusted for sex and age of the participant, paternal age and parental education. In addition, mothers of the VLBW-SGA men reported less coerciveness than mothers of the control men ( $p = 0.03$ ).

#### **4.6.3 Other modifying factors**

Additional adjustments for parental divorce/death and number of siblings had little effect on the results, but multiple births and neurosensory impairments contributed to some of the group differences in parenting. When non-singleton participants and those who had neurosensory impairments were excluded from the analyses, several of the group differences decreased and some of them rendered nonsignificant, including the higher paternal care in the VLBW-AGA group, the higher parental support in the VLBW group and the lesser maternal hostility in the VLBW-SGA group.

## 5 DISCUSSION

### 5.1 Summary of the main findings

The first aim of the thesis was to examine the differences in psychological and psychophysiological functioning between young adults born preterm with VLBW (as one group) and their counterparts born at term and AGA. We found that the VLBW group differed from those born at term in all areas of functioning included in the thesis. On average, the VLBW adults scored lower in neurocognitive tests measuring general intelligence, executive functioning, attention and memory processes and they had received more often remedial education. The VLBW adults also showed higher diastolic blood pressure reactivity to psychosocial stress. In terms of personality, the VLBW adults reported less fun seeking, indicating less behavioral approach, or in more specific, less spontaneous eagerness to approach new potentially rewarding events and actions. Related to their romantic attachment style, the VLBW adults reported less anxiety than the term-born controls indicating less concerns about being rejected or abandoned by the partner. In regard to the parental behavior, the VLBW adults reported their mothers to be more protective than the mothers of the term-born adults. In addition, the mothers and fathers of the VLBW adults reported more supportive parenting than parents of term-born adults.

The two other aims of the thesis were to examine whether intrauterine growth pattern and sex moderate the associations between VLBW and psychological functioning. While neurocognitive performance and blood pressure reactivity were mainly similarly altered for the VLBW men and women and for the VLBW adults born AGA and SGA, sex and whether the VLBW adult was born AGA or SGA did affect some of the outcomes in personality, romantic attachment style and parenting behaviors. Overall, female sex and being born SGA appeared to increase the risk of altered development. For example, the VLBW-SGA women reported more behavioral inhibition than the term-born women. They were also the only VLBW subgroup that did not score lower than the term-born adults on attachment-related anxiety and the only VLBW subgroup that scored higher than the term-born adults on attachment-related avoidance, indicating more discomfort being close to others and more avoidance of intimacy. In addition, in

comparison with the control group, only the VLBW women reported their mothers to be more protective and authoritarian. Moreover, in comparison with the control group, the fathers of the VLBW-AGA adults were rated by their children higher on care and marginally higher on protectiveness and authoritarianism, and by themselves, higher on supportive parenting.

## **5.2 Comparison between the current and previous findings**

Our findings show altered psychological and psychophysiological functioning in individuals born preterm. They are mainly in line with the existing research literature and expand them in several ways.

### **5.2.1 Neurocognitive abilities and academic performance**

Our findings regarding lower neurocognitive test scores are in accordance with previous results showing lower IQ scores, lower scores in both visual and verbal tests, poorer executive functioning and poorer encoding in memory process but adequate long-term memory in adults born preterm (Allin et al., 2008; Grunau et al., 2004; Hack et al., 2002; Hallin et al., 2010; Lohaugen et al., 2010; Lundgren et al., 2003; Nosarti et al., 2007). While previous studies have shown lower academic achievement among children and adults born preterm (Aarnoudse-Moens et al., 2011; Anderson & Doyle, 2008; Ericson & Källén, 1998; Hack et al., 2002; Hallin et al., 2010; Hille et al., 2007; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Lindström et al., 2007; Moster et al., 2008; Mulder et al., 2010; Nosarti et al., 2007; Reuner et al., 2009; Rickards et al., 2001; Saigal et al., 2000; Wolke et al., 2008), we found no group differences in grade point averages or in years of education. However, the VLBW group in our study had received more often remedial education, which is in line with some previous findings (Saigal et al., 2000). Remedial education may have improved the school performance of the VLBW group and resulted in comparable school grades with the term-born group.

In our study, the poorer neurocognitive performance concerned both the AGA and SGA subgroups born with VLBW while these two subgroups did not notably differ from each other. This is in contrast to a previous report showing lower IQ in the SGA

group in comparison to the AGA group within young adults born very preterm (Weisglas-Kuperus et al., 2009), and to reports showing an association between poorer cognitive performance and lower relative birth weight (Räikkönen et al., 2009) or SGA status (Lundgren et al., 2003) within male conscripts covering the whole birth weight range. However, it is possible that although poorer fetal growth (indicated by lower relative birth weight or being SGA) was related to poorer cognitive performance within the whole range of birth weights (Lundgren et al., 2003; Räikkönen et al., 2009), severe prematurity would override this effect. The effect of being SGA on the difference in neurocognitive performance between the preterm and term-born adults had not been reported before and our study now indicates that the poorer performance among the VLBW adults relates to prematurity rather than to the intrauterine growth pattern.

### **5.2.2 Blood pressure responses to psychosocial stress**

The higher blood pressure reactivity of the VLBW adults in our study fit together with previous studies showing higher office and ambulatory blood pressures among preterm adolescents and adults (Dalziel, Parag et al., 2007; F. de Jong et al., 2012; Edstedt Bonamy et al., 2008; Hack et al., 2005; Hovi et al., 2007; Hovi et al., 2010; Irving et al., 2000; Johansson et al., 2005; Keijzer-Veen et al., 2010; Kistner et al., 2005; Rossi et al., 2011; Rotteveel et al., 2008), although blood pressure responses to stress in particular have not been studied before. In contrast to these previous results, the VLBW adults in our current study did not differ statistically significantly from the term-born group in the baseline recording of blood pressure. This may relate to lack of statistical power in our study or to differing measuring techniques. Ambulatory blood pressure measurements include responses for every day stress. Also office blood pressure measurements performed by a research nurse may induce a stress response called “white coat hypertension” (Baguet, 2012). Instead, the baseline blood pressure in our study was measured with continuous measurement during the five minute period that the participant spent alone without intended external stressors. Thus, it may be possible that even the previous findings of elevated office and ambulatory blood pressures in preterm individuals were caused by elevated stress reactivity.



Among term-born adults, the associations between gestational age or birth weight and blood pressure response to stress appears to depend on sex, although results vary (Feldt et al., 2007; A. M. Ward et al., 2004). In one study, lower gestational age was related to higher response among women while among men the effect was the opposite (Feldt et al., 2007). Further, there was no significant association between birth weight and blood pressure response to stress (Feldt et al., 2007). In another study, gestational age was not related to blood pressure responses, but higher birth weight was related to lower blood pressure responses, although only among women (A. M. Ward et al., 2004). However, these results are not easily compared with those among VLBW adults, as their birth size derives from very different origins (severe prematurity versus normal variation) and thus the mechanisms connecting birth size to stress reactivity may also be different.

### **5.2.3 Personality**

Different personality dimensions derived from different personality frameworks may not be easily compared. However, in the same direction with our results showing lesser fun seeking in all VLBW adults and higher rate of behavioral inhibition in VLBW-SGA women, prematurely born adults have been found to be less extravert, less open to experience, less inclined to excitement seeking, less social and more shy and cautious in their behavior than their term-born peers (Allin et al., 2006; Pesonen et al., 2008; Schmidt et al., 2008). The modifying effect of being born SGA have not been reported in other preterm cohorts, but in contrast to our current result, the previous study on personality in the HeSVA cohort found no differences between the VLBW-SGA and VLBW-AGA groups (Pesonen et al., 2008).

### **5.2.4 Romantic attachment**

Our findings on romantic attachment showed more attachment-related avoidance in the VLBW-SGA women and less attachment-related anxiety in the other VLBW adults. Previous results concerning attachment are extremely scanty among preterm adults, but reports on early attachment patterns have shown varying results. Some studies indicate

slightly altered attachment patterns, although not necessarily difference in insecure vs. secure categorization, among preterm children (Goldberg et al., 1986; Hallin & Stjernqvist, 2011; Lubetzky & Gilat, 2002; Mangelsdorf et al., 1996; Sajaniemi et al., 2001; Wille, 1991) and some studies show no difference at all in contrast to term-born peers or normative data (Brisch et al., 2003; Brisch et al., 2005; Frodi & Thompson, 1985; Rode et al., 1981). Together the current and earlier results may suggest that preterm birth is not explicitly associated with a higher rate of insecure attachment style, but the higher avoidance which we found in VLBW-SGA women may make it less easy to form close relationships.

### **5.2.5 Parenting behavior**

The higher rate of parental protectiveness in recollections of the VLBW women fits together with the similar result reported previously among VLBW adolescents (Indredavik, Vik, Heyerdahl, Romundstad et al., 2005) and with other previous results showing increased sense of vulnerability (Perrin et al., 1989), protectiveness (Wightman et al., 2007) and controlling parenting (Forcada-Guex et al., 2006; Forcada-Guex et al., 2011) among parents of preterm children, although the moderating effects of SGA status and sex have not been reported before. It is of note, however, that, in comparison with the parents of the term-born adults, the parents of the VLBW adults in our study did not differ in care (similar result in the study by Indredavik et al., 2005) and reported more support in their own parenting behavior. This implies that the parents of the VLBW adults may not lack warmth and affectionate acceptance in their parenting behavior. It may be speculated that the supportive parenting reported by parents themselves was interpreted by their children as protectiveness, but this remains an issue for further studies.

### **5.3 Interpretation of the findings in the light of theoretical background and empirical evidence – Suggestions for underlying mechanisms**

Low birth weight is regarded as a crude summary marker of suboptimal fetal environment. Similarly, preterm birth can relate to a wide variety of adverse prenatal factors (see 1.1.2) and the physical and psychological consequences after preterm birth and VLBW may develop through a variety of pre- and postnatal mechanisms. While some infants may have been born with VLBW due to preterm birth without specific intrauterine adversity, particularly those VLBW infants who have suffered from IUGR may carry a burden of both pre- and postnatal adversity and they may be the most vulnerable to adverse development. The mechanisms relating VLBW to psychological outcomes may be both physiological and psychosocial. Altered physiological and biological mechanisms include potential effects on central nervous system, hormonal functioning and epigenetic effects on gene expression. Potential psychosocial mechanisms may relate to parenting and attachment development, for example. Further, biological and psychological mechanisms act together, for example, through temperament and personality which have biological and neural basis.

#### **5.3.1 Contribution of personality – perspective of the RST**

It is generally accepted that temperament and further personality refer to relatively stable and biologically based traits that have close regulatory connections with behavior and emotion. Accordingly, also part of the findings of this thesis can be viewed in relation to the RST, the personality theory we applied in our study. Based on the RST (Gray, 1991; Gray, 1994; Gray & McNaughton, 2000; for a review see Corr, 2004), the higher BIS scores that we found in the VLBW-SGA women could derive from either proneness to behavioral inhibition (relates to anxiety) or proneness to behavioral avoidance (relates to fear), or both. These VLBW-SGA women in our study also reported higher attachment-related avoidance but similar attachment-related anxiety in comparison with the control women. This may suggest that the result showing higher

BIS sensitivity in the VLBW-SGA women may in particular be due to processes causing behavioral avoidance, for example in romantic relationships.

Biologically based temperament that underlies personality is conceptually closely related to individual differences in psychological and physical reactivity (e.g., Rothbart & Derryberry, 1981). This may suggest that the lesser BAS sensitivity of the VLBW group, which refers to lesser sensitivity to potentially rewarding experiences, could promote the VLBW group to interpret psychosocial stress situations as less rewarding and thus more distressful, leading to increased stress responses. Reciprocally, higher physical stress reactivity may increase their subjective psychological distress proneness leading to lesser behavioral approach. This line of reasoning remains speculative, however, and remains to be confirmed by further studies.

Given that personality has a regulative effect on emotion and behavior, it may act as a vulnerability factor for the altered psychological outcomes that previous research has shown in young adults born preterm. Previous studies regarding the BIS and BAS, psychopathology (for a review see Bijttebier et al., 2009) and parenting offer useful perspective to our findings of personality and parenting in the VLBW adults. For example, high BIS scores have been related to a current depressive disorder while low BAS scores have been shown to predict the depressive vulnerability even more precisely (Kasch et al., 2002; McFarland et al., 2006; Pinto-Meza et al., 2006). BIS sensitivity is also shown to correlate with symptoms of anxiety (Kimbrel et al., 2007; Muris et al., 2005). Our finding of lower BAS sensitivity (manifested in lesser fun seeking) in the VLBW adults fits together with previous reports showing more often depression, anxiety and withdrawal in adults born preterm (M. H. Boyle et al., 2011; Indredavik et al., 2004; Indredavik et al., 2010; Levy-Shiff et al., 1994; Lund et al., 2011; Patton et al., 2004). In the HeSVA study this was true only for the VLBW adults born SGA, however (Räikkönen et al., 2008).

### **5.3.2 Contribution of parenting**

Severely preterm birth is often followed by neonatal illness and long time periods spent in NICU causing separation from normal contact with parents (Lemons et al., 2001; Rügger et al., 2012; R. M. Ward & Beachy, 2003). These altered postnatal conditions

as well as the trauma and emotional distress for parents (Eisengart et al., 2003; Miles & Holditch-Davis, 1997; Moore et al., 2006; Singer et al., 1999) pose a challenge to sensitive parenting and development of early attachment relationships, which in turn may affect psychosocial development of the child. The protective and authoritarian parenting that the VLBW adults, women in particular, reported for their mothers, may thus reflect the early parental worry related to preterm delivery as well as the vulnerability that the mothers perceived in their child born preterm.

It is of note that the child and the parent are in a reciprocal interaction both influencing each other. On one hand, difficult temperamental characteristics, which have been reported more in preterm than in term-born infants (Gennaro et al., 1990; Goldstein & Bracey, 1988; Hughes et al., 2002; Langkamp et al., 1998; Langkamp & Pascoe, 2001; Medoff-Cooper, 1986; Sajaniemi et al., 1998; Weiss et al., 2004), could elicit more negative parental emotions and actions, e.g. intrusiveness, towards the infant. On the other hand, sensitive and responsive parent perceives and interprets cues from the infant accurately and responds according to the infant's needs. Accordingly, the higher protectiveness that we found in the mothers of the VLBW women may have been an accurate response to higher vulnerability and temperamental sensitivity of a preterm infant. This correctly protective parenting style may, however, have turned into overprotectiveness as the child has gradually overcome his/her early illnesses and vulnerabilities. Our results imply that female sex of the child has increased the sense of vulnerability and protectiveness in mothers of the VLBW participants.

Specific parenting characteristics such as protectiveness and authoritarianism may link VLBW to the alterations in adult behavior and emotion. For example, overprotective parenting may reinforce the development of personality characterized by increased behavioral inhibition and restrained behavioral approach. Given our result on higher attachment-related avoidance in VLBW-SGA women, parental protectiveness may also restrict social experiences and formation of close relationships.

However, it is important to note that despite increased protectiveness, the sufficient parental care and warmth that the VLBW adults reported in their parents and the higher support that the parents reported in themselves indicate positive parenting. Caring and supportive parenting may, in fact, act as a protective factor against later psychopathology. This is in line with our result that in comparison with the controls, the

VLBW group in general did not report indications of more insecure attachment pattern in their romantic relationships. It is also in line with other reports showing no alterations in self-esteem (Grunau et al., 2004; Hack et al., 2007; Indredavik, Vik, Heyerdahl, Romundstad et al., 2005; Saigal et al., 2002) and less emotional and behavioral problems in self-reports than in parent-reports among preterm groups (Dahl et al., 2006; Hack et al., 2004; Hack et al., 2011; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Saigal et al., 2003; Zwicker & Harris, 2008).

Parenting may also contribute to the associations between low birth weight, personality and variety of outcomes. For example, preterm infants who were temperamentally prone to distress exhibited more externalizing behavior and lower cognitive test scores if paired with negative parenting and less externalizing behavior and higher cognitive test scores if paired with positive parenting (Poehlmann et al., 2012). Also in a sample including both very preterm and term-born children, higher maternal sensitivity at six years of age predicted better task persistence at 8 years of age (Jaekel et al., 2012). In addition, if maternal care had been low, lower birth weight has been related with smaller hippocampal volume in women (Buss et al., 2007). Moreover, in comparison to term-born infants, preterm infants demonstrated higher cortisol levels with depressed mothers and lower cortisol levels with non-depressed mothers (Bugental et al., 2008). Finally, in a cross-sectional study, higher maternal overprotection contributed to anxiety-depression symptoms through increased BIS sensitivity (Kimbrel et al., 2007).

Overall, the results of the thesis form a consistent picture of the VLBW adults, VLBW women born SGA in particular, who, in comparison with the controls born at term, report higher rates of maternal protection, more behavioral inhibition indicating avoidance of potentially aversive situations, and more avoidance related to their romantic attachment. In addition, the higher maternal protection in all VLBW women and higher BIS sensitivity in the VLBW-SGA women fits partly together with our previous reports showing less cohabiting with a partner in this same group of VLBW-SGA women (Kajantie et al., 2008) and increased risk of depression in the VLBW-SGA group as a whole (Räikkönen et al., 2008). The lower BAS sensitivity (manifested in lesser fun seeking) of the VLBW participants may set them more vulnerable for internalizing symptoms, and the higher maternal protection and increased BIS

sensitivity may emphasize this risk among those who are women and those born SGA within the VLBW group. Previously Patton et al. (2004) reported that the association between preterm birth and depression was reduced after controlling for pre-existing depression and anxiety and recent negative life events. Accordingly, through their personality and protective parenting, individuals born preterm may be more sensitive to adverse social experiences and develop depression in response. At the same time, however, parental care and support may act as protective factor against psychopathology.

### **5.3.3 Contribution of hormonal processes – focus on glucocorticoids**

Biological mechanisms relating to adverse intrauterine life may link prematurity and being SGA with adverse psychological outcomes in later life. Of the putative biological mechanisms, hormonal effects, in particular those relating to hypothalamic-pituitary-adrenal axis (HPAA), have been extensively studied. In response to stressful stimuli, HPAA becomes activated in its different levels and releases glucocorticoids, most importantly cortisol. To regulate further glucocorticoid release, glucocorticoids bind into glucocorticoid receptors and mineralocorticoid receptors on the HPAA, which consequently downshifts hormone secretion. In addition, hippocampus and frontal cortex participate in regulating the HPAA through their own glucocorticoid and mineralocorticoid receptors. While these simultaneous feedback loops operate to inactivate HPAA, amygdala operates to activate it. Activation of amygdala is related to fear and anxiety and purpose of its activating effect on HPAA is to elicit a stress response in order to cope with the threat.

In regard to HPAA, suboptimal fetal environment may be caused by undernutrition or overexposure to glucocorticoids due to maternal stress or placental dysfunction, for example. Increased activity of the maternal/fetal glucocorticoid system during pregnancy is shown to be associated with both preterm delivery (Inder et al., 2001; McLean et al., 1995) and poor fetal growth (Kajantie et al., 2003). In addition, due to its timing during gestation, preterm birth can be compared to prenatal stress. Prenatal stress and glucocorticoids are associated with reduced number of glucocorticoid and mineralocorticoid receptors in the hippocampus in female rats (Szuran et al., 2000) and

larger amygdala volume in human girls (Buss et al., 2012), which both may reduce inhibition of the HPA axis and therefore cause increased glucocorticoid levels in the offspring. Indeed, at least when the whole birth weight range has been included in the studies, poorer fetal growth has been linked with increased cortisol responses to stress (Jones et al., 2006; Wüst et al., 2005) and with increased fasting plasma cortisol concentrations in later life (Phillips et al., 2000; for a review see Kajantie & Räikkönen, 2010). In addition to prenatal stress, also early postnatal stress such as parental unavailability may increase the HPA axis activation of the offspring in animals (Sánchez et al., 2001) and humans (Bugental et al., 2003; Gunnar et al., 2001; Tyrka et al., 2008). Epigenetic modifications have been suggested to play a key role in these associations between the early environmental influences and later phenotype (Bloomfield, 2011; Meaney et al., 2007).

Regarding postnatal life, increased cortisol levels have been associated with increased blood pressure (Phillips et al., 2000; Whitworth et al., 2000), but they may also relate to increased vulnerability to respond to social adversity in a maladaptive manner. For example, in regard to personality, HPA axis and increased glucocorticoid activity are associated with traits such as lesser novelty seeking (a concept resembling fun seeking) (Tyrka et al., 2007) and lesser behavioral approach (Blair et al., 2004), as well as related disorders including depression (Brown et al., 2004). In regard to attachment, high attachment anxiety has been related to flattened cortisol responses to stress and flattened cortisol awakening responses, while avoidant and secure types have been similarly associated to the higher cortisol responses (Kidd et al., 2011; Oskis et al., 2011). Also in other studies, higher avoidance has been associated to increased cortisol reactivity (Powers et al., 2006; Rifkin-Graboi, 2008).

Increased HPA axis activation is thus one alternative mechanism to underlie physiological and psychological outcomes in preterm adults. Another alternative, as a consequence of increased HPA axis activation, is reduced HPA axis activation. Indeed, it has been suggested that long-lasting increase in HPA axis activation may lead to enhanced down regulation of the system. For example, children who have suffered from severe care deprivation and maltreatment show flattened cortisol activity (Carlson & Earls, 1997; Power et al., 2012; Tyrka et al., 2008). Similar findings have been made among patients suffering post-traumatic stress disorder, although not consistently (Meewisse et



al., 2007). Following this hypothesis of reduced HPAA activation, potential prenatal adversity, preterm birth and related postnatal treatments and parental separation could be compared to traumatic episode for the infant causing prolonged stress reactions with first increased and subsequently decreased glucocorticoid activation. The relationship between birth weight and later glucocorticoid activity could thus depend on severity of prematurity and other variables related to birth, pre- and perinatal life as suggested previously (Kajantie et al., 2002).

However, empirical evidence concerning HPAA activation in adults born severely preterm is scarce and partly inconsistent. In one study, middle-aged adults who were born preterm or with LBW had elevated evening and total diurnal cortisol levels, but similar cortisol awakening responses in comparison to term-born participants (Gustafsson et al., 2010). In another study, prematurely born young adults showed elevated awakening cortisol levels, but a trend towards blunted cortisol responses to psychosocial stress (Buske-Kirschbaum et al., 2007). Finally, in a study across the whole birth weight range, the group with the lowest birth weight in relation to the length of gestation showed the lowest cortisol responses to psychosocial stress (Kajantie et al., 2007). Together these three studies may suggest that those born preterm or SGA may have higher overall diurnal levels of glucocorticoids, but flattened responses to stress, although further research is needed to confirm and elaborate the associations between preterm birth and HPAA activation.

While the scarce evidence of HPAA activation in preterm adults shows consistencies with both hypotheses of increased and reduced HPAA activity, most of the results of this thesis fit to the hypothesis of increased HPAA activity. These results include elevated blood pressure responses to stress, lesser behavioral approach and low attachment-related anxiety in the whole group of VLBW adults as well as higher attachment-related avoidance in the VLBW-SGA women.

In summary, VLBW and/or being born SGA may at least partly be consequences of prenatal undernutrition or overexposure to glucocorticoids. In addition, adverse neonatal experiences due to prematurity and related illnesses can be considered as early stress which activates the glucocorticoid system of a neonate. Thus, both pre- and early postnatal adversities may have contributed to early acquired and persistent neurophysiological vulnerability, such as altered HPAA functioning, which in turn may

contribute to found differences in neurocognitive functioning, blood pressure reactivity, personality and attachment.

#### **5.3.4 Theoretical frameworks related to developmental plasticity**

Several closely related theoretical frameworks and concepts aim to explain the associations between early developmental factors and later health outcomes. These theories in general relate to evolutionary perspective as they describe the efforts of a system to increase chances to survive and reproduce in postnatal life. According to the 'Life History Theory', the body allocates energetic and material resources among the competing demands of survival and reproduction (Stearns, 1992). Increased allocation to one area of development decreases allocation to other areas. For example, in case of subnormal prenatal developmental resources (e.g. fetal undernutrition), brain growth is often prioritized at the expense of tissue development in other organs. This leads to smaller birth size, but it may also lead to altered functioning of the organs in later life.

Also the framework of 'Developmental Origins of Health and Disease' (DOHaD) follows evolutionary perspective. It originally evolved from the findings by Barker and others that highest rates of infant mortality, often following low birth weight, and mortality from coronary heart disease occurred in the same regions in England and Wales (Barker & Osmond, 1986). This and further findings led to the hypothesis that poor fetal growth was associated with increased risk of coronary heart disease (Barker et al., 1993), but also to other diseases including hypertension, stroke, type 2 diabetes and their risk factors (Barker, 2004). The theory of DOHaD states that development of the structure and functioning of different body organs may be permanently 'programmed' during their sensitive periods by certain stimuli or insults, e.g. fetal undernutrition or increased glucocorticoid exposure (de Boo & Harding, 2006). The term sensitive period refers to a period of fast growth or development during which the organ is highly sensitive and receptive to external stimuli that contributes to the development. The DOHaD thus rests on developmental plasticity, which refers to the phenomenon that one genotype can manifest in a variety of physiological and morphological forms in response to environmental factors affecting development (Barker, 2004).

Within the DOHaD framework, the ‘thrifty phenotype’ hypothesis originally described how undernutrition in pre- and early postnatal life programs organs to adapt to such environment which is low in nutrition and how this leads to disease if the later postnatal environment is, after all, abundant (Hales & Barker, 1992). In the thrifty phenotype model these adaptive changes are immediate responses to fetal environment in order to improve survival in that prevailing environment. The hypothesis of ‘predictive adaptive responses’ proposes that fetus is also able to make developmental adaptations according to predictions of the later postnatal environment (Gluckman & Hanson, 2004; Hanson & Gluckman, 2005). Accordingly, the predictive adaptive responses during the fetal development may not necessarily be advantageous immediately, but they would increase the chances of survival in later postnatal environment (Gluckman & Hanson, 2004).

‘The life cycle model of stress’ elaborates how the timing of stress or other adversity causing excess of glucocorticoids impacts on the programming effects, particularly those concerning brain, behavior and cognition (Lupien et al., 2009). While the models of thrifty phenotype and predictive adaptive responses emphasize the early life origins of health and disease, the life cycle model emphasize sensitive periods of different brain regions and differentiating effects of environment throughout life, from prenatal period till old age (Lupien et al., 2009). In more detail, regarding the brain regions that participate in regulating the HPA, amygdala continues to develop through all childhood and young adulthood, hippocampus develops through the first two years of life and frontal cortex has important volume increase during adolescence. Further, at old age all these brain regions have their sensitive periods of decline. Stress during a sensitive period of certain brain region alters the glucocorticoid-related functioning of that particular region. As the different brain regions have different impacts on behavior, the impact of stress on behavior depends on during which sensitive periods it takes place. In addition, type of the environmental stimuli counts for the direction of the glucocorticoid activation as have been shown in studies of parental separation or depression (increase in glucocorticoids) versus severe trauma (decrease in glucocorticoids).

Yet again related to developmental plasticity, the diathesis – distress model presents that some individuals may have increased vulnerability to negative environmental

influences. Accordingly, biological vulnerability interacts with negative life events to trigger adverse outcomes for example in terms of mental health. However, this model is further developed in the hypothesis of ‘differential susceptibility’ which proposes that individuals differ in developmental plasticity to both negative and positive directions. According to this hypothesis and some evidence, certain biological factors determine whether an individual is more susceptible than others to negative but also to positive environmental influences (Belsky & Pluess, 2009). For example, difficult temperament, more often reported in preterm infants, may be such biologically based factor. Indeed, as already mentioned in this thesis, preterm infants who were temperamentally prone to distress exhibited more externalizing behavior and lower cognitive test scores if they were paired with negative parenting and less externalizing behavior and higher cognitive test scores if they were paired with positive parenting (Poehlmann et al., 2012). In line, in an intervention study it was found that elements of social interaction were improved by intervention only among preterm infants who had temperament characterized by low regulatory competence (Olafsen et al., 2012). In addition, when compared to term-born infants, the preterm infants had higher cortisol levels with depressed mothers and lower cortisol levels with non-depressed mothers indicating that premature birth alters infants to be more sensitive to the “emotional climate” (both stress and warmth) in their environment (Bugental et al., 2008). These results imply that prenatal environment can, to some extent, program the postnatal plasticity of an individual (Pluess & Belsky, 2011).

Most of the evidence behind the theories described here comes from studies with no focus on preterm birth. Therefore suitability of these theories to preterm birth, VLBW and findings of this thesis is not self-evident, although it is possible. Accordingly, also preterm birth can be regarded as a byproduct of evolutionarily meaningful processes in order to increase survival in certain circumstances, for example in cases of infected or otherwise compromised pregnancy (Gluckman et al., 2005; Muglia & Katz, 2010). Moreover, preterm birth constitutes a specific early adversity, as it may originate in prenatal adversity and it often leads to early neonatal adversity. This adversity could relay a message of a hard life with restricted resources and direct development through adaptive responses to fit environment where it is better to be careful, inhibit behavior and be prepared to react to threatening cues effectively. In line with the life cycle model

of stress (Lupien et al., 2009) as well as hypotheses of diathesis – distress and differential susceptibility (Belsky & Pluess, 2009; Pluess & Belsky, 2011), it is presumable that in addition to the early adversity, development of the VLBW adults has also been directed by their differing social environment, most importantly parenting during childhood and adolescence. While the VLBW adults may be more vulnerable to disease, for example through their higher stress reactivity, they may in some regard also benefit more from the good parental care. Their lesser attachment-related anxiety and previously reported lesser risk-taking behavior and substance use (Strang-Karlsson et al., 2008) may be examples of the results after these kind of benefits. Altogether, the theories concerning developmental plasticity may together be applicable tools for interpreting some of the findings among preterm populations.

### **5.3.5 Contribution of altered brain development and neurocognitive consequences**

Some alterations in physical and psychological functioning of prematurely born individuals may relate to developmental plasticity and adaptive responses to fetal or perinatal environment as described in previous chapter. However, adaptive responses do not explain all outcomes. Some mechanisms underlying altered postnatal functioning are clearly disruptions in development and non-adaptive already in their origins in the pre- and perinatal period (Hanson & Gluckman, 2005). These include (a) altered brain maturation in the prenatal period, (b) perinatal brain injuries and (c) subsequent restrictions in postnatal brain maturation, which may underlie part of our findings, particularly those relating to neurocognitive abilities.

IUGR, in particular symmetric IUGR which is manifested early during pregnancy, restrict overall head growth (Nardozza et al., 2012), but also more subtle brain alterations may happen. Prenatal glucocorticoid activity affects brain maturation for which sufficient amount of glucocorticoids is essential, but excess of them is damaging. Animal studies have shown that glucocorticoid administration or stress during the prenatal period interrupts maturation processes of neurons (Huang et al., 2001) and causes structural and functional alterations in the brain (Antonow-Schlorke et al., 2003; S. G. Matthews, 2000), for example, reduced hippocampal volumes (Coe et al., 2003).

Also stressors related to neonatal intensive care may alter brain growth (G. C. Smith et al., 2011). However, it is of note that in one study among humans, lower birth weight in general was related with smaller hippocampal volume in adulthood, but only if maternal care had been low and only among women (Buss et al., 2007). This suggests that the consequences of small birth size or preterm birth on brain development may partly depend on postnatal environmental factors such as parenting and that girls may be more vulnerable than boys.

In addition to glucocorticoids, altered brain development in preterm individuals may relate to perinatal brain injuries caused by perinatal complications and prematurity-related neonatal illnesses. Neurocognitive development may follow one of several possible trajectories after an early brain injury. First, neurocognitive deficits may be absent although brain injury is evident. Second, the brain injury could be so severe that permanent neurocognitive impairments can be observed. Third, the brain could recover or compensate through neural plasticity and neurocognitive problems in infancy could resolve in process of time. Fourth, neurocognitive deficit could be absent or subtle but become more apparent in process of time implying limits in neural plasticity (Luciana, 2003). Accordingly, even apparently healthy preterm infants without obvious brain injuries may have had minor insults and interruptions to their brain development, which may become apparent in later life as they may restrict the normal brain maturation and development of higher cognitive skills (Luciana, 2003). However, the final developmental outcome could depend on several issues, including the exact timing, magnitude and nature of the injury as well as actions after the injury.

Although we do not have brain scans for our study participants, our results showing lower neurocognitive test scores in the VLBW than in the term-born group even in the absence of apparent neurosensory impairments indicate that brain plasticity does not fully recover the potential early insults to the brain. This is supported by previous neuroimaging studies demonstrating both structural and functional brain alterations in prematurely born children (Keunen et al., 2012; M. J. Taylor et al., 2012), adolescents (Caldú et al., 2006; Giménez et al., 2006; Martinussen et al., 2009; J. Parker et al., 2008) and young adults (Eikenes et al., 2011; Lawrence et al., 2010; J. Parker et al., 2008). Moreover, this is supported by studies showing correlations between the brain alterations and poorer neurocognitive performance within the preterm groups (Caldú et

al., 2006; Eikenes et al., 2011; Giménez et al., 2006; Iwata et al., 2012; Martinussen et al., 2009; Narberhaus et al., 2008; Skranes et al., 2008; Skranes et al., 2009), although not all studies have found such correlations (Rushe et al., 2001). Brain alterations in preterm groups concern mostly reduced volumes or altered microstructure in white matter, hippocampus, thalamus and corpus callosum (Caldú et al., 2006; Eikenes et al., 2011; Giménez et al., 2006; Lawrence et al., 2010; Martinussen et al., 2009; Narberhaus et al., 2008; J. Parker et al., 2008; Stewart et al., 1999).

Brain alterations and neurocognitive abilities may also affect psychosocial development. In general, lower hippocampal volume, for example, has been related to variety of neuropsychiatric outcomes (Geuze et al., 2005). In regard to VLBW, for example, lower IQ in childhood has been shown to predict internalizing symptoms in young adulthood among VLBW women (Hack et al., 2005). Similarly, IQ at adolescence tended to predict mental health in young adulthood among the VLBW group while it did not do so in the control group (Lund et al., 2012). Further, self-reported problems in VLBW adolescents were partly affected by their lower IQ (Levy-Shiff et al., 1994). Thus it is possible that through these poorer neurocognitive abilities the potential neural alterations also contribute to the personality characterized by lesser behavioral approach. Moreover, poorer neurocognitive abilities may account for the differing parenting, particularly for the more protective and authoritarian parenting that was reported by the VLBW participants in our study. In line with this, very preterm children's lower IQ has been shown to explain their mothers' higher verbal control and lesser sensitivity (Jaekel et al., 2012).

## **5.4 Limitations and strengths of the study**

Most of the limitations that concern all original studies of this thesis are related to our study cohort. First, our HeSVA cohort and preterm infants born today may differ, as knowledge of prematurity and its potential consequences has increased during the last decades and neonatal intensive care as well as other pre- and postnatal interventions have improved consequently. This may limit the generalizability of our results to the younger cohorts. Second, requirements for our VLBW participants were birth weight less than 1500 g and preterm birth, i.e. birth at less than 37 completed weeks of

gestation. One consequence of this is that belonging to a VLBW group may be due to severely preterm birth, slow intrauterine growth, or both resulting in a wide variety of gestational ages and relational birth weights. Therefore, our results do not precisely tell how the severity of prematurity affects the outcome. Another consequence is that being SGA was overrepresented in our sample, which may affect the results. However, we did aim to differentiate the effects of preterm birth and being SGA by examining the outcomes separately for the VLBW individuals born AGA and SGA and comparing these two groups with each other.

Third, due to attrition of the sample, selection bias cannot be ruled out, as we cannot compare the participants and nonparticipants in terms of other characteristics than those gathered from hospital records relating to pre- and perinatal period. Individuals can, for example, have health and functional problems that are not reported in early hospital records and attendance to the study could be more probable for those without such problems. Attendance could also be more probable for those interested in their health and well-being, as participants were given personal feedback concerning most of the measurements. Moreover, attendance could be more probable for those not working full time, as the clinical visits were carried out on office hours. At least in the subgroup who participated in the second clinical visit, the VLBW participants were marginally more often in gainful employment than the control participants (Strang-Karlsson, Kajantie et al., 2010).

Possible differences between participants and nonparticipants would, however, cause bias in the results only if they affected the associations between the grouping variable (VLBW, sex and being SGA) and the outcome measures. That is, if the biasing characteristic reduced or increased participation more in one group over the other and if it was associated to the outcome measure. A risk of this kind of bias in the results is largest in small subgroups differentiated by sex and being SGA. An example of a potentially biasing characteristic is neurosensory impairments which are more common among preterm individuals and could increase parental protection and controlling (Muller-Nix et al., 2004; Wightman et al., 2007). Protective parenting, in turn, could affect personality and attachment development of the child. However, the results of this thesis were essentially the same before and after excluding the VLBW participants with neurosensory impairments. For example, excluding participants with neurosensory



impairments did not explain the difference between the VLBW and control women in maternal protectiveness and authoritarianism. Yet the potential underrepresentation of CP and other functional limitations in the VLBW participants would, if anything, be expected to attenuate the group differences in most outcome measures from that what they would have been in the full cohort.

Fourth, the studies of this thesis give little information on the precise biological mechanisms underlying our findings. We did control for the effect of several potential confounding factors and examined the role of sex and being SGA. We found that while sex and being SGA did affect some outcomes (personality, romantic attachment, parental bonding), the effect of severely preterm birth presumably overran the potential effects of sex and being SGA in other outcome measures (neurocognitive abilities, blood pressure reactivity). However, the mechanisms underlying the findings remain to be clarified. As discussed in previous chapters, such mechanisms may relate, for example, to prenatal and postnatal hormonal programming, temperamental susceptibility, parenting, and perinatal brain insults. In addition, genetic factors that may underlie both prematurity and later biological and psychological outcomes cannot be ruled out (Hallman, 2012).

As a fifth limitation, we do not have follow-up data from childhood, which could be used to identify developmental pathways as well as factors that could contribute to the associations between VLBW and adulthood outcomes. Related to this, our results on parenting during childhood rely on retrospective questionnaire data, which are known to be easily biased. Particularly retrospective recollections of adverse childhood experiences often include false negatives. That is, in their retrospective assessments, respondents may underestimate negative parenting, for example (Hardt & Rutter, 2004). However, we do not know whether the potential bias caused by retrospective assessment is different in the VLBW and control groups and whether it therefore contributes to the group differences.

In addition, the results derived by questionnaires, namely results on personality, romantic attachment and parenting behavior, have to be viewed as subjective perceptions of the respondent. However, although the subjective perspective may differ from other people's perspective or from objective measures, it may be important in terms of the person's psychological wellbeing. This may particularly be true when

studying factors such as personality and attachment, which are based on individual's emotions and therefore may be difficult to measure objectively. Thus the subjective perspective on psychological functioning is justifiable. However, additional perspective of a partner or parents, for example, would give useful information given the discrepancy that has been found in earlier studies between the parent- and self-reports on psychiatric symptoms among VLBW adults and adolescents (Dahl et al., 2006; Hack et al., 2004; Indredavik, Vik, Heyerdahl, Kulseng et al., 2005; Saigal et al., 2003; Zwicker & Harris, 2008).

Strengths of the study include detailed birth data extracted from birth records, information on neonatal characteristics and well validated methods. In addition, important strengths come from the findings, as the studies of this thesis add to and expand on the previous findings in preterm populations in several ways. First, as most of the existing studies on effects of preterm birth have been conducted among children and adolescents, our studies offer important information on the long-term outcomes after severely preterm birth. Second, by assessing the effects of SGA status, sex and other confounding factors, we add information on the potential etiology of altered development after preterm birth, although the exact mechanisms remain open. Third, related to individual outcomes of the thesis, we used large test battery enabling an extensive overview on the neurocognitive functioning of VLBW adults (Study I). Fourth, we examined areas of psychological functioning that had not been examined previously in adults born preterm (parenting behavior; Study V) or in any groups born preterm (blood pressure reactivity to stress and romantic attachment style; Studies II and IV, respectively). Fifth, we offer a new perspective to personality development of VLBW individuals, as we examined it within a framework that has not been used before among preterm individuals (Study III).

## **5.5 Implications of the study**

Several clinical implications can be drawn from the results of this thesis. Firstly, prevention of preterm birth and IUGR is important. Despite considerable efforts to reduce the prevalence of preterm birth as well as the morbidity and mortality among those born preterm (Flood & Malone, 2012; Iams et al., 2008), very few of these

interventions have been evaluated as effective in reducing preterm birth rates (Barros et al., 2010; Simmons et al., 2010). Overall, smoking cessation and progesterone treatment for women at high risk of preterm delivery have shown the most consistent benefits (Barros et al., 2010; Simmons et al., 2010). Thus further research is necessary to develop and evaluate interventions that prevent preterm birth and improve fetal conditions.

Secondly, preterm birth at VLBW appears to increase parental involvement as was shown in recollections of increased parental protectiveness and support. As previous studies have shown high parental distress and anxiety after a severely preterm delivery, the readiness of parents to be involved could be utilized in specific NICU-based psychosocial interventions, which usually aim to relieve negative parental emotions and to optimize parents' interaction with the infant. Optimizing interaction includes improving parents' ability to recognize infant's cues of stress, readiness for interaction and different needs and responding to the cues appropriately in daily care (Milgrom et al., 2010; Newnham et al., 2009; Olafsen et al., 2012; Sajaniemi et al., 2001). Based on limited number of studies among preterm infants, these early interventions do have multiple benefits. For example, they can reduce parental distress (Melnik et al., 2006; Newnham et al., 2009). They also enhance sensitive and responsive parenting in infancy and improve the reciprocal interaction of an infant-parent dyad (Newnham et al., 2009), which in turn could reduce stress in the infant and support the development of secure parent-child attachment relationship (Sajaniemi et al., 2001), as well as reduce development of overprotective parenting behaviors. Early interventions also seem to affect brain maturation and cognitive development of the child. Indeed, sensitivity training for parents of preterm infants has been associated with improved cerebral white matter micro-structural development at term-equivalent age (Milgrom et al., 2010), lesser difficult temperament characteristics at three months of age, better communication at two years of age (Newnham et al., 2009) and better cognitive abilities at four years of age (Sajaniemi et al., 2001).

In addition to specific NICU-based interventions, it is justified to utilize parental involvement as much as possible as a routine and normal component of the neonatal care. For example, kangaroo care reduces neonatal mortality and morbidity (Lawn et al., 2011), improves parental sensitivity and decreases intrusiveness, decreases infant's

negative affect and improves parent-infant reciprocity (R. Feldman et al., 2003) and attachment (Charpak et al., 2005; Conde-Agudelo et al., 2011).

Thirdly, the thesis implies that recognizing the preterm infants that are most vulnerable (or susceptible) is important. Increased vulnerability concerns, for example, those who have potential double jeopardy due to both prenatal and environmental postnatal risks, for example IUGR in addition to prematurity-related neonatal illnesses and parental separation. Further, increased vulnerability may also concern those with certain type of temperament, for example increased proneness to distress, which have shown to sensitize children to adverse influences of intrusive and insensitive parenting (Poehlmann et al., 2012). However, according to the differential susceptibility hypothesis (Belsky & Pluess, 2009), these infants in the risk group may also benefit most from interventions. In line, sensitivity training for parents improved infant's social communication competence only in infants with low regulatory competence (Olafsen et al., 2012). Thus supporting sensitive and positive parenting is even more important among the children with increased susceptibility.

As a fourth implication of the thesis, the strengths of VLBW adults should be highlighted and acknowledged in potential interventions. After surviving the highly vulnerable neonatal period and prematurity-related illnesses, also supporting parenting of a normal healthy child could be valuable. Parents should be provided with information on the relatively good psychological well-being and functioning of the VLBW infants in adulthood in order to avoid excessive protectiveness. They should also be provided with the knowledge that parents are in general good in caring and supporting their preterm children, because this could reduce their distress and strengthen their confidence in parenting.

Fifth implication is that adequate support should be available also in later life for those who might need it. In terms of academic achievement, the VLBW adults without major impairments in our study had received more remedial education but did not differ from term-born adults in years of education or in grade point average at the end of comprehensive school. This may indicate that remedial education is beneficial in preventing adverse academic consequences in preterm individuals, although such association could not be directly tested. From another point of view, this may indicate that preterm individuals, at least if survived without major neurosensory impairments

and if supported by suitable measures, are capable of considerable resilience and adaptation in their school performance. This may relate to resilience and plasticity of the brain or it may relate to adaptation on individual's behavioral level.

In summary, preterm birth with VLBW is related to both vulnerabilities and protective factors. Some factors such as parenting may be regarded as either vulnerability or a protective factor. Both vulnerabilities and protective factors could be acknowledged in possible interventions among preterm children and their families. An immediate purpose of early psychosocial interventions is to buffer against the pre- and postnatal risk factors and utilize and harness the potential protective factors in order to support positive parenting, a child-parent relationship and optimal development of a preterm infant.

## **5.6 Suggestions for further studies**

Survival after severely preterm birth has substantially increased during the last few decades and consequently, the long-term outcomes in adulthood after a preterm birth have become an important subject to study. Although the studies of this thesis and other previous research in adults born preterm give valuable insight to the long-term outcomes in preterm infants, further research is essential to soundly understand the developmental processes related to preterm birth. While several developmental aspects still need to be studied or confirmed, a few questions rise from this thesis. First, based on the results, it may be speculated that certain characteristics of parenting could account for the psychosocial development of preterm infants. However, in terms of long-term development till adulthood, the predictive value of parenting for psychological outcomes should be examined in detailed. Second, the predictive value of other characteristics such as personality and stress reactivity for psychological well-being should be examined within the preterm group and in comparison to term-born controls. These questions on predictive factors lead to a third study suggestion which concerns different developmental trajectories within the preterm groups and in comparison to term-born groups. Studies differentiating developmental trajectories and factors that have led to certain trajectories could help identifying the most important risk factors and potential targets for interventions. Further, in regard to early psychosocial

interventions, the need for further long-term studies concerns also them. Most of the studies on the effectiveness of these interventions are limited to the first few years of the child's life. To see whether they are helpful in reducing the long-term developmental alterations, for example in cognitive and emotional functioning, and to develop the interventions further, follow-up studies are required.

Accordingly, long-term follow-up studies, large study samples and a large battery of outcome measures are required to be able to differentiate and follow several developmental trajectories and to examine the contribution of different risk factors and protective factors in the selection of a trajectory. To increase study samples, pooling data from several preterm cohorts may be useful. Outcome measures could include at least measures of neurocognitive abilities and psychological wellbeing including social outcomes and self-perceived quality of life. Importantly, outcome measures should also include areas of independent functioning in society, including education, employment and independent living. To identify the role of potential risk factors and protective factors, information could be gathered at different phases of development at least on temperament or personality, parenting and participation in any intervention programs.

## **5.7 General conclusions**

Results of the thesis demonstrate that young adults who were born preterm with VLBW differ from their peers born at term in several areas of development and that these differences are not explained by apparent neurosensory impairments, parental education or other major confounders. Lower neurocognitive performance and higher blood pressure responses to stress were found to the same extent in all VLBW adults. In contrast, areas with more psychosocial elements, i.e. personality, romantic attachment and parenting, appeared to be most affected in the VLBW women and in those born SGA reflecting poorer intrauterine growth. In detail, all VLBW adults showed lesser fun seeking and received more parental support according to their parents, but only the VLBW-SGA women showed more behavioral inhibition and more attachment-related avoidance and only the VLBW women reported more maternal protection and authoritarianism than their peers born at term. In addition, the VLBW-SGA women

were the only VLBW adults who did not report lesser attachment-related anxiety than the term-born adults.

The results thus imply that some of the apparent alterations in the functioning of VLBW adults are related to preterm birth per se while some others may relate to pronounced susceptibility particularly in VLBW women and/or in those born SGA. It is of note, however, that according to self-reports, in some areas the VLBW adults in general appeared to function similarly (e.g. parental care and most personality dimensions) or even better (e.g. attachment-related anxiety) than their term-born peers. Also the neurocognitive performance of the VLBW adults without major disabilities was on average in the normal range, although it was lower than that of the term-born adults. Overall, this thesis demonstrates that former VLBW infants function relatively well as young adults, although in some areas of psychosocial and cognitive functioning they show signs of adversity that may have an effect on their psychosocial wellbeing.

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