Very Low Birth Weight Infants as Young Adults

Focus on aspects of cognition, behavior and sleep

Sonja Strang-Karlsson

ACADEMIC DISSERTATION

To be publicly discussed, with permission of the Faculty of Medicine, University of Helsinki, in the Niilo Hallman Auditorium, Children’s Hospital, on February 17, 2011, at 12 noon.

Helsinki 2011
To my family

“Learn as if you were going to live forever.
Live as if you were going to die tomorrow.”
(Mahatma Gandhi)
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Abstract

Background and aims. Major advances in the treatment of preterm infants have occurred during the last three decades. Survival rates have increased, and the first generations of preterm infants born at very low birth weight (VLBW; < 1500 g) who profited from modern neonatal intensive care are now in young adulthood. The literature shows that VLBW children achieve on average lower scores on cognitive tests, even after exclusion of individuals with obvious neurosensory deficits. Evidence also exists for an increased risk in VLBW children for various neuropsychiatric disorders such as attention-deficit hyperactivity disorder (ADHD) and related behavioral symptoms. Up till now, studies extending into adulthood are sparse, and it remains to be seen whether these problems persist into adulthood. The aim of this thesis was to study ADHD-related symptoms and cognitive and executive functioning in young adults born at VLBW. In addition, we aimed to study sleep disturbances, known to adversely affect both cognition and attention. We hypothesized that preterm birth at VLBW interferes with early brain development in a way that alters the neuropsychological phenotype; this may manifest itself as ADHD symptoms and impaired cognitive abilities in young adulthood.

Methods. In this cohort study from a geographically defined region, we studied 166 VLBW adults and 172 term-born controls born from 1978 through 1985. At ages 18 to 27 years, the study participants took part in a clinic study during which their physical and psychological health was assessed in detail. Three years later, 213 of these individuals participated in a follow-up. The current study is part of a larger research project (The Helsinki Study of Very Low Birth Weight Adults), and the measurements of interest for this particular study include the following: 1) The Adult Problem Questionnaire (APQ), a self-rating scale of ADHD-related symptoms in adults; 2) A computerized cognitive test battery designed for population studies (CogState®) which measures core cognitive abilities such as reaction time, working memory, and visual learning; 3) Sleep assessment by actigraphy, the Basic Nordic Sleep Questionnaire, and the Morningness-Eveningness Questionnaire. Actigraphs are wrist-worn accelerometers that separate sleep from wakefulness by registering body movements.

Results and conclusions. Contrary to expectations, VLBW adults as a group reported no more ADHD-related behavioral symptoms than did controls. Further subdivision of the VLBW group into SGA (small for gestational age) and AGA (appropriate for gestational age) subgroups, however, revealed more symptoms on ADHD subscales pertaining to executive dysfunction and emotional instability among those born SGA. Thus, it seems that intrauterine growth retardation (for which SGA served as a proxy) is a more essential predictor for self-perceived ADHD symptoms in adulthood than is VLBW birth as such. In line with observations from other cohorts, the VLBW adults reported less risk-taking behavior in terms of substance use (alcohol, smoking, and recreational drugs), a finding reassuring for the VLBW individuals and their families.
On the cognitive test, VLBW adults free from neurosensory deficits had longer reaction times than did term-born peers on all tasks included in the test battery, and lower accuracy on the learning task, with no discernible effect of SGA status over and above the effect of VLBW. Altogether, on a group level, even high-functioning VLBW adults show subtle deficits in psychomotor processing speed, visual working memory, and learning abilities.

The sleep studies provided no evidence for differences in sleep quality or duration between the two groups. The VLBW adults were, however, at more than two-fold higher risk for sleep-disordered breathing (in terms of chronic snoring). Given the link between sleep-disordered breathing and health sequelae, these results suggest that VLBW individuals may benefit from an increased awareness among clinicians of this potential problem area. An unexpected finding from the sleep studies was the suggestion of an advanced sleep phase: The VLBW adults went to bed earlier according to the actigraphy registrations and also reported earlier wake-up times on the questionnaire. In further study of this issue in conjunction with the follow-up three years later, the VLBW group reported higher levels of morningness propensity, further corroborating the preliminary findings of an advanced sleep phase. Although the clinical implications are not entirely clear, the issue may be worth further study, since circadian rhythms are closely related to health and well-being.

In sum, we believe that increased understanding of long-term outcomes after VLBW, and identification of areas and subgroups that are particularly vulnerable, will allow earlier recognition of potential problems and ultimately lead to improved prevention strategies.

Key words: Very low birth weight, preterm, epidemiology, small for gestational age, intrauterine growth retardation, attention-deficit hyperactivity disorder, executive functions, risk-taking, cognition, processing speed, sleep, sleep-disordered breathing, sleep phase, morningness-eveningness, chronotype.
List of original publications

This thesis is based on the following publications referred to in the text by their roman numerals I-V:


These articles are reproduced with the kind permission of their copyright holders. (Study I: American Psychiatric Association; Studies II and IV: American Academy of Pediatrics; Study III: Oxford University Press on behalf of the Society of Pediatric Psychology; Study V: Informa Healthcare). Some previously unpublished results are also presented.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention-deficit hyperactivity disorder</td>
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<td>AGA</td>
<td>Appropriate for gestational age</td>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>APQ</td>
<td>Adult Problem Questionnaire</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>BMI</td>
<td>Body mass index, kg/m²</td>
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<td>BNSQ</td>
<td>Basic Nordic Sleep Questionnaire</td>
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<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>cm</td>
<td>centimeters</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CP</td>
<td>Cerebral palsy</td>
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<tr>
<td>e.g.</td>
<td>exempli gratia</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<td>ELBW</td>
<td>Extremely low birth weight (birth weight &lt; 1000 g)</td>
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<td>ES</td>
<td>Effect size</td>
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<td>IQ</td>
<td>Intelligence quotient</td>
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<td>IUGR</td>
<td>Intrauterine growth restriction</td>
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<td>kg</td>
<td>kilogram</td>
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<tr>
<td>LBW</td>
<td>Low birth weight (birth weight &lt; 2500 g)</td>
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<tr>
<td>MEQ</td>
<td>Morningness-eveningness questionnaire</td>
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<td>msec</td>
<td>milliseconds</td>
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<tr>
<td>N/A</td>
<td>Not available</td>
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<tr>
<td>NBW</td>
<td>Normal birth weight</td>
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<tr>
<td>NSI</td>
<td>Neurosensory impairment</td>
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<td>OSAS</td>
<td>Obstructive sleep apnea syndrome</td>
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<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>REM</td>
<td>Rapid eye movement</td>
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<tr>
<td>ROP</td>
<td>Retinopathy of prematurity</td>
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<tr>
<td>RT</td>
<td>Reaction time</td>
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<tr>
<td>SCN</td>
<td>Suprachiasmatic nucleus</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SDB</td>
<td>Sleep-disordered breathing</td>
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<tr>
<td>SES</td>
<td>Socioeconomic status</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<td>SWS</td>
<td>Slow wave sleep</td>
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<tr>
<td>VLBW</td>
<td>Very low birth weight (birth weight &lt; 1500 g)</td>
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1 Introduction

Along with the advent of modern neonatal intensive care from the 1970s and onwards, we have witnessed dramatic progress in the field of neonatology. While in the 1960s barely half the preterm infants born at very low birth weight (VLBW; birth weight < 1500 g) survived, almost 90% in high-income countries do so today (Järvenpää, 1982; Lee et al., 1995, meta-analysis; Rautava et al., 2007). At the same time, disability rates have fallen, a contrast to what was expected in terms of escalating disability rates as a consequence of this rise in survival (Lee et al., 1995, meta-analysis; Platt et al., 2007; Korvenranta et al., 2010). Mechanical support of ventilation has been a frontline determinant of the higher survival rates, followed by other therapeutic breakthroughs such as antenatal corticosteroids and surfactant. Only recently have the first generations of VLBW survivors who underwent modern neonatal intensive care reached adulthood, making their long-term outcomes increasingly relevant.

In Finland, 0.9% of infants are born at VLBW, with the corresponding figure in the USA being 1.5% (Official Statistics of Finland, Statistical Report 6/2010; Heron et al., 2010). From a global perspective, preterm birth (< 37 completed gestational weeks) is the leading cause of neonatal mortality, and one in ten births occur preterm (Black et al., 2010). Despite the revolutionizing advances in treatment, preterm birth at VLBW is still a high-risk condition even in high-income countries. The preterm infant is deprived of the last weeks or months of life in the womb – a period characterized by rapid development of, for example, the brain (Glenn, 2009; Kostovic & Vasung, 2009, reviews). Additionally, preterm birth is often accompanied by postnatal illness, prolonged hospitalization, infections, medications, and medical interventions. Some VLBW infants have suffered from growth retardation before birth, and many, if not all, even after birth. These factors may have adverse effects on their later health and well-being.

Studies on children born preterm show higher rates of health problems such as slow growth, respiratory illness, and impaired glucose tolerance, as compared with term-born controls (Hofman et al., 2004; Saigal et al., 2006c; Saigal & Doyle, 2008, review). Furthermore, VLBW children have on average poorer cognitive abilities and higher rates of psychiatric symptoms (Botting et al., 1997; Aarnoudse-Moens et al., 2009, meta-analysis; Johnson et al., 2010). Some of these adversities seem to persist beyond childhood and adolescence (Hack et al., 2002, Hovi et al., 2007). However, follow-up studies extending into adulthood are only now emerging, with more data needed. An increased understanding of long-term outcomes after VLBW birth may also serve as a general model for the ways in which incidents during fetal life and early childhood affect later health.

Within the confines of The Helsinki Study of Very Low Birth Weight Adults, we aimed to investigate health outcomes in young adults born prematurely at VLBW in the late 1970s and early 1980s. In the current thesis, health outcomes are addressed from a neurobehavioral point of view.
2 Review of the literature

2.1 Prematurity – general considerations

2.1.1 Definitions

In the early twentieth century, a noted Finnish pediatrician, Arvo Ylppö (Figure 1), defined prematurity as a birth weight of 2500 g or less, a definition that gained international acceptance (Ylppö, 1920). Today, the World Health Organization defines prematurity as birth before 37 completed gestational weeks (World Health Organization, 2007). The widely used classification according to birth weight is as follows: low birth weight (LBW; birth weight < 2500 g), very low birth weight (VLBW; < 1500 g), and extremely low birth weight (ELBW; < 1000 g). Prematurity can also be classified according to gestational age, designating those infants born before 32 weeks as very preterm, and those born before 28 weeks as extremely preterm. The abbreviation SGA (small for gestational age) refers in this text to an infant whose birth weight is < -2 standard deviations (SDs) of the population mean for a given gestational age, while AGA (appropriate for gestational age) refers to a birth weight within ± 2 SDs, and LGA (large for gestational age) to a birth weight > 2 SDs. (Pihkala et al., 1989). The definition of SGA is dependent on national standards and the choice of a cutoff limit, which usually ranges from -2 SD to the tenth percentile.

Figure 1  Archiater Arvo Ylppö as a medical student. Reproduced with permission from the photograph collection of the Children’s Castle Hospital Museum in Helsinki.
2.1.2 Etiology

“Few biological processes as central to the survival of a species as parturition are so incompletely understood.” (Roberto Romero, perinatologist, 2002)

Along with attempts to solve the enigma of spontaneous preterm birth, several subdivisions of preterm birth have been proposed. One common division is according to clinical presentation: 1) Preterm labor with intact membranes (45%), 2) premature preterm rupture of membranes (PPROM, 25%), and 3) medically induced delivery for fetal or maternal indications such as preeclampsia or intrauterine growth restriction (IUGR) of the fetus (30%). The first two together represent spontaneous preterm births (Goldenberg et al., 2008, review). In a report based on 1008 live births before 28 weeks of gestation, McElrath et al. (2008) proposed a classification into two broad groups according to features shared by pregnancy disorders that eventually lead to preterm birth. The “inflammatory” group included preterm labor, premature preterm rupture of membranes, placental abruption, and cervical insufficiency, and was characterized by signs of infection and inflammation in the absence of signs of placentation aberrations. The “placental dysfunction” group on the other hand included preeclampsia and fetal indication/IUGR, and was characterized by signs of placental dysfunction but relative absence of inflammation.

The pathogenesis of spontaneous preterm birth is incompletely understood, as are the mechanisms for timing of human parturition generally. Preterm birth could result from too early activation of the normal pathway that leads to term delivery, or alternatively, arise from mechanisms that activate distinctive pathways. The etiology is multifactorial, and preterm birth is nowadays considered a syndrome (Norwitz et al., 1999; Gotsch et al, 2009, reviews).

Although the cause remains unclear in most cases, among several factors associated with preterm birth, the most prominent, particularly at lower gestational ages, is intrauterine infection (Figure 2) (Goldenberg et al., 2008, review; Jones et al., 2009). Other major factors are multiple gestation with the majority of deliveries occurring before 37 completed weeks, and previous preterm delivery, which argues for a sturdy genetic component although shared environmental influences may also play a role (Wilcox et al., 2008). Several other risk factors have also been identified mainly from observational studies, including ethnicity, low and high maternal age (below 17 or above 35 years of age), low socioeconomic status, smoking, substance abuse, malnutrition, low pre-pregnancy body mass index (BMI), chronic medical conditions such as diabetes or hypertension, fetal or uterine anomalies, hydramnios/oligohydramnios, hard physical work, high levels of stress, history of cervical surgery, and extrauterine infections (Martin et al., 2006; Goldenberg et al., 2008, review). More recently, studies emphasizing an interaction between genes and environment in the etiology of preterm birth have begun to emerge (Gómez et al., 2010).
2.1.3 Epidemiological trends in prevalence, survival, morbidity, and treatment

Prevalence

Of the 8.8 million children globally who die before their fifth birthday, one million die due to preterm birth complications (Black et al., 2010). An estimated 10% of births worldwide occur preterm, and the greatest overall burden of prematurity, especially in terms of absolute numbers, is carried by developing countries (Beck et al., 2010, systematic review). In many Western countries, the incidence of preterm birth has increased during recent decades, partly explained by a rise in multiple gestations, in maternal age, in use of infertility therapies, and in obstetric interventions. The rate of preterm births in the USA has steadily risen from 10.6% in 1990 to 12.7% in 2007. The ethnic disparities in the USA are striking, with 18.3% of non-hispanic black women, in contrast to 11.5% of non-hispanic white women, delivering preterm (Heron et al., 2010). The rates of preterm birth in Europe range from about 5 to 11% (EURO-PERISTAT Project, 2008). Finland has one of the lowest rates: 5.7% of liveborn children born preterm in 2008, and this rate has remained relatively constant during the last few decades (Official Statistics of Finland, Statistical Summary 14/2010).

Preterm birth at VLBW, which is the main focus of this thesis, makes up a good 1% of births in high-income countries: 0.9% in Finland (Official Statistics of Finland, Statistical Report 6/2010), and 1.5% in the USA (Heron et al., 2010), while most European countries fall between these two (EURO-PERISTAT Project, 2008). The rate of ELBW in Finland is presently 0.4% (Official Statistics of Finland, Statistical Report 6/2010).
Survival

The improved survival of VLBW infants in high-income countries is a success story, thanks to introduction of neonatal intensive care and prenatal maternal care. While at best one-fifth of liveborn VLBW infants survived to hospital discharge in the 1950s (Drillien, 1961), about half survived in the 1960s, and more than two-thirds in the 1980s (Järvenpää, 1982; Lee et al., 1995, meta-analysis). During the course of the 1990s, survival increased from 80% to 85% (Horbar et al., 2002; Fanaroff et al., 2007). During the 21st century, the increase in survival has been only modest. Yet, survival rates today are historically high. Zeitlin and colleagues (2008) reported an average rate of 85.8% when studying survival until hospital discharge among liveborn very preterm infants in ten different European countries in 2003. Concurrently, the one-year survival among liveborn VLBW/very preterm infants in Finland was 89% (Rautava et al., 2007). Survival rates in developing countries are markedly lower, as illustrated by a 70% survival until hospital discharge among liveborn VLBW infants in an academic hospital in South Africa (Ballot et al., 2010). It is of note that a substantial heterogeneity exists in the design of studies reporting on survival rates.

Survival increases with increasing birth weight and gestational age. In a Swedish study reporting a one-year survival of 70% among infants born alive before 27 weeks of gestation, the survival was only 9.8% at 22 weeks, but as high as 85% at 26 weeks (EXPRESS group, 2009). Furthermore, being born in a level III hospital was related to increased survival, as shown by others as well (Rautava et al., 2007). Further factors related to increased survival in preterm infants include female sex and, at least in the USA, being black (Kaiser et al., 2004; Fanaroff et al, 2007).

Short-term morbidity

The increased survival as a result of improved neonatal care has raised concern about escalating disability rates. Several studies, however, show that this is not the case. The VLBW infant today has a better chance not only of surviving, but also surviving without severe neurologic impairment. The prevalence of cerebral palsy (CP) in European VLBW children has fallen during 1980-1996 from 6.1% to 4.0% in liveborns, and from 9.0% to 4.4% in neonatal survivors (Platt et al., 2007). More recent Finnish data also show CP rates of 4.4% (Korvenranta et al., 2010). Similarly, according to a meta-analysis spanning three decades, the prevalence of liveborn VLBW children who survived with an intact outcome rose from 14.7% in 1947-1965 to 49.8% in 1980-1987 (Lee et al., 1995, meta-analysis). On a par with this, most data from the 1990s and the very beginning of the 21st century fail to show a trend toward increasing short-term morbidities associated with the improved VLBW survival. Rather, morbidity rates in VLBW survivors decreased during the first half of the 1990s, and remained relatively unchanged later on (Horbar et al., 2002; Darlow et al., 2003; Fanaroff et al., 2007). Korvenranta et al. (2010) reported that no fewer than two-thirds of five-year-old VLBW/very preterm children born during 2001-2002 were free from morbidity.
With regard to common prematurity-related neonatal morbidities, the following rates have been reported in European VLBW/very preterm infants in 2006: bronchopulmonary dysplasia (BPD, defined as need for additional oxygen at 36 weeks postmenstrual age), 19.6%; grades III-IV intraventricular hemorrhage (IVH), 7.9%; cystic periventricular leukomalacia (PVL), 3.3%; necrotizing enterocolitis (NEC), 4.6%; stage III-IV retinopathy of prematurity (ROP), 5.5%; nosocomial infections, 22.6%; and patent symptomatic ductus arteriosus (PDA) that required surgery, 5.5% (EURO-PERISTAT Project, 2008, Data from the EuroNeoStat project 2006 cohort of VLBW/VLGA infants). Unsurprisingly, morbidities are inversely related to gestational age and birth weight. Whereas 70% of liveborn VLBW infants survived without major neonatal morbidity (defined as BPD, severe IVH, or NEC) during 1997-2002 (Fanaroff et al., 2007), during 2004-2007, among infants born alive at the limit of viability (< 27 weeks), one-year survival without major neonatal morbidities (severe IVH, ROP, BPD, PVL, or NEC) was 45% (EXPER group, 2009). Lately, the public health effects of moderately preterm and late preterm births (occurring between 32-37 and 34-37 weeks, respectively) have started to raise awareness. Late preterm infants are at higher risk for morbidity and mortality than are term borns, albeit not to the same extent as VLBW/very preterm infants. Given that late preterm infants comprise the lion’s share of all infants born preterm, this is an important population at risk (Engle et al., 2007; Saigal & Doyle, 2008, review).

Trends in treatment

The history of neonatology is short. Although the first incubator was invented in the 19th century, it was not until the 1960s that attitudes changed, and the field of neonatology took form – as illustrated by the term neonatology stemming from the 1960s. Before this, the main attention went to other causes of child mortality such as malnutrition, with the importance of early nutrition with breast feeding and clean milk emphasized (Riihola, 2010). Respiratory function was supported primarily by administration of supplemental oxygen. A milestone in the clinical care of preterm infants was the introduction in the mid 1960s of assisted mechanical ventilation to manage respiratory distress syndrome (RDS) (Philip, 2005, review). The introduction of mechanical ventilation was not trouble-free, however, and shortly thereafter, bronchopulmonary dysplasia (BPD) was described in the scientific literature (Northway, 1967). Other important advances in the early years of neonatal intensive care included improvements in delivery room care, parenteral nutrition, thermoregulation, and treatment of apnea and PDA (Philip, 2005, review).

In 1978, intensive care and follow-up of VLBW infants was initiated at the Children's Hospital in Helsinki (Anna-Liisa Järvenpää, personal communication), simultaneously with the birth of the first participants in The Helsinki Study of Very Low Birth Weight Infants. During the 1980s, cardiovascular monitoring improved, pulse oxygen-saturation monitors emerged, and clinical trials with antenatal corticosteroids were proceeding as a result of the 1972 Liggins report showing that corticosteroids for the mother before a preterm birth,
reduce RDS and IVH rates, and mortality (Liggins & Howie, 1972; Philip, 2005, review). Furthermore, administration of surfactant into the newborn’s lung proves effective in the treatment of RDS (Fujiwara et al., 1980; Hallman et al., 1985).

In the 1990s, often referred to as the post-surfactant era, antenatal corticosteroids and surfactant established their place in the treatment regimens. For example, the use of antenatal corticosteroids in VLBW births increased from 24% to 72% in 1991-1999, and use of surfactant went up from 53% to 62%. (Horbar et al., 2002, data from the Vermont Oxford Network). The post-surfactant era is further characterized by more active delivery room resuscitation, regionalization, more effective nutrition, improved ventilation regimens, and use of vasoactive substances. The use of postnatal steroids to reduce chronic lung disease is declining due to evidence of their adverse long-term effects on neurodevelopment (Yeh et al., 2004; Fanaroff et al., 2007). Nowadays, central themes in neonatology include protection of the developing brain and the yet unresolved ethical issues of the limits of viability (Martin et al., 2006).

2.2 Poor fetal growth

Intrauterine growth restriction (IUGR) occurs when the fetus fails to reach its genetically predetermined growth potential due to non- optimal fetal, uteroplacental, or maternal circumstances. An infant is classified as SGA when birth weight for gestational age is below a certain cut off value, usually below 2 SD of the population mean (or below the 10th percentile). The terms “IUGR” and “SGA” are not interchangeable, however: An SGA infant may have suffered from IUGR, although not necessarily; in that case the infant is simply small but otherwise healthy. Likewise, IUGR infants are not always SGA (Martin et al., 2005). In short, SGA can serve as a proxy for the pathological condition IUGR.

IUGR is a heterogenous condition with a wide range of etiologies. Fetal causes include chromosomal aberrations (e.g. Down syndrome), congenital infections (rubella, cytomegalovirus), and metabolic disorders and syndromes associated with low birth weight. Examples of uteroplacental causes are infections, preeclampsia, vascular anastomosis in twin pregnancies, and chronic placental abruption. Maternal determinants for IUGR include conditions such as hypertension, malnutrition, and tobacco smoking. Two patterns of IUGR can be discerned: symmetric and asymmetric growth restriction. In the first, measures of head circumference, weight, and length are proportionately affected. The onset is typically early in gestation, since the underlying causes (chromosomal aberrations, fetal infections) act at an early stage. Asymmetric IUGR, in turn, is more prevalent, characterized by brain sparing (large head size in relation to the body), later onset, and is caused by such problems as preeclampsia or maternal undernutrition. (Martin et al., 2005).

IUGR poses a risk for perinatal and neonatal complications in both term and preterm infants (Martin et al., 2005). In VLBW infants, SGA status more than doubles the mortality
risk (Bartels et al., 2005). IUGR/SGA has consequences beyond the neonatal period as well, including elevated risk for cardiovascular disease, depressive symptoms, and modestly impaired cognitive and neuropsychological functioning through childhood and adulthood (Kulseng et al., 2006; Räikkönen et al., 2008; Barker et al., 2009, de Bie et al., 2010, review). In a natural experiment during the Dutch famine in 1944 to 1945, characterized by a clearly defined period of severe famine, malnutrition in pregnant women was associated in their adult offspring with cardiovasular disease, glucose intolerance, and obesity (Roseboom et al., 2006). Taken together, these findings are consistent with the fetal origins theory, stating that adult health is already programmed during fetal life and early childhood as a result of developmental plasticity in response to malnutrition and impaired growth (Barker et al., 2009). With regard to this hypothesis, the VLBW participants of the current study constitute an interesting population, since while most of them have suffered from growth restriction postnatally, some have done so prenatally, as well.

2.3 Young adult outcomes of VLBW

“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” (World Health Organization, 1948)

2.3.1 Adult cohorts to date

Since the introduction of modern neonatal intensive care, a handful of studies have followed VLBW survivors into adulthood. Such long-term follow-up makes it possible to observe changes in outcomes over time, identify subtle deficits not noticed at younger ages, evaluate skills at coping in new environments encountered only after childhood (e.g. working life), and to obtain reports of perceived health from the adult patients themselves. That the existing cohorts differ in several aspects poses a challenge to comparison of outcomes across cohorts. While some are defined according to birth-weight limits such as VLBW or ELBW, others use a gestational age limit of < 32 weeks or more (Table 1). The cohorts may stem from a geographically defined region, be hospital-based, or national (Table 1). The outcomes studied and the methods used vary, as do the inclusion criteria. Some include all survivors (Lefebvre et al., 2005; Saigal et al., 2006); most include twins (Hack et al., 2002) and individuals with neurosensory impairments (Hack et al., 2002; Saigal et al., 2006; Hovi et al., 2007). The socioeconomic status (SES) of the study participants may differ both between and within cohorts; typically the controls come from families of higher SES than do the preterms (Lindström et al., 2007; Hack, 2009, review). Follow-up rates for the preterm groups range from 48% to 90% (Allin et al., 2006b; Saigal et al., 2006b, Gäddlin et al., 2009).

Figure 3 and Table 1 depict adult VLBW cohorts to date (including ELBW/very preterm cohorts). In the following text, adult outcomes after VLBW birth are summarized, with
emphasis on neurobehavioral outcomes relevant for the current work. We define adulthood as age 18 years or older. Data from ELBW/very preterm cohorts are included occasionally due to their overlap with VLBW, and a few essential studies covering later gestational are presented. For the sake of brevity, childhood and adolescent outcomes are mentioned only briefly.

Figure 3  Adult VLBW, very preterm, or ELBW cohorts to date. (The figure utilizes as background a world map freely licenced at Wikimedia Commons).
Table 1. Adult VLBW, very preterm, or ELBW cohorts to date. Portions adapted from Hack 2009, Journal of Developmental and Behavioral Disorders, 30(5):460-470, with permission from Wolters Kluwer Health.

<table>
<thead>
<tr>
<th>Origin</th>
<th>Reference</th>
<th>Study population (n, follow-up %)</th>
<th>Birth year</th>
<th>Age (y)</th>
<th>Control group (n)</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victoria, Australia</td>
<td>Doyle et al., 2003</td>
<td>VLBW (156, 74%)</td>
<td>1977-82</td>
<td>18+</td>
<td>38 (63%)</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Central-West Ontario, Canada</td>
<td>Saigal et al., 2006b</td>
<td>ELBW (149, 90%)</td>
<td>1977-82</td>
<td>22-25</td>
<td>133 (92%)</td>
<td>Regional</td>
</tr>
<tr>
<td>British Columbia, Canada</td>
<td>Grunau et al., 2004</td>
<td>&lt; 800 g (53, 54%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1981-86</td>
<td>17-19</td>
<td>31 (74%)</td>
<td>Regional</td>
</tr>
<tr>
<td>Mannitoba, Canada</td>
<td>Weiler et al., 2002</td>
<td>ELBW (25, 30%)</td>
<td>1978-82</td>
<td>16-19</td>
<td>25</td>
<td>Regional</td>
</tr>
<tr>
<td>Montreal, Canada</td>
<td>Lefebvre et al., 2005</td>
<td>ELBW (59, 72%)</td>
<td>1976-81</td>
<td>18</td>
<td>44 (56%)</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Copenhagen, Denmark</td>
<td>Mathiason et al., 2009</td>
<td>27 weeks to term (203 283; 1422 very preterm)</td>
<td>1974-76</td>
<td>27-29</td>
<td>Population</td>
<td>National register</td>
</tr>
<tr>
<td>Copenhagen, Denmark</td>
<td>Bjørager et al., 1995</td>
<td>VLBW (85, 72%)</td>
<td>1971-74</td>
<td>18-20</td>
<td>85 (77%)</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Copenhagen, Denmark</td>
<td>Dinesen &amp; Greisen, 2001</td>
<td>VLBW (92, 90%)</td>
<td>1980-82</td>
<td>18-20</td>
<td>69</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Liverpool, United Kingdom</td>
<td>Cooke, 2004</td>
<td>VLBW (79, 57%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1980-83</td>
<td>20</td>
<td>71 (44%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>London, United Kingdom</td>
<td>Walshe et al., 2008</td>
<td>Very preterm (169, 59%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1979-84</td>
<td>22</td>
<td>101</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Merseyside, United Kingdom</td>
<td>Pharoah et al., 2003</td>
<td>VLBW (143, 65%)</td>
<td>1980-81</td>
<td>20&lt;sup&gt;j&lt;/sup&gt;</td>
<td>16&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Regional</td>
</tr>
<tr>
<td>Helsinki, Finland</td>
<td>Hovi et al., 2007</td>
<td>VLBW (166, 65%)</td>
<td>1978-85</td>
<td>22</td>
<td>172 (55%)</td>
<td>Regional</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Hille et al. 2007 &quot;POPS Study&quot;</td>
<td>VLBW/very preterm (705, 74%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1983</td>
<td>19</td>
<td>Population data</td>
<td>National</td>
</tr>
<tr>
<td>Western Norway</td>
<td>Halvorsen et al., 2004</td>
<td>ELBW/extremely preterm (46, 90%)</td>
<td>1982-85</td>
<td>18</td>
<td>35 (76%)</td>
<td>Regional</td>
</tr>
<tr>
<td>Norway&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Moster et al., 2008</td>
<td>23 to ≥37 weeks (867 692, 88%)</td>
<td>1967-83</td>
<td>20-36</td>
<td>—</td>
<td>National register</td>
</tr>
<tr>
<td>Norway&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Swamy et al., 2008</td>
<td>22 to 43 weeks (586 832)</td>
<td>1967-88</td>
<td>16-37</td>
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<td>National register</td>
</tr>
<tr>
<td>Trondheim, Norway</td>
<td>Evensen et al., 2009</td>
<td>VLBW (37, 49%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1986-88</td>
<td>18</td>
<td>63 (70%)</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Sweden&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ericson &amp; Källén, 1998</td>
<td>VLBW men (260)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1973-75</td>
<td>19</td>
<td>Population</td>
<td>National register</td>
</tr>
<tr>
<td>South-East Sweden</td>
<td>Gäddlin et al., 2009</td>
<td>VLBW (77, 90%)</td>
<td>1987-88</td>
<td>20</td>
<td>69 (80%)</td>
<td>Prospective, regional</td>
</tr>
<tr>
<td>Sweden&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lindström et al., 2009</td>
<td>24 to 41 weeks (545 628, 95%)</td>
<td>1973-79</td>
<td>8-29</td>
<td>—</td>
<td>National register</td>
</tr>
<tr>
<td>Sweden&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ekeus et al., 2009</td>
<td>24 to 41 weeks men (119 664)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1973-76</td>
<td>18</td>
<td>—</td>
<td>National register</td>
</tr>
<tr>
<td>South-West Sweden</td>
<td>Hallin et al., 2010</td>
<td>~29 w (51, 78%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1985-86</td>
<td>18</td>
<td>54 (89%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Regional</td>
</tr>
<tr>
<td>Cleveland, USA</td>
<td>Hack et al., 2002</td>
<td>VLBW (242, 78%)</td>
<td>1977-79</td>
<td>20</td>
<td>233 (64%)</td>
<td>Hospital-based</td>
</tr>
</tbody>
</table>

<sup>a</sup> Individuals with major disability excluded; follow-up rate of eligible survivors 67%. <sup>b</sup> Includes those who attended mainstream schools; percentages refer to those from the childhood cohort followed up at age 20. <sup>c</sup> Percentages refer to those from the childhood cohort assessed at age 22. <sup>d</sup> Contacted at age 20, but study outcome assessed at age 16. <sup>e</sup> New controls included. <sup>f</sup> Varies according to outcome studied. <sup>g</sup>,<sup>h</sup> Overlapping cohorts. <sup>i</sup> Percentage of NICU survivors studied at age 18. <sup>j</sup> Military conscripts. <sup>k</sup> Percentages refer to preterms alive at age 10 and controls who participated in follow-up at age 10.
2.3.2 Neurodevelopmental outcomes

**Neurosensory impairment**

In the preterm follow-up literature, neurosensory impairment (NSI) usually refers to CP, severe visual or hearing deficit, or mental retardation. The rates in school-aged children are comparable to those reported in adulthood (Hack, 2009, review): CP rates among VLBW adults range from 5% to 8% (Ericson & Källén, 1998; Hack et al., 2002; Pesonen et al., 2008, Gäddlin et al., 2009), while the corresponding figure among ELBW adults is around 13% (Saigal et al., 2006). Blindness/severe visual impairment rates range from 2% to 13%, and deafness/severe hearing loss rates from 1% to 7% in ELBW/VLBW adults (Ericson & Källén, 1998; Hack et al., 2002; Lefebvre et al., 2005; Saigal et al., 2006b, 2007; Hille et al., 2007). These rates are, however, affected by loss to follow-up and the criteria used.

In VLBW adults, overall disability rates of 10% are reported (Hack et al., 2002). In ELBW adults the rates are higher; 12% and 27% according to two separate Canadian cohorts (Lefebvre et al., 2005; Saigal et al., 2006b). Upon a comprehensive neurological examination, Allin et al. (2006b) found more neurological abnormalities in very preterm young adults than in controls, although this study was limited by factors such as high attrition rate, lack of adjustment for confounders, and multiple comparisons. Disability rates are highest in those who were the most the most immature preterms, as illustrated by an overall disability rate of roughly one in four 1- to 10-year-old children born extremely preterm during the 1990s (Saigal & Doyle, 2008, review). Similarly, the risk for severe medical disability (including CP and mental retardation) in adulthood increased with decreasing gestational age in a large Norwegian register study spanning almost one million live births (Moster et al., 2008).

**Intelligence and executive functions**

It is well-established that in childhood, preterms as a group perform worse on intelligence quotient (IQ) tests than do their term-born peers, even when individuals with NSI are excluded (Korkman et al., 1996). According to a meta-analysis of case-control studies in school-aged children published between 1980 and 2001, the average difference between preterm and term-born groups was 11 IQ points, slightly less than one SD (Bhutta et al., 2002, meta-analysis). In a more recent meta-analysis of studies from the last decade, VLBW/very preterm children scored lower in tests of mathematics, reading, and spelling. The magnitudes of these decrements were 0.60, 0.48, and 0.76 SD respectively, which translates into 7 to 11 points (Aarnoudse-Moens et al., 2009, meta-analysis). Deficiencies in mathematics particularly seem to be a recurrent finding, for reasons poorly understood (Taylor et al., 2009, review).
Although catch-up occurs during childhood to some extent (Ment et al., 2003), the lower IQ scores persist into adulthood (Allin et al., 2008). Hack et al. (2002) reported a five-point lower IQ on average in VLBW adults, and a higher frequency of subnormal or borderline IQ. These findings persisted after exclusion of individuals with NSI. In a Swedish cohort of 119 664 military conscripts who took an intelligence test at ages 18 to 19, test scores decreased along a gradient of decreasing gestational age (Ekeus et al., 2010). Approximately one-third of the difference in test scores between preterms and term-borns was attributable to childhood SES, which underlines the importance of environmental factors when it comes to long-term outcomes of prematurity. A similar finding comes from the Dutch POPS Study (Weisglas-Kuperus et al., 2009), in which 562 VLBW/very preterm adults completed a computerized intelligence test; those with highest parental education scored 14 points higher than those with the lowest. This study also assessed the impact of early growth, and found that symmetrical rather than asymmetrical IUGR was a predictor of decreased intelligence in adulthood, and postnatal growth restriction exerted the strongest influence. Lefebvre et al. (2005) observed a one-SD (14 scores) decrease in IQ in ELBW adults as compared with controls, a difference that was, again, somewhat attenuated after controlling for parental SES. No catch-up in IQ from childhood was evident, nor any SGA vs. AGA difference. Notably, despite the lower average IQ score reported in most studies, the majority of VLBW/very preterm adults perform within the normal range (Hack et al., 2002; Nosarti et al., 2007). Only a few studies, mainly those examining moderately preterm adults, report a catch-up in IQ and a lack of any group difference between adult preterms and controls (Tideman, 2000; Dalziel et al., 2007).

Although a handful of studies highlight the importance of SES circumstances in relation to long-term outcomes of prematurity, SES indicators vary across studies with no agreement on the one most optimal (Daly et al., 2002; Lefebvre et al., 2005; Weisglas-Kuperus et al., 2009; Ekeus et al., 2010). SES can be measured in different ways (in terms of education, occupation, income), and at different time points (in childhood or adulthood, on single or multiple occasions). Cross-sectional SES estimates may be problematic, since they do not capture the dynamic nature of SES; for some, SES is not static but changes during their lifespan (Daly et al., 2002).

Deficits in executive functions have been reported in both preterm children (Mulder et al., 2009, meta-analysis) and VLBW/very preterm adults (Nosarti et al., 2007). Executive functions is an umbrella term referring to higher-order cognitive functions that maintain goal-directed behavior (including but not limited to working memory, initiation and inhibition of actions at appropriate times, set-shifting, abstract thinking, planning, and organization). Illustrating the clinical importance of executive functions, Mulder et al. (2010) found that in addition to full scale IQ, isolated deficits in specific areas of executive functions (verbal processing speed, working memory) also accounted for group differences in school attainment between very preterm children and term controls. Nosarti et al. reported impairments in several domains of executive functions (mental flexibility, response inhibition, visuomotor speed), in a group of high-functioning very preterm adults even after controlling for IQ (Nosarti et al., 2007).
School, educational, and occupational outcomes

A fairly robust finding in ex-preterms is poorer school outcomes in comparison with those of controls. Preterm children and adolescents leave school earlier (Ericson & Källén, 1998; Saigal et al., 2006b), and experience more grade repetition (Saigal et al., 2000; Hack et al., 2002; Farooqi et al., 2007); fewer graduate from high school or do so at a later age, although the vast majority do graduate (Hack et al., 2002; Lefebvre et al., 2005, Swamy et al., 2008). In one UK study, VLBW teens healthy enough to attend mainstream schools performed more poorly on a national examination (the general Certificate of Secondary Education) (Pharoah et al., 2003). All—teachers, parents and the children themselves—rate preterms as having lower school competencies (Grunau et al., 2004; Dahl et al., 2006; Mulder et al., 2010), and these children utilize more special educational resources (Saigal et al., 2000; Lefebvre et al., 2005; Farooqi et al., 2007; Mulder et al., 2010). In the current cohort, VLBW individuals free from NSI have also received special educational services more frequently and had marginally poorer high school grades, but they graduated from high school as frequently as did controls (Kajantie et al., 2008; Study II). However, not all studies show unfavorable results: As reported by Bjerager et al. (1995), poorer school outcomes occurred only among VLBW individuals with disabilities, and Saigal et al. (2006b) found similar rates of graduation from high school in ELBW teens, although some with NSI were included. In a prospective study of VLBW infants from satisfactory SES environments, similar rates of VLBW and controls young adults had graduated from upper secondary school (78% vs. 86%), or graduated from a theoretical program (23% vs. 30%) (non-significant, NSI included) (Gäddlin et al., 2009). In another study from the same country, adolescents born extremely preterm more often chose a practical program at upper secondary school than did their peers (50% vs. 26%) (Hallin et al., 2010).

After school age, fewer preterms than controls study at a university or obtain a university degree (Cooke, 2004; Saigal et al., 2006b), more obtain a vocational degree (Cooke, 2004), but most studies (Bjerager et al., 1995; Hack et al., 2002, Saigal et al., 2006b; Lindström et al., 2007; Gäddlin et al., 2009), although not all (Hille et al., 2007), report equal employment rates. Saigal et al. (2006b) found a higher proportion of ELBW adults who were neither employed nor at school, but this difference disappeared when adults with NSI were excluded. When employed, however, preterm adults free from major NSI were in less well-paid jobs and have lower salaries (Lindström et al., 2007; Moster et al., 2008; Mathiasen et al., 2009). A recent report from the McMaster cohort shows that the outcomes may differ by gender. When compared with controls, ELBW men aged 21 to 26 years reported lower educational attainment and lower weekly earnings, while ELBW women were less likely to be in school or to be employed (Goddeeris et al., 2010).

Brain imaging studies

Imaging studies have shed light on the long-term effects of prematurity on the developing brain. Several studies have reported on brain morphology pathologies among VLBW/very
preterm adolescents and adults, including ventricular dilatation, thinning of the corpus callosum and cortex, and aberrations in the distribution of gray and white matter, and reduced total and regional brain volumes (Stewart et al., 1999; Allin et al., 2004; Skranes et al., 2005; Nosarti et al., 2008; Ment et al., 2009; Nagy et al., 2010). More importantly, some of the brain pathologies observed have proven predictive of neurobehavioral impairments (Stewart et al., 1999; Nosarti et al., 2008). Skranes and colleagues (2007) used a diffusion tension imaging technique to study white matter trajectories, and found lower fractional anisotropy values in certain brain regions in VLBW adolescents than among controls. In the VLBW group, these lower values were associated with perceptual, cognitive, motor, or mental health impairments. Apart from the morphologic abnormalities, functional aberrations are reported as well. In a functional magnetic resonance image study, Lawrence et al. (2010) found altered neuronal activation in very preterm adults when compared with controls during a cognitive task, despite intact performance; this is suggestive of neuronal reorganization after early injury in the preterm brain.

2.3.3 Behavioral, social, and mental health outcomes

Mental health outcomes in childhood

A large body of research shows that children born preterm are at increased risk for mental health problems. Higher rates of internalizing problems such as anxiety, depressive symptoms, and withdrawn behavior are frequently reported (Botting et al., 1997; Elgen et al., 2002; Farooqi et al., 2007; Indredavik et al., 2010; Johnson et al., 2010). Inattention is extensively reported (Hille et al., 2001; Elgen et al., 2002; Mulder et al., 2009, meta-analysis; Indredavik et al., 2010; Johnson et al., 2010), and social and thought problems are more common than in controls as well (Botting et al., 1997; Hille et al., 2001, Elgen et al., 2002; Farooqi et al., 2007). The evidence for externalizing symptoms (such as hyperactive, aggressive, or delinquent behavior) is less straightforward. Some have found more externalizing symptoms in preterm children or adolescents (Bhutta et al., 2002 meta-analysis; Grunau et al., 2004; Indredavik et al., 2010), while others have not (Hille et al., 2001; Farooqi et al., 2007; Aarnoudse-Moens et al., 2009, meta-analysis; Johnson et al., 2010). As concluded by authors of the EPICURE study, who evaluated 11-year-old children born before 26 weeks in 1995 in the UK, their own and previous research points to an “extremely preterm phenotype” typified by inattention and by social and emotional problems (Johnson et al., 2010).

ADHD

The link between VLBW and ADHD in childhood is well-established, especially regarding inattention symptoms (Szatmari et al., 1993; Botting et al., 1997; Hille et al., 2001; Elgen et al., 2002; Saigal et al., 2003; Grunau et al., 2004; Indredavik et al., 2004; Farooqi et al., 2007; Aarnoudse-Moens et al., 2009, meta-analysis; Johnson et al., 2010). According to one meta-analysis, the risk
for ADHD in children born preterm is more than twofold (Bhutta et al., 2002 meta-analysis). It seems that the ADHD of preterm children differs from “common” ADHD, and a more “pure” form has been proposed (Szatmari et al., 1993). The ADHD in preterm children is less often associated with comorbid disorders, the gender distribution is more even, and the symptoms pertain mainly to inattention instead of hyperactivity (Szatmari et al., 1997; Elgen et al., 2002; Indredavik et al., 2004; Farooqi et al., 2007; Johnson et al., 2010). However, studies in adults have produced conflicting results, and whether the higher rates of ADHD persist into adulthood is far from written in stone. In the Cleveland cohort, VLBW adults themselves reported symptom scores and rates of ADHD on the ADHD Rating Scale for Adults similar to those of controls. According to parents’ reports, though, VLBW men showed more inattention, but this difference turned non-significant after adjusting for IQ, and after excluding those with NSI or those who were SGA (Hack et al., 2004). Dalziel et al. (2007) reported near-significantly less ADHD symptoms on the Brown Attention Deficit Disorder scale in moderately preterm adults with a mean gestational age of 34 weeks. In a recent Swedish study, adults born extremely preterm reported no more ADHD symptoms than did controls, when retrospectively assessing their own childhood symptoms using the Wender Utah Rating Scale (Hallin & Stjernqvist, 2010). In the Dutch POPS study, VLBW women reported no more above-borderline attention problems on the Young Adult Self Report when compared with population reference data, in contrast to their parents, who did report more inattention in their VLBW daughters (Hille et al., 2008). One reason for the conflicting results in adulthood, as opposed to the fairly uniform results of an increased ADHD risk in preterm children, may be a true decrease in symptoms over time. Attenuation of group differences between preterms and controls over time has been reported for other measures of psychopathology (Saigal et al., 2003; Cooke, 2004). Discrepancies between parental and self-reporting may be another explanation. Self-reporting is often used for adults, and studies using both parental and self-reporting show that parents of preterm young adults tend to report more mental health problems for their offspring than do the parents of controls, whereas the preterms themselves do not report more problems than do their control peers (Saigal et al., 2003; Hack et al., 2004, Dahl et al., 2006).

Other psychopathology

As is the case for ADHD, VLBW outcome studies extending into adulthood are sparse also regarding other mental health outcomes, and their results are not uniform. A Swedish register study revealed that rates of hospital admissions due to adult psychiatric disorders increased gradually with degree of prematurity, with higher ORs for organic/neuropsychiatric than for stress-related diagnoses (Lindström et al., 2009). A similar observation appeared in the Norwegian register study, showing that risk for disorders of psychological development, emotion, and behavior increased with degree of prematurity (Moster et al., 2008).

Moving to case-control studies, Cooke (2004) found no difference in self-reported anxiety, depression, or social activity between VLBW adults and controls. Neither did
Bjerager et al. (1995) observe any difference in the self-reported psychic health of VLBW adults and controls. In moderately preterm adults, Dalziel et al. (2007) found lower scores on the Beck Depression Inventory than for term-born controls. Equally promising for the preterm adults, Gäddlin et al. (2009) found no difference in self-reported mental health score on the Medical Outcomes Study, Short Form (SF-36) between VLBW and control adults, nor did they find any group differences on the Sense of Coherence questionnaire which measures ability to manage stressful situations and to maintain good health.

Not all results are in favor of the preterms, however. The parents of 16- to 19-year-olds with birth weight < 800 g and no major NSI reported more internalizing, externalizing, and total problems for their young adults than did the parents of controls (Grunau et al., 2004). Similarly, Hack et al. (2004) observed more symptoms of anxious and withdrawn behavior in VLBW women and more thought problems in VLBW men according to parental report, but according to self report, only more withdrawn behavior and internalizing problems in VLBW women. Parents of the POPS study participants reported scores higher than the reference values for their very preterm adults on almost all syndrome scales of the Achenbach Young Adult Behavior Checklist, and higher rates of above-borderline cutoff scores on several scales including internalizing problems. Their rates of psychopathology according to the very preterm adults themselves were no higher than reference values, except for withdrawn behavior in very preterm women (Hille et al., 2008). Walshe et al. (2008) are one of the few groups to have evaluated very preterm adults with a clinical interview (The Clinical Interview Schedule-Revised). They found higher rates of psychiatric diagnoses in very preterm adults, especially mood and anxiety disorders, than in controls. In the current cohort, VLBW adults reported less depression than did controls, although, importantly, this was confined only to the VLBW-AGA adults, whereas the VLBW-SGA adults reported more depressive symptoms, more diagnoses of depression, and more frequent use of antidepressants than did controls (Räikkönen et al., 2008). Thus, VLBW-SGA status, rather than VLBW status per se, was related to depression in adulthood. In a subsequent study, being born preterm, particularly if simultaneously SGA, elevated the risk for psychiatric hospitalizations in adolescent boys and adult men (Monfils Gustafsson et al., 2009). In one Australian study, VLBW adults assessed with a semi-structured clinical interview were at higher risk of psychopathology than were their normal birth-weight peers, and neonatal complications led to a further increase in risk (Westrupp et al., 2010, abstract).

At present, not enough evidence exists of an increased risk for schizophrenia or bipolar disorder in VLBW adults (Hack, 2009, review). Evidence for an increased risk for autism-spectrum disorder, in contrast, has emerged lately. For example, Indredavik et al. (2010) reported a higher mean score on the Autism Spectrum Screening Questionnaire in VLBW adolescents. Johnson et al (2010) found higher rates of autism spectrum disorder in ELBW children than in term controls by a structured psychiatric interview (8.0% vs. 0%). Moster et al. (2008) found an increasing risk for autism-spectrum disorders with decreasing gestational age in adults free from disability, although numbers were small. When it comes to eating disorders—another group of psychiatric disorder that occasionally have
been related to prematurity—the VLBW adults in our cohort reported less body size- and shape-related symptoms than did controls on the Eating Disorder Inventory-2 questionnaire, which potentially puts them at lower risk for eating disorders (Wehkalampi et al., 2010b).

**Risk-taking behavior**

Hack and co-workers were the first to show decreased risk-taking in VLBW adults compared with that of controls. VLBW adults used less alcohol and marijuana, had lower rates of sexual intercourse, pregnancy, and childbirth, fewer contacts with the police and less influence by delinquent peers, but they smoked equally often (Hack et al., 2002; 2007). Before that study, Bjerager et al. (1995) showed no difference in rates of alcohol and drug abuse in VLBW adults. Saigal et al. (2003) found less alcohol consumption in ELBW teens, and in the Liverpool study, VLBW adults had lower rates of alcohol and illicit drug use, but similar rates of sexual activity, police contact, and smoking (Cooke, 2004). In moderately preterm adults, smoking and illicit drug use was less common than in term borns, but alcohol use was similar (Dalziel et al., 2007). Our own results are analogous in demonstrating lower rates of smoking, drinking, illicit drug use, and sexual activity (Study I; Kajantie et al., 2008). In the Netherlands, VLBW/very preterm adults report less smoking, drinking, illicit drug use, and criminal activity, as compared with population data (Hille et al., 2008). Gäddlin et al. (2009) reported lower rates of alcohol use but similar rates of smoking in VLBW adults. Register studies from the Nordic countries report equal rates of criminal activity and drug-related hospital admission in preterm and term-born adults (Moster et al., 2008; Lindström et al., 2009).

These findings are consistent, and unexplainable by higher disability rates, since most studies exclude those with major impairments. Increased parental monitoring and resilience in the preterm individuals have been suggested as explanations (Hack et al., 2002; McCormick & Richardson, 2002; Hack et al., 2007, Pesonen et al., 2008). In our cohort, parents of VLBW adults rated their own parenting as more supportive than did the parents of controls, when all were recollecting parenting styles retrospectively. In addition, the VLBW women, compared with control women, rated their mothers as more protective and authoritarian (Pyhälä et al., 2010). Differences in personality may also be a cause. We and others have shown that preterm adults are more behaviorally inhibited, cautious, dutiful, shy, and risk averse, as well as less excitement-seeking and less open to new experience (Allin et al., 2006a; Pesonen et al., 2008; Schmidt et al., 2008; Pyhälä et al., 2009b).

**Health-related quality of life**

In attempts to evaluate outcomes more comprehensively, quality of life research has emerged as a complement to study of frank disease rates. Generally, these studies tell us that in childhood, parents report poorer physical, emotional, and social functioning of their
preterm children. In adolescence, differences are still discernible, although parental reports tend to provide a more pessimistic picture than do reports by the teens themselves (Indredavik et al., 2005; Zwicker & Harris, 2008, review). In adulthood, differences in health-related quality of life between preterms and controls have been attenuated, despite the higher chronic disease rates in preterms. Preterm adults, particularly those free from NSI, report a subjective health-related quality of life similar to that of controls, except for and in spite of impaired physical abilities (Bjerager et al., 1995; Dinesen et al., 2001; Cooke, 2004; Saigal et al., 2006a, 2007; Dalziel et al., 2007; Hack et al., 2007; Gäddlin et al., 2009). One study compared VLBW-SGA and VLBW-AGA adults, and found no difference in self-perceived physical or mental health score on the Medical Outcomes Study, Short Form (Gäddlin et al., 2009). The decrease in group differences over time may represent true catch-up, recalibration, or denial (Saigal et al., 2003), or a tendency among preterms to give more socially acceptable answers (Allin et al., 2006a; Schmidt et al., 2008), or may result from discrepancies between parent- and child reports. In a study on ELBW teens free from major disabilities, the ELBW rated themselves as less confident in areas usually important for teens (athletics, school achievement, romantic and job competencies), although interestingly, they also rated these areas as being of less social importance to them (Grunau et al., 2004). When it comes to quality of life research, attrition is expected to be particularly important, since non-responder preterms generally have higher NSI rates.

**Family outcomes and reproductive health**

Several studies show that ex-preterm young adults more often live at home with their parents (Cooke, 2004; Lindström et al., 2007; Kajantie et al. 2008). In one study, this was the case only among men (Saigal et al., 2006b), and in another, only among preterms with disabilities (Gäddlin et al., 2009). Preterm young adults are also at lower likelihood—or at least have a slower tempo—of finding a life partner, cohabiting with an intimate partner, getting married, and establishing a family (Lindström et al., 2007; Kajantie et al., 2008; Moster et al., 2008). Some of these studies excluded people with a major disability (Hack et al., 2002; Kajantie et al., 2008; Moster et al., 2008), and two studies report a gradient between gestational age and marriage (Lindström et al., 2007; Moster et al., 2008). Phillips et al. (2001) studied adult men from two separate cohorts and observed a relationship between small body size at birth and decreased likelihood of marrying, although it is not known whether the low birth weight men were born preterm or not. Moreover, rates of sexual activity (Hack et al., 2002; Kajantie et al., 2008; Hille et al., 2008) and reproduction (Hack et al., 2002; Ekholm et al., 2005; Moster et al., 2008; Swamy et al., 2008; Mathiasen et al., 2009) are lower than among term-born peers. Contradictory results exist as well: some found similar rates of marriage (Ekholm et al., 2005; Saigal et al., 2006), sexual activity (Cooke, 2004), parenthood (Saigal et al., 2006), cohabitation or living in the parental home (Gäddlin et al., 2009).

In a Norwegian register study of 0.58 million participants born in 1967-1976 and followed through 2004, absolute reproduction rates were 38.6% and 59.2% for men and women born at 28-32 weeks, versus 50.4% and 68.4% for term-borns. Additionally, the children
subsequently born to preterm women were at increased risk for prematurity as well as fetal and infant mortality, which underlines the far-reaching consequences of preterm birth. The authors discussed that psychosocial and economic factors, in addition to biological ones, may play a role in the diminished reproduction among preterms (Swamy et al., 2008).

2.3.4 Somatic health outcomes

Growth

In childhood, preterm survivors as a group are shorter and lighter than average. These differences are still discernible in adulthood, although some catch-up growth takes place and most achieve a body size within the expected range (Hack et al., 2003; Doyle et al., 2004, Saigal et al., 2006c). In the current cohort, VLBW adults were 5 to 6 cm shorter than their controls, which is by and large comparable with group differences reported from other cohorts with objectively measured height (Hack et al., 2003; Saigal et al., 2006c; Doyle & Anderson, 2010, review). The pubertal growth spurt of those born at VLBW also occurred at an earlier age (Wehkalampi et al., 2010a). Furthermore, VLBW adults in our study were lighter, and among men, their BMI was lower (Hovi et al., 2007). Saigal et al. (2006c) reported a 7-kg lower weight and similar BMI in ELBW adults as compared with controls. Doyle et al. (2004) compared ELBW adults with reference values and found no difference in weight or BMI. Hack et al. (2003) reported 11 kg lower weight and 2.6 units lower BMI for VLBW men than for controls, but found no corresponding group difference in women. Additionally, VLBW-SGA status was predictive of poorer growth in men. Doyle et al. (2004) measured parental heights and concluded that ELBW adults had reached a height consistent with that of their parents. In contrast to this, ELBW adults from the McMaster cohort lagged behind their mid-parental height and weight (Saigal et al., 2006c). The observations of shorter stature and lower weight in VLBW adults are further confirmed by studies confined only to men (Ericson & Källén, 1998), and to self-reports (Cooke, 2004; Gäddlin et al., 2009). Apart from BMI, studies indicate alterations in body composition in preterm adults. In our cohort, VLBW adults had a lower lean body mass but similar percentages of body fat as measured by dual-energy x-ray absorptiometry (Hovi et al., 2007; 2009). In the POPS Study, the very preterm had, on average, lower BMI but larger waist circumference, waist-to-hip ratio, and skinfold thickness than Dutch population means (Euser et al., 2005). Evensen et al. (2009) compared skinfold thickness and waist circumference across VLBW-SGA and VLBW-AGA adults, and found signs of a less favorable fat distribution in those born SGA. Similarly, ELBW adults from the McMaster cohort had a lower fat-free mass index than did controls (Atkinson et al., 2005, abstract).

Childhood studies point out subnormal bone mass in preterms compared with term-born peers (Zamora et al., 2001). These findings extend into adulthood as well: VLBW adults in our cohort had 0.51 units lower bone mineral density Z score in the lumbar spine, and 0.56 units lower in the femoral neck, as compared with controls. Furthermore, they were
twice as likely to have a lumbar spine Z score $\leq -1.0$ (Hovi et al., 2009). These results were not fully explained by smaller body size, as has been reported in some (Weiler et al., 2002), but not all (Zamora et al., 2001), previous studies.

**Glucose metabolism**

Prematurity is related to insulin resistance both in childhood and adulthood. Hofman et al. (2004) performed an intravenous glucose-tolerance test in 7-year-old very preterm children and controls and found reduced insulin sensitivity in the preterm group, irrespective of AGA/SGA status. In our cohort, VLBW adults had increased 2-hour glucose concentration, fasting insulin, and 2-hour insulin concentration in an oral glucose tolerance test (Hovi et al., 2007). Additionally, their insulin resistance index as determined by homeostatic model assessment (HOMA-IR) was higher. No significant difference emerged between VLBW-AGA and VLBW-SGA adults. In line with this, Finken et al. (2006) studied fasting glucose, insulin, C-peptide levels, and HOMA-IR in relation to growth patterns in VLBW/very preterm adults, and found relative birth weight to be unrelated to insulin resistance. However, adult fat accumulation predicted increased insulin resistance, an effect amplified in preterms with low relative birth weights. In a subsample from the same cohort, insulin sensitivity was evaluated by the hyperinsulinemic euglycemic clamp technique, replicating the observations of lower insulin sensitivity in VLBW/very preterm adults and adverse effects of catch-up growth on insulin sensitivity (Rotteveel et al., 2008).

**Cardiovascular health**

Elevated blood pressure in preterm survivors has been reported by many. In adolescents and young adults, the magnitude of the difference in systolic blood pressure between preterms and controls is 5 to 6 mmHg (range: 0 to 15) (Doyle & Anderson, 2010; Norman, 2010, reviews). Some authors have measured both clinical and ambulatory blood pressure, typically finding smaller group differences with ambulatory recordings. For example, Doyle et al. (2003) found higher systolic (8.6 mmHg) and diastolic (4.3 mmHg) clinical blood pressure in VLBW adults than in controls, although from ambulatory recordings, only higher mean systolic blood pressure (4.7 mmHg). No relationship between relative birth weight and blood pressure appeared in the VLBW group. Kistner et al. (2005), in a small sample of VLBW women, found higher systolic clinical and daily ambulatory blood pressure but no difference in diastolic blood pressure. In the current cohort, VLBW adults had higher systolic (4.6 mmHg) and diastolic (4.0 mmHg) clinical blood pressure, and in ambulatory recordings, higher systolic (2.4 mmHg) but not diastolic blood pressure (adjusted for gender, age, BMI). Moreover, the VLBW group had four-fold odds for hypertension (sex- and age-adjusted), with no SGA/AGA difference (Hovi et al., 2010). Interestingly, in the same cohort, Pyhälä et al. (2009a) found a higher blood pressure response to stress in the VLBW group. In the Cleveland cohort, systolic but not diastolic clinical blood pressure was elevated among VLBW adults, again unrelated to SGA/AGA
status (Hack et al., 2005). A Swedish study on military conscripts (n = 329,495) showed higher blood pressure with increasing degree of immaturity at birth: One gestational week less corresponded to 0.31 mmHg higher systolic blood pressure. SGA status was related to higher blood pressure, but only in preterms born after 32 weeks (Johansson et al., 2005).

Cardiovascular risk factors other than blood pressure have also been investigated in VLBW adults, although to a lesser extent. Evensen et al. (2009) measured flow-mediated dilatation of the brachial artery in VLBW adults, and found no evidence for endothelial dysfunction. Likewise, Hovi et al. (in press) found no impairment in flow-mediated dilatation in the brachial artery of VLBW adults in the current cohort, but when their smaller lumen size was accounted for, their carotid intima media was 0.5 percentage points thicker. Serum lipid levels in VLBW and control groups were similar (Hovi et al., 2007).

Respiratory health

During early childhood, the most common cause for rehospitalization in preterm survivors is respiratory illness (Underwood et al., 2007). In adults born VLBW/very preterm, higher rates of asthma are reported by some (Halvorsen et al., 2004; Vrijlandt et al., 2005; Saigal et al., 2007; Gåddlin et al., 2009), but not all (Northway et al., 1990; Doyle et al., 2006; Evensen et al., 2009). As a group, VLBW/very preterm adults have poorer values on spirometry variables reflecting airflow or obstruction, although most produce values within normal limits (Halvorsen et al., 2004; Doyle et al., 2006; Vrijlandt et al., 2006 Evensen et al., 2009). Particularly those preterms who smoke or were diagnosed with BPD are at a disadvantage (Northway et al., 1990; Halvorsen et al., 2004; Doyle et al., 2006). Evensen et al. (2009) observed lower carbon monoxide diffusion capacity in VLBW adults than in controls, as well as lower maximal oxygen uptake (VO$_{2\max}$) during exercise. Vrijlandt et al. (2006) also found lower diffusion capacity in VLBW/very preterm adults, but no difference in VO$_{2\max}$. Halvorsen et al. (2004) found increased metacholine bronchial hyperresponsiveness in ELBW adolescents compared with levels in controls, and in the same cohort, structural abnormalities on pulmonary high-resolution CT (HRCT) scans appeared in as much as 86% of those ELBW (Aukland et al., 2009). The HRCT abnormalities were predicted by a longer duration of oxygen treatment in the neonatal period, and correlated with lung-function impairments in adolescence.

Studies on atopy show either similar or lower rates of atopy in preterm adolescents or adults as compared with control rates (Northway et al., 1990; Halvorsen et al., 2004; Vrijlandt et al., 2006; Siltanen et al., 2010, in press).
Physical activity

Given the higher level of risk factors for cardiovascular disease in preterm adults (Hovi et al., 2007; Norman, 2010), observations on lower physical activity in this population are highly relevant, as this offers an opportunity for intervention. Rogers et al. (2005) studied ELBW teens free from NSI and found lower aerobic capacity, muscle strength, flexibility, sports participation, and poorer coordination than in controls. Even so, these ELBW teens were as satisfied as controls with their physical fitness. In the McMaster cohort, parents rated their ELBW teens lower in sport competencies (Saigal et al., 2003), and at 23 years of age, the ELBW adults had weaker hand-grip strength, reported less sports participation, lower physical self-efficacy, self-confidence, and perceived physical ability (Saigal et al., 2007). In parallel, Ericson & Källén (1998) noted reduced muscular strength and lower working capacity in 19-year-old VLBW men. VLBW adults in the Cleveland cohort reported poorer scores on the physical activity subscale of the CHIP-AE questionnaire (Hack et al., 2007). In our cohort, VLBW adults exercised less during their leisure time in terms of self-reported lower exercise frequency, intensity, and average session duration. Within the VLBW group, no SGA/AGA difference existed (Kajantie et al., 2010). Our findings were not explained by the higher BPD rates in the VLBW group, in accordance with the POPS study, where VLBW/very preterm adults had decreased exercise capacity on a bicycle ergometer test, unexplained by higher BPD rates (Vrijlandt et al., 2006). In that study, VLBW/very preterm adults also reported exercising less. Interestingly, in a meta-analysis spanning 13 Nordic cohorts, a U-shaped association between birth weight and leisure time physical activity was noted, implying that not only very low but also very high birth weight reduces the odds for engaging in leisure time physical activity (Andersen et al., 2009, meta-analysis).

2.3.5 Sleep outcomes

In school-aged children and adults born preterm, we know little about sleep. In a longitudinal, prospective study by Iglowstein et al. (2006), children born preterm or very preterm did not differ from term-born controls in regard to sleep duration, bed sharing, night wakings, bedtime resistance, or sleep-onset difficulties during their first 10 years of life according to parental reports. Natale et al. (2005) studied circadian typology in 13-year-olds born preterm (mean gestational age 34.8 weeks) by use of two questionnaires (Junior Composite Scale and Junior Morningness-Eveningness Questionnaire), and found a greater morningness propensity in preterms than in controls.

Sleep-disordered breathing (SDB, see paragraph 2.5.3 below) was investigated in a large sample of 8- to 11-year-old children by Rosen et al. (2003), who by in-home overnight cardiorespiratory monitoring observed a three- to five-fold prevalence of SDB in preterm children as compared with that of their term-born peers. The preterms had higher rates of prior tonsillectomy or adenoidectomy or both (13% vs. 3%), as well as higher rates of parental-reported snoring (21% vs. 14%). We extended these results into
adulthood, and, when controlling for confounding, showed a more than two-fold higher risk for chronic snoring in VLBW adults than in controls (Study IV). The crude prevalences of chronic snoring in our study, by the same criteria as in the Rosen group, was 15.8% in the VLBW and 13.6% in the control group, although this unadjusted difference was not statistically significant. In a subsequent study using polysomnography-defined SDB in school-aged children, these observations of an increased risk for SDB in preterm infants were replicable (Calhoun et al., 2010).

2.3.6 Summary of adult outcomes

To summarize, most VLBW adults do well, live comparatively normal lives, with perceived health-related quality of life similar to that of their term-born peers despite the fact that on a group level, VLBW is accompanied by various health sequelae.

2.4 ADHD

Epidemiology and diagnosis

Attention-deficit hyperactivity disorder (ADHD) is among the most common neurobehavioral disorders in children, characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity. The childhood prevalence worldwide is 5 to 10% (Polanczyk et al., 2007, and Skounti et al., 2007, systematic reviews; Merikangas et al., 2010). Although the symptoms decline with age, the course of ADHD is chronic; more than half the patients re-evaluated in young adulthood continue to have symptoms and to meet subthreshold or full diagnostic criteria (Biederman et al., 2006).

The diagnosis is clinical, in the absence of a specific diagnostic test. The evaluation includes in-depth history-taking, clinical examination, and an interview to rule out other causes and recognize contributing factors. Observer-ratings come from multiple sources, e.g. the child, parents, teachers, and other caregivers when it comes to pediatric patients, or the adult and spouse for adult patients. Behavior-rating scales are valuable, albeit not alone sufficient for diagnosis. The commonly used DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) include developmentally inappropriate symptoms for at least 6 months, not secondary to another disorder, and present in more than one setting and causing clinically significant impairment with onset before the age of 7. At least six of nine symptoms of inattention, or hyperactivity/impulsivity, or both, must be present. Three ADHD subtypes are identifiable: mainly inattentive, mainly hyperactive-impulsive, or combined (American Psychiatric Association, 1994). The ICD-10 (International Classification of Disease, 10th Edition) criteria for hyperkinetic disorder are somewhat
more stringent, requiring for example symptoms from both groups (inattention, hyperactive/impulsive).

The DSM-IV diagnostic criteria were originally developed for children, which needs to be considered when evaluating adults (American Academy of Pediatrics, 2000; Kliegman et al., 2007). To improve the diagnosis of adult ADHD, questionnaires designed for adults exist, as well. The role of self-rating questionnaires is considerably greater in adult than in pediatric populations, since in adults, the often self-referred patient herself is the main source of information, and observer-ratings are more scarce. Consequently, the clinician has to trust the patient’s subjective experience to a greater extent (De Quiros & Kinsbourne, 2001; Magnússon et al., 2006).

Clinical manifestations

ADHD manifests as long-lasting and pervasive distractibility, restlessness, and difficulties in sustaining attention and in inhibiting impulses. It is often associated with impairments in executive functions, which also have been proposed as endophenotypes for the disorder (Gau & Shang, 2010). The endophenotype concept refers to measurable elements located along the causal pathway between genotype and the clinical phenotype/disease. In other words, an endophenotype is a marker of a certain genotype that may lead to clinically overt disease (Gottesman & Gould, 2003, review). Executive functions, in turn, refer to higher-order cognitive functions that maintain goal-directed behavior (including but not limited to working memory, initiation and inhibition of actions at appropriate times, set-shifting, abstract thinking, planning, and organization). ADHD is more prevalent in males, especially in child populations (Merikangas et al., 2010). Gender differences exist in the clinical picture, with females being more likely to present with symptoms of inattention, possibly leading to under-identification of women with ADHD (Biederman et al., 2002b). The disorder is linked to substantial functional impairment and morbidity such as academic underachievement, social problems, sleep disorders, criminality, psychiatric comorbidity including mood-, anxiety-, antisocial-, and substance-use disorders, to mention a few (Biederman et al., 2006; 2010; Surman et al., 2009; Paavonen et al., 2009; Langley et al., 2010). Due to its broad impact on the patient, families, and society at large, the economic burden of ADHD is considerable (Matza et al., 2005, review).

Etiology, pathophysiology, and treatment

Based on twin studies, the heritability of ADHD is as high as 76% (Faraone et al., 2005, review). Its underlying genetic architecture is, however, multifaceted, and the contribution of individual risk genes is estimated to be small (Faraone et al., 2005; Franke et al., 2009, reviews). Numerous environmental risk factors occurring mostly early in development are, for example: ADHD associated with prenatal tobacco and alcohol exposure, toxins such as lead, psychosocial adversity, prematurity, low birth weight, and small body size at birth.
even within the term-born range (Bhutta et al., 2002 meta-analysis; Biederman et al., 2002a; Mick et al., 2002a, 2002b; Lahti et al., 2006; Hultman et al., 2007; Froehlich et al., 2009; Rodriguez, 2009). Yet conflicting results are also reported (Rodriguez et al., 2009), and future studies investigating the interaction between various environmental factors and genes may shed light on the background mechanisms of the disorder.

The pathophysiology of ADHD is still under debate. Functional neuroimaging studies support suggestions that dysfunction in frontostriatal neuronal circuits plays a role (Dickstein et al., 2006, meta-analysis). The dopamine hypothesis has arisen from the effectiveness in the treatment of ADHD of psychostimulants, which act through catecholaminergic pathways. Data on alterations in dopamine-rich brain regions among ADHD patients, as well as evidence from animal studies showing a therapeutic effect of psychostimulants on hyperactive dopamine transporter knock-out mice (Gainetdinov et al., 1999), corroborate this hypothesis. Further support is provided by genetic studies showing associations between dopamine receptor genes and ADHD (Faraone et al., 2005, review).

Treatment of ADHD is composed of medication, mainly psychostimulants such as methylphenidate, and individualized psychosocial and behavioral support for patients and families (Kliegman et al., 2007).

For a review of ADHD in adults born preterm, see section 2.3.3.

2.5 Sleep

2.5.1. Normal human sleep – an introduction

Sleep can be defined from a neurobehavioral point of view as a “reversible state of perceptual disengagement from and unresponsiveness to the environment” (Kryger et al., 2005). Sleep is nowadays acknowledged as an active brain process, not merely a passive state resulting from diminished wakefulness. According to the two-process model of sleep regulation proposed by Borbély, the timing and propensity of sleep is regulated by 1) a homeostatic sleep pressure component that builds up during wakefulness and diminishes during sleep (process S), and 2) an independent circadian timing system (process C) (Borbély, 1982). In another model of sleep regulation, Winfree’s three-oscillator model, more emphasis is on the circadian pacemaker, considered to underlie sleep-wake cycles (Kawato et al., 1982).

Sleep architecture is conventionally defined by three fundamental physiological parameters: brain activity waves (EEG; electroencephalogram), eye movements, and muscle tone (Rechtsaffen & Kales, 1968). The two principal sleep states are non-rapid eye movement (non-REM) and REM, which alternate during sleep in a cyclic fashion. Non-
REM is characterized by a synchronous EEG pattern including waveforms such as sleep spindles, K-complexes, and high-voltage slow-waves, and is divided into four stages (S1-S4) according to the waveforms. S1 represents light sleep, and when moving from S1 to S4, a gradual increase in high-voltage slow wave activity and sleep depth takes place (S3 and S4 are often called deep sleep or slow-wave sleep; SWS). REM sleep, on the other hand, is characterized by a highly activated and desynchronized EEG, muscle atonia, and sudden eruptions of eye movements. The normal sleep pattern in healthy young adults starts with non-REM S1 sleep, progresses through S2 to S4, and eventually enters REM sleep. Such a cycle lasts for approximately 90 minutes, and is repeated through the night. In healthy young adults, REM sleep comprises 20% to 25% of sleep and dominates during the last third of the night, whereas SWS dominates during the first third of the night (Ohayon et al., 2004, meta-analysis; Kryger et al., 2005).

Age affects sleep patterns markedly. In neonates, the sleep architecture in general is immature. The two principal sleep states are termed active sleep and quiet sleep (corresponding to REM and non-REM), and the proportion of sleep that cannot be classified as either of these is called indeterminate sleep. In preterm infants, sleep is characterized by a large proportion of indeterminate sleep (Lehtonen & Martin, 2004, review). Newborn infants usually enter sleep through active sleep, which comprises 50% of their total sleep time; the cycle is shorter (50 minutes) and their sleep evenly distributed throughout day and night (de Weerd & van den Bossche, 2003, review). As the central nervous system (CNS) matures, the sleep pattern changes. By the age of 4 months, SWS is discernible, and a day-night pattern becomes established. By 6 months, the amount of non-REM sleep has increased at the expense of REM sleep, which now accounts for only 30% of total sleep, indeterminate sleep has disappeared, and sleep is no longer entered through REM. Total sleep time falls with increasing age, from about 16 to 17 hours in newborns to 14 hours in 6-month-olds, 10 hours in 10-year-olds, and 7 to 8 hours in adults. (Iglowstein et al., 2003; de Weerd & van den Bossche, 2003, review; Ednick et al., 2009, review). The inter-individual variance is considerable, though. For instance in the study by Iglowstein et al. (2003), sleep times in 6-month-olds ranged from 10.4 to 18.1 hours (for 96% of all children studied). Sleep during early life is thought to play an important role in development of the CNS, but causality is difficult to prove (Mirmiran et al., 2003; Ednick et al., 2009, reviews).

The function of sleep—a key question in sleep research—is a much debated issue. The synaptic homestasis hypothesis proposed by Tononi & Cirelli (2003) is an interesting hypothesis to consider. It postulates that during wakefulness, when new synapses are formed, a net increase occurs in synaptic strength in several brain circuits. As a result, there also occurs an increase in energy consumption, space requirements, and cellular stress, as well as saturation of learning capacity. To renormalize cellular homeostasis and maintain only important synapses, a synaptic downscaling during SWS takes place.
2.5.2. How to measure sleep

The golden standard for objectively evaluating sleep is polysomnography (PSG), an electrophysiological technique that generates a multitude of sleep variables and, importantly, allows for separation of REM and non-REM sleep and staging of non-REM into S1-S4. PSG is usually performed in laboratory settings, and its chief components are EEG, electrooculograms, and electromyograms, supplemented with a varying number of additional measures such as electrocardiography and breathing monitors, depending on the purpose of the evaluation (Kryger et al., 2005). PSG is a prerequisite for proper diagnosis of many sleep disorders, including obstructive sleep apnea syndrome (OSAS), and is useful in evaluating treatment responses (Epstein et al., 2009, American Academy of Sleep Medicine guidelines). Yet, despite being presently the best method for evaluating sleep, PSG has disadvantages as well. It is a labored and costly procedure that involves risk for sampling bias, since a night spent in a sleep laboratory may not be representative of an average night at home. A manual scoring procedure means subjective evaluation of sleep stages, which adds a potential source of error: When the same PSG recording is scored by several evaluators, the concordance of the evaluation is on the order of 80%. Nowadays manual scoring procedures are often replaced with automatic scoring software.

When PSG is not feasible (e.g. when sleep patterns should be assessed longitudinally or in a larger sample), methods like the static charge-sensitive bed (SCSB) (Alihanka & Vahtoranta, 1979) or actigraphy are good substitutes for generating sleep estimates. The SCSB is a special kind of mattress that without any electrodes attached to the subject records body movements, breathing patterns, and heartbeat by registering the static charges formed when the subject moves in bed. An actigraph is a wristwatch-like accelerometer worn around the wrist, ankle or waist that distinguishes sleep from wakefulness by recording body movements per time unit. It is non-invasive and objective, and considered a valid and reliable method for determining sleep patterns in population studies: in infants, children, and adults (Morgenthaler et al., Standards of Practice Committee, American Academy of Sleep Medicine, 2007). In a systematic review of studies validating actigraphy against polysomnography, van de Water found that the overall agreement rate in healthy adult populations was 72.1% to 96.5%, the sensitivity (ability to detect sleep when PSG scores it as sleep) 86.5% to 98.7%, and the specificity (ability to detect wakening) 27.7% to 67.1%. Correlation coefficients for individual sleep variables were as follows: sleep onset latency ($r = 0.64-0.82$), total sleep time ($r = 0.43-0.97$), wake after sleep onset ($r = 0.36-0.39$), and sleep efficiency ($r = 0.39-0.91$). Agreement rates are influenced by the study population, device, and the scoring algorithm and sensitivity threshold, as well as the sleep variable of interest. As concluded by van de Water, its fairly low specificity is a weakness, and actigraphy tends to overestimate sleep especially in patients with low sleep efficiency, in whom quiet wakefulness may be falsely scored as sleep. Still, agreement rates for healthy adults and sleep-disordered breathing patients are high (van de Water et al., 2010, systematic review). However, different stages of sleep (REM vs. non-REM sleep) cannot be assessed with actigraphy. The minimum number of recorded nights needed is still a matter of debate. Although a minimum of three consecutive nights was recommended in 2003, recent reports suggest three is insufficient (Littner et al., Standards of Practice Committee of the American Academy of Sleep Medicine, 2003; van de Water et al., 2010, systematic review).
For subjective evaluation of sleep, clinical interviews, retrospective questionnaires, and sleep diaries and logs are useful. A variety of questionnaires and logs exist, some validated and published, others custom-made and unvalidated (Kryger et al., 2005). For evaluation of circadian preference (or chronotype, explained below in paragraph 2.5.4), the morningness-eveningness questionnaire (MEQ) is the most widely used (Horne & Östberg, 1976; Kryger et al., 2005).

2.5.3. Sleep, health, and well-being

Poor sleep is closely related to mental functions such as learning, memory, cognition, and mood and anxiety disorders (Kryger et al., 2005; Klockars & Porkka-Heiskanen, 2009; Palagini & Rosenlicht, 2010, review). Self-reported sleep duration (both short and long) is linked with decreased cognitive capacity (Kronholm et al., 2009). In a questionnaire-based study in adults, poor sleep quality was predictive of life dissatisfaction 6 years later (Paunio et al., 2009). ADHD and sleep disorders are often comorbid conditions. Those diagnosed with ADHD frequently report sleeping problems (Surman et al., 2009; Van Veen et al., 2010); conversely, poor sleep may manifest as a behavioral symptom of ADHD (Paavonen et al., 2009).

From a public health perspective, the link between poor sleep and accidents is of importance (Léger & Bayon, 2010, review). Poor sleep is also related to adverse somatic sequelae, as exemplified by the U-shaped relationship between sleep duration and mortality (Cappuccio et al., 2010, meta-analysis). This link is, however, merely associational and does not allow for conclusions about causality. Poor sleep has effects on cardiovascular health, endocrine and metabolic functions, and immunity (Kryger et al., 2005): To mention some examples, objectively measured sleep efficiency is associated with elevated blood pressure in healthy adolescents (Javaheri et al., 2008), and both epidemiological and laboratory studies show that poor sleep elevates the risk for type 2 diabetes and obesity (reviewed by Van Cauter in Klockars & Porkka-Heiskanen, 2009). In an experimental setting, poor sleep has led to increased susceptibility to the common cold (Cohen et al., 2009). Finally, epidemiological evidence exists for the role of poor sleep in cancer development (Thompson et al., 2010).

Sleep-disordered breathing

Of the many sleep disorders, insomnia is the most prevalent (Léger & Bayon, 2010, review). However, only sleep-disordered breathing (SDB) will be discussed here since it was the only disorder that we assessed in the present work (Study IV). SDB refers to abnormal breathing during sleep, characterized by episodes of upper airway obstruction (apneas or hypopneas) often associated with hypoxemia and disrupted sleep (Arens & Marcus, 2004, review). It is a spectrum of disorders, including but not limited to habitual snoring, obstructive sleep apnea syndrome (OSAS), and upper airway resistance syndrome.
Whereas intermittent snoring represents the mildest form of SDB, OSAS (often defined as an apnea-hypopnea index ≥ 10 in the presence of symptoms) is located at the more severe end of the spectrum (Kryger et al., 2005). The clinical importance of SDB is demonstrated by its associated morbidity, such as cardiovascular, cognitive, and mood sequelae (Nieto et al., 2000; Beebe et al., 2003, meta-analysis; Aronen et al., 2009).

SDB is a common sleep disorder, present at all ages. Prevalence estimates for OSAS range from 2% in childhood to 4% to 9% in adulthood (Arens & Marcus, 2004, review). Habitual snoring is clearly more prevalent, although estimates vary markedly. Known risk factors for SDB include obesity, large neck circumference, male gender, small upper airways, alterations in craniofacial morphology, and, particularly in children, adenotonsillar hypertrophy (Arens & Marcus, 2004, review; Kryger et al. 2005). Anatomical obstruction and abnormal neuromuscular tone (partially centrally regulated) of the upper airways are suggested as underlying mechanisms, although much concerning its pathophysiology is yet to be elucidated. The main treatment regimens in childhood are adenotonsillectomy, and in adulthood, CPAP (continuous positive airway pressure), surgery, weight reduction, and smoking cessation (Arens & Marcus, 2004, review).

2.5.4. Circadian rhythms and chronotype

Circadian rhythms refer to endogenously generated oscillating processes in the physiology and behavior of an organism, with a cycle of approximately 24 hours. At cellular level, these rhythms are generated through delicate transcription-translation feedback loops of clock genes. Circadian rhythms are highly conserved through evolution and confer a survival advantage on the organism, by making it possible to adjust physiology and behavior to the most appropriate time of day (Panda et al., 2002; Green et al., 2008, reviews). They are important in determining, for instance, sleep-wake patterns, food intake, alertness, and hormone secretion. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, is the principal pacemaker of the human brain and orchestrates rhythmicity in cells via humoral and neural output. The SCN is entrained by environmental cues, of which light is the most important time-keeper (zeitgeber) (Kryger et al., 2005). Both experimental and epidemiological research point out the importance of circadian rhythms and clock genes for health. Sheer and co-workers (2009) showed that experimentally induced circadian misalignment simulating that of shift work was linked to adverse cardiometabolic sequelae, including unfavorable changes in leptin, glucose, cortisol, mean arterial pressure, and sleep efficiency. In a meta-analysis, night shift work was associated in women with a 48% increased risk for breast cancer (Megdal et al., 2005). Additionally, polymorphisms in circadian clock genes are associated with clinical disease such as mood disorders (Partonen et al., 2007; Utge et al., 2010) and hypertension (Woon et al., 2007). Recently, clock gene evidence has emerged from genome-wide association studies aimed at identifying type 2 diabetes risk genes (Dupuis et al., 2010, meta-analysis), which
parallels knockout mouse experiments showing that inactivation of clock genes in pancreatic islets causes diabetes (Marcheva et al., 2010). Further studies in mice have established an intimate relationship between clock genes and metabolic and prothrombotic pathways (Hatanaka et al., 2010; Somanath et al., 2011).

**Chronotype** (also designated circadian typology, diurnal preference, or morningness-eveningness) represents one behavioral consequence of the circadian pacemaker, and can be considered a proxy for the circadian phase. Chronotype refers to interindividual time preferences for going to bed and waking up, and for performing cognitive and physical activities, in other words, the individual “feeling best” rhythm. It corresponds with physiological markers of the circadian rhythm including core body temperature, heart rate, and particularly, melatonin secretion (Duffy et al., 2001 Griefahn et al., 2002). Chronotype is considered to have a genetic basis, as indicated by twin studies that report a heritability of almost 50% (Vink et al., 2001; Koskenvuo et al., 2007). It is a continuum showing a near-Gaussian distribution, with people positioned somewhere between definitive eveningness and definitive morningness. Morningness is more prevalent in women (Randler, 2007, meta-analysis) and, as suggested based on cross-sectional studies, with increasing age: Most children are morningness types, but during pubertal maturation the sleep phase is temporarily delayed before the final chronotype establishes itself (Carskadon et al., 1993; Roenneberg 2007, review). Polymorphisms in circadian clock-related genes have been associated with the chronotype (Katzenberg et al., 1998, Johansson et al., 2003).

Morningness is more often related to beneficial health outcomes than is eveningness (Taillard et al, 2001). For example, early chronotypes (more morningness) report healthier lifestyle and eating habits, and report higher life satisfaction (Wittmann et al., 2006; Randler, 2008; Fleig & Randler, 2009). Conversely, late chronotypes (more eveningness) report more psychiatric morbidity such as bipolar disorder, ADHD, depressive symptoms, and sleep disturbances (Rybak et al., 2007; Ong et al., 2007; Lehnkering & Siegmund, 2007; Wood et al., 2009; Hidalgo et al., 2009; Van Veen et al., 2010). With regard to personality traits, morningness has been fairly consistently related to conscientiousness, agreeableness, and a low level of neuroticism (Tonetti et al., 2009).

Sleep outcomes and chronotype in ex-preterm individuals are reviewed in section 2.3.5.
3 Aims of the study

The general aim of this thesis was to study, from a neurobehavioral point of view, adult outcomes after being born prematurely with very low birth weight. In order to elucidate the role of poor fetal growth in modulating the outcomes, another aim was to separately evaluate those born appropriate or small for gestational age (reflecting poor fetal growth). The study outcomes included symptoms of ADHD and cognitive functioning, and given that sleep disturbances may interact with these outcomes, a further aim was to assess sleep characteristics.

More specifically, the aims were as follows:

- To learn whether self-perceived behavioral symptoms of ADHD and risk-taking in terms of substance use are more common in VLBW adults.
- To evaluate core cognitive functions of VLBW adults.
- To discover whether VLBW adults differ from controls in sleep quality, duration, sleep-disordered breathing, or chronotype.
4 Methods

4.1 Study participants

All participants belonged to The Helsinki Study of Very Low Birth Weight Adults, a longitudinal retrospective cohort study, outlined in Figure 4 (Hovi et al. 2007, 2009, 2010, in press; Kajantie et al. 2008, 2010; Rääkkönen et al., 2008; Pesonen et al., 2008; Pyhältö et al. 2009a, 2009b, 2010; Siltanen et al., in press; Wehkalampi et al., 2010a, 2010b). Below follows a description of the establishment of the cohort.

The original cohort comprised 474 consecutive VLBW infants born in the province of Uusimaa, Finland, from January 1978 through December 1985, and admitted to the Children’s Hospital at Helsinki University Central Hospital. Of them, 335 (70.7%) were discharged alive from the neonatal intensive care unit and followed up during early childhood (Järvenpää 1982; 1987).

When these VLBW individuals had reached young adulthood, we traced them through data from the Population Register Centre of Finland. A control group was created by manually searching the birth records (handwritten books) of all consecutive births in the maternity hospitals: For each VLBW survivor, the next available singleton infant of the same gender, born at term (gestational age ≥ 37 weeks), and not SGA, was included as a control. Mortality rates from hospital discharge to June 2004 were 1.8% for the VLBW group and 1% for their controls. We were able to contact 95.1% of the VLBW young adults and 96.8% of the controls. Thereafter, those 255 VLBW survivors and 314 controls living in the greater Helsinki area were invited to participate in a clinical study during 2004-2005 (Studies I-IV). Of those invited, 166 (65.1%) VLBW individuals and 172 (54.8%) controls agreed to participate. The age range of the participants was 18 to 27 years (mean 21.4, SD 2.2). Participants did not differ from nonparticipants with regard to the following variables: birth weight, birth weight SD score, gestational age, maternal pre-eclampsia, days of mechanical ventilation, oxygen treatment, days of age at hospital discharge, or bronchopulmonary dysplasia (p-values ≥ 0.30). They did, however, differ in rates of cerebral palsy at 15 months of age (6.0% among participants and 19.1% among nonparticipants, p = 0.005), and, among the VLBW group, in maternal smoking during pregnancy (19.9% and 31.8% respectively, p = 0.04).

Three years later, in 2007-2008, we carried out a follow-up study (Study V). We invited 313 (92.6%) of those who participated in the first clinical study, after exclusion of one individual with developmental delay, two who could not be traced, four who had refused to be contacted again in the future, eleven who lived abroad, and seven who failed to fulfill the inclusion criteria for the metabolic assessments conducted in conjunction with the follow-up. A total of 218 (69.6% of those invited and eligible) participated, at ages 21 to 29 years (mean 25.0, SD 2.2).
Figure 4  Flow chart of the study cohort.
Maternal and neonatal characteristics of the participants are shown in Table 2. We interviewed two study participants on their subjective experience of taking part in the clinical study, and their stories are retold in Box 1.

**Table 2. Maternal and neonatal characteristics of the participants in the Helsinki Study of Very Low Birth Weight Adults.**

<table>
<thead>
<tr>
<th></th>
<th>Participants in the first clinical study</th>
<th>Participants in the follow-up study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLBW n = 166</td>
<td>Term controls n = 172</td>
</tr>
<tr>
<td></td>
<td>VLBW n = 113</td>
<td>Term controls n = 105</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>29.3 (4.8)</td>
<td>29.2 (4.9)</td>
</tr>
<tr>
<td>Primiparity a</td>
<td>80 (48.2)</td>
<td>85 (49.7)</td>
</tr>
<tr>
<td>Multiparity a</td>
<td>86 (51.8)</td>
<td>86 (50.3)</td>
</tr>
<tr>
<td>Twin or triplet pregnancy</td>
<td>28 (16.9)</td>
<td>0 **</td>
</tr>
<tr>
<td>Maternal preeclampsia</td>
<td>35 (21.1)</td>
<td>13 (7.6)**</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy b</td>
<td>31 (19.9)</td>
<td>28 (16.7)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>103 (62.0)</td>
<td>20 (11.6)**</td>
</tr>
<tr>
<td>Birth weight, grams</td>
<td>1120 (221)</td>
<td>3593 (471) **</td>
</tr>
<tr>
<td>Birth weight SD score</td>
<td>-1.3 (1.5)</td>
<td>0.0 (1.0)**</td>
</tr>
<tr>
<td>Birth head circumference, cm c</td>
<td>26.2 (1.9)</td>
<td>35.1 (1.3)**</td>
</tr>
<tr>
<td>SGA (birth weight &lt; -2 SD)</td>
<td>55 (33.1)</td>
<td>0 **</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>95 (57.2)</td>
<td>103 (59.9)</td>
</tr>
<tr>
<td>Male</td>
<td>71 (42.8)</td>
<td>69 (40.1)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>30 (18.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sepsis in the neonatal period, blood culture-verified</td>
<td>12 (7.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mechanical ventilation, days d median (interquartile range)</td>
<td>5 (0 to 14)</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxygen treatment, days c median (interquartile range)</td>
<td>13 (4 to 34)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age at hospital discharge, days f median (interquartile range)</td>
<td>70 (53 to 90)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) or frequency (%) unless otherwise specified. * p < 0.05, ** p < 0.001
Missing values for the first clinical visit and follow-up: a n=1 and n=0 missing values respectively, b n=14 and n=11, c n=4 and n=3, d n=3 and n=3, e n=8 and n=8, f n=72 and n=53.

43
**Mr. A** was born small for gestational age at week 43 weighing only 1360 g, after a pregnancy complicated by preeclampsia. Today, this 22-year-old young man possesses a vocational qualification in information technology and is temporarily employed. He will live with his parents until he finds a permanent job. He participated in the study out of his own good will: “I help people in my work all the time, and when I got the study invitation I thought I wanted to help again,” he says. His experience from the study is positive, and participating caused him no distress. He could well imagine participating in something similar again.

He hasn’t thought much about the fact that he was born preterm. He acknowledges he was born approximately a month too soon, but cannot recall his birth weight. Neither can he recall any hospital visits during childhood, since fortunately he has been quite healthy. He doesn’t think that being born preterm has affected his lie in any particular way. “I was born small but grew tall,” smiles the young man, nowadays 185 cm tall.

**Ms. B** participated in the study as a term-born control at the age of 26. She now lives with her partner and works as a package designer. She doesn’t know anyone born preterm, and admits that despite actually disliking doctors, she decided to participate out of pure curiosity. She found it easy to answer the questionnaires, and didn’t perceive them as uncomfortable or intrusive. She was surprised, though, by the most extreme alternatives, and felt sad that “some people can actually feel that bad inside.” She doesn’t think participating in this study affected her in any way, although she to some extent thought about her own questionnaire answers afterwards.

**Box 1.** Two participants reflect on their experiences of taking part in the Helsinki Study of Very Low Birth Weight Adults.

### 4.2 Measures

#### 4.2.1 Background characteristics (Studies I-V)

We collected maternal and perinatal data from maternal welfare clinics and hospital records. Maternal preeclampsia was diagnosed if the mother met current preeclampsia criteria of blood pressure > 140/90 mmHg, occurring for the first time after mid-gestation, in addition to having proteinuria (≥ 0.3 g in a 24-hour specimen or a positive dipstick) (NHBPEP Working Group Report, 2000). Data on cigarette smoking during pregnancy (yes/no, inquired about prior to delivery) was also drawn from hospital records. We defined SGA
as birth weight below -2 SD of the Finnish mean, corrected for gestational age and gender, and AGA as birth weight within ± 2 SD (Pihkala et al. 1989). Bronchopulmonary dysplasia (BPD) was defined using the standard criteria of those days (clinical picture, chest radiographs, and dependency on supplementary oxygen at 28 days of age) (Northway et al. 1967).

We gathered information on health, medications, schooling and family background of all participants by self-report as adults. We defined parental education as the highest educational level attained by either parent, and used it as a proxy for socioeconomic status. In conjunction with the clinic visits, the participants underwent extensive somatic and psychological examinations. The questionnaires administered included the Beck Depression Inventory (BDI) (Beck et al. 1961) for assessment of depressive symptoms, and the NEO-Personality Inventory (Costa & McCrae, 1985) for assessment of personality traits. The most important of the adult background variables used in this thesis are presented in Table 3.
Table 3. Adult characteristics of the participants in the Helsinki Study of Very Low Birth Weight Adults.

<table>
<thead>
<tr>
<th></th>
<th>Participants in the first clinical study in the years 2004-2005</th>
<th>Participants in the follow-up study in the years 2007-2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLBW n = 166 Term controls n = 172</td>
<td>VLBW n = 113 Term controls n = 105</td>
</tr>
<tr>
<td>Age, years a</td>
<td>22.4 (2.1) 22.5 (2.2)</td>
<td>25.0 (2.1) 25.0 (2.2)</td>
</tr>
<tr>
<td>Weight, kg a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>58.7 (12.0) 63.8 (10.9) *</td>
<td>59.9 (13.0) 64.3 (14.4)</td>
</tr>
<tr>
<td>Men</td>
<td>67.2 (13.1) 76.1 (11.7) **</td>
<td>70.3 (12.0) 79.4 (11.3) **</td>
</tr>
<tr>
<td>Height, cm a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>162.0 (7.7) 167.3 (6.8) **</td>
<td>162.0 (7.7) 166.1 (6.1) *</td>
</tr>
<tr>
<td>Men</td>
<td>174.7 (7.7) 180.6 (6.4) **</td>
<td>174.7 (7.7) 180.4 (6.1) **</td>
</tr>
<tr>
<td>Body mass index, kg/m² a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>22.3 (4.0) 22.8 (3.7)</td>
<td>22.8 (4.5) 23.3 (5.0)</td>
</tr>
<tr>
<td>Men</td>
<td>22.0 (3.6) 23.3 (3.2) *</td>
<td>23.0 (3.6) 24.4 (3.4)</td>
</tr>
<tr>
<td>Adult head circumference, cm b, c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>54.3 (1.5) 55.5 (1.2) **</td>
<td>54.4 (1.6) 55.5 (1.2) **</td>
</tr>
<tr>
<td>Men</td>
<td>56.3 (1.7) 57.5 (1.5) **</td>
<td>56.5 (1.7) 57.5 (1.3) *</td>
</tr>
<tr>
<td>School grade average in comprehensive school (scale 4 to 10) c,d</td>
<td>8.0 (0.8) 8.2 (0.9) *</td>
<td>8.0 (0.8) 8.2 (0.8)</td>
</tr>
<tr>
<td>Helped by a special educational teacher at school c,e</td>
<td>35 (22.9) 21 (12.5) *</td>
<td>23 (21.9) 12 (11.7) *</td>
</tr>
<tr>
<td>Highest educational attainment c,f of either parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>17 (10.4) 11 (6.4)</td>
<td>11 (9.9) 6 (5.7)</td>
</tr>
<tr>
<td>High school</td>
<td>42 (25.8) 31 (18.1)</td>
<td>28 (25.2) 19 (18.1)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>59 (36.2) 56 (32.7)</td>
<td>37 (33.3) 34 (32.4)</td>
</tr>
<tr>
<td>University</td>
<td>45 (27.6) 73 (42.7) *</td>
<td>35 (31.5) 46 (43.8)</td>
</tr>
<tr>
<td>Cerebral palsy c</td>
<td>14 (8.4) 0 **</td>
<td>6 (5.3) 0 *</td>
</tr>
<tr>
<td>Current psychoactive medication d</td>
<td>11 (6.7) 7 (4.1)</td>
<td>11 (9.9) 6 (5.8)</td>
</tr>
<tr>
<td>Psychiatric comorbidity b</td>
<td>19 (11.7) 27 (15.8)</td>
<td>18 (16.2) 22 (21.2)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) or frequency (%) unless otherwise specified. * p < 0.05, ** p < 0.001
Missing values for the first clinical study and the follow-up, respectively: a 0 and 1, b 19 and 10, c 17 and 10, d 22 and 10, e 4 and 0, f 3 and 3.

We measured current symptoms of ADHD with the Adult Problem Questionnaire (APQ) (De Quiros & Kinsbourne 2001), a self-rating instrument designed to assess ADHD symptoms in adulthood. Given that the diagnosis of ADHD is clinical (American Academy of Pediatrics, 2000; De Quiros & Kinsbourne 2001; Kliegman et al., 2007), the APQ is insufficient for diagnosing...
ADHD; it rather serves as a tool for quantifying the symptoms. It includes 43 items representing various behavioral symptoms of ADHD, rated on a 0 to 3-point Likert scale, with response alternatives ranging from “Not at all present” to “Very much.” The internal consistency of the APQ in this study was high, as indicated by the general coefficient of reliability of 0.96, calculated according to the procedure described by Tarkkonen and Vehkalahti (2005).

In order to uncover the latent structure of the APQ, we carried out an exploratory factor analysis. The basic idea of factor analysis is to describe the variance in a large set of variables (in this case, items) using a considerably smaller number of factors (here called subscales), that are created by grouping strongly inter-correlated variables. In other words, factor analysis aims at crystallizing the information from many variables into a few usable factors, and at identifying what these factors represent conceptually. It enables extraction of latent variables in the dataset that can be measured only indirectly (Ranta et al. 1989). In the current study, the factor analysis yielded six subscales: 1) Executive Dysfunction, 2) Emotional Instability, 3) Anger Out, 4) Social Problems, 5) Inattention/restlessness, 6) Alcohol Use. The general coefficients of reliability for the subscales ranged from 0.93 to 0.96. We used both total APQ sumscore (all items summed) and subscale-specific factor scores (items belonging to a certain factor are weighted by their loadings on that factor, and then summed) as outcome variables in subsequent analyses.

The participants also completed a questionnaire on risk-taking behaviors in terms of substance use. We asked them about alcohol (quantity and frequency of use and of getting drunk), tobacco smoking (frequency; response alternatives ranging from “never smoked” to “smoke ≥ 20 cigarettes/day”), and recreational drugs (“how many times have you tried hash, marijuana, or other narcotics, or for instance sniffed glue?”; response alternatives ranging from “never” to “≥ 20 times”). We dichotomized the outcome variables prior to analyses.

Of the 338 individuals who participated in the first clinical study in 2004-2005, two failed to return the questionnaires, one did not respond to the substance-use questions, and another two who had attended training school due to developmental delay were excluded from analyses. Altogether, the ADHD analyses comprised 334, and the substance use analyses 333 young adults.

4.2.3 Cognitive assessment (Study II)

For assessment of cognitive functions, we utilized a computerized test battery (CogState Ltd., Melbourne, Australia, version CogHealth 3.0.5.). This test battery focuses on major cognitive areas including psychomotor speed, working memory, attention, learning, and facets of executive functions. It has proven reliable, valid, and sensitive, with only small practice effects usually occurring between the first and second administration but seldom
Afterwards (Darby et al. 2002; Collie et al. 2003a, 2003b; Cysique et al. 2006; Falleti et al. 2006). Being computerized, it has the advantage of being faster and less instructor-dependent than conventional “paper-and-pencil” neuropsychological tests and enables registration of reaction times with high accuracy (milliseconds). The battery we used in the current study is made up of five tasks (Table 4), presented on the computer screen in the form of card games in order to be neutral with respect to the culture, language, and socioeconomic background of the subject. For each task, mean reaction times (milliseconds) and accuracies (% correct responses) were recorded.

The participants all started with at least one practice round, following oral instructions by a research nurse blinded to birth status. When the testing round began, the participants sat alone at a computer and wore headphones in order to optimize concentration. During the test, before each task to be recorded, familiarization trials with written instructions were presented on the computer screen, and false responses were followed by error beeps and true responses by visual feedback. When the actual recording of the trial started, instructions and error beeps were no longer provided. Total test duration was 15 to 20 minutes.

Since we explicitly aimed at comparing the cognitive performance of unimpaired VLBW young adults with that of their term-born peers, we excluded from the analyses participants with neurosensory impairments (deafness, blindness, cerebral palsy or developmental delay) (18 individuals in the VLBW group and one control). An additional one was excluded due to equipment-related technical problems. Altogether, we included in the analyses 318 unimpaired young adults (147 VLBW and 171 term controls).
Table 4. *Tasks included in the cognitive test battery.*

<table>
<thead>
<tr>
<th>Task</th>
<th>Cognitive target domain</th>
<th>Procedure *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time</td>
<td>Psychomotor speed</td>
<td>A playing card face down on the screen; press the &quot;Yes&quot; key as quickly as possible when the card turns face up.</td>
</tr>
<tr>
<td>Choice reaction time</td>
<td>Simple visual attention (Psychomotor speed)</td>
<td>When a face-down card flips over, determine quickly whether it is red or not and press &quot;Yes&quot; or &quot;No.&quot;</td>
</tr>
<tr>
<td>One-back working memory</td>
<td>Working memory (Psychomotor speed) (Visual attention)</td>
<td>Does the card match the previous one? Press &quot;Yes&quot; or &quot;No&quot; quickly when face-down card flips over.</td>
</tr>
<tr>
<td>Divided attention</td>
<td>Divided visual attention (psychomotor speed)</td>
<td>Five cards in a row, one horizontal line above them and one below. When the cards start moving randomly, press &quot;Yes&quot; quickly when any card touches either white line.</td>
</tr>
<tr>
<td>Associate learning</td>
<td>Visual learning Declarative memory</td>
<td>The most difficult task of the test. Requires ability to memorize cards and learn through feedback during the task.</td>
</tr>
</tbody>
</table>

* The simple reaction time procedure was randomly repeated 30 times, the associate learning 50 times, the others 35 times.

4.2.4. Sleep assessments (Studies III-V)

*Actigraphy (Study III)*

For objective sleep assessment, we used actigraphy (Actiwatch AW4, Cambridge Neurotechnology Ltd., UK) (Figure 5). For an overview of this methodology, see section 2.5.2. In the current study, we scored the data with Actiwatch Activity & Sleep Analysis V 5.42 software, using one-minute epochs and medium sensitivity as recommended by the manufacturer. The scoring algorithm (incorporated in the software) and the AW4 model
have been validated against polysomnography in adults by Kushida et al. (2001), who performed epoch-by-epoch comparisons of actigraphy with polysomnography and reported a sensitivity (ability to detect sleep when polysomnography scores it as sleep) of 0.96, specificity (ability to detect an awake state) of 0.38, and accuracy (ability to detect sleep and wakefulness) of 0.77. When in the aforementioned study the actigraphy-derived estimates for sleep duration and sleep efficiency were analyzed in combination with subjective data from sleep logs, the actigraphy-derived estimates were similar to those derived by polysomnography. The principle of the scoring algorithm is as follows: The activity-counts for the epoch being scored and those within 2 minutes on each side of it are compared with a threshold sensitivity value. If the activity count exceeds the threshold value, the epoch is scored as awake, otherwise as sleep.

According to the study protocol, we instructed the participants to wear the actigraph on the non-dominant wrist for at least three consecutive days. During that period, they were also instructed to keep a sleep log on bedtimes (closing the eyes), wake-up times (opening the eyes), as well as on monitor removal times (e.g. in the shower, swimming or sauna), and to simultaneously press the actigraph event marker button.

![An actigraph](image)

We performed the scoring procedure blinded to group assignment. First, to cover the whole sleeping period, we set the analysis window to start ≥ 20 minutes before bedtime, and to end ≥ 20 minutes after wake-up time. Next, we visually inspected the activity plot to detect discrepancies in sleep logs, event-marker pressings and the activity pattern. Although both sleep logs and event markers were taken into account when scoring the activity data, we prioritized event markers since they turned out to be more reliable in the age group of the current study sample. We excluded a night if the actigraph was not in use or had been taken off; if bedtime information was missing; if wake-up time information was missing, and activity data were not unequivocally interpretable; if sleep log information was missing, and event markers were not unequivocally interpretable; if both sleep log information and event markers were missing despite the actigraphy's having been in use; and if the activity data did not match the sleep log or event markers.
We used the following actigraphy-derived sleep estimates as outcome variables: *Sleep duration* (total sleep length minus wake time); *sleep latency* (time before falling asleep); *sleep efficiency* (percentage of minutes spent asleep while in bed, including sleep latency); and *fragmentation index* (a marker of restlessness). We derived estimates of *bedtimes* and *wake-up times* from the actigraph registration marks or the sleep logs.

In conjunction with the first clinic visit, we offered all 338 study participants an actigraph provided there was one available, resulting in a subsample of 211 individuals who participated in the actigraphy study. The subsample did not differ in maternal or perinatal variables from the rest of the study sample. From the subsample, we excluded 27 (12.8%) from analyses due to equipment-related technical problems or lack of reliable nights according to the exclusion criteria, and 17 (8.1%) because they had only one reliable night. The remaining 167 individuals (89 VLBW and 78 term controls) had at least two reliable nights (range: 2 to 9) that were averaged and included in analyses.

*Basic Nordic Sleep Questionnaire (Studies III and IV)*

We derived subjective sleep assessments using the Basic Nordic Sleep Questionnaire (BNSQ) (Partinen & Gislason, 1995). The BNSQ is a 21-item scale on frequency of sleep problems during the preceding 3 months, rated on a five-point scale. For Study III, in line with the objectives of that study, we analyzed items related to sleep duration, latency, daytime napping, bedtimes and wake-up times.

Sleep-disordered breathing (SDB) was operationalized in terms of chronic snoring – one of its manifestations (Study IV). Three BNSQ items related to snoring were analyzed. The first question was: “Do you snore while sleeping (ask others, if you are not sure)?”. Chronic snoring was defined as snoring ≥ 1 to 2 times per week, and served as a dichotomized principal outcome variable. The other items concerned the quality of snoring “How do you snore? (Ask others about the quality of your snoring)”, and frequencies of apneas “Have you had breathing pauses (sleep apnea) during sleep (or have other people noticed that you have pauses in respiration while you sleep)?”.

We administered the BNSQ during the first clinical visit in 2004-2005. Of the 338 participants, 7 failed to complete the questionnaire, and we excluded another 4 from analyses due to conditions likely to interfere with snoring (panhypopituitarism, diabetes mellitus, pregnancy). Thus, we included a total of 327 participants (158 VLBW and 169 term controls) in the SDB analyses (Study IV).
As the findings from Study III suggested an advanced sleep phase, a result we had not anticipated, we investigated this matter further by administering the morningness-eveningness questionnaire (MEQ) (Horne & Östberg, 1976) in conjunction with the follow-up study 3 years later. The MEQ is the method most widely used to assess circadian typology (chronotype), which refers to individual time preferences for going to bed, waking up, and for performing physical and cognitive activities. It asks, for instance, “Considering your own feeling-best rhythm, at what time would you get up if you were entirely free to plan your own day?” and “Assuming adequate environmental conditions, how easy do you find getting up in the morning?” Validation studies show that the MEQ correlates well with physiological markers of the endogenous circadian rhythm such as heart rate, core body temperature, and, in particular, with melatonin-secretion rhythmicity (Griefahn, 2002). It is a 19-item self-report questionnaire, which produces a morningness-eveningness score (MES) ranging from 18 to 86, with higher scores indicating a propensity towards morningness and lower scores a propensity towards eveningness. Due to a typographical error in the questionnaire interfering with the interpretation of item number 17 in the current study, we discarded that item when calculating the MES; this needs to be kept in mind when comparing MES from this study with that of other studies. The internal consistency of the MEQ in this data was good (Crohnbach’s alpha = 0.85).

As outlined in Figure 4, we administered the MEQ during the follow-up study in 2007-2008. Of the 218 follow-up participants, 190 (87.2%) completed the MEQ. Those completing the MEQ did not differ from the 139 non-participants (defined as those who declined to participate in the follow-up or who participated without completing the MEQ) regarding the following variables: VLBW status, gender, gestational age, birth weight, relative birth weight, age in days at hospital discharge, and duration of mechanical ventilation (VLBW group), cesarean section, or maternal preeclampsia (p-values > 0.05). The rate of maternal smoking during pregnancy differed between groups, being more common among mothers of non-participants (14.0% vs. 23.5%, p = 0.03). Since neurosensory impairments are likely to interfere with sleep and chronotype, we excluded six MEQ-responders with blindness or cerebral palsy. Thus, we included a total of 184 young adults (58.8% of those invited) in Study V analyses.

4.3 Statistical analyses

In all studies (I-V), crude group comparisons of categorical variables were performed with the Chi-square test, or Fischer’s exact test when appropriate. Regarding continuous variables, groups were compared by use of Student’s t-test (two groups) or ANOVA (three groups). Skewed outcome variables were compared with the Mann-Whitney U-test, or Student’s t-test after normality was first improved by logarithm-transformation. Correlations were explored with Pearson’s (normally distributed variables) or Spearman’s

52
(skewed or dichotomized variables) correlations. When exploring correlations while controlling for confounders, bipartial correlation or multiple linear regression analyses were utilized. Interactions between gender and study group were examined by entering the following variables into the statistical models as independent predictors: gender, study group, and their product (gender x study group). Where no significant interaction term existed, the results were presented with men and women pooled. Next follows a study-specific description of the raw-data processing, the main statistical models applied, and the covariates chosen.

In Study I, APQ items with missing values (n=11, < 0.001%) were imputed by aid of the participant’s individual mean score. The total sumscore of the APQ was calculated by simply adding together the raw scores of all items. The APQ was then subjected to exploratory factor analysis, by the maximum likelihood extraction method. Based on inclusion of factors with eigenvalues > 1, and inspection of the scree plot, as well as critical analysis of the theoretical rationale for the factors, a six-factor solution was agreed upon. Items with communalities < 0.3 were dropped (item numbers 26-28, 34, 38-41), and the factor solution was varimax-rotated for ease of interpretation. The factor structure is shown in Table 5. Factor scores were calculated and served as outcome variables in analyses. When group differences in ADHD symptoms were tested in the presence of covariates, analysis of covariance (ANCOVA) was applied. The covariates were chosen on theoretical grounds and included the following: Gender, age, parental education (entered into the models as a dummy-coded variable with the lowest group as reference), maternal smoking during pregnancy, body mass index (BMI; kg/m²), and participation in a modified school curriculum (serving as a proxy of cognitive performance). Finally, all analyses were re-run after exclusion of participants with severe depression (four with ≥ 30 BDI scores), and with neurosensory impairments (13 with cerebral palsy, two deaf, one blind, and two with developmental delay who were initially included in analyses because their disorder was mild enough to allow participation in a normal school curriculum). When examining group differences in substance use while adjusting for these confounders, logistic regression models were applied, due to dichotomized outcome variables.
Table 5.  

<table>
<thead>
<tr>
<th>APQ item number</th>
<th>Item</th>
<th>Factor 1 Executive Dysfunctioning</th>
<th>Factor 2 Emotional Instability</th>
<th>Factor 3 Anger Out</th>
<th>Factor 4 Social Problems</th>
<th>Factor 5 Inattention/Restlessness</th>
<th>Factor 6 Alcohol Use</th>
<th>Communality</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Have difficulty finishing tasks</td>
<td>0.79</td>
<td>0.15</td>
<td>0.08</td>
<td>0.17</td>
<td>0.11</td>
<td>0.09</td>
<td>0.70</td>
</tr>
<tr>
<td>13</td>
<td>Have difficulty organizing daily activities</td>
<td>0.71</td>
<td>0.22</td>
<td>0.10</td>
<td>0.17</td>
<td>0.14</td>
<td>0.09</td>
<td>0.61</td>
</tr>
<tr>
<td>12</td>
<td>Jump from one task to another without finishing it</td>
<td>0.63</td>
<td>0.08</td>
<td>0.07</td>
<td>0.21</td>
<td>0.14</td>
<td>0.13</td>
<td>0.49</td>
</tr>
<tr>
<td>30</td>
<td>Frequently put off tasks that should be completed sooner</td>
<td>0.63</td>
<td>0.15</td>
<td>0.09</td>
<td>0.09</td>
<td>0.16</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>Have difficulty in organizing time</td>
<td>0.57</td>
<td>0.23</td>
<td>0.11</td>
<td>0.15</td>
<td>0.14</td>
<td>0.02</td>
<td>0.44</td>
</tr>
<tr>
<td>14</td>
<td>Have difficulty solving problems</td>
<td>0.51</td>
<td>0.38</td>
<td>0.18</td>
<td>0.26</td>
<td>0.11</td>
<td>-0.03</td>
<td>0.52</td>
</tr>
<tr>
<td>7</td>
<td>Have difficulty remembering</td>
<td>0.46</td>
<td>0.15</td>
<td>0.13</td>
<td>0.14</td>
<td>0.32</td>
<td>0.07</td>
<td>0.37</td>
</tr>
<tr>
<td>36</td>
<td>Poor job performance</td>
<td>0.44</td>
<td>0.30</td>
<td>0.05</td>
<td>0.37</td>
<td>0.05</td>
<td>0.05</td>
<td>0.42</td>
</tr>
<tr>
<td>8</td>
<td>Misplace items frequently</td>
<td>0.41</td>
<td>0.09</td>
<td>0.26</td>
<td>0.02</td>
<td>0.29</td>
<td>0.09</td>
<td>0.33</td>
</tr>
<tr>
<td>31</td>
<td>React strongly and excessively to stressful situations</td>
<td>0.20</td>
<td>0.68</td>
<td>0.20</td>
<td>0.16</td>
<td>0.23</td>
<td>0.14</td>
<td>0.64</td>
</tr>
<tr>
<td>33</td>
<td>Experience repeated crises in dealing with routine life stresses</td>
<td>0.26</td>
<td>0.65</td>
<td>0.11</td>
<td>0.30</td>
<td>0.18</td>
<td>0.14</td>
<td>0.64</td>
</tr>
<tr>
<td>37</td>
<td>Get easily depressed</td>
<td>0.29</td>
<td>0.63</td>
<td>0.16</td>
<td>0.30</td>
<td>0.19</td>
<td>0.09</td>
<td>0.65</td>
</tr>
<tr>
<td>9</td>
<td>Have frequent mood swings</td>
<td>0.24</td>
<td>0.57</td>
<td>0.40</td>
<td>0.09</td>
<td>0.27</td>
<td>0.12</td>
<td>0.64</td>
</tr>
<tr>
<td>42</td>
<td>Emotional responses easily triggered</td>
<td>0.21</td>
<td>0.46</td>
<td>0.40</td>
<td>0.03</td>
<td>0.17</td>
<td>0.03</td>
<td>0.45</td>
</tr>
<tr>
<td>16</td>
<td>Have difficulty making decisions</td>
<td>0.39</td>
<td>0.43</td>
<td>0.13</td>
<td>0.20</td>
<td>0.14</td>
<td>-0.03</td>
<td>0.41</td>
</tr>
<tr>
<td>23</td>
<td>Frequently later regret and worry about own behavior</td>
<td>0.20</td>
<td>0.32</td>
<td>0.26</td>
<td>0.26</td>
<td>0.21</td>
<td>0.12</td>
<td>0.33</td>
</tr>
<tr>
<td>17</td>
<td>Easily angered</td>
<td>0.14</td>
<td>0.21</td>
<td>0.78</td>
<td>0.13</td>
<td>0.18</td>
<td>0.04</td>
<td>0.72</td>
</tr>
<tr>
<td>18</td>
<td>Have frequent temper outbursts</td>
<td>0.13</td>
<td>0.17</td>
<td>0.74</td>
<td>0.15</td>
<td>0.22</td>
<td>0.03</td>
<td>0.67</td>
</tr>
<tr>
<td>24</td>
<td>Get angry over trivial matters</td>
<td>0.12</td>
<td>0.15</td>
<td>0.72</td>
<td>0.22</td>
<td>0.13</td>
<td>0.04</td>
<td>0.62</td>
</tr>
<tr>
<td>22</td>
<td>Lose control of behavior frequently</td>
<td>0.13</td>
<td>0.14</td>
<td>0.49</td>
<td>0.45</td>
<td>0.24</td>
<td>0.14</td>
<td>0.55</td>
</tr>
<tr>
<td>21</td>
<td>Have difficulty maintaining friendships</td>
<td>0.19</td>
<td>0.16</td>
<td>0.06</td>
<td>0.70</td>
<td>0.10</td>
<td>-0.09</td>
<td>0.58</td>
</tr>
<tr>
<td>19</td>
<td>Have unstable personal relationships</td>
<td>0.25</td>
<td>0.20</td>
<td>0.09</td>
<td>0.68</td>
<td>0.12</td>
<td>0.18</td>
<td>0.62</td>
</tr>
<tr>
<td>25</td>
<td>Temper interferes with personal relations</td>
<td>0.25</td>
<td>0.18</td>
<td>0.21</td>
<td>0.66</td>
<td>0.15</td>
<td>0.16</td>
<td>0.61</td>
</tr>
<tr>
<td>20</td>
<td>Break off personal relationships over trivial matters</td>
<td>0.13</td>
<td>0.15</td>
<td>0.34</td>
<td>0.62</td>
<td>0.10</td>
<td>0.08</td>
<td>0.55</td>
</tr>
<tr>
<td>4</td>
<td>Mind wanders when reading or watching TV</td>
<td>0.28</td>
<td>0.18</td>
<td>0.08</td>
<td>0.12</td>
<td>0.61</td>
<td>0.07</td>
<td>0.51</td>
</tr>
<tr>
<td>1</td>
<td>Restless</td>
<td>0.24</td>
<td>0.30</td>
<td>0.15</td>
<td>0.10</td>
<td>0.60</td>
<td>0.11</td>
<td>0.55</td>
</tr>
<tr>
<td>5</td>
<td>Mind wanders during conversations</td>
<td>0.34</td>
<td>0.10</td>
<td>0.10</td>
<td>0.17</td>
<td>0.57</td>
<td>0.11</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>Cannot sit still and do nothing</td>
<td>-0.05</td>
<td>0.04</td>
<td>0.20</td>
<td>0.01</td>
<td>0.52</td>
<td>0.10</td>
<td>0.33</td>
</tr>
<tr>
<td>6</td>
<td>Easily distracted</td>
<td>0.38</td>
<td>0.18</td>
<td>0.18</td>
<td>0.10</td>
<td>0.49</td>
<td>-0.02</td>
<td>0.47</td>
</tr>
<tr>
<td>2</td>
<td>Cannot seem to relax</td>
<td>0.07</td>
<td>0.39</td>
<td>0.10</td>
<td>0.16</td>
<td>0.49</td>
<td>-0.01</td>
<td>0.43</td>
</tr>
<tr>
<td>10</td>
<td>Easily bored in situations others feel comfortable in</td>
<td>0.31</td>
<td>0.09</td>
<td>0.16</td>
<td>0.33</td>
<td>0.43</td>
<td>0.05</td>
<td>0.42</td>
</tr>
<tr>
<td>35</td>
<td>Frequently drink to intoxication</td>
<td>0.08</td>
<td>0.08</td>
<td>0.03</td>
<td>0.05</td>
<td>0.07</td>
<td>0.86</td>
<td>0.77</td>
</tr>
<tr>
<td>32</td>
<td>Drink too much alcohol</td>
<td>0.14</td>
<td>0.12</td>
<td>0.03</td>
<td>0.12</td>
<td>0.11</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td>29</td>
<td>Have trouble sticking to a budget</td>
<td>0.30</td>
<td>0.05</td>
<td>0.23</td>
<td>0.08</td>
<td>0.16</td>
<td>0.40</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Factor Eigenvalues: 4.49, 3.19, 3.02, 3.00, 2.97, 1.94
% of variance explained: 12.84, 9.10, 8.62, 8.56, 8.50, 5.55
Cumulative % of variance explained: 12.84, 21.94, 30.57, 39.13, 47.62, 53.17
General Coefficient of Reliability: 0.95, 0.96, 0.95, 0.95, 0.94, 0.93

Rotated six factor solution. * When generating the factor scores, all items shown were used.
In Study II, mean reaction time (RT) and accuracy (% correct) served as variables of interest for the five tasks included in the CogState test. Initial data inspection revealed two participants with > 40 errors on the working-memory task (indicating they did not understand the task); therefore, their working-memory tasks were excluded from further analyses. The associate learning task for another participant was excluded due to an exceptionally slow response (RT > 4500 msec). The simple reaction time task was administered twice during the test and calculated as the mean of two identical tasks, but because four participants failed to complete the second task, their simple reaction time was based exclusively on the first task. Due to slightly positively skewed distributions, all RTs were logarithm-transformed (base 10), and their mean values served as outcome variables. Accuracy for the associate learning task showed a normal distribution and thus served as an untransformed continuous variable. Accuracies for other than the associate learning task were omitted from analyses because they were negatively skewed and showed a ceiling effect (with most participants performing near the optimal accuracy, indicating the test was too easy), and the usefulness of such variables is questionable. Group differences were analyzed by multiple linear regression, with adjustment for gender, age, parental education, and adult head circumference. The covariates adjusted for were chosen on theoretical grounds. To facilitate the interpretation of the relative magnitude of the group differences, Cohen’s $d$ effect size (ES) measures were calculated (Thalheimer et al., 2002). Cohen’s $d$ is calculated as the mean group difference divided by the pooled SD of the two groups.

In Study III, the raw data processing and scoring procedure was performed as explained in section 4.2.4. The actigraphy-derived sleep latency variable was logarithm-transformed due to its skewed distribution and thereafter explored as a continuous variable. Group differences in actigraphy-derived sleep estimates were examined using multiple linear regression models when adjustments for covariates were made. Age, gender, parental education, BDI score, standardized birth weight, current smoking, and, additionally, frequently getting drunk served as covariates. Individuals with and without neurosensory impairment were compared, and analyses were re-run after exclusion of those 11 individuals with neurosensory impairment. To assess the effects of gestational age and birth measures (birth weight, standardized birth weight) on sleep, multiple linear regression models were fit for the VLBW and control groups separately (due to the study design). Finally, groups were compared with regard to BNSQ-derived sleep estimates.

In Study IV, chronic snoring served as the principal and dichotomized outcome variable. A series of multivariate logistic regression models were fitted to predict chronic snoring. Group differences between VLBW and controls were tested while controlling for significant background factors and comorbidity, namely age, gender, current smoking, parental education, height, BMI, and depressive symptoms in the form of logarithm-transformed BDI score, $\ln(BDI + 1)$. To examine the roles of perinatal (standardized birth weight, SGA status, mechanical ventilation) and maternal (preeclampsia, smoking during pregnancy) variables as predictors of chronic snoring, a set of separate models were fitted
while controlling for the confounders. Finally, a full model was constructed by entering all explaining variables of interest into the model.

In Study V, a morningness-eveningness sumscore was calculated according to instructions provided by Horne & Östberg (1976). It was normally distributed and thus served as an untransformed continuous outcome variable in comparisons of group differences by ANCOVA. Gender, age, current gainful employment (yes/no), and night shifts at work (yes/no) served as covariates. Additionally, based on the literature showing associations of morningness with depression, ADHD symptoms, and personality (Chelminski et al., 1999; Rybak et al., 2007; Tonetti et al., 2009, Hidalgo et al., 2009), we also explored correlations between morningness and these psychological variables in our study, while adjusting for birth status. Depressive symptoms were explored as a categorized variable (raw BDI scores from the follow-up study were divided into four categories due to skewed distributions), while personality traits and ADHD symptoms were explored as untransformed continuous variables (these assessments were derived from the first clinic visit, 3 years prior to the follow-up).

All analyses (Studies I-V) were performed with SPSS for Windows (SPSS, Chicago) versions 13.0 to 17.0. Survo MM served for calculating the general coefficients of reliability (Study I). All significance tests were based on two-sided p-values, and the significance level was set at p < 0.05 (Study I, III-V), or p < 0.01 (Study II).

4.4 Ethical considerations

The study protocol was approved by the ethics committee for Children´s and Adolescents´ Diseases and Psychiatry, Helsinki and Uusimaa Hospital District. Each participant signed a written informed consent.
5 Results

5.1 Is VLBW related to ADHD symptoms and substance use in young adulthood? (Study I)

ADHD-related behavioral traits

Comparisons of the VLBW and term control groups indicated a lower total sumscore (fewer symptoms) on the APQ among VLBW young adults (Table 6 and 7). When the two groups were compared with respect to the factor analysis-derived subscales (each representing a behavioral dimension of ADHD), it became clear that the VLBW group scored lower only on the Alcohol-use subscale, which contributed to their lower total sumscore. No group differences on other subscales existed.

Further comparisons of VLBW young adults born AGA and SGA against term controls and against each other revealed the following significant differences: As shown in Table 7 and Figure 6, the VLBW-AGA subgroup had a lower total sumscore than did either the VLBW-SGA or the term control group. On the Executive Dysfunction subscale, VLBW-SGA scored higher than did term controls or VLBW-AGA young adults. Furthermore, the scores on Emotional Instability were highest in the VLBW-SGA group and lowest in the AGA-VLBW group, while the corresponding scores in term controls fell between the scores of those groups. On the Alcohol-use subscale, both VLBW-SGA and VLBW-AGA scored lower than term controls. No group differences on other subscales emerged. The results in Table 7 were similar even without adjustment for confounders.

Thereafter, the analyses reported in Table 7 were re-run after exclusion of 21 individuals with neurosensory impairment or severe depression. Group differences in total sumscore became attenuated and were no longer significant. However, the VLBW-SGA still scored higher (more symptoms) than the VLBW-AGA on the Executive Dysfunction subscale (p = 0.019, adjusted), higher than VLBW-AGA and term controls on Emotional Instability (p = 0.002 and p = 0.02, adjusted), and lower than term controls on Alcohol Use (p = 0.04, adjusted).

Among pregnancy-related factors, maternal smoking was related to higher total sumscore (p = 0.005) and higher scores on Executive Dysfunction (p = 0.003), whereas preeclampsia was related to higher scores on Emotional Instability (p = 0.05).

<table>
<thead>
<tr>
<th></th>
<th>VLBW All</th>
<th>VLBW-AGA</th>
<th>VLBW-SGA</th>
<th>Term Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 162</td>
<td>n = 110</td>
<td>n = 52</td>
<td>n = 172</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Total Sumscore on APQ (all items)</td>
<td>37.6 (17.6)</td>
<td>35.5 (17.3)</td>
<td>42.1 (17.5)</td>
<td>43.1 (19.8)</td>
</tr>
<tr>
<td>Factor Scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Dysfunction</td>
<td>-0.05 (0.90)</td>
<td>-0.17 (0.84)</td>
<td>0.20 (0.97)</td>
<td>0.03 (0.91)</td>
</tr>
<tr>
<td>Emotional Instability</td>
<td>-0.01 (0.90)</td>
<td>-0.16 (0.82)</td>
<td>0.29 (0.99)</td>
<td>0.02 (0.85)</td>
</tr>
<tr>
<td>Anger Out</td>
<td>-0.08 (0.81)</td>
<td>-0.06 (0.81)</td>
<td>-0.12 (0.82)</td>
<td>0.05 (0.96)</td>
</tr>
<tr>
<td>Social Problems</td>
<td>-0.06 (0.81)</td>
<td>-0.05 (0.70)</td>
<td>-0.07 (1.02)</td>
<td>0.03 (0.94)</td>
</tr>
<tr>
<td>Inattention/Restlessness</td>
<td>-0.06 (0.89)</td>
<td>-0.08 (0.92)</td>
<td>-0.02 (0.82)</td>
<td>0.06 (0.82)</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>-0.14 (0.87)</td>
<td>-0.11 (0.88)</td>
<td>-0.22 (0.84)</td>
<td>0.15 (0.97)</td>
</tr>
</tbody>
</table>

Figure 6 Adjusted group mean scores on the Adult Problem Questionnaire. Adapted and reprinted, with permission, from Strang-Karlsson et al., American Journal of Psychiatry, 33:387-395. (Copyright 2008). American Psychiatric Association.

<table>
<thead>
<tr>
<th></th>
<th>VLBW vs. Term Controls</th>
<th>VLBW-AGA vs. Term Controls</th>
<th>VLBW-SGA vs. Term Controls</th>
<th>VLBW-AGA vs. VLBW-SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sum score on APQ</strong></td>
<td>0.04 (-0.33 to 0.25, 0.04)</td>
<td>0.04 (-0.33 to 0.25, 0.04)</td>
<td>0.04 (-0.33 to 0.25, 0.04)</td>
<td>0.04 (-0.33 to 0.25, 0.04)</td>
</tr>
<tr>
<td><strong>Factor scores</strong></td>
<td>0.29 (0.01 to 0.58)</td>
<td>0.29 (0.01 to 0.58)</td>
<td>0.29 (0.01 to 0.58)</td>
<td>0.29 (0.01 to 0.58)</td>
</tr>
<tr>
<td><strong>Executive Dysfunction</strong></td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
</tr>
<tr>
<td><strong>Emotional Instability</strong></td>
<td>0.04 (-0.23 to 0.24)</td>
<td>0.04 (-0.23 to 0.24)</td>
<td>0.04 (-0.23 to 0.24)</td>
<td>0.04 (-0.23 to 0.24)</td>
</tr>
<tr>
<td><strong>Anger Out</strong></td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
</tr>
<tr>
<td><strong>Social Problems</strong></td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
<td>0.02 (-0.22 to 0.13)</td>
</tr>
<tr>
<td><strong>Inattention/Restlessness</strong></td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Alcohol Use</strong></td>
<td>0.29 (-0.30 to 0.00)</td>
<td>0.29 (-0.30 to 0.00)</td>
<td>0.29 (-0.30 to 0.00)</td>
<td>0.29 (-0.30 to 0.00)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, age, BMI, parental education, attending a modified curriculum when school-aged, and maternal smoking during pregnancy. (The maternal smoking variable had 14 missing values. The results were similar even without adjustment for this variable).  

\(^{a}\) p = 0.03 for interaction term between VLBW and gender. Among women, those born at VLBW scored higher than did term controls (p = 0.03), and among men those born at VLBW scored lower than did term controls (p = 0.11).  

\(^{b}\) p = 0.018 for interaction between gender and birth status. No significant group differences were found among women, whereas among men, term controls scored higher than did VLBW-AGA (p = 0.002).
Risk-taking in terms of substance use

In accordance with the results from the APQ, VLBW young adults reported less smoking, drinking, and recreational drug use than did term controls on the substance use questionnaire (Table 8). These findings applied to both the VLBW-SGA and VLBW-AGA groups, which did not differ from each other in this regard. The results remained similar after exclusion of individuals with neurosensory impairment or severe depression or both (with the exception of “daily smoking,” which became non-significant), and regardless of adjustment for confounders.


<table>
<thead>
<tr>
<th>Statement</th>
<th>VLBW n = 162</th>
<th>Term n = 172</th>
<th>Adjusted Odds Ratio (95% CI) **</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use alcohol</td>
<td>131 (81.4)</td>
<td>150 (93.0)</td>
<td>0.28 (0.13 to 0.62)</td>
<td>0.002</td>
</tr>
<tr>
<td>Get drunk monthly</td>
<td>68 (42.2)</td>
<td>111 (64.9)</td>
<td>0.41 (0.25 to 0.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Have tried smoking</td>
<td>75 (46.6)</td>
<td>110 (64.0)</td>
<td>0.48 (0.30 to 0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoke daily</td>
<td>38 (23.6)</td>
<td>55 (32.0)</td>
<td>0.58 (0.34 to 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Have tried recreational drugs</td>
<td>35 (21.7)</td>
<td>66 (38.4)</td>
<td>0.39 (0.22 to 0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>(sniffing, marijuana, hasch or other)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have tried recreational drugs ≥ 10 times</td>
<td>11 (6.8)</td>
<td>19 (11.0)</td>
<td>0.60 (0.26 to 1.38)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The odds ratios denote the risk of VLBW individuals for responding positively to the statement, when compared with term controls.

* Self-reported, questionnaire-derived statements. Two missing values on the alcohol questions, one on the others.

** Adjusted for gender, age, BMI, parental education, attending modified curriculum when school-aged, and maternal smoking during pregnancy.

5.2 Does VLBW predict cognitive test performance in young adulthood? (Study II)

As illustrated in Table 9, and in Figure 2 in Study II (Strang-Karlsson et al., 2010), VLBW young adults free from neurosensory impairment had longer reaction times on all tasks of the cognitive test battery when compared with term controls. Additionally, they had lower accuracy (% correct) on the learning task. Adjustment for gender, age, and parental educational attainment had little effect on the results, while adjustment for adult head circumference (which was smaller in the VLBW group) marginally attenuated some of the
group differences (simple reaction time, choice reaction time, divided attention, and associate learning). The effect sizes (Cohen’s $d$) of the group differences ranged from 0.24 to 0.63, which are considered small- or medium-sized effects (Cohen, 1992). Within the VLBW group, the VLBW-AGA and VLBW-SGA subgroups did not differ from each other (p’s > 0.30, unadjusted).

On exploration of background variables as predictors of test performance, the following gender differences were observed: Men had shorter reaction times but higher error rates than did women on some tasks, while no gender difference existed with regard to accuracy on the associate learning task. Older age was related to longer associate learning reaction time, maternal smoking to shorter choice reaction times and working memory reaction times, and higher school grades to higher accuracy on the learning task (one school grade corresponded to 1.7 percentage points’ higher accuracy, p = 0.01, adjusted). No associations with test performance emerged for current smoking, handedness, parental educational attainment, being first born, or maternal preeclampsia. Few neonatal factors turned out to be associated with test performance: Increased duration of mechanical ventilation was associated with longer divided attention reaction time ($r = 0.27$, $p < 0.01$), whereas BPD, ROP, and sepsis were unrelated.

Since sleep-disordered breathing (SDB) is linked with impaired cognitive performance (Beebe et al., 2003, meta-analysis; Kryger et al., 2005; Aronen et al., 2009), and our results from Study IV showed that VLBW adults are at increased risk for SDB, we also tested whether the association between VLBW and impaired cognitive performance was mediated by SDB. When controlling for SDB (Table 9, model 4), the result remained similar, however, indicating that the impaired cognitive performance among VLBW adults was not mediated by SDB (unpublished results).
### Table 9

Multiple linear regression models comparing cognitive performance of VLBW and term born young adults, Adapted and reprinted, with permission, from Strang-Karlsson et al., Pediatrics 125:e74-82, Copyright © 2010 by the AAP.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Task</th>
<th>VLBW mean (SD)</th>
<th>Term born mean (SD)</th>
<th>Group difference in % ** (95% CI)</th>
<th>p-value</th>
<th>Effect Size Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time * (msec)</td>
<td>Simple Reaction time Unadjusted</td>
<td>285 (1.15)</td>
<td>274 (1.13)</td>
<td>4.0 % (1.1 to 7.0)</td>
<td>&lt;0.01</td>
<td>0.30</td>
</tr>
<tr>
<td>Model 1</td>
<td>4.2 % (1.4 to 7.1)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>3.5 % (0.7 to 6.3)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>3.1 % (-0.1 to 0.3)</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>4.3 % (1.5 to 7.2)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choice reaction time Unadjusted</td>
<td>468 (1.16)</td>
<td>454 (1.12)</td>
<td>3.2 % (0.3 to 6.2)</td>
<td>0.03</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>3.3 % (0.3 to 6.3)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>3.0 % (-0.01 to 6.0)</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>3.1 % (-0.3 to 6.6)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>3.5 % (0.5 to 6.5)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory Unadjusted</td>
<td>655 (1.23)</td>
<td>604 (1.22)</td>
<td>8.4 % (3.7 to 13.4)</td>
<td>&lt;0.001</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>8.7 % (4.1 to 13.5)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>8.2 % (3.6 to 13.0)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>9.2 % (3.9 to 14.7)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>8.7 % (4.0 to 13.5)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divided attention Unadjusted</td>
<td>336 (1.22)</td>
<td>314 (1.21)</td>
<td>7.2 % (2.7 to 11.9)</td>
<td>&lt;0.01</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>7.4 % (3.0 to 12.1)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>6.6 % (2.2 to 11.3)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>4.0 % (-0.8 to 9.1)</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>7.5 % (3.0 to 12.1)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate learning Unadjusted</td>
<td>1299 (1.25)</td>
<td>1220 (1.26)</td>
<td>6.4 % (1.3 to 11.9)</td>
<td>0.01</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>6.8 % (1.9 to 12.0)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>6.2 % (1.3 to 11.3)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>5.7 % (0.1 to 11.6)</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>7.3 % (2.3 to 12.6)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy *** Associate learning (% correct) Unadjusted</td>
<td>80.2 (10.1)</td>
<td>85.7 (7.5)</td>
<td>-5.5 (-7.5 to -3.6)</td>
<td>&lt;0.001</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-5.6 (-7.5 to -3.6)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>-5.5 (-7.5 to -3.5)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-5.3 (-7.5 to 3.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>-5.4 (-7.3 to -3.4)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: Adjusted for gender, age (n=318).
Model 2: Adjusted for gender, age, and parental educational attainment (n = 314)
Model 3: Model 2 and adult head circumference (n = 295).
Model 4: Model 1 and sleep-disordered breathing (SDB) (n=312).

* Linear regression comparing logarithmed (log 10) reaction times on CogState-tasks. Due to skewed distributions, geometric means (SD) are reported. ** A positive value indicates a longer reaction time for VLBW individuals.
*** The group mean difference is in absolute percent. A negative value means lower accuracy for VLBW individuals.
5.3 Do VLBW young adults differ from their term-born peers with regard to sleep characteristics? (Studies III-V)

Sleep quality, duration, and sleep phase (Study III)

As shown in Table 10, the actigraphy recordings revealed no group differences in sleep duration, sleep latency, sleep efficiency, or fragmentation index. The VLBW young adults did, however, go to bed on average 36 minutes earlier than did the term controls (95% CI: 6 to 66 minutes, \( p = 0.02 \)). This difference remained similar after adjustment for covariates (\( p = 0.03 \)). The questionnaire-derived sleep characteristics corroborated these preliminary suggestions of an advanced sleep phase; VLBW young adults reported earlier wake-up times on free days and working days, as well as a nearly-significant earlier bedtime on free days (\( p = 0.06 \)), but no group difference existed in self-reported sleep duration or in difficulties in falling asleep. Within the VLBW group, the VLBW-AGA and VLBW-SGA subgroups did not significantly differ from each other with regard to the sleep variable presented in Table 8, with exception of the self-reported “bedtime on working days,” which was earlier among VLBW-AGA individuals (unadjusted \( p \)-value = 0.03, unpublished result).

Individuals with neurosensory impairments had generally poorer sleep: Compared with unimpaired individuals, their sleep duration was shorter (mean difference: 0.72 hours, 95% CI 0.20 to 1.25, \( p = 0.007 \)), their sleep efficiency lower (mean difference: 3.6 percentage points, 95% CI: 0.4 to 6.8, \( p = 0.03 \)), and their sleep latency longer (mean difference: 60.2%, 95% CI: 26.9 to 78.4, \( p = 0.003 \)). Exclusion of individuals with neurosensory impairment left the results reported in Table 10 essentially unchanged.

Finally, relationships between sleep quality, duration, and birth measures (standardized birth weight, gestational age) were explored separately in the VLBW and control groups. No relationship existed for sleep duration, sleep efficiency, or fragmentation index (\( p \)-values > 0.12). A longer sleep latency, however, was related to shorter gestational age in the control group (\( r = -0.32, p = 0.004 \)), but not significantly so in the VLBW group (\( r = -0.14, p = 0.20 \)). After adjustment for confounders, this relationship remained significant in the control group (standardized regression coefficient \( \beta = -0.25, p = 0.03 \)), and became significant in the VLBW group (\( \beta = -0.36, p = 0.04 \)).
Table 10.  Sleep characteristics of VLBW young adults and term controls, unadjusted. Adapted and reprinted, with permission, from Strang-Karlsson et al., Journal of Pediatric Psychology 33:387-395, 2008, by Oxford University Press on behalf of the Society of Pediatric Psychology.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing values</th>
<th>VLBW n = 89 mean (SD)</th>
<th>Term Controls n = 78 mean (SD)</th>
<th>Mean difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actigraphy-derived sleep variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency (minutes: seconds) *</td>
<td>0</td>
<td>11:20 (2.75)</td>
<td>9:11 (2.73)</td>
<td>19.0 % (-10.3 to 40.5) *</td>
<td>0.18</td>
</tr>
<tr>
<td>Sleep duration (hours: minutes)</td>
<td>0</td>
<td>7:11 (0:53)</td>
<td>7:09 (0:50)</td>
<td>0:02 (-0:14 to 0:18)</td>
<td>0.78</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>0</td>
<td>81.8 (5.2)</td>
<td>83.0 (5.3)</td>
<td>1.2 (-0.5 to 2.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td>0</td>
<td>30.3 (9.4)</td>
<td>31.1 (14.6)</td>
<td>0.8 (-2.9 to 4.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Bed time (hours: minutes **)</td>
<td>0</td>
<td>-0:01 (1:19)</td>
<td>0:35 (1:52)</td>
<td>0:36 (0:06 to 1:06)</td>
<td>0.02</td>
</tr>
<tr>
<td>Wake-up time (hours: minutes **)</td>
<td>0</td>
<td>8:45 (1:28)</td>
<td>9:05 (1:48)</td>
<td>0:20 (-0:10 to 0:50)</td>
<td>0.19</td>
</tr>
<tr>
<td>Questionnaire-derived sleep variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep duration (hours: minutes)</td>
<td>2</td>
<td>7:36 (1:18)</td>
<td>7:54 (1:18)</td>
<td>0:18 (-0:06 to 0:42)</td>
<td>0.15</td>
</tr>
<tr>
<td>Bed time, working day **</td>
<td>5</td>
<td>-1:00 (1:06)</td>
<td>-0:42 (1:18)</td>
<td>0:18 (-0:06 to 0:42)</td>
<td>0.12</td>
</tr>
<tr>
<td>Bed time, free day **</td>
<td>0</td>
<td>0:12 (1:24)</td>
<td>0:36 (1:18)</td>
<td>0:24 (0:00 to 0:48)</td>
<td>0.06</td>
</tr>
<tr>
<td>Wake-up time, working day **</td>
<td>8</td>
<td>7:00 (1:2)</td>
<td>7:30 (1:36)</td>
<td>0:30 (0:02 to 0:54)</td>
<td>0.04</td>
</tr>
<tr>
<td>Wake-up time, free day **</td>
<td>3</td>
<td>9:54 (1:24)</td>
<td>10:18 (1:18)</td>
<td>0:24 (0:001 to 0:48)</td>
<td>0.049</td>
</tr>
<tr>
<td>Difficulties to fall asleep, n (%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Less than once a week ¹</td>
<td></td>
<td>59 (66.3)</td>
<td>53 (67.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least once a week ²</td>
<td></td>
<td>30 (33.7)</td>
<td>25 (32.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of daytime napping, n (%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Less than once a week ¹</td>
<td></td>
<td>65 (73.0)</td>
<td>53 (67.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least once a week ²</td>
<td></td>
<td>24 (27.0)</td>
<td>25 (32.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Due to log-normal distribution of the sleep latency variable, geometric means (SD) are reported and the mean difference is shown as percent

** Hours: minutes. Negative values indicate time before midnight, positive values after midnight.

¹ Categories “never or less than once a month” and “less than once weekly” combined.

² Categories “once or twice weekly”, “3-5 times weekly”, “daily or almost daily” combined.

Sleep-disordered breathing (Study IV)

Initially, those classified as chronic snorers were compared to non-snorers with regard to various clinical characteristics (crude comparisons). Chronic snoring was more common among men (58.3% of snorers vs. 39.4% of non-snorers were men, p = 0.01). Among men, snoring was related to taller height (181.7 cm vs. 176.7 cm, p = 0.002), heavier weight (81.8 kg vs. 69.4 kg, p < 0.01), and higher BMI (24.7 vs. 22.2, p = 0.001). In both genders, snoring was related to depressive symptoms (mean BDI score for men: 4.9 vs. 2.7, p = 0.02; and for women: 9.2 vs. 5.5, p = 0.05). A history of maternal smoking during
pregnancy was more common among snorers than non-snorers (34.1% vs. 15.6%, p = 0.003). Snoring was unrelated to age, current smoking, parental education, maternal preeclampsia, gestational age, birth weight, standardized birth weight, and, within the VLBW group, to mechanical ventilation in the neonatal period and SGA status (p-values $\geq 0.05$).

The VLBW and control groups were then compared with regard to chronic snoring. The crude prevalence of snoring was similar: 15.8% (95% CI: 8.4 to 18.8) for the VLBW group and 13.6% (95% CI: 10.1 to 21.5) for the control group (p = 0.57). After controlling for confounding variables, the odds for snoring among VLBW adults were 2.2-fold (95% CI: 1.1 to 4.5, p = 0.03) that of term-born controls (Table 11).

The groups did not differ with respect to the quality of snoring, nor to the frequency of apneas: 97.5% in the VLBW group and 97.6% in the control group reported no sleep apneas.

Thereafter, perinatal and maternal variables were explored as predictors of chronic snoring while controlling for confounders. As reported in Table 11, maternal smoking during pregnancy remained a significant predictor of chronic snoring in adjusted analyses as well: Those young adults whose mothers smoked during pregnancy had a 2.6-fold likelihood of chronic snoring. Preeclampsia, standardized birth weight, and, within the VLBW group, SGA status and mechanical ventilation, remained unrelated to chronic snoring. Lastly, when all explanatory variables of interest were entered into the full model, VLBW remained a significant predictor of snoring (aOR: 2.7; 95% CI: 1.5 to 6.2, p = 0.02).
Table 11. Chronic snoring predicted by logistic regression models. Adapted and reprinted, with permission, from Paavonen et al., Pediatrics 120:778-784, Copyright © 2008 by the AAP.

<table>
<thead>
<tr>
<th>Model</th>
<th>Term/Condition</th>
<th>aOR</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Term controls (reference) vs. VLBW adults</td>
<td>2.21</td>
<td>1.07 to 4.54</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal smoking during pregnancy (no vs. yes)</td>
<td>2.64</td>
<td>1.17 to 5.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Preeclampsia (no vs. yes)</td>
<td>1.09</td>
<td>0.44 to 2.68</td>
<td>0.85</td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Standardized birth weight</td>
<td>1.11</td>
<td>0.84 to 1.46</td>
<td>0.47</td>
</tr>
<tr>
<td>Model 5 (VLBW group only)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AGA vs. SGA</td>
<td>0.84</td>
<td>0.30 to 2.34</td>
<td>0.74</td>
</tr>
<tr>
<td>Model 6 (VLBW group only)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mechanical ventilation (no vs. yes)</td>
<td>1.59</td>
<td>0.52 to 4.86</td>
<td>0.42</td>
</tr>
<tr>
<td>Model 7 (VLBW group only)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Duration of mechanical ventilation (&lt; 10 days vs. &gt;10 day)</td>
<td>1.64</td>
<td>0.56 to 4.83</td>
<td>0.37</td>
</tr>
<tr>
<td>Full model&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Term Controls (reference) vs. VLBW</td>
<td>2.67</td>
<td>1.45 to 6.20</td>
<td>0.02</td>
</tr>
</tbody>
</table>

aOR; adjusted odds ratio.

<sup>a</sup> Data were adjusted for age, gender, current smoking, parental education, height, BMI, and depression (logarithmed BDI score).

<sup>b</sup> Data were adjusted for age, gender, current smoking, parental education, height, BMI, depression (logarithmed BDI score), and prematurity.

<sup>c</sup> Full model = Model 1 + maternal smoking during pregnancy, preeclampsia, and standardized birth weight

Morningness propensity (Study V)

As compared with controls, the VLBW adults scored higher on the MEQ, indicating morningness propensity (mean score [SD] for VLBW and control groups: 45.7 [9.6] vs. 42.9 [9.0]). This finding particularly characterized VLBW-AGA adults (47.0 [9.7]), who scored higher in morningness than did either VLBW-SGA adults (43.5 [9.2]) or controls, whereas the latter two scored comparably. The results remained similar after controlling for gender, age, or working conditions (Table 12, Figure 7).

In a search for background variables potentially associated with morningness, we found no significant relationships for age, gender, maternal smoking during pregnancy, birth weight, relative birth weight, gestational age, adult BMI, current smoking, frequent use of alcohol, having children currently living in the same household, current gainful employment (yes/no), or currently doing night shifts (yes/no) (p-values > 0.13, adjusted for birth status). Of perinatal risk factors within the VLBW group, a longer duration of mechanical ventilation and blood culture-verified sepsis correlated with morningness.
propensity (r = 0.31, p = 0.004; and r = 0.24, p = 0.022), but BPD and gestational age did not (p-values > 0.32).

As expected based on the literature (Chelminski et al., 1999; Rybak et al., 2007; Tonetti et al., 2009, Hidalgo et al., 2009), morningness correlated with fewer symptoms of ADHD (total sumscore: r = -0.21, p = 0.004; Executive Dysfunction: r = -0.28, p < 0.001), a personality profile characterized by conscientiousness, agreeableness, and lower levels of neuroticism (r = 0.29, p < 0.001; r = 0.18, p = 0.015; r = -0.15, p = 0.04), as well as non-significantly with fewer depressive symptoms (r = -0.13, p = 0.085).

**Table 12.** Comparison of morningness-eveningness scores across groups. Adapted and reprinted, with permission, from Strang-Karlsson et al., Chronobiology International 27:1829-1842, 2010, by Informa Healthcare.

<table>
<thead>
<tr>
<th></th>
<th>VLBW vs. Controls</th>
<th>VLBW-AGA vs. Controls</th>
<th>VLBW-SGA vs. Controls</th>
<th>VLBW-SGA vs. VLBW-AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean group difference</td>
<td>(95% CI), p-value</td>
<td>Mean group difference</td>
<td>(95% CI), p-value</td>
<td>Mean group difference</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.8 (0.1 to 5.5), 0.04</td>
<td>4.1 (1.0 to 7.1), 0.01</td>
<td>0.6 (-3.1 to 4.3), 0.75</td>
<td>3.5 (-0.5 to 7.4), 0.09</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.8 (0.1 to 5.5), 0.04</td>
<td>4.1 (1.1 to 7.2), 0.01</td>
<td>0.5 (-3.2 to 4.2), 0.79</td>
<td>3.6 (-0.3 to 7.6), 0.07</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.8 (-0.02 to 5.5), 0.05</td>
<td>4.1 (1.0 to 7.2), 0.01</td>
<td>0.4 (-3.3 to 4.2), 0.82</td>
<td>3.7 (-0.3 to 7.7), 0.07</td>
</tr>
<tr>
<td>Model 3</td>
<td>2.8 (0.05 to 5.5), 0.05</td>
<td>4.1 (1.0 to 7.2), 0.01</td>
<td>0.5 (-3.2 to 4.2), 0.80</td>
<td>3.6 (-0.4 to 7.6), 0.08</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, gender.
Model 2: Model 1 + gainful employment (yes/no). Missing values n=2.
Model 3: Model 1 + currently doing night shifts (yes/no). Missing values n=2.

**Figure 7** Distribution of morningness-eveningness scores. In boxplots, horizontal lines indicate median and interquartile range, and whiskers the minimum and maximum values.
5.5 Summary of key findings

- Being born both too early and too small in relation to gestational age (VLBW-SGA) was associated with more self-perceived behavioral symptoms of ADHD in young adulthood, more specifically, with executive dysfunction and emotional instability. The VLBW group as a whole did not report more symptoms; in fact those born VLBW-AGA tended to report the least symptoms. In sum, this indicates that growth retardation in utero—for which SGA served as a proxy—might be a more important risk factor for symptoms related to ADHD than is VLBW *per se*.

- VLBW young adults reported less risk-taking behavior in terms of substance use than did their term-born peers.

- Being born at VLBW, even when neurosensory impairments were absent, constituted a risk factor for poorer cognitive outcomes (slower psychomotor processing speed, impaired visual learning abilities) in young adulthood, irrespective of AGA/SGA status.

- VLBW young adults did not differ from term controls with respect to sleep quality or duration. They did, however, have a two-fold risk for sleep-disordered breathing. The VLBW had earlier bedtimes, suggestive of an advanced sleep phase. In a follow-up study three years later, further elucidating the suggested advanced sleep phase, VLBW young adults rated themselves as having an earlier chronotype (morningness propensity) than did the term controls.
6 Discussion

Because the initial VLBW survivors who experienced modern neonatal intensive care have now become adults, there is a growing need for follow-up into adulthood in order to gain knowledge about their long-term outcomes. In this clinical-epidemiological study, we investigated outcomes pertaining to behavioral symptoms of ADHD, cognitive abilities, and sleep characteristics in a cohort of young adults born at VLBW or at term during the years 1978 to 1985.

6.1 VLBW birth and behavioral symptoms of ADHD in young adulthood

Contrary to expectations based on the higher rates of ADHD in preterm children (Bhutta et al., 2002, meta-analysis), we found no increase in self-reported ADHD symptoms in the VLBW group as a whole. In fact, the VLBW adults reported lower total ADHD scores, partly attributable to their lower scores on items related to alcohol use. Our finding is in agreement with those of other self-report studies in adolescents or adults that find no difference between preterms and controls (Saigal et al., 2003; Hack et al., 2004; Dalziel et al., 2007; Hille et al., 2008; Hallin & Stjernqvist, 2010). Ours is in disagreement, however, with reports of more ADHD symptoms based on parental reporting (Saigal et al., 2003; Hack et al., 2004; Dahl et al., 2006).

The oft-appearing discrepancy between parent- and adult offspring ratings is intriguing, and it remains unclear whether one is more trustworthy than the other, or whether they simply represent different but nonetheless equally valid interpretations. It may be that parental concerns about their preterm babies growing up lead to over-reporting of symptoms, or, conversely, that the preterm adults themselves under-report symptoms due to recalibration, denial (Saigal et al., 2003), or a desire to give socially acceptable answers, which has been proposed in the literature (Allin et al., 2006a). It can also be the case that the APQ fails to measure what it is supposed to measure. In the validation study, APQ scores correlated strongly (r = 0.67) with scores on the Conners Hyperactivity Index, and the APQ correctly classified most of the ADHD patients and healthy controls who participated in the study (De Quiros & Kinsbourne, 2001). The study was, however, limited by the self-referred sample and failure to report reliability. Alternatively, our findings may simply reflect the true absence of symptoms, perhaps due to individuals’ outgrowing symptoms over time.

Exploration of the VLBW-AGA and VLBW-SGA subgroups separately increased our understanding of how VLBW relates to ADHD symptoms in adulthood. The VLBW adults born SGA—but not those born AGA—reported more problems on the Executive Dysfunction and Emotional Instability subscale of the APQ. This suggests that intrauterine growth retardation (IUGR, for which SGA served as a proxy) may be a more important predictor for later ADHD-related symptoms than is VLBW per se. It parallels those
studies in term borns reporting that SGA is related to increased psychiatric hospitalization later in life (Monfils Gustafsson et al., 2009). It also parallels the relatively few preterm studies beyond childhood that have compared AGA and SGA preterms separately and found poorer psychological outcomes for those SGA (Dahl et al., 2006).

We found no group difference on subscales designated Anger Out, Social Problems, or Inattention, which disagrees with previous reports on inattention as an area of weakness in preterm children (Mulder et al., 2009, meta-analysis). This discrepancy may be attributed to failure of our Inattention subscale to identify the symptoms, or perhaps to a catch-up during development. Evidence for catch-up in attention skills among preterm children has indeed been reported (Mulder et al., 2009, meta-analysis). We emphasize that we aimed to study self-perceived symptoms of ADHD—not diagnoses—and hence our results do require replication in future studies using a structured diagnostic interview. However, based on our findings, a hypothetical model of risk factors for ADHD is proposed in Figure 8. As for prenatal smoking as a risk factor for ADHD, we found a correlation between maternal smoking during pregnancy and ADHD symptoms in the adult offspring, which is in agreement with other reports on prenatal smoking exposure as a predictor of subsequent psychiatric morbidity (Ekblad et al., 2010). Preeclampsia, on the other hand, was not linked here with ADHD symptoms, despite the fact that preeclampsia often is related to SGA status and IUGR.

VLBW adults (both SGA and AGA) scored lower on the Alcohol subscale of the APQ, entirely in line with their lower rates of drinking, smoking, and recreational drug experimentation according to the substance use questionnaire. This finding, in combination with more ADHD symptoms in the VLBW-SGA group, reinforce suggestions of a more “pure” form of ADHD in ex-preterms, characterized by fewer comorbid disorders (Szatmari et al., 1993), such as substance use. Possible reasons for lower risk-taking include increased parental monitoring, social isolation or lack of opportunities, and personality features that make ex-preterms less prone to risk-taking (Hack et al., 2002; Harrison, 2002; McCormick & Richardson, 2002; Hack et al., 2007, Pesonen et al., 2008; Pyhälä et al., 2010). Speculatively, preterms may also be characterized by personality features that translate into a greater interest in certain types of hobbies that in turn may be prove protective against engagement in risk-taking.
6.2 Cognitive test performance of VLBW young adults

In the present study, we used a computerized cognitive test battery (CogState) focused on visual attentional and memory domains. Ostensibly unimpaired VLBW adults as a group had slower psychomotor processing speed and poorer visual learning abilities than did controls. The effect sizes were moderate; the VLBW group performed between one-fourth and two-thirds SD lower than did the control group. Our results parallel previous findings from different measures for comparing cognitive abilities in VLBW/very preterm adults and controls. Typically, those studies report group differences ranging from one-tenth SD
to one SD in favor of the controls (Hack et al., 2002; Lefebvre et al., 2005; Allin et al., 2008, Weisglas-Kuperus et al., 2009). Also in agreement with our findings, Nosarti et al. (2007) found impairments in several aspects of executive functions in very preterm adults, such as visuomotor processing speed. The existing studies, however, are still few in number and usually focus on limited aspects of cognition. Hence, the comprehensive profile of cognitive abilities in preterm adults, including areas of weakness, strength, and potential catch-up, still remains to be determined. The current study does not provide a complete outline of cognitive abilities in preterm adults. Nevertheless, it adds to the literature by showing that the deficits in processing speed, working memory, and learning, previously observed in preterm children (Rose & Feldman, 1996; Rickards et al., 2001; Aarnoudse-Moens et al., 2009, meta-analysis), persist into adulthood even in apparently healthy individuals.

Contradictory to some findings (Korkman et al., 1996; Lundgren et al., 2001; Weisglas-Kuperus et al., 2009), although in agreements with others (Lefebvre et al., 2005), we found no difference in cognitive abilities between VLBW-AGA and VLBW-SGA adults, suggesting that the group differences were attributable to VLBW per se rather than to IUGR. Although we did not examine the effects of postnatal or childhood growth, it may well be that growth patterns after a preterm birth are more important for determining cognitive abilities in adulthood, as pointed out by some (Weisglas-Kuperus et al., 2009). Few perinatal factors were associated with test performance in our study, nor did SDB mediate the effect. Moreover, it is unknown whether personality-related factors influenced our participants’ responses in our cognitive testing. Hypothetically, the cautiousness and low impulsivity among our VLBW adults (Pesonen et al., 2008) may translate into longer reaction times caused by their fear of giving an incorrect response. In one controlled study in school-aged children, psychologists evaluated ELBW children confronted with novel cognitive tasks and found a tendency to back off and show maladaptive behaviors (Whitfield et al., 1997).

The relevance of longer reaction times is highlighted by a recent study showing that in very preterm children as compared with controls, slower processing speed explains their lower academic attainment (Mulder et al., 2010). Another study found that poorer memory and processing speed accounted for much of the IQ difference between VLBW and control children (Rose & Feldman, 1996). Interestingly, in a study exploring the role of processing speed with respect to the well-known association between IQ and longevity, longer reaction time was an even stronger predictor for mortality than was IQ (Deary & Der, 2005). As we lacked data on a formal assessment of IQ, we were thus unable to test the association between full-scale IQ and cognitive abilities. In conclusion, our finding of subtle cognitive deficits in VLBW adults underscores the importance of maintaining a low threshold for support such as special educational assistance for preterm children.

6.3 Sleep characteristics of VLBW young adults

Many adverse outcomes related to prematurity are also related to poor sleep, or to circadian clock abnormalities that result in disrupted sleep-wake cycles and poor sleep.
Such outcomes include elevated blood pressure, impaired glucose tolerance, and cognitive impairment (Kryger et al., 2005; Hovi et al., 2007; Javaheeri et al., 2008; Aarnoudse-Moens et al., 2009, meta-analysis; Kronholm et al., 2009; Sheer et al., 2009). Hence, poor sleep may be one factor that potentially mediates or modifies the link between prematurity and adverse outcomes. Studies in term-born children suggest prenatal origins of sleep disturbances, and programming of sleep patterns as occurring early in life (Kennaway, 2002; Pesonen et al., 2009; Stone et al., 2010). Evidence from animal studies corroborates these findings. For example, prenatally malnourished rats display altered sleep quality and quantity in adulthood (Datta et al., 2000). Studies on sleep in individuals born prematurely may offer further insight into the early origins of sleep. However, a gap exists in knowledge of sleep in ex-preterms, particularly beyond infancy. In the current work, we investigated sleep characteristics of VLBW adults by both objective and subjective measures.

6.3.1 Sleep duration, quality, and timing

In contrast to the few findings on disrupted sleep and shorter sleep duration in VLBW children during their first years of life (Gössel-Symank et al., 2004; Asaka & Takada, 2010), we found no evidence of altered sleep duration or quality (in terms of sleep efficiency, sleep latency, or fragmentation index) in our VLBW adults. Thus, that disturbances in sleep quality or duration mediate the link between prematurity and adverse health outcomes later in life seems implausible. Unlike Hoppenbrouwers et al. (2005), who studied preterm infants beyond the neonatal period with polysomnography (PSG) and observed disrupted sleep architecture in preterms born SGA, we found no difference in sleep duration or quality between our VLBW-SGA and VLBW-AGA subgroups. Our findings parallel two previous studies’ findings based on parental report that failed to show differences in the sleep of preterm/very preterm children from the sleep of term controls (Wolke et al., 1995; Iglowstein et al., 2006). However, Iglowstein et al. (2006), found no correlation between gestational age and questionnaire-based sleep-onset problems, whereas in our study, lower gestational age correlated with longer actigraphy-derived sleep latency.

Unexpectedly, our findings suggest that VLBW individuals are characterized by an advanced sleep phase. The VLBW went to bed earlier according to the actigraphy recordings, and also reported earlier wake-up times on the questionnaire. Due to the preliminary nature of these findings, we pursued this issue further using a different methodology in a follow-up study three years later and found that on the morningness-eveningness questionnaire, the VLBW group reported a higher morningness propensity (Horne & Östberg, 1976). Thus, we observed no alterations in sleep, but in sleep-wake cycles. This suggests that it is the circadian clock abnormalities that are associated with prematurity. To our knowledge, these findings are novel, since altered sleep rhythmicity in VLBW adults has not been previously reported. One study reported a greater morningness propensity in 13-year-old preterms than in their term-born peers (Natale et al., 2005), a result in line with ours. In a subsequent actigraphy study on 12-month-old children, our suggestions of an advanced sleep phase were replicated: the VLBW/very preterm group
had earlier onset and offset of night-time sleep than did full-term controls, and the magnitude of the group difference was comparable to what we found (Asaka & Takada, 2010).

The mechanisms behind our findings of an advanced sleep phase and morningness preference in VLBW adults may be related to inappropriate and more or less constant postnatal light exposure in the neonatal intensive care units in the era in which our study participants were born. Several animal studies speak for such a link. Prichard et al. (2004) found that adult rats reared in constant light prenatally and for a certain period postnatally, as opposed to rats reared in cyclic light-dark or in constant darkness, showed as adults stronger circadian sleep-wake patterns that were less easily affected by acute changes in environmental light. Interestingly, despite the effect on timing of sleep, no difference appeared with regard to sleep duration, a result in line with ours. In a study on mouse pups, constant light postnatally had adverse effects on subsequent circadian rhythmicity of the SCN in vitro (Ohta et al., 2006).

Further support for long-term programming effects of light comes from reports on plastic changes in SCN astrocytes (Canal et al., 2009) and a more stable circadian rhythm of locomotor activity (Smith & Canal, 2009) in adult mice exposed to constant light postnatally. A study in preterm baboons provides evidence that the SCN of primates is responsive to light at ages equivalent to 24 postconceptional weeks in humans (Hao & Rivkees, 1999). In humans, the SCN is present prenatally and continues to mature after birth, suggesting that it may be sensitive to programming both pre- and postnatally (Swaab, 1995; Kennaway, 2002, reviews). However, some studies also argue against any effect of postnatal light exposure on subsequent rhythmicity (Mirmiran et al., 2003). Besides inappropriate light exposure, there may also be other “exposures” during early life to explain the mechanism behind our finding of an advanced sleep phase. For example, animal studies report phase advance in circadian rhythms after prenatal stress, prenatal protein malnutrition, and prenatal hypoxia (Koehl et al., 1997; Joseph et al., 2002; Durán et al., 2005). Another such “exposure” may be the prolonged absence of melatonin experienced by preterm infants. During pregnancy, the human fetus receives melatonin from the mother (Okatani et al., 1998). The first months postnatally are characterized by a transient melatonin deficiency, which in preterm infants is prolonged (Jan et al., 2007, review). In support of potential programming effects of melatonin, animal models show that maternal melatonin acts as a timekeeper for the fetal SCN in monkeys, and that its absence may alter clock gene expression in the SCN (Torres-Farfan et al., 2006).

Potentially, the mechanisms underlying the advanced sleep phase are to be found in the correlation between certain personality traits and morningness, described fairly consistently in the literature (Tonetti et al., 2009) and seen in our Study V as well. If this is the case, possible mechanisms include alterations in clock genes or their functions, given that personality traits (agreeableness) have been associated in genome-wide association scans with genes such as the CLOCK gene (Terracciano et al., 2010) and morningness-eveningness associates with polymorphisms in the same gene (Katzenberg et al., 1998), or includes a higher level of serotonergic activity, which has been linked with personality
traits in humans (DeYoung et al., 2002) and the circadian system in Drosophila (Yuan et al., 2005). In support of the latter mechanism, clock genes are known to regulate monoamine oxidase A, which in turn regulates serotonin levels (Albrecht, 2010, review). In our study, the morningness propensity in VLBW adults was confined to those born AGA—a finding for which we have no ready explanation. It may be related to the higher level of immaturity at birth, since AGA preterms are born at lower gestational ages and experience a postnatal course different from that of the SGA. Whatever the cause, notably the same pattern of more favorable outcomes for the AGA group (presuming that morningness represents a favorable outcome) is true for depression and ADHD symptoms, as well, in our cohort (Räikkönen et al., 2008; Study I). When it comes to the correlation between gestational age and sleep latency in both our VLBW and control groups (Study III), this, hypothetically, may relate to programming of the hypothalamus-pituitary-adrenal-axis (HPAA). Previous studies have found HPAA function to be dependent on gestational age (Kajantie et al., 2003; Kajantie & Räikkönen, 2010, review), and a tight interplay occur between HPAA function and sleep disturbances (Buckley & Schatzberg, 2005, review).

In short, these possible mechanisms remain speculative. If replicated in future studies, our findings of an advanced sleep rhythmicity and higher level of morningness may be clinically important, given the clinical significance of circadian rhythms for cardiovascular and metabolic health (Cohen et al., 1997; Sheer et al., 2009) and the association between eveningness and mood disorders, sleep disorders, and substance use disorders (Wood et al., 2009; Broms et al., 2010; Van Veen et al., 2010).

### 6.3.2 Sleep-disordered breathing

In a study of 850 children, utilizing overnight in-home cardiorespiratory monitoring and parental questionnaires, SDB rates were three to five times as high in preterms as in controls, depending on the criteria applied (Rosen et al., 2003). We replicated these findings in VLBW adults by showing a more than two-fold risk for SDB, in terms of self-reported chronic snoring (Study IV). A few subsequent studies have reported analogous findings. Calhoun et al. (2010), examined an impressive number of 613 school-aged children with PSG and found prematurity to be a predictor of SDB, the OR being 3.6 (95% CI: 1.7 to 7.4, adjusted for race, SES, and BMI). Other pre- or perinatal determinants of SDB included maternal smoking during pregnancy, need for oxygen at birth, and NICU stay after birth. Montgomery-Downs et al. (2010) explored SDB at 9 months’ corrected age in 173 infants born prematurely. According to parental reports (previously validated only in children older than 2 years), 8.6% of the preterm infants snored at least three times weekly and were classified as having SDB. That study was limited by the lack of a control group, but nevertheless suggests that SDB can already be present in infancy in preterm children. In line with this, in a study aimed at exploring OSAS (obstructive sleep apnea syndrome) due to adenotonsillar hypertrophy in infants, preterms were over-represented (at 24%) in the clinically referred study sample of 29 infants with PSG-diagnosed OSAS (Greenfeld et al., 2003).
The elevated SDB risk may be related to such occurrences as alterations in craniofacial development impacting on the size of the upper airways, or to abnormal respiratory control or ventilatory drive. These mechanistic pathways may in turn stem from the preterm birth or from its associated morbidity or medical intervention. As for craniofacial development, Paulsson et al. (2008, 2009) found altered craniofacial morphology, more malocclusion traits, deep bites, and orthodontic treatment need in extremely or very preterm children than in controls. Supporting the suggestion of smaller upper airway size, Monahan et al. (2002) measured smaller pharyngeal dimensions (minimum cross-sectional pharyngeal area) in children born preterm by use of acoustic pharyngometry and also noted an inverse relationship between this measure and the degree of SDB in the whole sample. The same cohort showed higher rates of prior adenoidectomy or tonsillectomy in preterms (Rosen et al., 2003). With regard to abnormal respiratory control and ventilatory drive as potential mechanisms, a series of animal studies show attenuated ventilatory responses to hypoxia in adults rats exposed to hyperoxia perinatally (Ling et al., 1997). The authors concluded that peripheral chemoreceptor deficits was the main cause, and that early life determinants may be important for ventilatory control in adults. In a study on human very preterm infants, those who needed oxygen treatment for more than 3 weeks postantally showed an altered ventilatory response to oxygen at 36 weeks postconception, especially if diagnosed with chronic lung disease (Katz-Salomon & Lagercrantz, 1994). In this context, the effect of prenatal smoking exposure on subsequent SDB (Study IV; Calhoun et al., 2010) is interesting, particularly in the light of a recent study showing that, in sleeping preterm neonates evaluated near term, prenatal smoking exposure impairs peripheral chemoreceptor function, manifested as a reduced and delayed ventilatory response to hyperoxia (Stéphan-Blanchard et al., 2010).

The clinical implications of an increased risk for SDB in ex-preterms are apparent when considering the cognitive and behavioral sequelae of SDB and the improvement in outcomes after treatment (Wei et al., 2007). Emancipator et al. (2006) found that SDB was related to poorer cognitive performance in children, an effect only partly attributable to lower SES in the SDB group. The effect of SDB defined as chronic snoring was even stronger than that of SDB defined according to objective criteria, which adds validity to our study. Importantly, the SDB-related poorer cognitive performance was more marked in the preterm than in the full-term group, indicating that preterms may face a double hazard. Based on the relatively small number of studies to date that have reported higher rates of SDB in ex-preterms, this patient group may thus benefit from more intensive screening for SDB and increased awareness among health professionals.

6.4 Study limitations

The current work has several limitations, mainly pertaining to the methods used and to loss to follow-up. As in all epidemiological studies with cross-sectional observations, no conclusions about causality are possible. Nevertheless, epidemiological observations do
act as invaluable hypothesis-generators whereupon associations can be confirmed in prospective studies and the mechanisms elucidated by use of experimental designs. Our results are not directly applicable to contemporary cohorts, since our study participants were born more than two decades previously, and treatment regimens as well as survival rates have changed. Attrition bias cannot be ruled out, despite the fact that participants and nonparticipant were similar in regard to most perinatal variables. It is possible that VLBW individuals lost to follow-up had poorer health than those who agreed to participate, as suggested by the higher rates of CP at age 15 months among the non-participants (Hovi et al., 2007). For practical reasons, only adults who resided within 110 km from Helsinki were invited to participate in the study; hence, urban dwellers may have been slightly over-represented in our sample. However, whether such a potential source of sampling bias would affect the results is unclear.

Another limitation is the definition of SGA, which serves as a proxy for IUGR. We defined SGA as a birth weight for gestational age below – 2 SD of the Finnish sex-specific mean (Pihkala et al., 1989). Gestational age is susceptible to recall bias, being based on the last menstrual period, and growth charts are limited by the decreasing number of observations at lower gestational ages. However, we used a stringent definition of SGA (compared with the commonly used 10th percentile limit), which reduces the likelihood of misclassification bias in the SGA group. This stringent definition reduces the risk that normally growing, genetically small-sized preterm infants are falsely classified as SGA. On the other hand, our AGA group may include individuals who were actually growth retarded but who due to their genetically determined relatively large body size did not meet SGA criteria. Our preterm group was defined by birth weight rather than gestational age, which has the advantage of avoiding recall bias of gestational ages, but on the other hand, tends to raise the proportion of near-term SGA infants. The large proportion of SGA in our cohort, though, permits valuable comparisons of SGA and AGA preterms. Since gestational age < 37 weeks was one inclusion criteria, we made sure that all VLBW infants in the current cohort were born preterm.

We had no access to intermediate assessments after early childhood and before adulthood, which would have been informative. Related to the retrospective longitudinal design, it is possible that the findings were confounded by some variable we were unable to measure, such as genes that predispose both to prematurity and to the outcome of interest. Moreover, we used parental educational attainment as a proxy for SES, which may not suffice to describe the social circumstances of the study participants’ childhoods.

Study I is limited by the lack of retrospective data on ADHD symptoms in childhood, and lack of data on parental ADHD. We emphasize that since the study is based on self-report, no diagnosis of ADHD is possible. Nevertheless, the outcome represents ADHD-related behavioral symptoms as perceived by the adults themselves. The psychometric properties of the APQ are at present insufficiently studied. Since no factor structure of the APQ had previously been proposed, we were unable to compare our factor solution with that of others. Moreover, factor analysis contains subjective elements; for instance, the
number of factors included is in the end determined by the investigator. Study II is restricted by ceiling effects which prevented us from examining accuracies of some of the cognitive test tasks. Potentially, participants familiar with video games may have a head start over others when performing the test, however, we do not know whether the proportions of such participants differed between groups. Additionally, lack of data on full-scale IQ precluded study of test performance while controlling for IQ. The actigraphy study (III) is limited primarily by the number of low-quality recordings discarded in attempts to keep a high standard for the recordings included in analyses.

Ideally—but unfeasibly—the sleep assessment should have been performed with PSG. The actigraphy study was carried out in only a subsample of the cohort, which further downsized the sample. In attempts to keep the subsample as representative of the whole cohort as possible, we analyzed those with at least two recorded nights despite our original aim of at least three nights. Recent reports propose that a larger number of consecutively recorded nights may be necessary, but no consensus on the minimum number of nights has been agreed upon (van de Water et al., 2010, systematic review). We failed to account for possible differences in weekend and weekday sleep. Because the actigraphy study was not designed to assess circadian rhythms, replications of the advanced sleep phase finding are therefore vital. The major limitation of the SDB study (IV) is the lack of objective measurements such as PSG. The morningness-eveningness study (V) is limited by attrition, because the study was performed on only a subsample of the cohort. We had no data on mothers working night shifts during pregnancy, something that speculatively could relate to morningness-eveningness in the offspring and thus might be interesting to explore in future studies. Moreover, the exclusion of item 17 due to a typographical error in the questionnaire precludes our comparing morniness-eveningness scores across cohorts, although it is unlikely affect the group differences within our cohort.

6.5 Future prospects

Future follow-up studies extending beyond young adulthood are necessary to discern the ultimate impact of prematurity on outcomes such as reproduction, occupation, and cardiovascular and psychiatric diseases, to mention only a few. Collaboration between cohorts (like the one planned between the Canadian McMaster cohort and the current cohort) should be initiated in order to increase power and to untangle differences and similarities in results. To prevent potential adverse outcomes, upcoming studies should put special emphasis on elucidating mechanisms, causal pathways, the role of genes, and protective factors. Indeed, Norman (2010) argued that perhaps we should start asking the question why preterm birth is an excellent start for the life of some individuals. Studies of long-term outcomes of peri- and neonatal treatments are crucial and best performed in prospective settings. More knowledge on the interaction between family functioning and outcomes of prematurity is also crucial, since this area may offer an opportunity for intervention. In the current cohort, certain outcomes differed markedly between preterms born AGA and SGA, a fact deserving notice in future studies, preferably ones using
refined measures of IUGR. Moderately preterm individuals comprise another understudied population whose long-term health outcomes need attention in upcoming studies.

Given the few and inconsistent reports on ADHD in adult preterm survivors, findings from our ADHD study need replication through in-depth psychiatric interviews. The suggestions of an advanced sleep phase and morningness propensity also await replication, for instance by use of objective markers of circadian rhythms such as melatonin secretion. Modern brain imaging techniques may shed light on the neural correlates of impaired cognitive abilities in VLBW adults, and relating their cognitive performance to their postnatal growth pattern may be informative and ideally may open another window for intervention.
7 Summary and conclusions

This thesis shows that in young adults born prematurely at VLBW, their intrauterine growth pattern (as reflected in their SGA status), rather than VLBW per se, confers a risk for behavioral symptoms of ADHD. Like previous findings from other cohorts, the VLBW adults in the current study engaged less in risk-taking behaviors in terms of substance use, which is encouraging for the parents, families, and the preterm survivors themselves. With regard to cognitive abilities, subtle deficits in processing speed and visual learning abilities existed in VLBW adults on a group level, with no effect of SGA status over and above the effect of prematurity. Notably, these deficits appeared in apparently healthy VLBW adults without neurosensory impairments, which highlights the importance of keeping a low threshold for various kinds of support. With regard to sleep characteristics, we found an increased risk for sleep-disordered breathing in VLBW adults as compared with risk in controls, which underlines the need for increased awareness among clinicians of this potential problem area, as well as a low threshold for screening. Sleep quality or duration showed no differences. Finally, our sleep studies carried out at different time points, on different subsamples of the cohorts, and by different methodologies, all point towards an advanced sleep phase in the VLBW group. The underlying mechanisms and the clinical implications for this remain to be elucidated.

Thus, the current work confirms findings (Gäddlin et al., 2009; Hack et al., 2009, review) that on the whole, most VLBW adults do relatively well, although a smaller proportion do present with sequelae ranging from subtle to severe.
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References


**Grunau RE, Whitfield MF, Fay TB.** Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics* 114:e725-732, 2004.


Järvenpää AL., Granström ML. The development, social behavior and prognosis of premature infants. *Duodecim* 103:1238-1246, 1987. [In Finnish].


Ylppö A. Synnytyksen aiheuttamista aivo- ja keskushermostovioista keskosilla. *Duodecim* 10-12:172-181, 1920. [In Finnish]


