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The Effect of Intrauterine Growth Restriction on Long-Term Outcome in Very or Extremely Low Birth Weight Infants

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Academic dissertation
To be presented, with the permission of the Medical Faculty of the University of Helsinki in the Niilo Hallman Auditorium of the Hospital for Children and Adolescents, on September 28 2007, at 12 noon.

Helsinki 2007
To families with preterm infants
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Abstract

The survival of preterm infants has increased during the recent decades. Thus, the number of children at risk for adverse neurological development has increased. In term-born children, small size at birth is later in life associated with an increased risk for cardiovascular morbidity. Whether intrauterine growth restriction causes an increase in such risk in preterm-born children is unclear. In these prospective studies, we assessed the neurodevelopmental and cardiovascular outcome of 5-year-old children born preterm. Our special interest was the effect of intrauterine growth restriction on outcome. Because tools for early recognition and prediction of cognitive dysfunction in preterm children are lacking, we studied the relationship of auditory event-related potentials (AERP) to long-term outcome.

The neurodevelopmental outcome of a national cohort of 203 extremely low birth weight (ELBW, birth weight less than 1000 g) children born in Finland from 1996 to 1997 showed that 9% had cognitive impairment (intelligence quotient less than 70), 14% cerebral palsy, and 4% needed a hearing aid; 10% had been treated with laser/cryo for retinopathy of prematurity, and 81% of them had abnormal ophthalmic findings. The mean full-scale (96 ± 19) and performance intelligence quotients (94 ± 18) of the preterm children, despite being within normal limits, differed significantly (p < 0.05) from the normal population mean (100 ± 15). Attention, language, and sensorimotor, visuospatial, and verbal memory values in a neuropsychological assessment were poorer than normal population values. Of the whole cohort, 20% exhibited major and 19% minor disabilities, and 61% showed development with no functional abnormalities. In this cohort, being small for gestational age (SGA) at birth was associated with continuing sub-optimal growth. In all ELBW children born before 27 gestational weeks, the SGA had poorer mean language values, and more often minor neuropsychological disabilities than did the appropriate for gestational age (AGA) children.

Echocardiographic results showed an increased thickness of the interventricular septum and a decreased left ventricular end-diastolic diameter standard deviation score (SDS) in both SGA and AGA very low birth weight (VLBW, ≤ 1500 g) preterm children when compared to normal reference values. Further, the preterm children had systolic blood pressure (BP) higher than normal population reference values. In laser Doppler flowmetry, endothelium-dependent perfusion response reached a plateau earlier in the AGA than in the control children. Maximal endothelium-independent perfusion response as well as the response to temperature provocation was higher in the AGA than in the control children. SGA was not associated with cardiovascular abnormalities.

In an AERP maturation study, we assessed responses in SGA and AGA VLBW preterm and healthy term infants at term, at 6 and 12 months of age corrected for prematurity, and at 5 years of age. In the easy oddball paradigm used for infants, the standard was a harmonic tone of 500-Hz fundamental frequency (i.e., 500, 1000, and 1500 Hz
sinusoidals), and the deviant of 750-Hz fundamental frequency (750, 1500, 2250 Hz sinusoidals, probability of 10%). At term age, the main positive peak (P350) was lower in both preterm groups than in the controls. In response to the deviant, the late negative component (Nc) was smaller in the SGA than in the AGA, or the control infants. The N250 amplitude was also smaller in the SGA infants. At 12 months, the mismatch negativity peak (MMN) was observed in the control, but not in the preterm infants, who had a broad difference positivity instead. This amplitude of positive voltage correlated positively with the Bayley developmental index. At 5 years of age, the P1 amplitudes to the frequency deviant were smaller in the preterm than in the control children. MMN was larger in the preterm than in the control children. In the preterm children, several positive correlations were found with P1 or MMN and language performance.

At age 5, in a more challenging paradigm using either a slight frequency, or a short duration deviant, no differences appeared in P1 between the SGA and the AGA, but P1 responses to the standard, frequency, and duration stimuli were smaller in the preterm than in the control children. The SGA had smaller P1 responses to the challenging frequency deviant than did controls. In this paradigm, no group differences occurred in MMN responses. In either the easy or the challenging oddball paradigm, no differences existed between the SGA and AGA children.

In an AERP distraction paradigm, the sound-discrimination task showed longer reaction times to the deviant than to the standard sound source in both preterm and control children, indicating involuntary distraction; the SGA and AGA did not differ from each other. AERP amplitudes in the P1 interval and in the P3a interval elicited by standard and deviant stimuli were smaller in the preterm than in the control children. Deviants elicited P3a (indicating attentional orienting) and reorienting negativity (RON, indicating attentional reorienting after distraction) in both groups. Comparable involuntary attentional orienting, distraction, and reorienting suggest similar maturation processes in preterm and full-term children. In those born preterm, smaller AERP amplitudes in P1 and P3a intervals may suggest altered processing of auditory stimuli.

In conclusion, preterm birth is a major risk factor for brain damage, inflicted by perinatal and postnatal mechanisms. At age 5, preterm children showed signs of cardiovascular abnormality suggestive of later morbidity. That no significant differences between SGA and AGA groups emerged, however, may mean that prematurity has an independent effect on later cardiovascular morbidity. The association of aberrations in AERPs with language performance suggest a possibility to identify risk groups by this method, but the distraction task paradigm appeared to be too difficult for one-fourth of the preterm infants to perform. The predictive value of AERP aberrations for cognitive dysfunction thus must be assessed with further developed stimulus paradigms in a larger population.
1. List of original publications

This thesis is based on the following publications:


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2. Abbreviations

ACh  Acetylcholine
ADHD  Attention deficit and hyperactivity disorder
AERP  Auditory event-related potential
AGA  appropriate for gestational age
ANOVA  analysis of variance
AUC  area under the curve
BMI  body mass index
BP  blood pressure
BPD  bronchopulmonary dysplasia
BW  birth weight
CI  confidence interval
CP  cerebral palsy
EEG  electroencephalography
ELBW  extremely low birth weight
ERP  event-related potential
GW  gestational weeks
IQ  intelligence quotient
IUGR  intrauterine growth restriction
IVH  intraventricular hemorrhage
IVS  interventricular septum
LDF  laser Doppler flowmetry
LVEDD  left ventricular end-diastolic diameter
LVSD  left ventricular systolic diameter
LVPW  left ventricular posterior wall
MND  minor neurological dysfunction
MMN  mismatch negativity
NEPSY  neuropsychological test battery
PU  perfusion units
RON  reorienting negativity
ROP  retinopathy of prematurity
SGA  small for gestational age
SD  standard deviation
SDS  standard deviation score
SOA  stimulus onset asynchrony
WPPSI-R  the Wechsler Preschool and Primary Scale of Intelligence-Revised
SNP  Sodium nitroprusside
VLBW  very low birth weight
3. Introduction

During recent decades, the survival rate of extremely low birth weight (ELBW, birth weight, BW, < 1000 g) infants and especially that of the very preterm infants with gestational age < 28 weeks has increased (Darlow et al., 2003; Tin et al., 1997). Factors contributing to this increased survival include antenatal steroids, surfactant treatment for respiratory distress syndrome, improved ventilation techniques, and proactive optimal delivery planning with centralized management for very immature infants (Håkansson et al., 2004). The proportion of adverse neurological outcome has remained almost unchanged, despite the increased survival rate of the extremely low gestational age infants (Hack and Fanaroff, 2000; Marlow et al., 2005). Intrauterine growth restriction (IUGR) in preterm infants is a risk factor for increased mortality (Bartels et al., 2005; Regev et al., 2003) and for cognitive dysfunction (McCarton et al., 1996).

In Finland, very low birth weight (VLBW, BW ≤ 1500 g) infants accounted for 0.8% and ELBW infants for 0.5% of all births according to the National Birth Register from 1995 to 2005. In the year 2005, a total of 56,963 infants were born in Finland, of whom 480 (0.8%) were VLBW and 209 (0.4%) ELBW infants. Despite advanced perinatal treatment strategies, the incidence of cognitive impairment in ELBW children is still considerable, up to 16.5 to 32%, and the incidence of cerebral palsy (CP) 11 to 16% in the survivors (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). Even in preterm children with normal intelligence and without major neurosensory impairments, cognitive dysfunction and learning disabilities as well as behavioral and attention problems are common (Anderson et al., 2004; Hille et al., 2001; Saigal et al., 2000; 2003; Taylor et al., 2000). In a large cohort study of 6-year-old children born at less than 26 gestational weeks (GW), 41% of the children performed below -2 SD in intelligence testing when compared to control children (Marlow et al., 2005).

Follow-up studies of well-defined cohorts are needed to assess long-term effects of prematurity and perinatal care, since many preterm-born children have later school problems despite being classified as non-disabled during infancy. Several risk factors have been identified for adverse outcome in preterm infants, depending on the timing of the follow-up studies. Even with modern perinatal care, the main risk factor remains the grade of immaturity. However, several studies emphasize the additional effect of infection, inflammation (Cornette, 2004), and hypoxia-reperfusion mechanisms (Inder and Volpe, 2000). New treatment improving the respiratory situation (Stevens et al., 2004), as well as proactive treatment of the very immature (Costeloe and EPICure Study Group, 2006; Håkansson et al., 2004) have improved the outcome. New treatments may, however, have unrecognized long-term adverse effects, as illustrated by the postnatal dexamethasone
treatment commonly used in the 1990s to ameliorate respiratory problems, which resulted in an increased cerebral palsy (CP) rate (Halliday, 2002).

Recent improvements in brain imaging techniques have provided new knowledge of cerebral structural and functional associations in preterm children (Dyet et al., 2006; Woodward et al., 2006), though methods to assess and predict cognitive function early are lacking. Cognitive assessment during the second year of life correlates poorly with later cognition (Hack et al., 2005c). More informative and predictive tests even in children with normal intelligence can be performed at preschool age (Braaten and Norman, 2006). Identification of infants at risk is, however, needed for effective screening and for designing favorable rehabilitation. Auditory event related potentials (AERPs) reflect the brain electrical activity, and can be used as a functional measure of brain response to auditory stimuli. AERPs can objectively and non-invasively be measured without attention or behavioral response at an early age, even in sleeping neonates (Alho et al., 1990; Huotilainen et al., 2003; Kushnerenko et al., 2001; 2002).

Epidemiological studies show that in term infants low weight at birth and in infancy associates with later cardiovascular morbidity (Barker et al., 1989). Whether this is true in preterm infants is unclear.

The aims of this project were to assess the effect of IUGR on the one hand on 5-year outcome in a national cohort of ELBW infants and on the other to assess in a prospective follow-up study whether growth restriction in VLBW infants was a risk factor for adverse neurocognitive and cardiovascular outcome and whether AERP findings are related to cognitive dysfunction.
4. Review of the literature

4.1 Definitions

According to the WHO International Classification of Diseases, preterm birth is defined as gestational age less than 37 weeks, and extreme immaturity as less than 28 weeks. VLBW is defined as birth weight less than 1500 g, and ELBW as less than 1000 g. SGA is considered as a birth weight less than -2 standard deviation score (SDS) of the mean birth weight adjusted to gestational age (World Health Organization, Finnish version 1995). IUGR is defined as diminished fetal growth velocity (Lee et al., 2003).

Neonatal risk factors considered here include intraventricular hemorrhage (IVH) (Papile et al., 1978), necrotizing enterocolitis (Bell et al., 1978), bronchopulmonary dysplasia (BPD) with oxygen dependency at 36 GW (Shennan et al., 1988), and retinopathy of prematurity (ROP) (The Committee for the Classification of Retinopathy of Prematurity, 1984), all risk factors defined according to international criteria.

Cognitive impairment, formerly called mental retardation, is considered as intelligence quotient (IQ) less than -2 SD of the population mean. CP is defined as “a disorder of movement and posture due to a defect or lesion of the immature brain” (Bax, 1964).

4.2. Maturation of the central nervous system and preterm infants

During the embryonic period, the closure of the neural tube occurs by the end of the fourth GW. Thereafter, the neural tube bulges to form the vesicles of the brain, and the spinal cord. The cells within the neural tube wall rearrange, and the stem cells of the germinal neuroepithelium divide and differentiate into neurons and supportive glial cells. By the end of the sixth GW all the five vesicles have formed; the telencephalon (the cerebral hemispheres) have grown over the diencephalon, mesencephalon, metencephalon (the cerebellum and pons), and myelencephalon. Thereafter, the plexus choroid arises and secretes cerebrospinal fluid (Gilbert, 2003).

During the early fetal period, the organogenesis of the brain is very active. The neuroblasts and glioblasts originate from the germinal matrix, a highly vascularized area during the proliferative phase up to 30 GW. Up to 24 GW the neuroblasts migrate to their final cell layer destination, where the neurons initiate dendritic growth to form synapses. Thereafter,
the glioblasts migrate, and the oligodendroglial cells wrap a myelin sheath around the neuronal axons. Myelin causes increased neural conduction velocity. Myelination starts during the second trimester and continues up to adulthood (Gilbert, 2003).

The axonal and dendritic growths are initiated during the second trimester, and synaptogenesis with neurotransmitter production is highly active. Cerebral sulci and gyri start to fold during the third trimester, continuing postnatally (Gilbert, 2003). In term infants, the synaptic density reaches its maximum in the primary auditory cortex at the age of 3 months, in the visual cortex at 8 months, and in the frontal lobes at the age of 2 years. Thereafter, the excess of synaptic connections will be deleted with programmed apoptosis (Huttenlocher and Dabholkar, 1997). In the human brain, cortical maturation occurs heterochronously in different cortical regions, but this is atypical in other species (Huttenlocher and Dabholkar, 1997). The prefrontal maturation continues until late adolescence (Bunge et al., 2002).

Preterm birth is a risk factor for normal brain development. The germinal matrix is located subependymally beside the lateral ventricles, and it practically disappears before term age (Greisen, 1992). In preterm infants, during the functionally active phase of the germinal matrix, the highly vascularized area is prone to vascular insults because of impaired cerebral autoregulation and mechanical fragility of the vascular bed leading to ischemia and hemorrhage. These vascular insults may disturb the neural and especially the glial migration, and may be diagnosed later as periventricular leukomalasia or cysts, enlarged ventricular size, and reduced white and gray matter (Inder et al., 1999). Other causes for abnormal brain development include inflammation, hypoxia, reperfusion injury, or postnatal disorders such as cerebrovascular insults or nutritional deficiency (Amin, 2004; Folkert, 2005; Lucas et al., 1998; Murphy et al., 2001; Raman et al., 2006; Vollmer et al., 2006).

4.3 Mortality

During the last two decades, the neonatal mortality has decreased in the very preterm children (Meadow et al., 2004; Tin et al., 1997; Whitfield et al., 1997; Wood et al., 2000). In the Victoria cohort in Australia, the mortality rate of ELBW infants was 75% in 1979-80, 62% in 1985-1987, and 44% in 1991-1992 (The Victorian infant collaborative study group, 1997). Between two American regional ELBW cohorts in 1982-1989 and in 1990-1998, the mortality fell by 18% (Wilson-Costello et al., 2005). A large multicenter study from 1993 to 1998 of more than 7000 ELBW infants showed a mortality rate of 36% (Vohr et al., 2005). In these very immature infants with a gestational age less than 27 weeks, the mortality decreased from 45% to 39% in those 6 years (Vohr et al., 2005).
Advanced proactive treatment and perinatal care have improved the short-term outcome (Håkansson et al., 2004). Antenatal steroids and surfactant treatment have played an important role in reduction of mortality (Crowley, 2006). Major risk factors for perinatal mortality include low gestational age, IUGR, and male sex (Evans et al., 2007). It is expected that further improvement of perinatal care will reduce the number of preterm stillbirths in the future. Follow-up studies of extremely immature or ELBW infants should therefore include stillbirths and delivery-room deaths, as already have been reported in some studies (Markestad et al., 2005; Tin et al., 1997; Tommiska et al., 2001) The ELBW mortality rate in 1999-2000, including stillborn infants, is reported to be 56% in Finland (Tommiska et al., 2007), and 41% in Norway (Markestad et al., 2005).

4.4. Major neurosensory impairment

The proportion of major neurosensory impairments has decreased during the last 30 years (Doyle et al., 2005) but has remained unchanged in the last 20 years (Hack and Fanaroff, 2000; Marlow et al., 2005, Table 1). Thus the number of children with impairment is increasing, as the rate of survivors has increased. Major impairments of preterm children include CP, cognitive impairment, progressive hydrocephalus, and visual and hearing impairments (Avery et al., 1999).

The most commonly used standardized age-adjusted test to evaluate cognitive development at age 18 to 24 months is Bayley Infant Scale mental assessment (Bayley, 1993). The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Wechsler, 1995) is commonly used at preschool age, and the Kaufman Assessment Battery for Children (K-ABC; Kaufman and Kaufman, 1983) or Wechsler Intelligence Scale for Children (Wechsler, 1991) at school age.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Region/Country</th>
<th>BW or GW Year of birth (N at birth)</th>
<th>N at birth</th>
<th>Mortality, % (N assessed)</th>
<th>Age (N assessed)</th>
<th>Cognitive impairment, %</th>
<th>CP, %</th>
<th>Deafness, %</th>
<th>Blindness, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saigal et al., 1989</td>
<td>Ontario, Canada</td>
<td>&lt; 1000 g 1977-84 (521)</td>
<td>521</td>
<td>53</td>
<td>3 yrs (232)</td>
<td>1*</td>
<td>14</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Veen et al., 1991</td>
<td>Holland</td>
<td>&lt; 1500 g or &lt; 32 GW 1983 (1338)</td>
<td>1338</td>
<td>29</td>
<td>5 yrs (927)</td>
<td>6 (D)**</td>
<td>5 **</td>
<td>1 **</td>
<td>1 **</td>
</tr>
<tr>
<td>Doyle and Anderson, 2005</td>
<td>Victoria, Australia</td>
<td>&lt; 1000 g 1979-80 (351)</td>
<td>351</td>
<td>75</td>
<td>8 yrs (87)</td>
<td>(WISC)</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1985-87 (560)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1991-92 (429)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Finnström et al., 1998</td>
<td>Sweden</td>
<td>&lt; 1000 g 1990-92 (633)</td>
<td>633</td>
<td>42</td>
<td>3 yrs (362)</td>
<td>-</td>
<td>7</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Hack et al., 2005a</td>
<td>Cleveland, USA</td>
<td>&lt; 1000 g 1992-1995 (344)</td>
<td>344</td>
<td>31</td>
<td>8 yrs (200)</td>
<td>15 (K)</td>
<td>14</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Marlow et al., 2005</td>
<td>United Kingdom, Ireland</td>
<td>&lt; 26 GW 1995 (811)</td>
<td>811</td>
<td>62</td>
<td>6 yrs (241)</td>
<td>21 (K)</td>
<td>12</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Farooqi et al., 2006a</td>
<td>Sweden</td>
<td>&lt; 26 GW 1990-1992 (247)</td>
<td>247</td>
<td>64</td>
<td>11 yrs (86)</td>
<td>not assessed</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

* Test not defined
** According to WHO international classification of handicaps (World Health Organisation, 1980)
WISC Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1991)
K Kaufman assessment Battery for Children (Kaufman and Kaufman, 1983)
D Denver developmental screening test
4.4.1 Cerebral palsy

Depending on cohorts studied, the incidence of CP has varied between 10.7 and 15.5% in reports published after 2000 (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). In an ELBW cohort study, in those infants with gestational age less than 27 weeks born in the 1990s, the CP rate was 18% (Vohr et al., 2005) Spastic CP, especially diplegia affecting the lower extremities, is typical for prematurity (Hagberg et al., 1996).

In a large follow-up study of preterm infants, the most important risk factor for severe CP was periventricular leukomalacia, with a 10-fold increased risk for CP. Other risk factors were IVH grade III to IV, postnatal steroids, BPD, and male sex. Birth outside a tertiary hospital and multiple births raised the risk for CP, whereas antenatal steroid was a protective factor (Vohr et al., 2005). During the 1990s, the incidence of severe IVH grade III to IV decreased significantly from 28% to 17%, but the incidence of periventricular leukomalacia remained unchanged in the very preterm infants (Vohr et al., 2005). An important predisposing factor for CP is a maternal infection in pregnancy (Bax et al., 2006), as well as neonatal sepsis or intrapartal hypoxia (Greenwood et al., 2005; Jacobsson et al., 2002). In preterm children born at less than 32 GW, pre-eclampsia was not a risk factor for CP, as it was in term-born infants (Greenwood et al., 2005). Male sex is a risk factor for CP in very preterm infants (Wood et al., 2000). In preterm infants born at less than 28 GW, the risk for CP was higher in infants with a birth weight large for gestational age than in infants with IUGR, whereas in full-term infants, those SGA had a higher the risk for CP (Bax et al., 2006).

4.4.2 Cognitive impairment

The prevalence of mental retardation, or cognitive impairment as is preferable nowadays, was reported to be between 12 and 15% in infants born in the early 1990s (Doyle and Victorian Infant Collaborative Study Group, 2001; Pleacher et al., 2004). In studies published later, the incidence of cognitive impairment is reported to be higher, up to 16.5 to 32% (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). Risk factors for cognitive impairment are periventricular leukomalacia, BPD, multiple birth, male sex, IVH grade III to IV, high frequency ventilation, and postnatal steroids (Vohr et al., 2005). In long-term outcome studies, the rate of cognitive impairment tends to vary depending on study age, as the evaluation becomes more accurate according to developmental level of cognition (Table 3).
4.4.3 Sensory impairment

The rate of blindness has declined in ELBW cohorts during the last 20 years. In the early 1980s, it was 6% (Doyle et al., 2001), whereas nowadays the rate is reported to range between 0.8 and 1.3% (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). The incidence and severity of ROP declined when surfactant treatment started. Risk factors for ROP are low gestational age and the number of days on supplemental oxygen postnatally (Hussain et al., 1999). An advanced ROP, especially in very preterm infants is a complication of prematurity with life-long sequelae (Smith and Tasman, 2005). Advanced ROP associates positively with later ophthalmic abnormalities, with poorer motor skills, and even with poorer intelligence (Cooke et al., 2004; Powls et al., 1997). ROP treatment has had beneficial effects for both eye structure and vision, but in the long run a risk for retinal detachment persists (Palmer et al., 2005).

Hearing impairment is considered major, if a hearing aid is needed. The need for a hearing aid is reported to range from 1.3 to 7% in the most recent studies (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). An otoacoustic emission screening in a VLBW cohort in infancy showed a 0.3% frequency in bilateral sensory-neural hearing loss, but a conductive hearing loss rate up to 2.7% (Ari-Even Roth et al., 2006).

4.5 Minor neurosensory impairment

Minor impairments in preterm children include delays or disorders in cognitive or perceptual development such as lower intelligence, minor neurological dysfunction (MND) including balance and coordination problems, speech/language disorders, or problems in visuomotor or visuospatial perception. Behavioral sequelae include attention deficit and hyperactivity disorder, other behavioral problems, and later problems in achieving academic milestones (Avery et al., 1999). The definitions of minor neurological impairments are not uniform, and study ages of different cohorts vary; thus the direct comparison of results is impossible. Table 2 shows the overall cognitive performance of ELBW children in follow-up studies.
Table 2. Full-scale intelligence quotient (IQ) in long-term follow-up studies of ELBW children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Region/Country</th>
<th>BW or GW Year of birth</th>
<th>Age</th>
<th>Test</th>
<th>IQ preterm (N)</th>
<th>IQ controls (N)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saigal et al., 1991</td>
<td>Ontario, Canada</td>
<td>&lt;1000 g 1977-1981</td>
<td>8 yrs</td>
<td>WISC</td>
<td>91±16 (113)</td>
<td>104±12 (145)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kilbride et al., 2004</td>
<td>Kansas-City, USA</td>
<td>450-800 g 1983-1990</td>
<td>5 yrs</td>
<td>SB</td>
<td>85±12 (25)</td>
<td>95±11 (25)*</td>
<td>0.005</td>
</tr>
<tr>
<td>Grunau et al., 2002</td>
<td>Vancouver, Canada</td>
<td>≤ 800 g 1982-1987</td>
<td>9 yrs</td>
<td>WISC</td>
<td>99±11 (74)</td>
<td>117±13 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anderson et al., 2003</td>
<td>State Victoria, Australia</td>
<td>&lt;1000 g 1991-1992</td>
<td>8 yrs</td>
<td>WISC</td>
<td>96±16 (258)</td>
<td>105±14 (220)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hack et al., 2005a</td>
<td>Cleveland, USA</td>
<td>&lt;1000 g 1992-1995</td>
<td>8 yrs</td>
<td>K</td>
<td>88±18 (200)</td>
<td>100±15 (176)</td>
<td>0.001</td>
</tr>
<tr>
<td>Marlow et al., 2005</td>
<td>United Kingdom, Ireland</td>
<td>&lt;26 weeks 1995</td>
<td>6 yrs</td>
<td>K</td>
<td>82±19 (241)</td>
<td>106±12 (160)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Siblings
K Kaufman assessment Battery for Children (Kaufman and Kaufman, 1983)
WISC Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1991)
SB Stanford-Binet IQ (Thorndike et al., 1986)

The proportion of children in an American regional cohort with IQ < 85 (1 SD from mean IQ score) was 38% in preterm and 14% in term-born control children at age 8 (Hack et al., 2005b). The mean full-scale IQ of ELBW school-aged children has been shown to be below that of control children although within normal population limits, and those ELBW
children with birth weight below 750 g had lower full-scale IQ than those with a greater birth weight (Anderson et al., 2003).

Preterm children often have disorders in specific cognitive areas despite normal intelligence. Performance based on visual perception, such as visuomotor or visuospatial tasks, is vulnerable in ELBW children (Grunau et al., 2002; Kilbride et al., 2004; Taylor et al., 2004). These associate with periventricular leukomalacia in MRI, especially with posterior ventricular enlargement (Olsen et al., 1997) and with thinning of parietal and occipital white matter (Goto et al., 1994). Tasks based on verbal skills are better performed, but at school age the ELBW children have problems with receptive language (Kilbride et al., 2004). Learning problems are common; ELBW children have problems in reading, spelling, and mathematics (Anderson et al., 2003; 2004; Grunau et al., 2002; Hack et al., 2005b; Kilbride et al., 2004; Saigal et al., 2000). The arithmetic skills have even been shown to deteriorate over time when compared to those in control children (Saigal et al., 2000).

Impairments in attention and executive functions, and behavioral problems are frequent in preterm children (Anderson et al., 2004; Hack et al., 2005b; Hille et al., 2001; Saigal et al., 2003; Taylor et al., 2000). Executive functions refer to goal-directed performance with an ability not to get distracted. The prefrontal cortex and related connections are considered important regions for executive functions (Anderson, 2002). Because ELBW children aged 4 to 11 years in cohorts of four different countries had difficulties in social, thinking, and attention-demanding tasks, they seem not to originate in cultural background (Hille et al., 2001). All these skills requiring multiple simultaneous information processing are considered to be associated with the impaired cognitive function of preterm children (Wolke and Meyer, 1999). Minor neurological dysfunctions have been shown to associate with poor performance in the neuropsychological assessment (Olsen et al., 1997) and predict problems at school (Marlow et al., 1993).

4.6 Intrauterine growth restriction, mortality, and neurodevelopmental outcome

In VLBW infant cohorts born in the 1990s, IUGR caused a three- to five-fold increased risk for mortality (Bartels et al., 2005; Regev et al., 2003).

In preterm infants with gestational age over 31 weeks, SGA causes a four- to five-fold increased risk for CP. In a VLBW cohort, the incidence of CP was lower in SGA than in appropriate for gestational age (AGA) children, but the logistic regression risk analysis showed fetal growth restriction not to be associated with a reduced CP risk; gestational
age was the main risk factor for increased CP rate (Dammann et al., 2001). VLBW SGA infants have had a two- to five-fold risk for severe ROP (Regev et al., 2003; Zaw et al., 2003).

In a follow-up of VLBW children, the SGA were compared with gestational age- or birth weight-matched AGA groups. At the age of 5 years, SGA children had better IQ scores than did the birth weight-matched AGA, but poorer verbal performance than the gestational age-matched controls (Gutbrod et al., 2000). Thus, the early gestation with increased number of neonatal complications is suggested to have a larger effect on long-term outcome than does the SGA factor alone (Gutbrod et al., 2000). However, in a study cohort with all preterm infants included, i.e., also those of more mature gestational age, SGA turned out to be an independent risk factor for lower IQ at preschool age (McCarton et al., 1996). Good postnatal catch-up growth associates with better neurodevelopmental outcome in both SGA and AGA infants (Latal-Hajnal et al., 2003). In a follow-up of SGA and AGA ELBW twins and triplets, when socio-economic factors were matched, the SGA-born children were smaller at adolescence, and they had more visual abnormalities, behavioral disturbances, and speech problems than did the AGA co-twin or triplet (Monset-Couchard et al., 2004).

In IUGR, reduced umbilical flow leads to chronic hypoxia that is responsible for fetal blood flow redistribution, i.e., brain sparing. The blood circulation focuses on the brain, heart, and adrenal glands. In a study of growth-restricted infants with an abnormal velocity in the umbilical artery, a retrograde flow in the aortic isthmus associated strongly with non-optimal neurodevelopmental outcome at ages 2 and 4 years, suggesting hypoxic intrauterine brain damage (Fouron et al., 2001).

### 4.6.1 Longitudinal follow-up

Repeated longitudinal outcome assessments of preterm cohorts are important, since the degree of neurological and developmental abnormalities varies depending on study age (Table 3). Cognitive assessment at the age of 2 years poorly predicts school-age cognitive function (Hack et al., 2005c). Outcome measures should be internationally accepted and nationally validated, and age-matched term-born controls should be included for comparison. Table 3 shows the difference in major neurosensory impairment at age 2 and age 8 years in three Victorian ELBW cohorts. During the time course, the incidence of major neurological impairments tends to decrease.
Table 3. Longitudinal publications of ELBW cohort from Victoria, Australia, showing different outcome rates according to study age in three cohorts from different time periods: I (1979-80, N=351), II (1985-87, N=560), and III (1991-1992, N=429).

<table>
<thead>
<tr>
<th>BW &lt; 1000 g</th>
<th>Cohort</th>
<th>2 years age</th>
<th>8 years age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>The Victorian study group, 1997</td>
<td>Doyle et al., 2005</td>
</tr>
<tr>
<td>N survivors (% of live born)</td>
<td>I 89 (25%)</td>
<td>89 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 212 (38%)</td>
<td>212 (38%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 241 (56%)</td>
<td>241 (56%)</td>
<td></td>
</tr>
<tr>
<td>N assessed (% of survivors)</td>
<td>I 89 (100%)</td>
<td>87 (98%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 211 (99%)</td>
<td>206 (97%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 237 (98%)</td>
<td>224 (93%)</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment, %</td>
<td>I 15 *</td>
<td>10 **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 11*</td>
<td>5 **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 12*</td>
<td>9 **</td>
<td></td>
</tr>
<tr>
<td>CP, %</td>
<td>I 14</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Deafness/hearing aid, %</td>
<td>I 3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Blindness, %</td>
<td>I 7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III 2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Bayley Scales of Infant Development (Bayley, 1993)


4.7 Growth

Postnatal growth of preterm children is reported to be poor, and is positively related to birth weight (Cooke and Foulder-Hughes, 2003; Gutbrod et al., 2000; Hack et al., 2003; Kitchen et al., 1992). In a recent follow-up of growth pattern in ELBW children, the weight SDS declined during childhood, but a catch-up to adolescence occurred during the time that height SDS remained below that of control children. This led to higher body mass index (BMI) from age 3 to adulthood than in controls; the study of ELBW children showed no sex-specific differences (Saigal et al., 2006), in contrast to a VLBW cohort study showing a gender difference, with females having a greater ability to catch up later in growth until adolescence (Hack et al., 2003). In extremely immature children born
under gestational week 26, weight, height, and head circumference SDS in the early teenage years were smaller than in control children, but the BMI increased faster than in the control children (Farooqi et al., 2006b). As BMI has been considered a good measure of body fatness, this may be connected with increased insulin resistance (Hofman et al., 2004) and later cardiovascular sequelae (Doyle et al., 2003; Irving et al., 2000; Johansson et al., 2005).

Many VLBW follow-up studies have found an association of poor postnatal growth (Connors et al., 1999) or of catch-up growth (Ehrenkranz et al., 2006) with lower intelligence and higher rate of major and minor neurosensory impairments. Good postnatal catch-up growth associates with better neurodevelopmental outcome on both SGA and AGA infants (Latal-Hajnal et al., 2003).

4.7.1 Intrauterine growth restriction and later growth

In a follow-up of VLBW children, the SGA were compared with the gestational age- or birth weight-matched AGA groups, and at the age of 5 the SGA children had an SDS significantly lower on all growth measures than did the gestational age-matched control children, but an SDS similar than that of birth weight-matched but more immature AGA controls (Gutbrod et al., 2000). The postnatal growth of VLBW infants born SGA is suboptimal up to adulthood when compared to AGA growth (Hack et al., 2003).

4.8 Low birth weight and cardiovascular outcome

Large epidemiological studies have shown that small size at birth and in infancy, especially when combined with accelerated weight gain in childhood until the teens, is associated with an increased risk for cardiovascular morbidity later in life (Barker et al., 1989; 2002; 2005). Low gestational age has been associated with increased systolic blood pressure (BP) in early adulthood (Johansson et al., 2005). In the Finnish population, two different growth phenotypes in childhood seem to lead to different kinds of morbidity in adulthood. Those thin and short at birth and in infancy but with rapid growth in childhood, reaching the average size at age 11, became, as adults, severely hypertensive, overweight, and insulin resistant, with a coronary heart disease risk. The others who were short at birth with poor growth at age 11 became, as adults, hypertensive, overweight, and with a high lipid profile with a stroke risk (Eriksson et al., 2007).

Endothelial dysfunction early in childhood has been considered a risk factor for later cardiovascular disease (Celermajer et al., 1992; Martin et al., 2000b). Flow-mediated
dilation studies by ultrasound have shown a low birth weight to associate with impaired endothelial function at 10 years of age (Leeson et al., 1997). The pathophysiological mechanism of the disease process that may develop from the initial endothelial dysfunction is, however, unclear.

Noninvasive methods to evaluate the macrocirculation include BP measurement and echocardiography. Large population-based reference values of healthy children are available for both BP (Allen et al., 1995; Forsén et al., 1998; Taittonen et al., 1996) and echocardiography (Kampmann et al., 2000).

Noninvasive methods to study microcirculation include laser Doppler flowmetry (LDF) (Nilsson et al., 1980), flow-mediated vasodilatation of the brachial artery during post-occlusive hyperemia (Celermajer et al., 1992; Sörensen et al., 1995), and flow-mediated diameter of the intima-media thickness of the abdominal aorta (Järvisalo et al., 2001). LDF is a non-invasive assessment of endothelial function, and feasible even in newborns (Martin and Norman, 1997). With the LDF method, cutaneous microvascular blood flux can be measured; the reflection of Doppler shift in the illuminated area of the superficial microcirculation is proportionate to the number of blood cells and their velocity, with perfusion expressed as arbitrary perfusion units (PU) (Nilsson et al., 1980).

Use of LDF combined with iontophoresis makes it possible to examine the skin perfusion response to a charged drug delivered locally through the skin by a direct low-intensity electric current (Morris and Shore, 1996). Cholinergic endothelium-dependent skin perfusion has been assessed with acetylcholine (ACh), which induces endothelial vasoactive production; and the endothelium-independent perfusion response has been assessed with sodium nitroprusside (SNP), a nitric oxide donor itself causing smooth muscle relaxation (Morris and Shore, 1996). The drug provocations with LDF are reproducible when the repeated recordings are standardized to the recording site (Kubli et al., 2000). Measurement of flow-mediated vasodilatation of the brachial artery during post-occlusive hyperemia is a standardized method to study shear-stress-induced, endothelium-mediated vasodilation non-invasively (Sorensen et al., 1995). The ACh-induced skin perfusion change in LDF correlates with the flow-mediated vasodilation of the brachial artery and with LDF post-occlusive peak perfusion (Hansell et al., 2004).

4.8.1 Blood pressure

Systolic BP increases with advancing age (Law et al., 1993), and correlates inversely with birth weight in adults (Ylihärsilä et al., 2003). At the age of 5 years, this inverse correlation is weaker than in adults (Taittonen et al., 1996). Previously reported data of BP after prematurity are contradictory. In adolescents, a regional study in the United Kingdom showed no difference in BP between preterm SGA, AGA, and term controls (Singhal et
al., 2001), whereas elevated BP in preterm compared to term-born children with normal birth weight was a finding in Sweden, Australia, Scotland, and the Netherlands (Doyle et al., 2003; Irving et al., 2000; Johansson et al., 2005; Keijzer-Veen et al., 2005). In a 30-year follow-up study performed in New Zealand, preterm-born adults exposed to antenatal steroid treatment had a similar BP and cardiovascular history to that of preterm controls without exposure (Dalziel et al., 2005). A study from Finland showed elevated higher systolic BP in VLBW young adults than in the controls (Hovi et al., 2007). In Finnish children (Forsén et al., 1998; Taittonen et al., 1996) BP has been reported to be slightly higher than in the American pediatric literature (Allen et al., 1995). This suggests that population-specific differences may have both a genetic background and exogenous influences.

4.8.2 Echocardiography

Echocardiographic long-term follow-up studies on preterm children are scarce, performed before the surfactant era (MacLusky et al., 1986; McConnell et al., 1990). In infancy, postnatal dexamethasone treatment has caused transient left ventricular hypertrophy, (Skelton et al., 1998; Yeh et al., 1997; Zecca et al., 2001). In school-aged term-born children, adolescents, and young adults in France, left ventricular mass correlated inversely with growth in infancy, independent of systolic pressure. Increased ventricular mass resulted mainly from the thickening of the posterior wall and interventricular septum (IVS), and was evident in both sexes in all age groups (Zureik et al., 1996). In a Finnish study of VLBW children at school age, the IVS was thickened in children without BPD compared to thickness in control children, but no other significant echocardiographic finding appeared in that study between the preterm and control children (Korhonen et al., 2005).

4.8.3 Endothelial function

Endothelium plays a central role in vascular reactivity. Endothelial function mainly implies the endothelial production of vasoactive substances such as vasodilating nitric oxide, prostaglandins, endothelium-derived hyperpolarizing factor, and vasoconstricting factors. In addition, it regulates vascular tone, permeability, cellular transmigration, smooth muscle cell proliferation, and platelet aggregation (Cracowski et al., 2006).

Endothelial dysfunction has been associated with vascular and metabolic disorders: The endothelium-dependent flow-mediated dilation of the brachial artery correlates inversely with the thickness of the carotid intima media in healthy young adults (Juonala et al., 2004). In high-risk children with hypercholesterolemia or type 1 diabetes, the increased
intima-medial thickness of the abdominal aorta was already evident already at the age of 10 years (Järvisalo et al., 2001). Obese children have shown increased carotid artery stiffness or thickness and diminished flow-mediated dilation of the brachial artery (Tounian et al., 2001; Woo et al., 2004). In a LDF study of normal teens, the endothelium-dependent vasodilation response to ACh, and the smooth muscle-dependent vasodilation response to SNP was diminished in those who had the highest post-feeding glucose levels, and in that study cohort this response correlated negatively with body fat (Khan et al., 2003).

4.8.4 Intrauterine growth restriction and cardiovascular outcome

IUGR is often associated with placental insufficiency. As placental circulatory resistance increases, the umbilical blood flow decreases. In cases of retrograde umbilical flow, hypoxia and acidosis of the fetus emerge (Hecher et al., 1995). High vascular resistance in the placenta raises the cardiac afterload in the fetus, and is associated with arterial stiffness in the preterm and full-term SGA infants (Mori et al., 2006; Tauzin et al., 2006). Full-term growth-retarded infants have an increased aortic wall thickness from an increased intrauterine cardiac workload at the time of birth (Skilton et al., 2005). In the VLBW infant during the first week of life, SGA infants showed cardiac hypertrophy and elevated initial left ventricle output compared to AGA infants as signs of increased cardiac workload and compromised capacity for hemodynamic adaptation (Leipälä et al., 2003).

Fetal growth restriction has not been associated with elevated BP in adolescents born prematurely (Doyle et al., 2003; Hack et al., 2005). Earlier LDF studies have shown an impaired relative response to ACh-induced vasodilation in full-term IUGR infants during the first week of life compared to the response in normal birth weight controls (Martin et al., 2000a). Furthermore, term-born children with IUGR had signs of endothelial dysfunction, whereas preterm IUGR infants and preterm and term controls did not. That study showed no differences between the SGA and AGA preterm infants (Norman and Martin, 2003). However, term-born IUGR children, when prepubertal, had impaired endothelium-dependent vasodilation and increased carotid artery stiffness (Martin et al., 2000b). Prematurely born SGA adolescents did not differ from term-born controls when their endothelial function was studied for flow-mediated brachial artery vasodilation response. The SGA preterm adolescents had, however, a lower vasodilation response than did the AGA group (Singhal et al., 2001). In other studies, both female adolescents who were born prematurely (Bonamy et al., 2005) and term-born IUGR adolescents (Brodzski et al., 2005) had a diminished abdominal aortic diameter compared to controls’ diameters. Neither study, however, showed differences in vascular stiffness or endothelium-dependent vasodilatation.
4.9 Auditory event-related potentials

4.9.1 Development of the auditory system

The auditory system includes the outer ear, middle ear, cochlea, and neural pathways that all develop in parallel from disparate embryonic tissues. The auditory function that depends on cochlear development starts gradually around 20 GW. The innervation of the cochlear hair cells is completed after 22 GW, and the cochlea matures by 35 GW. It is postulated that, because of the amniotic fluid, the outer and middle ears do not participate in fetal hearing. The middle ear ossicles develop until 32 GW, and the tympanic membrane starts to fuse to the temporal bone at 34 GW (Lasky and Williams, 2005). The auditory cortex is located in the superior temporal gyrus. The auditory processing continues from Heschl’s gyrus, the primary auditory cortex, to the secondary cortical areas as well as to other auditory areas and connections to the frontal, parietal, and occipital lobes.

The earliest fetal response has been observed with ultrasound at about 20 GW to a 500-Hz tone of 110 dB (Hepper and Shahidullah, 1994). According to magnetoencephalographic studies, a normally developing brain can detect and even discriminate auditory information after the second trimester of fetal life (Draganova et al., 2005; Huotilainen et al., 2005).

4.9.2 AERP waveforms

AERPs are time-locked, transient synchronized electrical potentials of only a few microvolts in the ongoing electroencephalogram (EEG) induced by auditory stimuli. AERPs of scalp electrodes represent activity of cortical pyramidal neurons, and they can be extracted from the EEG background by repeating the event numerous times. The repeated EEG epochs must be summed and averaged to identify the AERPs and to minimize the activity unrelated to the stimuli (Näätänen, 1992; Stapells and Kurtzberg, 1991).

AERPs with latencies of more than 50 ms after the stimulus onset are called long-latency responses and thought to reflect cortical electrical activity. They are classified into obligatory exogenous or more cognitive endogenous components. The exogenous responses include positive (P) and negative (N) electrical deflections that are determined by the physical characteristics of the stimuli presented. The endogenous components reflect the more cognitive processing of the stimulus paradigm; these responses are related
to learning, memory, and discrimination ability. The oddball paradigms can be used to study endogenous components such as mismatch negativity (MMN), P3a, or late negative responses. In the oddball paradigm, the infrequent stimuli are represented randomly in the repetitive stream of standard sounds (Näätänen, 1992).

In children, several neurodevelopmental disorders or neuropsychiatric diseases have been connected with abnormal auditory processing, such as specific language impairment (Korpilahti and Lang, 1994; Tonnquist-Uhlen, 1996), dyslexia (Guttorm et al., 2005), cleft palate (Cheour et al., 1999), Asperger syndrome (Jansson-Verkasalo et al., 2005; Lepistö et al., 2006), autism (Čeponienė et al., 2003; Gomot et al., 2006; Lepistö et al., 2005), attention-deficit and hyperactivity disorder (AHDH) (Gumenyuk et al., 2005), and depression (Lepistö et al., 2004).

4.9.3 Maturation of AERPs

Exogenous AERPs change in children with the maturation of the auditory system. AERPs of newborns and infants do not consist of the same waveforms as adult AERPs; they are characterized by a large broad positivity at 200-300 ms (P2) followed by late negativity at 300-600 ms (N2) (Kurtzberg et al., 1984). AERPs reflect the maturation of the primary auditory cortex first and later the secondary auditory cortical areas. During the maturation, the AERP waveforms change in infancy first at midline and later at temporal electrodes (Kurtzberg et al., 1984). During infancy, the peak amplitudes increase and latencies decrease, and this is thought to be related to the increase in myelination and synaptic density, and better electrical synchronization of co-working neurons (Eggermont, 1988).

In children, AERPs consist of P1 (at 85-120 ms), N2 (at 200-240 ms), and N4 (at about 450 ms) when the interstimulus interval is less than one second (Čeponienė et al., 1998; Korpilahti and Lang, 1994). In childhood, P1 is large in amplitude (Cunningham et al., 2000; Kushnerenko et al., 2002). P1 is generated in Heschl’s gyrus and is suggested to reflect primary auditory processing (Godey et al., 2001; Liegeois-Chauvel et al., 1994). It decreases in latency and amplitude up to the age of 20 years, reaching the adult latency of approximately 50 ms (Ponton et al., 2002; Sharma et al., 1997). At the age of 5 years, the first typical negative deflection in adults (N1) is not yet detectable (Ponton et al., 2002), whereas the negative peak N2 at approximately 250 ms is large, and diminishes thereafter (Čeponienė et al., 2001).

The MMN is an endogenous AERP response to an infrequent deviant sound in a continuously repeated standard sound stream. During the time the repeated standard sound produces a memory trace, the MMN reflects preconscious sound discrimination and
memory functions (Näätänen, 1992). The MMN is obtained by subtracting the response to the standard from that to the deviant stimuli. In newborns, MMN is elicited during sleep or while awake, peaking at 200-400 ms (Alho et al., 1990). At the age of one to three months, the MMN amplitude increases, despite the stable latency of 200-250 ms with vocal stimuli (Cheour et al., 1998). In infancy, at time windows typical for MMN, positive responses have also appeared (Leppänen et al., 2004). MMN latency is in children about 100-200 ms; it includes both temporal and frontal components (Gomot et al., 2000).

AERPs at different ages of healthy term-born control children that participated in the studies included in this thesis are shown in Figure 1.

**Figure 1.** Auditory event-related potentials to the standard and deviant tone, and the difference wave in term-born healthy infants at term age (A), at 6 months (B), at 12 months (C), and at 5 years (D) of age. The oddball paradigm was used with a standard (probability of 85%) of 100-ms harmonic tone of 500-Hz fundamental frequency (500, 1000, and 1500 Hz) and a deviant (probability of 15%) of 750-Hz fundamental frequency with a SOA of 800 ms.
B) ERPs at 6 months

C) ERPs at 12 months
Other endogenous components include P3a and reorienting negativity, RON. When a novel sound is presented, attention is automatically partially shifted towards the sound. Responses to novel sounds reflect the child’s capacity to allocate attention. This involuntary, automatic attention shift is suggested to elicit the P3a in AERP at around 300 ms (Alho et al., 1998; Escera et al., 1998). The P3a generators are located in the left auditory cortex with association regions bilaterally prefrontally, temporoparietally, and possibly in hippocampal and parahippocampal areas (Escera et al., 2000; Yago et al., 2003). The RON is observed in distraction paradigms, indicating reorienting from task-irrelevant sounds or sound features back to task-relevant sounds or sound features. The frontal RON is considered to reflect reorienting and refocusing on the primary task (Berti and Schröger, 2001; Escera et al., 2001). RON has been observed in adults (Gissler et al., 1998; Munka and Berti, 2006) and children aged 5-12 years (Wetzel et al., 2004; 2006).

4.9.4 Auditory event-related potentials in preterm children

Preterm children develop structural cerebral abnormalities, such as enlarged ventricles with reduced white matter volume, periventricular leukomalacia and cysts, myelination delay, thin cortical gray matter with poor gyration, and corpus callosum dysgenesis (Inder et al., 1999; 2003). The white matter damage is known to be related to adverse long-term neurodevelopment (Inder et al., 2003; Woodward et al., 2006). To evaluate how the
abnormal structure affects the cerebral function, a few AERP studies have been performed on preterm-born children.

Preterm infants have at term age less mature AERPs than do full-term infants (Kurtzberg et al., 1984; Therien et al., 2004). In childhood, MMN to syllables has been smaller in preterm than in control children, and the absence of MMN at the age of 4 years has predicted object-naming difficulties at age 6 (Jansson-Verkasalo et al., 2004). In a distraction study, 5-year-old preterm children had lower correct hit rates and smaller P3a than did control children (Dupin et al., 2000). Preterm children with ADHD had the smallest P1 and P3, and those preterm without ADHD had the second smallest P1 and P3 compared to amplitudes in full-term children with and without ADHD (Potgieter et al., 2003). In 9-year-old preterm-born children the amplitude of the N250 response to standard stimuli was smaller, and it was associated with lower activity in frontal and left supratemporal generators suggesting left temporal impairment in preterm children (Gomot et al., 2007).

Brain sparing in growth-restricted preterm infants has been studied with visual evoked potentials. Those children who had a brain sparing effect verified with fetal Doppler ultrasound had an increased neural maturation during the first year of life, as indicated by shorter latencies (Scherjon et al., 1996). At the age of 5 years, however, the IQ of the children with brain sparing was lower than in those without (Scherjon et al., 2000). Similar signs of accelerated neural maturation has been obtained for IUGR children born at 34 to 38 GW in a recognition memory test (Black et al., 2004).
5. Aims of the study

The aims of this study were:

1. To assess the 5-year outcome in a national ELBW infant cohort and to investigate whether SGA is a risk factor for adverse outcome.

2. To assess the maturation of sound discrimination in VLBW infants during the first year of life, and to evaluate the effect of IUGR on the responses.

3. To investigate whether aberrations in AERPs elicited by a passive oddball paradigm are related to cognitive dysfunction assessed with neuropsychological tests in 5-year-old VLBW children. We also wanted to evaluate the distractibility of VLBW children by the use of AERPS to a distraction paradigm at age 5.

4. To assess whether growth-restricted VLBW infants show cardiovascular dysfunction at age 5.
6. Subjects and methods

6.1 National ELBW cohort (I)

6.1.1 Subjects

The study population consisted of 5-year-old ELBW survivors from a national cohort of ELBW infants born in Finland between 1 January 1996 and 31 December 1997. During that time, a total of 120,025 infants were born including 351 live-born infants and 178 stillborn infants of a gestational age at least 22 full weeks or BW 500 g or more. Data on all ELBW infants were prospectively collected during the perinatal period, during infancy, at 1.5 years of corrected age, and at age 5 years into a research register maintained by the Finnish National Research and Development Centre for Welfare and Health. Figure 2 shows the number of children assessed for outcome of the national ELBW cohort (I).

Figure 2. Flow chart of the survivors in a national cohort of ELBW infants born in Finland, 1996-1997 (I)

The inclusion criterion, BW less than 1000 g, resulted in enrollment of both AGA and SGA infants of a gestational age < 27 weeks, but a rising proportion of SGA infants have a higher GW. In addition to assessing all ELBW children, we analyzed the subgroup of children born at less than 27 GW to evaluate the effect of IUGR on later outcome (Table 4).
Table 4. Perinatal characteristics of the whole national ELBW cohort and of the subgroup of SGA and AGA children born at gestational age less than 27 weeks (I, adapted from Mikkola et al: Neurodevelopmental Outcome at 5 Years of Age of a National Cohort of Extremely Low Birth Weight Infants Who Were Born in 1996-1997. Pediatrics 2005; 116:1391-1400)).

<table>
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<tr>
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<th>All ELBW infants N = 206</th>
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<tbody>
<tr>
<td>Maternal age, years</td>
<td>31.6 ± 5.8</td>
<td>31±6</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>Multiparity (%)</td>
<td>92 (45)</td>
<td>39 (49)</td>
<td>5 (22) *</td>
</tr>
<tr>
<td>Multiple birth (%)</td>
<td>54 (26)</td>
<td>22(28)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Antenatal steroids (%)</td>
<td>163 (79)</td>
<td>63(79)</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Premature rupture of membranes &gt;24 h (%)</td>
<td>48 (23)</td>
<td>35(44)</td>
<td>3 (13) †</td>
</tr>
<tr>
<td>Vaginal delivery (%)</td>
<td>66 (32)</td>
<td>48 (60)</td>
<td>5 (22) †</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>27.3 ± 2.1</td>
<td>25.6 ± 0.9</td>
<td>25.8 ± 1.0</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>806 ± 136</td>
<td>816 ± 116</td>
<td>595 ± 82 ‡</td>
</tr>
<tr>
<td>Birth weight SDS</td>
<td>-2.1 ± 1.4</td>
<td>-0.7 ± 0.8</td>
<td>-2.9 ± 0.5 ‡</td>
</tr>
<tr>
<td>SGA &lt; -2 SDS (%)</td>
<td>106 (51)</td>
<td>0</td>
<td>23 (100) ‡</td>
</tr>
<tr>
<td>Male (%)</td>
<td>95 (46)</td>
<td>45 (56)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Surfactant treatment (%)</td>
<td>126 (61)</td>
<td>50 (62)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Respirator treatment (%)</td>
<td>189 (92)</td>
<td>80 (100)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Respirator treatment in days</td>
<td>19 ± 18</td>
<td>26 ± 20</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>IVH grade III to IV (%)</td>
<td>23 (11)</td>
<td>16 (20)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Perforated necrotizing enterocolitis (%)</td>
<td>12 (6)</td>
<td>9 (11)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Oxygen dependency at 36 GW (%)</td>
<td>80 (39)</td>
<td>39 (49)</td>
<td>11 (48)</td>
</tr>
</tbody>
</table>

SGA vs. AGA:  * P < 0.05, † P < 0.01, ‡ P < 0.001
6.1.2 Methods

Health data at 5 years of age were collected from hospital records and child welfare clinics. CP was defined as a non-progressive motor disorder with abnormal muscle tone, persistent or exaggerated primitive reflexes or a positive Babinsky sign associated with delayed motor development (Hagberg et al., 1996). A modified partial Touwen test (Touwen, 1979) was used for the neurological assessment to detect MND, which is a developmental coordination disorder without major neurological impairment or cognitive abnormalities (Hadders-Algra et al., 2004). Findings of the neurological examination were scored into six functional categories according to Hadders-Algra: 1) mildly abnormal muscle tone regulation assessed from posture maintenance during standing, sitting, and walking; 2) mildly abnormal reflexes; 3) involuntary choreiform movements; 4) mild coordination problems in finger-nose and fingertip touching, diadochokinesia, walking a straight line, and standing on one leg; 5) mild abnormalities in fine manipulation; and 6) other miscellaneous abnormalities, such as brain nerve dysfunction or excess of associated movements (Hadders-Algra, 2002). Results of the neurological examination were classified as normal outcome, simple minor neurological dysfunction (MND-Simple), meaning that one or two of the six main categories were abnormal, complex minor neurological dysfunction (MND-Complex) with three or more abnormal, and CP (Hadders-Algra et al., 2004).

Cognitive development was assessed by the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Wechsler, 1995). Cognitive impairment was classified as severe if the IQ was less than 34, moderate at 35 to 49, mild at 50 to 69.

Neuropsychological performance was assessed with a neuropsychological test battery, the NEPSY test (Korkman et al., 1997; 1998). Mean scores were calculated from the following domains: attention and executive functions (the Auditory Attention and Response Set, Visual Attention, and Statue subtests); language (the Phonological Processing, Comprehension of Instructions, and Speeded Naming subtests); sensory-motor function (the Imitating Hand Positions, Visuomotor Precision, and Manual Motor Sequences subtests); visuospatial perception (the Design Copying, and the Block Construction subtests); and memory and learning (the Memory for Names, Narrative Memory, and Sentence Repetition subtests). Clinical diagnoses of attention deficit and hyperkinesia disorder and dysphasia were collected from patient files.
6.2 Regional VLBW cohort (II-V)

6.2.1 Subjects

In a regional tertiary neonatal intensive care unit, the Hospital for Children and Adolescents, Helsinki University Hospital, a cohort (n=80) of very low birth weight infants was enrolled in 1998-2000 for a follow-up study of cardiovascular, metabolic, and neurocognitive functions. The inclusion criteria were a birth weight less than 1500 g, an indwelling arterial line, and a birth weight \( \leq -2 \) (SGA) or within \( \pm 1.5 \) SDS (AGA) according to Finnish birth weight standards (Pihkala et al., 1989, Table 5). Children with major malformations were excluded. Health data including growth parameters and outcome were prospectively collected from hospital records. The parents of VLBW children were requested to have them participate in the cardiovascular examination and in the AERP recordings with neurocognitive assessments (Tables 6, 7).

Table 5. Perinatal characteristics of VLBW infants participating in the cardiovascular (V) and AERP follow-up (III) at age 5. Data expressed as a number (%) or mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular cohort</th>
<th>AERP cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGA</td>
<td>AGA</td>
</tr>
<tr>
<td>Antenatal steroids, (%)</td>
<td>N=22</td>
<td>N=25</td>
</tr>
<tr>
<td>Pre-eclampsia, (%)</td>
<td>17 (78)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Age, gestational weeks</td>
<td>28.5 ± 2.5</td>
<td>27.6 ± 0.8</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>821 ± 248</td>
<td>1065 ± 241</td>
</tr>
<tr>
<td>Male gender, (%)</td>
<td>15 (68)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Respiratory distress syndrome, (%)</td>
<td>15 (68)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Oxygen dependency at 36 GW, (%)</td>
<td>12 (55)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Postnatal dexamethasone, (%)</td>
<td>7 (32)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Laser treatment of retinopathy, (%)</td>
<td>2 (9)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>
Echocardiography (n=61/80, 76%) and blood volume measurements (n=37/80, 46%) were performed during the first 2 weeks of life. Of the original cohort of 80 preterm children, 45 (56%) were assessed with echocardiography and 47 (59%) with LDF at 5 years of age. For the LDF measurements, full-term infants (n=13) born at the same time in the same hospital were recruited to a control group (Table 6).

Table 6. Participants in cardiovascular follow-up of VLBW children (V).

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal echocardiography</td>
<td>31</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>5-year echocardiography</td>
<td>21</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>5-year laser Doppler flowmetry</td>
<td>22</td>
<td>25</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 7. Numbers of participants in the auditory event-related potential studies: Altogether 41 preterm children arrived for recordings, among whom 37 could be recorded, and of these recordings 28 fulfilled the acceptance criteria for analysis in the passive AERP paradigm. Only 28 of the 37 were able to perform the active task paradigm, and of these recordings only 24 were acceptable (II, III, IV).

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term-age (corrected for prematurity): passive</td>
<td>15</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>1-year (corrected for prematurity): passive</td>
<td>15</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>5-year: passive (N accepted/ N recorded)</td>
<td>13 / 19</td>
<td>15 / 18</td>
<td>13 / 15</td>
</tr>
<tr>
<td>5-year: active (N accepted/N recorded)</td>
<td>12 / 13</td>
<td>12 / 15</td>
<td>11 / 15</td>
</tr>
</tbody>
</table>
6.2.2 Methods

6.2.2.1 Cardiovascular assessments at 5 years of age (V)

Blood pressure was measured oscillometrically (Dinamap) from the right upper arm in a recumbent position after a 20-minute rest. Echocardiography included two-dimensional, M-mode, and Doppler measurements in the standard projections. The left and right ventricular dimensions, thickness and motion of the ventricular walls, left ventricular ejection fraction, and fractional shortening were measured. The internal diameter of the aortic annulus and the flow velocity integral of the ascending aorta were measured for calculation of left ventricular output. All echocardiography measurements were performed by the same pediatric cardiologist.

The laser Doppler flowmetry recordings (Figure 3) were performed at room temperature, 22 to 23°C. The child was sitting with one arm at a time immobilized with pillows to prevent any movement artifact. At first, the right forearm was used for physiological provocations; then the corresponding site of the left forearm for ACh, and finally the right forearm for SNP provocations. After skin-cleaning with 70% alcohol, skin perfusion was measured on the proximal volar side of the forearm where no larger veins were visible. The illuminated skin area was 1 mm², the probe temperature was 32 °C, a single-spot laser Doppler with a wavelength of 780 nm was used. After a baseline measurement at 32 °C for 2 minutes, arterial occlusion was applied for 2 minutes, inducing suprasystolic pressure with a pneumatic cuff. The peak perfusion during the post-occlusive hyperemia, the time-to-peak after cuff release, and the relative perfusion change during the reactive hyperemia (percentage of the peak-baseline difference in relation to baseline) were measured. After the original baseline perfusion was achieved, the perfusion change to local warming from 32 to 44 °C was assessed. Absolute perfusions and relative perfusion change were calculated.

Iontophoretical transdermal drug provocations were performed at 32 °C with 2% ACh for the endothelium-dependent perfusion change, with an anodal current of 0.1 mA for 20 seconds six times, at 40-second intervals. Endothelium-independent perfusion change to 1% SNP was assessed similarly with a cathodal current of 0.2 mA for 20 seconds nine times, at 40-second intervals. Perfusion responses to drug provocations were measured during the 40-second intervals. Maximal perfusion was defined as the perfusion following the last drug provocation. Drug concentrations were those recommended by the manufacturer. The SNP dosage used topically was estimated to have no systemic effects.
6.2.2.2 Neurocognitive assessments (II-IV)

At the age of 24 months, the infants underwent a neurological and developmental assessment (Bayley scale of infant development) at the Hospital for Children and Adolescents; 14 infants were followed up at their local hospital and were therefore not assessed with the Bayley scale.

At the age of 5 years, neurocognitive development of the preterm children was assessed by the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, Wechsler, 1995), and the NEPSY test (Korkman et al., 1997; 1998).
6.2.2.3 AERP follow-up (II-IV)

AERPs were recorded at the age corresponding to 40 (± 2) GW at the Hospital for Children and Adolescents. During infancy, at the age of 6 and 12 months (± 2 weeks), corrected for prematurity, and at chronological age of 5 years the recordings were performed at the Cognitive Brain Research Unit, University of Helsinki.

All children had passed a hearing test in infancy. Full-term infants born close to the same time in the same hospital were recruited to a control group. Numbers of participants in different AERP studies are shown in Table 7.

Ag/Ag-Cl electrodes were attached to nine standard scalp sites according to the International 10-20 system: F3, Fz, F4, C3, Cz, C4, Pz, right (M2), and left mastoid (M1). One nose, one frontal, and two electro-oculogram electrodes were placed. EEG [at bandpass 0.1-30 Hz, sampling rate 250 Hz (II, III), or 500 Hz (IV)] was recorded by use of the NeuroScan 3.4 system. Positivity in AERP figures is located below the horizontal axis.

An easy passive oddball paradigm was performed in infancy (II) and at the age of 5 years (III). A three-partial harmonic tone of 500 Hz fundamental frequency (i.e., 500, 1000, and 1500 Hz sinusoids, 70 dB) served as the standard tone, and a harmonic tone of 750 Hz (i.e., 750, 1500, and 2250 Hz sinusoids) fundamental frequency served as an easy deviant. All sounds were 100 ms in duration and were presented with an 800-ms stimulus onset asynchrony (from onset to onset). The paradigm contained a total of 800 stimuli, and the frequency deviants were randomly presented with a probability of 10%. At 5 years of age, novel sounds (each sound was different) representing environmental noises were included at a probability of 10%.

A challenging passive oddball paradigm was included in the 5-year recording (III). A 75-ms harmonic tone of 1000 Hz fundamental frequency (higher harmonics at 2000 and 3000 Hz sinusoids, 70 dB) served as the standard at a probability of 80%. Two deviants were used: a duration deviant of 35 ms similar in frequency to the standard, occurring at a probability of 10%, and a challenging frequency deviant of 1080 Hz fundamental frequency (including 2160, 3240 Hz sinusoids) with an 8% frequency difference but similar in duration to the standard, at a probability of 10%. This paradigm consisted of 1800 stimuli. All tones in the challenging paradigm were presented with a stimulus onset asynchrony (SOA) of 300 ms with an intensity of 70 dB.

Further, an active distraction paradigm was used to study distractibility at age 5 (IV). Dog barking, cat mewing, and bird crowing sounds (70 dB, duration 400 ms) were presented via loudspeakers located on the right and left side of the screen; loudspeakers and screen
were at head level. The task-irrelevant standard stimuli came from one loudspeaker, and the deviant (11%) sounds from the other direction. The task-relevant issue was to distinguish two animal sounds by clicking computer mouse buttons rapidly and accurately (pictures of the animals were located to the right and left of each mouse button). The paradigm contained three 12-minute sessions, plus training with 12 stimuli prior to and a short break after each session. Each session comprised 18 blocks, and 36 stimuli with two different animal sounds were presented per block with SOA of 3800 ms. After each response, the child received feedback on the screen as a happy or sad smiley. With this feedback, the children were able to concentrate for about one hour.

In the distraction paradigm (IV) EEG was filtered offline (1-20 Hz) and averaged into epochs of 700 ms and a pre-stimulus baseline of 100 ms. Epochs including amplitude differences larger than 100 µV (200 µV in eye electrodes) were rejected. Epochs were separated for stimulus type and groups. The data for MMN, P3a, RON, and P1 were averaged from the three frontal electrodes (F3, Fz, F4). The mean amplitudes were computed around the maximal peak in the grand average, with time windows for P1 at 90-120 ms, in the difference wave (deviant minus standard amplitude) time window for MMN at 180-200 ms, for P3a at 330-360 ms, and for RON at 500-570 ms.

6.3 Statistics

Statistical analyses were performed with SPSS 12.0.1 for Windows and Statistica 5.1. for AERP results.

In the national follow-up, analysis of variance (ANOVA), χ², student´s independent t-test, and Fisher´s exact test were used to distinguish group differences. Multiple linear and binary logistic regressions were used to assess risk factors. For assessing growth, Finnish growth charts were available (Pihkala et al., 1989; Sorva et al., 1990).

In the cardiovascular follow-up, ANOVA, Student´s t-test, and the Mann-Whitney U-test were used to test group differences of continuous variables. The associations of perinatal factors with the 5-year findings were assessed with multiple linear regression analysis. The multivariate general linear model for repeated measurements with log-transformed perfusion values was used to analyze drug provocation responses. Published normal values for BP of Finnish children (Taittonen et al., 1996) and echocardiographic measurements (Kampmann et al., 2000) served as references. Height SDS was calculated by dividing the difference of the observed height and the mean height for age divided by SD, and the weight-to-height ratio (weight-for-height index, kg/cm) was calculated as a
percentage of the mean weight for height for the normal population of the same chronological age and gender (Pere, 2000).

In the AERP studies, the behavioral data and AERPs were analyzed using two-way ANOVAs with the within-factor type (standard, deviant) and the between-factor group (preterm, controls); significant results were post-hoc tested. The clinical data were tested with the t-test, chi-square, or Pearson correlations. A p-value less than 0.05 was statistically significant in all studies.

6.4 Ethics

All the studies represented here were approved by the Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa. Written informed parental consent was obtained before inclusion postnatally and at recruitment for the 5-year follow-up. For ethical reasons we did not recruit control children to echocardiography and neuropsychological assessments, since adjusted population-based reference values were available.
7. Results

7.1 National ELBW cohort (I)

7.1.1 Survival and major neurosensory impairments (I)

The overall 5-year survival rate among the 351 infants was 59% (n=206). In 18 children (9%), congenital anomalies or syndromes were evident. CP was diagnosed in 28 (14%) children; diplegia in 19, tetraplegia in 3, hemiplegia in 2, dystonic CP in 3, and triplegia in one. Ten children (5%) had epilepsy. The main risk factor for any major impairment was IVH grade III-IV (9.7-fold risk).

Of all ELBW infants, 21 (10%) had ROP needing laser or cryo treatment. Of 173 assessed children, 17 (10%) had strabism, 21 (12%) myopia, 14 (8%) astigmatism, 4 (2%) hypermetropia, 7 (4%) amblyopia, 4 (2%) unilateral amaurosis, and one (0.6%) bilateral amaurosis. Eight children (4%) needed a hearing aid.

According to the neurological assessment, 110 children (57%) had a normal outcome, 41 (21%) had MND-Simple, 14 (7%) had MND-Complex, and 28 (14%) had CP. Abnormalities were common in the detailed Touwen functional categories: abnormal posture was evident in 37 children (20%), abnormal reflexes in 33 (18%), exceptional involuntary movements in 31 (17%), coordination problems in 94 (51%), fine manipulative disorders in 28 (15%), and abnormal brain nerve function findings in 20 (11%).

With growth parameters adjusted by age and gender, the weight for height was -7± 11%, height SDS -1.0 ± 1.1, and head circumference SDS -1.2 ± 1.1; All parameters remained significantly (p < 0.05) below the normal Finnish growth curves (Sorva et al., 1990).

7.1.2 Neurocognitive outcome (I)

Cognitive impairment was diagnosed in 19 (9%) children, 13 of whom (68%) were males (gender difference p = 0.04). The mean full-scale IQ of the WPPSI-R-tested children (n=172) was 96 ± 19 (p < 0.05 compared to the normal population WPPSI-R mean 100 ± 15 SD). Regression analysis using perinatal risk factors (multiparity, maternal smoking,
high social class, pre-eclampsia, absence of antenatal steroids, multiple birth, gestational age, birth weight, gender, SGA, vaginal delivery, Apgar score < 4 at 5 minutes of age, university hospital area A, B, C, D, or E, birth outside a tertiary-level hospital, IVH grade III to IV, perforated necrotizing enterocolitis, BPD, ROP grade 3 to 4) explained 55% of full-scale IQ. With a baseline full-scale IQ of 100, presuming only one variable changing at a time, high social class would raise the expected IQ by 14 points (p < 0.001, 95% confidence interval, CI, 9-20), whereas IVH grade III to IV would cause a decrease of 20 points (p = 0.001, 95% CI -32 to -9). Other factors reducing IQ were male gender (8 points, p = 0.002, 95% CI -14 to -3), multiparity (8 points, p = 0.003, 95% CI -14 to -3), multiple pregnancy (7 points, p = 0.02, 95% CI -13 to -1), vaginal delivery (7 points, p = 0.016, 95% CI -12 to -1), and lack of antenatal steroids (8 points, p = 0.04, 95% CI -15 to -0.3). Each BW increment of 100 grams raised IQ by 2 points (p = 0.025, 95% CI 0.3 - 4).

The verbal IQ for all ELBW infants was 99 ± 20, and the performance IQ 94 ± 18 (p < 0.05 compared to the normal population mean 100 ± 15 SD).

The mean of all five NEPSY main domain scores in ELBW children was below the age-corrected normal population mean (Table 8). The number of children achieving test results below the normal average (≤ -1 SD) was 84 (54%) in the visuospatial main domain; 78 (50%) in the sensorimotor domain; 72 (47%) in the attention domain; 45 (29%) in the language domain; and 48 (31%) in the memory and learning domain. Only one-fifth of the ELBW children had a neuropsychological profile within age-correlated norms. Males performed significantly worse (p = 0.01) than females in attention (6.6 ± 3.4 vs. 7.9 ± 3.0) and sensorimotor (6.6 ± 2.2 vs. 7.6 ± 2.5) tasks.

In the ELBW cohort, all the means of NEPSY subtests were significantly (p < 0.001) lower than the age-adjusted normal population mean except for Narrative Memory (Figure 4). Poor performance was common, especially in design copying (mean score 6.4 ± 3.2), auditory attention (mean 6.6 ± 3.8), imitating hand positions (mean 6.8 ± 3.3), and visuomotor precision (mean 6.9 ± 2.7).
Table 8. Neuropsychological test scores (mean ± SD) for ELBW infant cohort at the age of five years (I, adapted from Mikkola et al: Neurodevelopmental Outcome at 5 Years of Age of a National Cohort of Extremely Low Birth Weight Infants Who Were Born in 1996-1997. Pediatrics 2005; 116:1391-1400)

<table>
<thead>
<tr>
<th>NEPSY</th>
<th>ELBW infants 166 / 203 (82%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>8.6 ± 3.0*</td>
</tr>
<tr>
<td>Language</td>
<td>7.7 ± 2.3*</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>7.1 ± 2.4*</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>7.1 ± 2.6*</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>8.4 ± 2.9*</td>
</tr>
</tbody>
</table>

*P < 0.05; ELBW infants compared to normal population NEPSY mean 10 ± 3 SD

Figure 4. Boxplots illustrating the median and the interquartile ranges of performance of ELBW children in NEPSY subtests (normal mean reference values 10 ± 3 SD).
**7.1.3. Intrauterine growth restriction and later outcome**

Neurocognitive performance, Table 9, showed mean language domain NEPSY scores in the SGA children to be significantly poorer than in the AGA.


<table>
<thead>
<tr>
<th></th>
<th>AGA, GW &lt; 27</th>
<th>SGA, GW &lt; 27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WPPSI-R</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>performed on N/N children</td>
<td>68 of 80 (85%)</td>
<td>20 of 23 (87%)</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>96 ± 20</td>
<td>89 ± 16*</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>97 ± 23</td>
<td>91 ± 16*</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>94 ± 19*</td>
<td>94 ± 20*</td>
</tr>
<tr>
<td>Retarded, not tested</td>
<td>3 of 80 (4%)</td>
<td>1 of 20 (5%)</td>
</tr>
<tr>
<td><strong>NEPSY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>performed on N/N children</td>
<td>63 of 80 (79%)</td>
<td>20 of 23 (87%)</td>
</tr>
<tr>
<td>Attention</td>
<td>8.4 ± 3.0†</td>
<td>7.6 ± 2.0†</td>
</tr>
<tr>
<td>Language</td>
<td>7.7 ± 1.9†</td>
<td>6.5 ± 2.2 †‡</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>7.0 ± 2.3†</td>
<td>6.3 ± 2.2†</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>6.9 ± 2.7†</td>
<td>6.4 ± 2.4†</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>8.4 ± 3.0†</td>
<td>6.5 ± 2.2†</td>
</tr>
</tbody>
</table>

* p< 0.05 AGA or SGA compared to normal population WPPSI-R mean 100 ± 15 SD
† p< 0.05 AGA or SGA compared to normal population NEPSY mean 10 ± 3 SD
‡ p< 0.05 SGA compared to AGA
In the subgroup born before 27 GW, the SGA children had significantly lower growth parameters (weight to height%, height and head SDS, and BMI) at the age of 5 years than did the AGA children (Table 10).


<table>
<thead>
<tr>
<th>5-year growth</th>
<th>AGA</th>
<th>SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight%</td>
<td>-5 ±12 (82)</td>
<td>-9 ±11 (91) ‡</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-0.7 ± 1.0 (85)</td>
<td>-1.4 ±1.1 (91) *</td>
</tr>
<tr>
<td>Head circumference, SDS</td>
<td>-1 ± 1.1 (57)</td>
<td>-1.4 ± 1.2*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>14.8 ± 1.6</td>
<td>14.3 ± 1.7 ‡</td>
</tr>
</tbody>
</table>

* p<0.01, ‡ p<0.05

7.2. VLBW infants (II, III, IV, V)

7.2.1 Blood pressure and echocardiography (V)

Systolic BP in the SGA (110 ± 15 mmHg, n=21) and AGA children (109 ± 7 mmHg, n=21) did not differ from population reference values (106 ± 8 mmHg), nor did the diastolic BP (SGA 63 ± 13 mmHg, AGA 63 ± 9 mmHg,) differ from the reference of 65 ± 9 mmHg (Taittonen et al., 1996). However, when both preterm groups were pooled (n=42), systolic BP was slightly higher than the population reference (110 ± 11 mmHg vs. 106 ± 8 mmHg, p = 0.040).

In echocardiography, the SDS of IVS thickness was significantly higher, and the left ventricular end-diastolic diameter (LVEDD) SDS lower in both preterm groups than the reference values (p < 0.05), with no differences between SGA and AGA children (Table 11). Left ventricular fractional shortening and ejection fraction as well as left ventricle stroke index and left ventricle cardiac index were similar in the SGA and AGA children, and within the reference range. The IVS correlated with the LVEDD (r = -0.43, p = 0.003) and systolic (r = -0.31, p = 0.038) diameters, and posterior wall (r = 0.45, p = 0.002), when
adjusted to body surface area. The neonatal echocardiographic measurements did not correlate with the 5-year results.

Table 11. Echocardiographic measurements (mean ± SD) of preterm SGA and AGA children at the age of 5 years (V. from Mikkola et al: Fetal Growth Restriction in Preterm Infants and Cardiovascular Function and Five Years of Age. Journal of Pediatrics 2007, in press).

<table>
<thead>
<tr>
<th></th>
<th>SGA (N = 21)</th>
<th>AGA (N = 24)</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septum (mm)</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td></td>
</tr>
<tr>
<td>Interventricular septum diameter (SD)</td>
<td>0.6 ± 1.2*</td>
<td>0.7 ± 1.3*</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Left ventricle end-diastolic diameter (mm)</td>
<td>32 ± 4</td>
<td>32 ± 2</td>
<td></td>
</tr>
<tr>
<td>Left ventricle end-diastolic diameter (SD)</td>
<td>-0.6 ± 1.0*</td>
<td>-0.9 ± 0.7*</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Left ventricle systolic diameter (mm)</td>
<td>21 ± 3</td>
<td>21 ± 2</td>
<td></td>
</tr>
<tr>
<td>Left ventricle systolic diameter (SD)</td>
<td>-0.2 ± 1.0</td>
<td>-0.4 ± 0.9</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Left ventricle posterior wall diameter (mm)</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td></td>
</tr>
<tr>
<td>Left ventricle posterior wall diameter (SD)</td>
<td>0.1 ± 1.1</td>
<td>0.2 ± 1.1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Left ventricle fractional shortening (%)</td>
<td>35 ± 6</td>
<td>37 ± 5</td>
<td>28 - 40</td>
</tr>
<tr>
<td>Left ventricle ejection fraction (%)</td>
<td>66 ± 7</td>
<td>66 ± 7</td>
<td>50 - 70</td>
</tr>
<tr>
<td>Left ventricle stroke index (ml/m²)</td>
<td>55 ± 11</td>
<td>52 ± 10</td>
<td>40 - 60</td>
</tr>
<tr>
<td>Left ventricle cardiac index (l/[min x m²])</td>
<td>5.2 ± 1.3</td>
<td>5.4 ± 1.7</td>
<td>2 - 5</td>
</tr>
</tbody>
</table>

* p < 0.05 as compared to population reference
7.2.2 Laser Doppler flowmetry (V)

All the physiologic provocation results in the SGA and AGA children were similar, but the heat provocation response was higher in the AGA children than in the SGA and control children (p < 0.05). When the results for all preterm children were pooled, the post-occlusive relative perfusion was lower in girls than in boys (p = 0.023).

All groups showed a significant perfusion change to ACh (p = 0.029, Figure 5). The perfusion baseline of ACh provocation predicted the maximum perfusion response to ACh (p = 0.006). The response reached a plateau earlier in the AGA than in the control group (p = 0.014), but the summarized mean perfusion response to Ach compared between the groups was similar (p = 0.70). The area under the curve, AUC, (SGA 699 ± 431, AGA 648 ± 211, controls 672 ± 273), and the maximal perfusion response (SGA149 ± 89, AGA 132 ± 62, controls 145 ± 64 PU) in all groups were similar. In the preterm groups, systolic BP was a significant cofactor (p = 0.032) in the multivariate analysis. Perfusion change to SNP (Figure 5) was significant in all groups (p = 0.008), and basal perfusion predicted the response (p = 0.03). No significant difference appeared in the velocity of the perfusion response (p = 0.53) or in the summarized mean perfusion response between groups (p = 0.24). The AUC was larger in the AGA than in the control children (AGA 761 ± 294, controls 537 ± 234, p = 0.046), but similar to the AUC of the SGA children (688 ± 374, p = 0.26). The maximal perfusion response was higher in the AGA than in the control children (AGA 119 ± 46, controls 78 ± 35, p = 0.022, SGA 100 ± 59 PU).
Figure 5. Absolute mean skin perfusion responses (perfusion units, PU) at 5 years of age in preterm AGA, SGA, and term-born control children (V. from Mikkola et al: Fetal Growth Restriction in Preterm Infants and Cardiovascular Function and Five Years of Age. Journal of Pediatrics 2007, in press).

A. Endothelium-dependent response to six times repeated doses of topical 2% acetylcholine. The response plateau was achieved earlier in AGA than in control children ($p=0.016$).

B. Smooth muscle–dependent response to nine times repeated 1% sodium nitroprusside. Area under the curve was larger ($p=0.046$) and maximal perfusion response higher ($p=0.022$) in the AGA than in controls.
The growth of the preterm children was sub-optimal at 5 years of age. In the SGA group, 19 of 22 (86%), in the AGA group 18 of 25 (72%) and in the control group 3 of 13 (23%) children had a height SDS smaller than the midparental target height. The mean 5-year height SDS of the preterm children was -1.9 ± 0.8, and the midparental target height SDS was -0.1 ± 0.6. In the preterm children, birth weight SDS correlated significantly with weight-to-height percentage ($r = 0.38$, $p = 0.008$) and with head circumference SDS ($r = 0.47$, $p = 0.002$). Family history of diabetes, hypercholesterolemia, hypertension, or obesity was unrelated to growth variables at age 5.

In the general linear model multivariate analysis using absolute perfusion values, preterm children with height SDS < -1 had a different ACh response profile with a slower vasodilation increase and a lower plateau ($p = 0.033$) than did preterm children with height SDS ≥ -1 or the controls. The maximal vasodilation (height SDS < -1: 112 ± 56 vs. height SDS ≥ -1 148 ± 67, $p = 0.16$; vs. controls 145 ± 65 PU, $p = 0.25$) and the AUC (540 ± 291 vs. 715 ± 373, $p = 0.16$; vs. 672 ± 274 $p = 0.30$) did not, however, differ significantly between groups. The smooth-muscle response to 1% SNP, the maximal vasodilation (105 ± 38 vs. 112 ± 57, $p=0.73$; vs. 78 ± 36, $p = 0.14$), and the AUC (655 ± 155 vs. 756 ± 373, $p = 0.47$; vs. 537 ± 234, $p = 0.23$) did not differ significantly. These nine preterm children with height SDS < -1 were all male, and their mean gestational age was 27.8 ± 2.8 weeks, birth weight 876 ± 256 g, and BMI at 5 years 14.9 ± 2.2%. Eight of them had postnatal corticosteroid treatment. The mean height SDS of this group was 1.9 ± 0.8, and the midparental target height SDS was -0.1 ± 0.6.
7.2.3 AERP maturation in infancy (II)

At term age (Figure 6), the preterm children had an AERP main positive peak to the three-partial harmonic standard tone (mean amplitude over the 150-250 ms and 250-350 ms) similar to that of the 2-to 4-day-old full-term infants, but smaller than in the control children of the same postnatal age (p = 0.0001 at 150-250 ms, p=0.028 at 250-350 ms). The positive peak to the standard stimuli at the parietal electrodes correlated with the 2-year Bayley developmental index, both over the 150-250 ms (r = 0.6 p = 0.048) and the 250-350 ms (r = 0.64, p = 0.032). At term age, the AGA children had a more positive response to the deviant than to the standard at 150-250 ms (p = 0.046). No such differences were obtained in the SGA group. The late negative Nc over 550-650 ms to the deviant was smaller in amplitude in the SGA infants than in the AGA or control infants (p = 0.030).

A precursor of the N250 peak was seen in the AGA group at 6 months of corrected age, but not in the SGA group between 6 and 9 months (Figure 7). The mean voltage over the 250-350 ms interval was significantly more positive in the SGA than in the AGA infants. In the 250-350 ms latency (the latency of the P3a), the positive difference wave voltage was larger in the AGA than in the SGA and the 6-month-old control infants, but not larger than in the 9-month-old controls. Bayley MDI correlated negatively with Nc at 250-350 ms (r = -0.63, p < 0.0.41) to the standard stimuli at the frontal electrodes.

At 12 months, the MMN peak (at 200 ms) was observed in the control, but not in the preterm infants, who had difference positivity instead (Figure 8). In the AGA infants the response to the deviant was significantly more positive than that to the standard over both the 150-250 ms (p < 0.01) and the 250-350 ms periods (p < 0.001); thus, the MMN was indistinguishable. In the SGA infants, the difference between the responses to the deviant and standard was not significant. The mean voltage over the 150-250 ms period in the difference wave was more positive in both preterm groups (p < 0.001) than in the controls. The mean P3a in this latency window correlated positively with the MDI at the frontal (r = 0.61, p = 0.037) and central (r = 0.64, p = 0.025) electrodes.
Figure 6. AERPs and the difference wave in control infants at term and at 3 months of age, and in preterm SGA and AGA infants at corrected term age (II, from Fellman V, et al. Atypical auditory event-related potentials in preterm infants during the first year of life: A possible sign of cognitive dysfunction? Pediatr Res.2004;56:291-7)
Figure 7. AERPs and the difference wave in control infants at 6 and 9 months of age, and in preterm SGA and AGA infants at corrected age of 6 months (II, from Fellman V, et al. Atypical auditory event-related potentials in preterm infants during the first year of life: A possible sign of cognitive dysfunction? Pediatr Res.2004;56:291-7)
Figure 8. AERPs and the difference wave at one-year corrected age in preterm children and in control infants at 12 and 15 months of age. In the difference wave, the preterm infants have no MMN but a broad positivity instead (II, from Fellman V, et al. Atypical auditory event-related potentials in preterm infants during the first year of life: A possible sign of cognitive dysfunction? Pediatr Res. 2004;56:291-7)
7.2.4 AERPs to passive paradigm at 5 years of age (III)

In the easy paradigm, the positive P1 mean amplitudes to the frequency deviant in the SGA and AGA children were similar, but were significantly smaller in the preterm than in the control children (Table 12). The MMN to the frequency deviant was similar in the SGA and AGA, but it was larger in the preterm than in the control children. No differences existed in P3a response amplitudes.

In the challenging paradigm with a fast presentation rate, both preterm groups had smaller P1 responses to standard stimuli than did the control children (Table 12). P1 responses to the frequency deviants were smaller, and P1 responses to the duration deviants both were smaller in the preterm than in the control children. N2 responses to the frequency deviants were larger in the preterm than in the control children. No difference appeared between AERP latencies or any significant lateralization in any group.

Table 12. AERP components P1, N2 (grand averaged over C3, Cz, C4, and Fz), and MMN (at Fz) between preterm and control children at five years of age (For mean values, see Study III, adapted from Mikkola et al., Auditory event-related potentials and cognitive function of preterm children at five years of age. Clinical Neurophysiology. 2007; 118:1494-1502).

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Stimulus</th>
<th>AERP</th>
<th>ANOVA Electrode x Group (Preterm vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Easy</td>
<td>Standard</td>
<td>P1</td>
<td>F(1,38) = 4.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N2</td>
<td>F(1,38) = 0.04</td>
</tr>
<tr>
<td>Frequency</td>
<td>P1</td>
<td>F(1,38) = 8.95</td>
<td>0.005†</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>F(1,38) = 0.01</td>
<td>0.923</td>
</tr>
<tr>
<td></td>
<td>MMN</td>
<td>F(1,38) = 4.88</td>
<td>0.033*</td>
</tr>
<tr>
<td>Novel</td>
<td>P1</td>
<td>F(1,38) = 3.57</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>F(1,38) = 0.46</td>
<td>0.502</td>
</tr>
<tr>
<td>Challenging</td>
<td>Standard</td>
<td>P1</td>
<td>F(1,37) = 17.0</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>F(1,37) = 0.03</td>
<td>0.866</td>
</tr>
<tr>
<td>Frequency</td>
<td>P1</td>
<td>F(1,37) = 9.20</td>
<td>0.004†</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>F(1,37) = 8.29</td>
<td>0.007†</td>
</tr>
<tr>
<td></td>
<td>MMN</td>
<td>F(1,37) = 0.04</td>
<td>0.854</td>
</tr>
<tr>
<td>Duration</td>
<td>P1</td>
<td>F(1,37) = 5.09</td>
<td>0.030*</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>F(1,37) = 0.00</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td>MMN</td>
<td>F(1,37) = 0.29</td>
<td>0.595</td>
</tr>
</tbody>
</table>

Preterm vs. control children; * p < 0.05  † p < 0.01
In the preterm children, several correlations were found with 5-year AERP components and performance based on language. In the easy paradigm, P1 amplitude to standard tone correlated with NEPSY sentence repetition (r = 0.43, p = 0.04), and P1 to novel deviant with NEPSY verbal fluency (r = 0.57, p = 0.001). MMN to frequency deviant correlated with NEPSY verbal fluency (r = 0.50, p = 0.04) and with verbal IQ (r = 0.43, p = 0.03). In the challenging paradigm, the amplitude of N2 to frequency deviant correlated with verbal fluency (r = 0.54, p = 0.03), and P1 to duration deviant with NEPSY language main domain (r = 0.44, p = 0.04) and with phonological processing (r = 0.52, p = 0.02). Results of cognitive assessments are shown in Table 13.

Table 13. Intelligence quotient (IQ) and neuropsychological test results at 5 years of age (mean ± SD) of the VLBW children of the AERP studies.

<table>
<thead>
<tr>
<th></th>
<th>AERP passive paradigm</th>
<th>AERP active paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SGA</td>
<td>AGA</td>
</tr>
<tr>
<td><strong>WPPSI-R</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 12/13 (92%)</td>
<td>N = 14/15(93%)</td>
<td>N = 20/24 (83%)</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>97 ± 24</td>
<td>98±15</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>98 ± 20</td>
<td>104 ± 12</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>96 ± 21</td>
<td>96 ± 17</td>
</tr>
<tr>
<td><strong>NEPSY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 11/13 (85%)</td>
<td>N =14/15(93%)</td>
<td>N = 20/24 (83%)</td>
</tr>
<tr>
<td>Attention</td>
<td>6 ± 4 *</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Language</td>
<td>7 ± 2*</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>6 ± 3*</td>
<td>7 ± 3*</td>
</tr>
<tr>
<td>Visuomotor</td>
<td>7 ± 2*</td>
<td>6 ± 2*</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>8 ± 3</td>
<td>11 ± 3</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01 compared to WPPSI-R reference values 100± 15 or NEPSY 10± 3.

7.2.5 AERPs to active distraction paradigm (IV)

The reaction times to the deviant stimuli were longer than to the standard F(1, 33) = 8.51, p < 0.006), i.e., the expected distraction effect in both groups with no group x type interaction. Correct hit rates to deviant and standard stimuli were similar. The preterm
children had a tendency to be more error-prone than did the controls (F(1,33) = 3.5, p < 0.069). For mean values of reaction times, correct hit rates, and AERP components, see Table in Study IV. Hit rates for the standard stimuli correlated positively with performance IQ (r = 0.534, p = 0.015) and with full-scale IQ (r = 0.509, p = 0.044) in the preterm children. Hit rates for the deviant stimuli correlated even more positively with these IQ measures (r = 0.681, p = 0.001, and r = 0.685, p = 0.003, respectively). Neuropsychological test results are shown in Table 13.

As no significant differences were found between SGA and AGA children, they were considered as one group. These preterm children had smaller P1 amplitudes than the controls: 4.4 µV vs. 6.7µV, F(1,33) = 4.40, p < 0.044 (Figure 9). In the time window for MMN, more negative AERPs were observable in the preterm than in the control group: F(1,33) = 14.5, p < 0.001. No mismatch response-like effect of the stimulus was apparent at the frontal electrodes in either group. In the P3a interval task-irrelevant deviants elicited larger responses than did standards (F(1,33) = 5.62, p < 0.024). In addition, AERPs in the P3a interval were less positive in the preterm than in the control children (F(1,33) = 9.40, p<0.004). No indication of a difference in P3a appeared between groups. For the RON interval, there was a main effect of type, F(1,33) = 4.30, p < 0.046, due to enlarged negativity in the AERPs elicited by the deviant stimuli relative to those elicited by the standard stimuli. Again, no group x type interaction occurred, indicating that the RON in both groups was of comparable size.
Figure 9. Auditory event-related potentials to standard and deviant sound source stimuli at frontal electrodes for the preterm (N=24), and control (N=11) children at age 5. In the frontal electrodes, P1 and P3a were smaller for the preterm than for control children, whereas RON was similar (IV).
8. Discussion

8.1. Methodological considerations

8.1.1 Subjects

In the national ELBW cohort (I), the inclusion criterion BW less than 1000 g resulted in enrollment of all SGA and AGA infants with a gestational age less than 27 weeks, but an increasing proportion of SGA infants at higher GW (Tommiska et al., 2001). Since SGA children are overrepresented among ELBW children with a gestational age over 27 weeks, the effect of gestational age has been considered only in children born before 27 weeks. The inclusion criteria based on birth weight depends on historical reasons, since the majority of comparable cohorts were so defined. Accurate birth weight can be obtained for every newborn, but before systematic fetal ultrasound assessments were introduced, gestational age may have been incorrect. Thus, even though fetal ultrasound was available for the majority of the ELBW children, the birth weight criterion was used for enrollment. Nowadays when gestational age is estimated by fetal ultrasound, inclusion criteria of follow-up studies should be based on gestational age. In future, as serial routine antenatal ultrasound are available (at GW 10-14 and 18-21 in Finland since 2007), even more accurate assessment of IUGR can be achieved.

In the national follow-up study, we used population-standardized age-matched neuropsychological tests. A comparison with controls born after normal pregnancies and deliveries in the same hospitals might have been more precise, as shown by other studies (Marlow et al., 2005). The strength in our cohort is the inclusion of all deliveries, including stillbirths, providing a true prognosis of ELBW pregnancies. Another strength was the low drop-out rate of 1%, and the low proportion, 5%, of only locally assessed children.

In the VLBW studies (II-V), one of the original inclusion criteria was an indwelling arterial line, because in the neonatal period the infants underwent a minimal model insulin sensitivity test (Leipälä et al., 2002). Thus, the infants recruited represent VLBW infants with considerable neonatal morbidity and not a population-based cohort. Their neurodevelopmental outcome was therefore poorer than the average for VLBW infants, as was expected. In the AERP studies during infancy, the control infants participated in all repeated recordings, but at age 5 for only half could we obtain consent. At ages 2 and 5...
years, assessing the control children with neuropsychological tests might have provided a more accurate comparison, but because the AERP recording was time-consuming, the extensive neuropsychological test was not included for ethical reasons. This strategy is acceptable, since the tests used are well standardized in the population.

In the cardiovascular study (V), the participants were mainly the same preterm and control children as in the AERP studies. As BP and echocardiographic age- and sex-matched reference values were available, we recruited control children only for the LDF assessments. Case-control assessment on every method would have been the best design, but was an unrealistic approach when dealing with 5-year-old children.

8.1.2 Methods

The national ELBW cohort (I) used standardized Touwen assessment (Touwen, 1979). As this test is complex, we used a modified, more unambiguous Touwen test (Hadders-Algra, 2002). A common international sensitive outcome assessment of neurological status is lacking. As motor coordination disorders are common, there is a need for a high-quality measurement tool to evaluate functional disability precisely.

In the VLBW AERP studies (II-IV), the EEG recordings contained artefacts (technical errors such as detachment of an electrode, movement artefacts, poor impedance) or too few epochs leading to several exclusions of recordings. A minimum of 35 epochs for the easy, and 75 for the challenging paradigm were required. The distraction paradigm was considerably challenging because it was long-lasting, and required good cognitive and concentration ability from the child. Many of the children with a successful passive AERP recording could not perform the active task paradigm. This might be explained by the fact that the participants represent preterm VLBW children with only fairly good cognitive ability. A further AERP methodological drawback to be considered is the rate of missing responses in control infants; e.g., previous studies have detected MMN at term in only 80% of infants categorized to be healthy term newborns (Fellman, 2006). Whether this finding is a technical issue or related to later language difficulties remains to be assessed.

In the cardiovascular study (V), BP was only measured on one visit. A 24-hour BP registration would have provided more information. We compared the results of BP and echocardiography of preterm children to published data, since we considered such reference values superior to those of a small control group. LDF measurements, however, were performed both on preterm and control children. LDF was challenging to complete due to movement artefacts caused by the tickling of iontophoresis, and impaired cooperation during the one-hour procedure. The success rate in the ACh and in SNP
provocations in the preterm children were 72% and 62%, leaving a possibility of beta error in the analysis.

The variability in LDF is substantial (Kubli et al., 2000), so several factors should be taken into account when interpreting LDF recordings. Iontophoresis may induce sensory nociceptive C fibers (axon reflex) to produce vasodilative substances, and the vehicle itself may cause non-specific vasodilation (Droog and Sjöberg, 2003; Droog et al., 2004). In our study, the voltages of the anodal and cathodal currents were low, in accordance with recommendations for iontophoresis (Droog et al., 2004). Previously, iontophoresis with sodium chloride with the same magnitude of anodal current as in our study produced no skin perfusion change (Martin et al., 2000a). It has been suggested that application of local anesthetic creme and antihistamine prior to recording would reduce involvement of sensory nerves and histamine-related reactions (Horiuchi et al., 2004), but these agents may have other confounding effects, as well (Droog et al., 2004).

8.2. Neurodevelopmental outcome of the national ELBW cohort (I)

8.2.1 Mortality and major neurosensory impairments

The 5-year survival rate in our study increased as gestational age and BW increased, and was similar to that reported in the mid-1990s (Doyle and Victorian Infant Collaborative Study Group., 2001; Meadow et al., 2004; Tin et al., 1997; Wood et al., 2000). Of this entire ELBW cohort, 61% were considered normal, 19% had minor, and 20% major disabilities. When the results of the Epicure study (Marlow et al., 2005) of 6-year-old preterm children born at less than 26 GW is categorized according to our follow-up classification, their outcome would be 46% with no disabilities, 29% with minor, and 24% with major disabilities. The slightly higher rates can be ascribed to the one-week younger inclusion criterion.

The cognitive impairment rate cannot reliably be determined at 1.5 years of age, but is rather well assessed at 5. The prevalence of cognitive impairment of 9% is slightly less than the 12 to 15% reported in infants born in the early 1990s (Doyle and Victorian Infant Collaborative Study Group., 2001; Pleacher et al., 2004). The CP rate was 14%, in accordance with other studies with rates of 11 to 16% (Doyle and Anderson, 2005; Vohr et al., 2005; Wilson-Costello et al., 2005). A ROP treated in infancy was a significant risk for later visual impairment, in accordance with findings that ROP treatment reduces the incidence of poor visual outcome without an increase in the rate of normal visual acuity.
(Reynolds et al., 1993). In this study, the rate of ELBW children’s needing a hearing aid was 4%. The rate of hearing deficits has largely ranged, e.g., in ELBW cohorts of the 1990s, from 9% (Hack et al., 2000) to less than 1% in infants of GW < 27 (Doyle and Victorian Infant Collaborative Study Group., 2001). To obtain reliable results on hearing deficits, long-term outcome studies are needed, since the study age is important (Table 3). In this study, when BW was the inclusion criterion without any exclusion of syndromes or genetic causes of hearing disabilities, about half the children using a hearing aid appeared to have a primary cause for the hearing deficit other than prematurity.

8.2.2 Minor neurosensory impairments

The performance of all five NEPSY main domain scores in ELBW children were below the age-corrected normal population mean of 10. Studies have shown that specific problems may occur in practically all domains of neurocognitive development, however, with the exception of verbal expression and memory (Anderson et al., 2003; Grunau et al., 2002; Hille et al., 2001; Kilbride et al., 2004; Saigal et al., 2003). Despite normally rated performance on language tasks in intelligence tests, the ELBW children often have reading and spelling problems (Anderson et al., 2003; Grunau et al., 2002; Kilbride et al., 2004; Saigal et al., 2003). Studies have also shown deficits in ELBW children in receptive language (Kilbride et al., 2004) and verbal memory (Taylor et al., 2004). In our national follow-up, the children with spastic diplegia performed well on tasks based on verbal skills, but had difficulties in attention, sensorimotor, and visuosconstructive function, which is dependent on visual perception. Similarly, other studies have showed that children with CP have impairments in tasks based on visual perception (van den Hout et al., 2000; van den Hout et al., 2004).

The association of diffusely subnormal neuropsychological performance with MND is an important finding, since in follow-up studies these children would be classified as normal. Minor neurological dysfunction and neurological soft signs are also associated with decreased cognitive performance in school-aged children, even when the neurological background is normal (Fellick et al., 2001). The children in our follow-up were considered normal at the age of 18 months, since no neurological abnormality or developmental delays occurred (Tommiska et al., 2003). In addition, a diffusely subnormal neuropsychological profile within several NEPSY domains predisposes later learning disorders (Friedman et al., 2003; Mayes et al., 2000).

Our specific aim was to evaluate the effect of IUGR on outcome. In the ELBW follow-up, at the age of 5 years the growth of SGA children was still sub-optimal compared to that of AGA children. In ELBW children born at less than 27 GW, all means of NEPSY main domains remained below the population reference, but the SGA children performed
significantly (p < 0.05) poorer in the NEPSY language domain than did the AGA children. All mean scores of WPPSI-R and NEPSY main domains were in the SGA group significantly lower than for the reference. However, in regression analyses of risk factor for IQ, SGA did not appear as an independent risk factor. In another study, immaturity with many-fold neonatal complications is suggested to have a larger effect on long-term outcome than does the SGA factor only (Gutbrod et al., 2000).

8.3. AERP studies of VLBW children (II, III, and IV)

8.3.1. AERPs in infancy (II)

The maturation pattern of the AERP during the first year of life in control infants was in line with other findings (Kushnerenko et al., 2002; Novak et al., 1989). AERPs of the preterm infants at 40 GW to standard stimuli were similar to those of full-term newborns, but not to those of the 3-month-old controls, suggesting that exposure to extrauterine auditory stimulation for a mean duration of about 3 months did not influence the infants’ maturation of auditory processing. Thus, AERPs of preterm infants should be compared to AERPs of controls of a similar postconceptional rather than postnatal age. Scalp-recorded AERPs represent cortical synaptic activity, and postnatal synaptic density correlates with the postconceptional age rather than postnatal experience (Zecevic and Rakic, 1991).

At the age of 12 months, AERP positivity in the difference wave may reflect a delayed AERP maturation in preterm infants (Kushnerenko et al., 2002). The absence of MMN in preterm children may be connected to altered auditory change detection.

8.3.2. AERPs to a passive paradigm (III)

In this study, P1 amplitude was diminished in the preterm children at 5 years. P1 amplitude is normally large at age 5 and increases up to age 10, which may reflect the high synaptic density and increased intracortical myelination (Čeponienė et al., 2002; Ponton et al., 2002). Decreased P1 amplitude has been reported in children with ADHD (Jonkman et al., 1997; Kemner et al., 1996), with Asperger syndrome (Jansson-Verkasalo et al., 2003), and with autism (Čeponienė et al., 2003). In one study using visual event-related potentials, preterm children had a smaller P1 than did control children (Potgieter et al., 2003). In the present study, P1 amplitude correlated positively with the NEPSY language tests. One study found that in children with learning difficulties, P1, N1, and N2 correlated with spelling, auditory processing, and listening comprehension (Cunningham et al., 2003).
The small P1 peaks observed in the preterm children in our study may thus suggest impaired primary auditory encoding.

The MMN amplitude to the easy frequency deviant was larger in the preterm than in the control group. Since the P1 peak preceding the MMN was smaller in response both to the standard and deviant in the preterm children, it may have enhanced the MMN deflection. Interference from adjacent peaks is possible, since surface-recorded deflections represent the algebraic sum of overlapping positive and negative components. Alternatively, it is possible that the response to auditory change was genuinely enhanced in preterm children, both during their first year of life, when MMN may be of positive polarity (Fellman et al., 2004), and at the age of 5, when consistent MMN appears (Shafer et al., 2000). In a study of dyslexic children (Kujala et al., 2001), training-induced enhancement in MMN amplitude correlated with reading-skill scores. The association observed in this study between the amplitude of MMN and verbal IQ and fluency may be a true sign of cortical discrimination. Small positive P1 amplitudes and enlarged MMN amplitude to the easy frequency deviant in preterm children may reflect impaired early auditory processing that may also affect verbal skills. AERP alterations in preterm children may arise from perinatal brain damage. White matter lesions acquired in childhood have recently been shown to affect AERPs, although cortical structure is normal (Hogan et al., 2006).

No considerable differences appeared between SGA and AGA children in AERPs at any age. This may be a true finding and be more related to the neonatal morbidity, which was marked and similar in both groups, than the growth restriction per se (Gutbrod et al., 2000).

8.3.3 AERPs to an active task paradigm (IV)

Using an active task distraction paradigm, no differences in AERPs appeared between SGA and AGA infants, and thus the groups were combined in the preterm group. Due to the small number, however, a beta error cannot be excluded.

P1 response was smaller in the preterm than in the control children, similarly to the passive paradigm results. Small P1 might reflect a different pre-attentive stage between the groups, and might be a sign of attenuated auditory processing or impaired voluntary attention. The long stimulus onset asynchrony (SOA) in the present study (3800 ms) may have affected MMN generation. Unclear MMN with long SOAs in children was also observed in other studies (Ćeponienė et al., 2004; Gumenyuk et al., 2004; Wetzel et al., 2006). That P3a was present in both our study groups suggests involuntary orienting towards task-irrelevant deviants. The P3a is expected to be present at age 5 in normal children (Gumenyuk et al., 2004). We found that even preterm children of this age have
P3a. This result confirms a finding of no group difference in P3a when deviants are task-irrelevant (Dupin et al., 2000). However, when deviants are task-relevant, or when attention is not controlled, some have found group differences in the P3a (Lavoie et al., 1997; Potgieter et al., 2003). Combined behavioral and AERP studies suggest that frontal P3a reflects involuntary attentional orienting (Escera et al., 1998; Escera et al., 2000; Schröger et al., 2000). We suggest that also in preterm children, P3a indicates involuntary attention. This interpretation is consistent with the behavioral distraction effect. Our AERPs were generally smaller in the P3a interval in those born preterm, which may possibly relate to our P1 results. Thus, because the P1 is larger in control children, the subsequent AERP maintains this shift in positive polarity. Thus, the group effect on the P3a interval may be of no functional relevance. Here RON was observable in both groups, indicating that cognitive attentional reorienting after distraction is functional in 5-year-old children. No differences appeared between the groups, suggesting similar executive control following distraction.

**8.4 Cardiovascular outcome in VLBW children (V)**

The preterm children showed signs of increased cardiac afterload. Systolic BP in the preterm children was higher than the population reference, but no differences appeared between the SGA and the AGA. Similarly, elevated BP has been found in preterm compared to term-born children with normal birth weight (Doyle et al., 2003; Irving et al., 2000; Johansson et al., 2005; Keijzer-Veen et al., 2005), especially in female subjects (Bonamy et al., 2005; Hack et al., 2005). IUGR has not, however, been associated with elevated BP in preterm adolescents (Doyle et al., 2003; Irving et al., 2000; Keijzer-Veen et al., 2005).

Repeated echocardiography during the first 2 postnatal weeks showed that the preterm SGA infants had cardiac hypertrophy that the AGA lacked (Leipälä et al., 2003). In echocardiography at 5 years of age, both preterm groups had increased IVS thickness and decreased LVEDD with no associations with neonatal echocardiography, IUGR, or any other perinatal risk factors. Postnatal dexamethasone treatment was not associated with hypertrophy at 5 years of age. Combined with the finding of systolic BP, prematurity per se may be an independent risk factor for these signs of increased cardiac workload.

In the present study, the endothelium-dependent vasodilative response was slower and the endothelium-independent response higher in the AGA children than in the controls. No differences emerged between the SGA and the AGA. Because neonatal LDF studies have shown an impaired relative response to ACh-induced perfusion response in full-term IUGR infants (Martin et al., 2000a; Norman and Martin, 2003), but not in preterm IUGR.
infants (Norman and Martin, 2003), one might speculate that preterm birth may protect the child from abnormal fetal programming concerning cardiovascular status.

Endothelium-independent, SNP-induced maximal perfusion response was higher in the AGA than in the control children. A study on vascular smooth muscle function in children showed that the smooth muscle response induced by glyceryl trinitrate correlated inversely with vessel diameter (Pena et al., 2006). Female prematurely born adolescents (Bonamy et al., 2005) and term-born adolescents with IUGR (Brodszki et al., 2005) had diminished abdominal aortic diameters when compared to those of controls. We did not measure vessel diameter. Repeated SNP- and ACh-induced perfusion responses during pregnancy in pre-eclamptic women have shown an increase in SNP-induced perfusion preceding pre-eclamptic syndromes, and have later shown an increase in ACh-induced perfusion during the hypertensive state (Khan et al., 2005). It has been speculated that the increased sensitivity to nitric oxide preceding pre-eclamptic symptoms may be a compensatory mechanism of the smooth muscle layer (Khan et al., 2005). Our finding of the enhanced SNP-induced perfusion combined with higher systolic BP and increased IVS thickness in the AGA children may indicate a compensatory smooth muscle function probably because of diminished blood vessel diameters. Our preterm children had no signs of metabolic disorders such as obesity or diabetes; and no associations appeared between endothelial dysfunction and family history of diabetes, hypercholesterolemia, hypertension, or overweight. Whether our finding of an association between sub-optimal growth in boys and decreased reactivity in the endothelium-dependent perfusion response is a sign of a developmental trajectory that links early life events with adult cardiovascular disease (Barker et al., 1989; Barker et al., 2002) remains to be clarified in a long-term follow-up study in a larger population.

8.5 Future

During the last 20 years, the mortality of ELBW and extremely immature infants has decreased, and even the rate of neurosensory impairments has slightly decreased. As late handicaps and disabilities are inversely related to gestational age (Veen et al., 1991), improvement in the perinatal care of very immature infants is crucial (Håkansson et al., 2004; Vohr et al., 2004). Despite the importance of early intensive care, numerous other factors affect outcome, such as epigenetic effects, or rehabilitation, environmental, or socioeconomic factors (Dammann et al., 1996; Escobar et al., 1991). Studies on possibilities to improve post-discharge factors are, however, still scarce.

Perinatal care undergoes continuous development, and therefore new population-based cohorts are needed, with detailed perinatal characteristics and outcome variables over a
long time course. Follow-up registers including data from hospitals, child welfare clinics, and schools are warranted. In addition to perinatal risk factors, late postnatal factors should also be taken into consideration. Benchmarking multicenter studies are needed to clarify differences in treatment strategies between centers and countries. To be able to compare study results, uniform follow-up schedule, i.e., defined study ages and methods, are also necessary.
9. Conclusions

I
In the national ELBW cohort, 61% of the survivors were considered functionally normal, 19% had minor, and 20% major disabilities. The incidence of cognitive impairment was 9% and of CP 14%. Considering the IUGR effects on preterm children at 5 years of age, SGA alone was not a risk factor for a low intelligence quotient. However, the SGA children in the ELBW national cohort with a gestational age less than 27 weeks had poorer performance on all neurocognitive test means in WPPSI-R and NEPSY when compared to reference values, and they performed more poorly in the NEPSY verbal main domain than did the AGA children.

The high rate of cognitive dysfunction in the neuropsychological test profile suggests an increased risk for learning difficulties that needs to be evaluated at a later age. In addition, the SGA infants still showed poorer growth at 5 years of age. Extended follow-up should be the rule in outcome studies of ELBW infant cohorts to elucidate the impact of immaturity on school achievement and social behavior later in life.

II
During the first year of life, the AERPs in VLBW infants differed from those of control infants, being more positive in overall voltage. At the age of one year, preterm children’s AERPs showed broad difference positivity, whereas the control children had MMN. This difference positivity correlated positively with the 2-year Bayley developmental index. The broad difference positivity at one year of age may indicate atypical cortical auditory processing.

Auditory evoked-response potentials in 5-year-old VLBW children showed small P1 responses that appear to be typical for preterm children, and these may suggest altered primary auditory processing. Small positive P1 amplitudes and enlarged MMN amplitude to the easy frequency deviant in preterm children may reflect impaired early auditory processing that may also affect verbal skills. The association of aberrations in AERPs with language performance suggest a possibility to identify risk groups by this method.

In an active distraction paradigm, the 5-year-old VLBW children tended to be more error-prone than did control children, but revealed behavioral and AERP distraction effects similar to those of controls. Attention AERP components were recognizable in the control children and in those preterm children who successfully completed the task. Smaller AERP amplitudes in the P1 and P3a interval suggest altered processing of auditory stimuli in those born preterm. However, involuntary attention shift and distraction in those born preterm and full term seem to be similar. The pathophysiology behind AERP aberrations
is not clarified. Thus, this method is still a research tool, and the clinical applicability needs to be evaluated in further studies.

III
Compared to reference values, 5-year-old VLBW children had increased systolic BP and a thickened IVS. These findings did not correlate with perinatal risk factors. Altered cardiac dimensions and differences in perfusion responses may reflect increased cardiac afterload. We found differences in LDF perfusion responses, especially between the AGA and control children, which may indicate altered function at a microvascular level.

Growth-restricted VLBW children appeared to differ very little from the AGA children. No differences in cardiovascular function or vasoreactivity existed between them at 5 years of age. Interestingly, prematurity per se may impair cardiovascular function independently of intrauterine growth restriction. Neither were any distinct differences found in AERP studies between growth-restricted and AGA-born children. Since the infants represented those with considerable postnatal morbidity, the growth restriction effect appeared less important than other risk factors.
Acknowledgements

The studies were carried out at the Hospital for Children and Adolescents, Helsinki University Central Hospital, in collaboration with the National Research and Development Center for Welfare and Health, Helsinki, and with the Cognitive Brain Research Unit, Department of Psychology, University of Helsinki. I sincerely thank Head Professor Mikael Knip, and the Administrative Head of the Hospital, Veli Ylitalo, at the Hospital for Children and Adolescents, and Professor Risto Näätänen, Head of the Cognitive Brain Research Unit at the University of Helsinki, for maintaining the excellent research facilities. I am very grateful to Professor Markku Heikinheimo, the director of the Pediatric Graduate School, for effectively promoting support for doctoral students. I also thank the Heads of the Division in Stakes Information, Hannu Hämäläinen and Olli Nylander, and the Developmental Manager, Mika Gissler, at the National Research and Development Center for Welfare and Health.

I wish to express my warmest gratitude to all who made these studies possible, and I especially wish to thank:

My supervisor Professor Vineta Fellman for excellent guidance and patience with this work. I admire her scientific insight and her ability to adapt the most recent scientific results to new practices. I am very grateful for her encouragement and support for these studies.

The reviewers of the manuscript of the thesis, Professor Pirjo Korpilahti and Docent Ville Jäntti, for their constructive comments and advice.

Docent Anna-Liisa Järvenpää and Docent Jaana Leipälä for participating in the follow-up group of my studies. I am grateful for the meetings and conversations on this work, and for encouragement and optimism. I also wish to thank Anna-Liisa for reviewing the thesis from the neonatological point of view.

Dr. Viena Tommiska, who had collected the perinatal and two-year data of the national cohort, for help and support in good times and bad times. I want to thank pediatric neurologist Teija Salokorpi for teaching me the neurological study method and good consultation in neurologic aspects. I also thank neuropsychologist Niina Ritari for assessing the children of the Helsinki area, and for the collaboration with other neuropsychologists in other university hospitals. I am grateful to research assistant Marita Suni, and all the personnel in the Lastenlinna wards for outstanding assistance.

All collaborative colleagues and co-workers in the national ELBW follow-up study in other university hospital areas: Docents Leena Lehtonen and Leena Haataja from Turku, Docent Outi Tammela, Drs. Manta Tolvanen and Outi Saarenpää-Heikkillä from Tampere Docent Kirsti Heinonen and Dr. Leena Pääkkönen from Kuopio, and Drs. Tero Saarelä, and Päivi Olsen from Oulu University Hospitals for good collaboration in the national follow-up study. I also want to thank all the neurophysiologists and nurses all over Finland for taking part in the follow-up study.
Docent Minna Huotilainen, Dr. Helen Kushnerenko, Eino Partanen, MSc., and Dr. Rita Ėponienė at the Cognitive Brain Research Unit. All the meetings and discussions concerning these studies introduced me an interesting scientific branch of clinical neurophysiology. Especially I wish to thank Eino for his kindness and patience.

My German co-workers Dr. Nicole Wetzel and Professor Erich ("Erkki") Schröger from the Institute of Psychology I, University of Leipzig. International collaboration by using email worked well and rapidly. I am grateful to neuropsychologist Silve Serenius-Sirve for performing the psychological assessments in the AERP studies. And I especially thank research assistant Leena Wallendahr. I miss the nice working hours with you; your personal character created such a positive and pleasant atmosphere.

Pediatric cardiologist Talvikki Boldt for performing all the echocardiographic examinations for the cardiovascular study.

Dr. Carol Norris for skillful editing of the language of the original articles and the thesis.

All my colleagues and friends at the Hospital for Children and Adolescents for their support, help, and refreshing humor. I want to thank all my peers in the Pediatric Graduate School for refreshing and supportive lunch conversations, help, and being such good company. Especially I want to thank Dr. Eero Kajantie for the statistical discussions concerning the data analyses.

The children and their families participating in these studies.

My friends: Many thanks to “Laaksolahden Martat,” to “Levi’s Ladies,” to “Secret Sisters,” to “Cooper-naiset,” as well as to friends from school and student times.

I want to express my deepest gratitude to my beloved family. My parents Hilkka and Esko have encouraged me in all areas of life, and they have been wonderful grandparents for my children. The family of my brother (Mikko, Sirpa, Julius and Karoliina) bring joy into our lives.

I want to express my love to my children Oskari, Emilia, and Ursula - And surely to my little poodle Väinö. They provide the core happiness of my life.

Helsinki, September 2007.

Kaija Mikkola
Literature cited


Crowley P. 2006. Prophylactic corticosteroids for preterm birth. Cochrane Database of Systematic Reviews 4:


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