EXTREMELY LOW BIRTHWEIGHT INFANTS IN FINLAND

Early outcome, costs of care, and parental distress with infants of birth weight below 1000 g

Viena Tommiska

ACADEMIC DISSERTATION

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ABSTRACT
To assess short- and long-term consequences of extremely low birth weight, in 1996 all five university hospitals and the National Research and Development Centre of Welfare and Health established a national register for extremely low birthweight infants (ELBW, <1000 g) born in Finland. Using this register, this prospective nation-wide investigation determined the birth rate, mortality, short-term morbidity, and neurodevelopmental outcome of ELBW born during 1996 and 1997, and analysed factors associated with unfavourable outcome. The overall costs of care and parental coping in families of ELBW born in the Helsinki University Hospital were also evaluated.

The national study cohort consisted of all live and stillborn ELBW born in Finland between 1 January 1996 and 31 December 1997, and the regional subcohort of ELBW born in Helsinki University Hospital. Full-term infants born next to each ELBW in Helsinki University Hospital were eligible for the control group.

The national prospective data from all maternity hospitals (n=44) comprised information on pregnancy, delivery, neonatal morbidity, treatment, and short-term outcome to an age corresponding to 40 gestational weeks (GW).

Follow-up data from all attending hospitals included ophthalmological assessments at the age of 12 months and neurological and speech therapists’ assessments at the age of 18 months. Both ELBW and control infants born in Helsinki University Hospital were assessed by the Bayley Infant Scale, 2nd edition (mental index), at the age of two years, and during this visit parents of both groups completed a parenting distress questionnaire (Swedish Parenthood Stress Questionnaire).

The costs of care for ELBW and controls were obtained from the Helsinki University Hospital Patient Accounts Office, from hospitals responsible for care and follow-up, and from families by a mailed questionnaire.

Of the 529 ELBW (0.4% of all newborns, n=120 025) born in Finland during the study period, 34% (n=178) were stillborn and 22% (n=115) died on day 0-6. Neonatal mortality was 38% (n=133) and post-neonatal mortality 2% (n=7). Of all live-born infants, 60% (n=211) survived until an age of 40 GW.

At 18 months’ of age, 42% of the 208 surviving infants were classified as normally developed, 40% as mildly impaired and 18% as severely impaired. The rate of cerebral
Abstract

Palsy was 11%, motor impairment 24%, ophthalmic abnormalities 23%, speech delay 42%, and hearing impairment necessitating a hearing aid 3%. In the regional subcohorts, Bayley scores were significantly lower among ELBWI (n=78) than among controls (n=75), but the scores of ELBWI seemed to improve during the follow-up period.

Mortality and short-term morbidity decreased with increasing birth weight. Moreover, abnormalities in vision assessment correlated negatively with birth weight, but the rates of other impairments at the age of 18 months were not related to weight at birth. Significant differences in survival, short- and long-term morbidity were found between the five university hospital areas.

Most parents in the subcohort of ELBWI appeared to have recovered well, as the parenthood stress in these families did not significantly differ from the stress experienced in control families. Due to the small number of infants with a handicap, no conclusions could be drawn about distress in families with an impaired infant.

The two-year costs of care even for normally developed ELBWI were higher (25-fold) than for their full-term counterparts. Among the mildly impaired, the costs were 33-fold and among the severely impaired, 68-fold those of control infants. The initial hospital care costs accounted for 64% of overall costs and correlated negatively with birth weight. However, among ELBWI, no correlation between the costs of care and birth weight was found after the initial hospitalisation.

In conclusion, mortality, short-term morbidity, visual impairment at the age of 18 months, and costs of initial hospital care correlated negatively with birth weight, but rates of other impairments at the age of 18 months and costs of care following initial hospitalisation did not. In surviving infants, the high rates of neurological deficits necessitate long-term follow-up. Differences in regional outcome and detected improvement in Bayley mental scores warrant assessments of new cohorts and continuous evaluation of treatment practices.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals (I-IV):


IV Tommiska V, Tuominen R, Fellman V. Economic costs of care in extremely low birthweight infants during the first two years of life. Ped Critic Care Med 2002; in press.
ABBREVIATIONS

B Bayley Mental Index
BPD bronchopulmonary dysplasia
CI confidence interval
CP cerebral palsy
CRIBS Clinical Risk Index for Babies
ELBW I extremely low birthweight infant
G Griffiths Mental Developmental Scale
GW gestational week
HUCH Helsinki University Central Hospital
ID intellectual disability
IQ intelligence quotient
iqr range interquartile range
IVH intraventricular haemorrhage
LBW low birthweight infant
McC McCarthy Scales
NA not available
NEC necrotising enterocolitis
NICU neonatal intensive care unit
OR odds ratio
PDA persistent ductus arteriosus
PSI Parental Stress Index
PVL periventricular leukomalasia
RDS respiratory distress syndrome
ROP retinopathy of prematurity
SB Stanford-Binet Intelligence Scale
SD standard deviation
SE standard error
SGA small for gestational age
SIDS sudden infant death syndrome
SPSQ Swedish Parenthood Stress Questionnaire
VLBW I very low birthweight infant
W Wescler Preschool and Primary Scale of Intelligence
INTRODUCTION

The outcome of very low birthweight infants (VLBW, birth weight <1500 g) born 50 years ago was poor (Lubchenco et al. 1963). Of the infants admitted to the Colorado General Hospital Premature Infant Centre, only 50% survived the first year of life and the impairment rate in the 63 VLBWI followed until the age of ten years was high. Visual impairment was found in 60%, spastic diplegia in 35%, intelligence quotient (IQ) below 90 in 42%, and of those who had had electroencephalograms (n=55), 60% had abnormalities in it. All five extremely low birthweight infant (ELBW, birth weight <1000g) survivors were neurologically or intellectually impaired: one mildly, others moderately or severely (Lubchenco et al. 1963).

The introduction of neonatal intensive care in the 1960s together with better knowledge of physiology and methods for treating and controlling such conditions as hypoxia, acidosis, hyperthermia, hypoglycaemia, and hyperbilirubinaemia improved survival of preterm infants (Rawlings et al. 1971). The initial outcome results in ELBW were, however, modest and contradictory, with some investigators reporting declined mortality and morbidity rates, but others claming no advances (Alden et al. 1972; Jones et al. 1979; Stewart et al. 1977). During the 1970s increasing number of studies provided evidence of better survival in ELBW. Hack et al. reported significantly increased survival in ELBW (26% vs. 47%) born at University Hospitals of Cleveland when two three-year study periods, from 1973 to 1975 and from 1976 to 1978, were compared (Hack et al. 1979). Moreover, the outcome of surviving infants appeared to improve over time (Hack et al. 1979).

In the 1980s, the survival of ELBW continued to improve, initially among ELBW with a birth weight of more than 750 g, but by the end of decade the greatest improvement in survival was found in infants with a birth weight from 500 to 750 g (French et al. 1995; La Pine et al. 1995; Philip 1995; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a). Although more ELBW also seemed to have survived without impairment when infants born during the 1970s were compared with those born in the early 1980s, no further decline in overall impairment rates was found during the 1980s (Blaymore-Bier et al. 1994; Grogaard et al. 1990; Hack et al. 1996; Cshea et al. 1997; The Victorian Infant
Introduction

Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997).

Recent advances in care, such as antenatal steroid treatment for mothers with threatening preterm labour, surfactant treatment for infants with respiratory distress syndrome (RDS), and new modes of respiratory support, taken into common use during the 1990s have further declined mortality. However, as the overall impairment rate has remained unchanged or has slightly decreased, a growing absolute number of infants with impairments due to higher survival have resulted (Lefebvre et al. 1996; Lemons et al. 2001; Svenningsen et al. 1997).

Today, in developed countries with modern neonatal intensive care, most ELBWIs survive. Nevertheless, high rates of various disabilities among ELBWIs cause high economic costs and continuous concern for parents. Increasing attention has been paid to the burden that preterm birth imposes on the family. Awareness of the importance of parental distress has grown as recent studies have shown that family well-being is crucial for later outcome and academic achievement of these fragile infants (Thompson et al. 1994).

This prospective study focuses on the early outcome of a national cohort of ELBWIs, including assessment of parental well-being and estimation of overall costs from birth up to the age of two years.
REVIEW OF THE LITERATURE

1. Definitions

**Preterm birth**
Infants born after 37 but before 42 full weeks of gestation are known as full-term deliveries. Preterm birth is commonly defined as birth at a gestational age of less than 37 full weeks, and extremely preterm birth as at a gestational age of less than 29 full weeks.

**Low birth weight**
Low birthweight infant (LBWI) is a term used for newborns with a birth weight of less than 2500 g, which is the average weight for Finnish infants born at a gestational age of 34 weeks (± 2SD, from 32 to 38 weeks) (Pihkala et al. 1989).

Very low birthweight infants (VLBW1) have a birth weight of less than 1500 g, a weight which in the Finnish population is, on average, reached at a gestational age of 29 to 30 weeks (± 2SD, from 28 to 32 weeks) (Pihkala et al. 1989). Newborns with a birth weight of less than 1000 g are called extremely low birthweight infants (ELBWI) and the mean gestational age of these infants in the Finnish population is 27 weeks (± 2SD, from 24 to 29 weeks).

Small for gestational age (SGA) are those infants with a birth weight of less than 2SD below the mean birth weight for each gestational week. Infants with a birth weight within the range of mean ± 2SD are called appropriate for gestational age (AGA) and those with a birth weight of more than 2SD over the gestational-age specific mean value are referred to as large for gestational age (LGA).

According to the latest report by the Nordic Medical Statistical Committee, the birth rates of infants with a birth weight of less than 2500 g in Nordic countries during the 1980s have varied between 3.0% and 5.9% of all births, of those with a birth weight of less than 1500 g between 0.5% and 1.5%, and those weighing less than 1000 g at birth between 0.2% and 0.5% (Nordic Medical Statistical Committee 1993). In addition to real differences in birth rates for different birthweight categories, also differences in registration practices of extremely preterm infants in Nordic countries may have some influence on reported rates (Nordic Medical Statistical Committee 1993).
**Perinatal and neonatal mortality**

The perinatal period extends from the 20\textsuperscript{th} week of gestation to the age of seven full days after birth (Nelson et al. 1990). Perinatal mortality rate includes infants who die during the perinatal period and is expressed as the number of deaths per 1000 births, or, in a target population, as the number of deaths per all births. The neonatal period begins at birth and includes the first 28 days. Neonatal mortality refers to deaths during the neonatal period and is expressed as number of deaths per 1000 live-born infants, or, in target population, as number of deaths per all live-born infants.

2. **Short-term outcome**

2.1. **Mortality**


Presumably owing to difficulties in obtaining reliable data on stillbirth rates, most studies report only neonatal mortality rates. Table 1 summarises mortality rates in outcome studies published between 1993 and 2003. Survival of live-born infants up to first discharge is most often used in survival rates. In studies performed in neonatal intensive care units (NICU), survival is typically determined from those admitted to NICU; however, neonatal survival rate is occasionally reported.

In live-born ELBWIs and in infants born alive before a gestational age of 27 GW, mortality is highest during the first days of life (Agustines et al. 2000; Meadow et al. 1996; Philip 1995; Sauve et al. 1998; Stevenson et al. 1998; Whyte et al. 1993). Mean survival time has been shown to decrease with decreasing birth weight and gestational age (Battin et al. 1998; Cartlidge et al. 1997; El-Metwally et al. 2000; Hack et al. 1991; Hagan et al. 1996). Concomitantly with decreasing neonatal mortality, some investigators have, however, demonstrated that time to death has increased in non-
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<th>Live-births (n)</th>
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<th>IVH (%)</th>
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<tr>
<td>Bardin et al. (1997)</td>
<td>NICU</td>
<td>24-26 GW (AGA)</td>
<td>1983-92</td>
<td>147</td>
<td>65</td>
<td>23 m (gr 3-4)</td>
<td>50 n / 32 b (gr 3-4)</td>
<td>7 j</td>
<td>55 l n (st 3-4)</td>
<td>12</td>
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<td>NICU</td>
<td>24-26 GW (SGA)</td>
<td>1983-92</td>
<td>37</td>
<td>54</td>
<td>12 m (gr 3-4)</td>
<td>50 m / 65 b (gr 3-4)</td>
<td>15 l</td>
<td>75 l n (st 3-4)</td>
<td>65</td>
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<td>23-26 GW (surfactant tr.)</td>
<td>1986-90</td>
<td>154</td>
<td>73</td>
<td>23 (gr 3-4)</td>
<td>NA / 88 e NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Holmsgaard et al. (1996)</td>
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<td>≤ 28GW</td>
<td>1987-90</td>
<td>197</td>
<td>71 m (gr 3-4)</td>
<td>18 m (gr 3-4)</td>
<td>NA / 24 e m</td>
<td>5 m</td>
<td>11 m</td>
<td>5 m</td>
</tr>
<tr>
<td>Kilpatrick et al. (1997)</td>
<td>NICU</td>
<td>24-26 GW</td>
<td>1990-94</td>
<td>138 b</td>
<td>68</td>
<td>10 l (gr 3-4)</td>
<td>NA / 15 b (gr 3-4)</td>
<td>7 l</td>
<td>NA</td>
<td>13 (st 3-4)</td>
</tr>
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<td>O’Shea et al. (1997)</td>
<td>NICU</td>
<td>501-800g</td>
<td>1989-94</td>
<td>218</td>
<td>59 n (gr 3-4)</td>
<td>12 n (gr 3-4)</td>
<td>NA / 61 h n</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Msall et al. (1993)</td>
<td>Hospital</td>
<td>23-28 GW</td>
<td>1983-86</td>
<td>194</td>
<td>79</td>
<td>9 l (gr 3-4)</td>
<td>NA / 65 e</td>
<td>9 l</td>
<td>12 l</td>
<td>NA</td>
</tr>
<tr>
<td>Synnes et al. (1994)</td>
<td>Hospital</td>
<td>23-28 GW</td>
<td>1983-89</td>
<td>911</td>
<td>65</td>
<td>21 b (gr 3-4)</td>
<td>NA / 85 c</td>
<td>5 m (meningitis)</td>
<td>13 m</td>
<td>NA</td>
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<tr>
<td>Allen et al. (1993)</td>
<td>Hospital</td>
<td>22-25 GW</td>
<td>1988-91</td>
<td>142</td>
<td>39 e (gr 3-4)</td>
<td>23 e (gr 3-4)</td>
<td>NA / NA</td>
<td>NA</td>
<td>NA</td>
<td>45 e (gr 2-4)</td>
</tr>
<tr>
<td>Battin et al. (1998)</td>
<td>Hospital</td>
<td>23-28 GW</td>
<td>1991-93</td>
<td>333</td>
<td>72</td>
<td>7 l (gr 3-4)</td>
<td>NA / 74 e</td>
<td>5 m</td>
<td>24 m</td>
<td>3 (gr 4)</td>
</tr>
<tr>
<td>El-Metwally et al. (2000)</td>
<td>Hospital</td>
<td>22-25 GW</td>
<td>1993-97</td>
<td>211</td>
<td>60</td>
<td>21 l (gr 3-4/PVL)</td>
<td>NA / 35 b</td>
<td>10 l</td>
<td>NA</td>
<td>21 (st 3-4)</td>
</tr>
</tbody>
</table>
| Author                  | Cohort | Definitions | Birth years | Live-births (n) | Survival to discharge (%) | IVH (%) | RDS/BPD (%) | NEC (%) | Septicaemia (%) | ROP (%) at discharge (%)
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<td>Hack et al. (1996)</td>
<td>Hospital</td>
<td>500-750g</td>
<td>1990-92</td>
<td>114</td>
<td>43 (^i)</td>
<td>41 (^j)</td>
<td>NA / 41 (^h)</td>
<td>4 (^j)</td>
<td>53 (^l)</td>
<td>12 (st 3-4)</td>
</tr>
<tr>
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<td>Hospital</td>
<td>500-750g</td>
<td>1990-95</td>
<td>167</td>
<td>38</td>
<td>17</td>
<td>64 / 21 (^h)</td>
<td>14</td>
<td>8</td>
<td>8 (^l) (gr 3-4)</td>
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<tr>
<td>Sauve et al. (1998)</td>
<td>Regional</td>
<td>≤500g and ≥20GW</td>
<td>1983-94</td>
<td>382</td>
<td>4.7</td>
<td>44 (^j)</td>
<td>NA / 89</td>
<td>22 (^j)</td>
<td>NA</td>
<td>33 (st 3-4)</td>
</tr>
<tr>
<td>Finnström et al. (1997)</td>
<td>Regional</td>
<td>≤1000g</td>
<td>1990-92</td>
<td>633</td>
<td>63 (^a)</td>
<td>8 (^n)</td>
<td>NA / 26 (^h)</td>
<td>2 (^a)</td>
<td>NA</td>
<td>10 (^n) (st 3-4)</td>
</tr>
<tr>
<td>Costeloe et al. (2000)</td>
<td>Regional</td>
<td>20-25 GW</td>
<td>1995</td>
<td>811</td>
<td>39 (^m)</td>
<td>37 (^j)</td>
<td>93 (^m) / 74 (^h)</td>
<td>NA</td>
<td>NA</td>
<td>15 (treated)</td>
</tr>
<tr>
<td>Cust et al. (2003)</td>
<td>Regional</td>
<td>&lt;28 ([&lt;32])</td>
<td>1998-99</td>
<td>397</td>
<td>79 (^m)</td>
<td>11 (^m) (gr 3-4)</td>
<td>NA / 27 (^h)</td>
<td>7 (^n)</td>
<td>46 (^p)</td>
<td>5 (st3-4)</td>
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<tr>
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<td>Multicenter</td>
<td>≤1000g (singletons)</td>
<td>1992-93</td>
<td>679</td>
<td>59 (^a)</td>
<td>13 (^j)</td>
<td>/ 27 (^i)</td>
<td>3 (^j)</td>
<td>NA</td>
<td>21 (st3-4)</td>
</tr>
<tr>
<td>Tyson et al. (1996)</td>
<td>Multicenter</td>
<td>501-800</td>
<td>1994-95</td>
<td>1126</td>
<td>57</td>
<td>16 (^j)</td>
<td>/ 49 (^a)</td>
<td>4 (^j)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

a. Neonatal survival  
b. Severe malformations excluded  
c. Survival to the age of six months/ Calculated from those alive at the age of six months  
d. Survival to the corrected age 20 months  
e. Supplementary oxygen at the age of 28 days  
f. Supplementary oxygen at discharge or at the age of 120 days  
g. Supplementary oxygen at the age corresponding to 36 GW  
h. Calculated from all live-born infants  
i. Calculated from those alive at discharge  
j. Calculated from those with at least one assessment  
k. Calculated from those admitted to NICU  
m. Calculated from those alive at the age of one year  
o. Sepsis after the first week of life  
p. Proven systemic infection  
NA = Data not available  
BPD = Bronchopulmonary dysplasia  
IVH = Intraventricular haemorrhage  
NEC = Necrotising enterocolitis  
RDS = Respiratory distress syndrome  
ROP = Retinopathy of prematurity
surviving ELBW. Hack et al. have reported that with increased survival of infants with a birth weight of less than 750 g born in 1990-1992 compared with those born in 1983-1989, the number of deaths during the first day of life decreased and the number of deaths after the neonatal period increased (Hack et al. 1996). Similarly, Sauve et al. found a tendency of delayed deaths during the 1990s in infants with a birth weight of less than 500 g (Sauve et al. 1998), and El-Metwally in infants born at 22 to 25 gestational weeks (GW) whose mothers had received intensive perinatal care, including antenatal steroids (El-Metwally et al. 2000). In an American study, the average time to death increased between 1987 and 1993 in ELBW with a birth weight of 750-999 g but not in those weighting less than 750 g at birth (Gould et al. 2000).

In previous studies, the main reported specific causes of neonatal deaths in ELBWI and in infants born extremely preterm have been respiratory distress syndrome (RDS), its consequences and infections (Barton et al. 1999; Doyle et al. 1999a; Doyle et al. 1999b; Erkkola et al. 1991; Finnstrom et al. 1997; Hack et al. 1996; Philip 1995). Doyle et al. compared the causes of death in infants born before 28 GW in 1983-1990 to those in infants born in 1992-1996 and noted that with advancements made in respiratory care deaths caused by pulmonary insufficiency had decreased and those resulting from septicaemia had increased (Doyle et al. 1999a). Barton et al. reported infections to account for half of all deaths in ELBWI. To explain the higher proportion of septic deaths than in other studies, the authors suggest that most infections were clinically silent or masked by other problems related to prematurity and that the signs of infection were only found in careful autopsy, including comprehensive histopathological analysis (Barton et al. 1999).

Malformations have been reported to account for 5-17% of neonatal deaths in ELBWI (Barton et al. 1999; Cartlidge et al. 1997; Finnstrom et al. 1997; Hack et al. 1996). Doyle et al. found lethal anomalies to have increased importance as a cause of death with increasing gestational age, but even in infants born at 23 to 27 GW, they were one of the leading causes (Doyle et al. 1999a).

The majority of postneonatal deaths both among ELBW and VLBW have been ascribed to bronchopulmonary dysplasia (BPD), infections, sudden infant death syndrome (SIDS), central nervous system abnormalities, necrotising enterocolitis
(NEC), and malformations (Barton et al. 1999; Cartlidge et al. 1997; Fillmore et al. 1998).

2.2. Neonatal morbidity

The rate of major morbidity [severe IVH (grades II-IV), BPD, confirmed NEC] declined among ELBW survivors cared for in National Institute of Child Health and Human Development Neonatal Research Network Centres in USA between 1988 and 1994 (Stevenson et al. 1998). A declining rate for BPD and grade III to IV IVH has also been reported from Sweden (Svenningsen et al. 1997). On contrary, Lemons et al. reported recently elevated rate of BPD among ELBW survivors in USA (Lemons et al. 2001).

Table 1 shows the neonatal morbidity rates in follow-up studies in preterm and ELBW infants born in the late 1980s and 1990s. Retinopathy of prematurity (ROP) and BPD are mostly reported in infants surviving to discharge, whereas other disease rates are generally determined from live-born infants or those admitted to NICU. Several exceptions exist, and in some cases, it is difficult to identify the populations for which the disease or mortality rates were reported.

Comparison between studies warrants caution because the definitions for disease states vary, as do selection criteria for study populations. For example, gestational age and birth weight limits differ, some studies exclude multiple pregnancy infants or infants with malformations, and some exclude those who died in the delivery room. Studies are also performed at different times, with a wide range in the duration of follow-ups. Furthermore, the origin of the cohort (population-based, hospital, or NICU) influences study results.
3. Outcome during the infancy

3.1 Mortality

Although mortality both in VLBWI and ELBWI declines sharply after the first days and weeks of life, these infants continue to have increased mortality rate after the first discharge. Fillmore and Cartlidge studied the causes of late deaths in VLBWI: BPD alone accounted for 32%, pulmonary infections 24%, SIDS 15%, non-pulmonary infections 10%, and other causes, such as NEC, congenital heart disease, hypoxic ischaemic encephalopathy, and cerebral degeneration, for 19% of deaths during infancy, i.e. after the neonatal period up to the postconceptional age of one year (Fillmore et al. 1998).

The mortality rates during the first two years in ELBW populations have varied between 0% and 3%, the main reported causes of late deaths being SIDS and cardiac or respiratory insufficiency related to BPD (Dezoete et al. 1997; French et al. 1995; Hack et al. 1996; Piecuch et al. 1997b; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000).

3.2 Morbidity

The long-term outcome of preterm infants has become more and more important with the decline in the neonatal mortality. Besides increased risks for developmental delays, poor growth, and neurosensory and cognitive impairments (Battin et al. 1998; Emsley et al. 1998; Finnstrom et al. 1998; Finnstrom et al. 1999; French et al. 1995; Hack et al. 2000; Lagercrantz 1999; Lorenz et al. 1998; Piecuch et al. 1997a; Salokorpi et al. 2001; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000; Wood et al. 2000) these infants have a tendency to develop learning problems and behavioural and psychiatric disorders (Stjernqvist et al. 1999).

ELBW1 have commonly been classified according to outcome status as normally developed, mildly disabled, and severely disabled, with definitions varying markedly between studies. Escobar et al. in their meta-analysis showed that from the 1960s to the beginning of the 1990s the incidence of disabilities in ELBW1 population remained
stable at 27% (Escobar et al. 1991). The overall reported rates of severe handicap, including cerebral palsy (CP), hearing loss, blindness, and intelligence disability with an IQ of more than 2SD below the mean, have, in recent studies, varied from 15% to 24% (Hack et al. 2000; La Pine et al. 1995; Lee et al. 1995; O’Shea et al. 1997). The rates have remained fairly constant in the 1980s and the 1990s and resulted with a concurrent increase in survival rates in the increased absolute number of disabled infants. Although most studies (Battin et al. 1998; Blaymore-Bier et al. 1994; Hack et al. 1989; Hack et al. 1996; La Pine et al. 1995; Lefebvre et al. 1996; Lorenz et al. 1998; O’Shea et al. 1997; Perlman et al. 1995; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a) confirm no significant changes in major disability rates in ELBW1 and in extremely preterm infants, some investigators have contrary findings. Grøgaard et al. detected a decrease in the overall rate of major handicaps [cerebral palsy (CP), cicatricial retinopathy of prematurity (ROP) or blindness, neurosensory hearing loss, mental retardation (Bayley scores <70)] in ELBW1 admitted to the Vanderbilt Medical Centre NICU between 1976 and 1985 (Grogaard et al. 1990). In Australia, sensory-neural outcome improved for ELBW1 survivors born in 1985-1987 compared with those born in 1979-1980, but no further improvement was detected in infants born at the beginning of the 1990s (The Victorian Infant Collaborative Study Group 1997a; The Victorian Infant Collaborative Study Group 1997c). Furthermore, the differences in disability rates between ELBW1 birthweight groups seemed to decrease over time (La Pine et al. 1995). In Victoria state, in the late 1970s, the outcome of infants with a birth weight of less than 750 g was significantly worse than that of infants with a birth weight from 750 to 999 g, but after the mid 1980s, no difference could be detected in outcomes between these groups (The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a).

3.2.1 Motor impairments

In studies reporting outcomes in VLBWI, ELBWI, and extremely preterm infants, cerebral palsy (CP) is commonly defined as spastic diplegia, hemiplegia, dihemiplegia, or quadriplegia (Cooke 1994; Emsley et al. 1998; Finnstrom et al. 1998; Hack et al. 1996; Hack et al. 2000; Lefebvre et al. 1996; Ment et al. 2000; Msall et al. 1991; Piecuch et al. 1997a; Piecuch et al. 1997b; Wood et al. 2000). The definition of CP may
also include a combination of the following features: motor delay, abnormal muscle tone and reflexes, persistent primitive reflexes, positive Babinsky sign, and abnormal posture (Ambalavanan et al. 2001; Battin et al. 1998; French et al. 1995; Ment et al. 2000; Msall et al. 1991; O’Shea et al. 1997; Salokorpi et al. 2001; Synnes et al. 1994; Vohr et al. 2000). A few investigators have included only severe CP with disabling motor impairment (O’Shea et al. 1997), others have reported CP in conjunction with other motor impairments or neurosensory disabilities (Johnson et al. 1993).

The prevalence of CP in the south-western region of Finland increased between the late sixties and early eighties from 1.6/1000 to 2.5/1000 live-births. The investigators assumed that the main reason for the increase was the better survival of low birthweight infants (birth weight <2500 g) (Riikonen et al. 1989). A regional survey from England reported an increase in the rates of CP per neonatal survivors born in 1990-1994 compared with those born in 1970-1975. The rise occurred mainly among preterm infants, from 5.5/1000 to 16.8/1000 singleton neonatal survivors, and was the highest among those born at less than 28 GW from 0/1000 to 112.7/1000 singleton neonatal survivors (Drummond et al. 2002).

Hagberg et al. found similar trends in CP rates in Sweden: in preterm infants, the prevalence of CP increased between the late sixties and early eighties but remained stable or declined slightly from the early eighties to the nineties (Hagberg et al. 1996). Likewise, increased rates of CP between 1975 and 1985 have been reported in Western Australia (Stanley et al. 1992).

However, several studies from the 1980s and 1990s have shown that the concomitant decrease in mortality rates is not always associated with the increase in CP rates. The rate of CP in VLBWI survivors did not significantly change between 1962 and 1985 according to a meta-analysis from the United States (Escobar et al. 1991). Grögaard et al. confirmed that the CP rate remained stable in VLBWI born between 1976 and 1985 (Grogaard et al. 1990), and Robertson et al. in infants with a birth weight of less than 1250 g born in 1978-1989 (Robertson et al. 1992). In a regional study from Scotland and England, no significant time trends in prevalence of CP were detected between 1984 and 1989 (Pharoah et al. 1998) in any birthweight groups.
Moreover, decreasing CP rates have been reported recently. Although in Denmark the CP rate increased among preterm infants born before GW 31 in 1970 to 1982 and in 1983 to 1986, a declining rate was detected in infants born between 1987 and 1990 (Topp et al. 2001; Topp et al. 1997). O’Shea showed that between 1982 and 1994 the CP rate declined in a regional cohort of VLBWI born in North Carolina both among live-born and surviving infants (O’Shea et al. 1998). As survival increased from 63.2% to 86.2%, the prevalence of CP decreased from 11.3% to 5.2%. The decline remained significant even when adjusted for gestational age, surfactant use, gender, and race. Similar results among VLBWI have also been reported from Britain (Cooke 1999).

In agreement with results of VLBWI, stable CP rates have also been reported in ELBWIs populations from the early 1990s. O’Shea et al. found no increase in CP rates in infants with a birth weight of 500-800 g born between 1979 and 1994 (O’Shea et al. 1997), nor did Emsley in extremely preterm infants born at 23-25 GW delivered between 1984 and 1994 (Emsley et al. 1998). The CP rates did not either significantly change among ELBWIs born in Australia between 1979 and 1992 (French et al. 1995; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a). Contradictory reports do, however, exist: Hack and Fanaroff reported higher CP, mental retardation, and neurodevelopmental impairment rates in infants with a birth weight of 500-749 g born in 1993-1995 compared with those born in 1990-1992 (Hack et al. 1999).

Recent CP rates have varied from 6.7% to 7.1% among VLBWI survivors (Grogard et al. 1990; Ment et al. 2000; O’Shea et al. 1998; Robertson et al. 1994). In ELBWIs, the corresponding rate has varied between 6% and 19% (Finnstrom et al. 1998; French et al. 1995; Grogard et al. 1990; Hack et al. 1996; Hack et al. 2000; Kitchen et al. 1987; O’Shea et al. 1997; Piecuch et al. 1997b; Robertson et al. 1994; Salokorpi et al. 2001; The Victorian Infant Collaborative Study Group 1991; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000) and from 7.8% to 20% in infants born extremely preterm (Battin et al. 1998; Cooke 1994; Lefebvre et al. 1996; Msall et al. 1991; Piecuch et al. 1997a; Synnes et al. 1994; Wood et al. 2000). These wide variations partly result from differences in study populations, study settings, assessment ages, duration of follow-up, comprehensiveness of follow-up, and variations in the definition of CP.
The frequency distribution of different CP types in preterm infants differs from that of term infants, in whom hemiplegic syndrome predominates (Hagberg et al. 1996). Hagberg et al have reported that in extremely preterm infants born at less than 28 GW, diplegia accounted for 80% of all CP, followed by hemiplegic syndrome (10%) (Hagberg et al. 1996). Although this finding is supported by some studies (Finnstrom et al. 1998), in other recent reports, the rate of tetraplegia has been similar to that of diplegia in study populations including ELBW and extremely preterm infants (Emsley et al. 1998; Hack et al. 2000; Kuban et al. 1994; Msall et al. 1991; Vohr et al. 2000; Wood et al. 2000).

Infants with CP are also susceptible to other disabilities (La Pine et al. 1995; Piecuch et al. 1997a), such as behavioural, (McDermott et al. 1996) sensory, or neurological problems (Hagberg et al. 1996; Johnson et al. 1993; Lanzè et al. 1998; Msall et al. 1991; Nordmark et al. 2001; Pennefather et al. 2000), deafness (Johnson et al. 1993), epilepsy (Hadjipanayis et al. 1997; Hagberg et al. 1996; Nordmark et al. 2001), and mental retardation (Hagberg et al. 1996; Johnson et al. 1993; Kitchen et al. 1987; Msall et al. 1991). In a Finnish study, mental retardation occurred in 52% of ELBW with CP, whereas in ELBW without CP, mental retardation was found only in 4% (Salokorpi et al. 2001).

Motor impairment other than CP usually comprises developmental delay in motor age-specific milestones, clumsiness, hypotonia, hypertonia, and/or tremor. In a study from USA, abnormal motor assessment was detected in 25% of ELBW and CP in 17% (Vohr et al. 2000). Similarly, of the 67 infants with abnormal motor development born at 22 to 25 GW in the United Kingdom or Ireland, 75% had CP and 25% another motor deficit (Wood et al. 2000). As motor impairments other than CP are also common in preterm infants CP alone might be a poor measure of overall motor outcome.

The reported rates of all motor abnormalities, including CP and milder motor abnormalities, have varied among ELBW between 20% and 25% (Hack et al. 2000; Vohr et al. 2000), among those with a birth weight under 800 g between 16% and 58% (Agustines et al. 2000; O’Shea et al. 1997), and among cohorts including extremely preterm infants born before 29 full GW between 21% and 24% (Piecuch et al. 1997a; Wood et al. 2000).
3.2.2. Ophthalmological abnormalities

In the United States, retinopathy of prematurity (ROP) and cortical visual impairment are among the main causes of childhood blindness (Steinkuller et al. 1999). Besides blindness, preterm infants are also prone to other ophthalmological abnormalities, such as myopia, strabismus, and amblyopia, which are, in turn, associated with ROP (Arroe et al. 1994; Darlow et al. 1997; Maly 1993; O’Connor et al. 2002a; Pennefather et al. 1999).

In a Swedish study, infants with a birth weight of less than 1000 g had a higher frequency of ROP and subsequent ocular complications compared with infants with a birth weight from 1000 to 1500 g (severe ROP 11.6% vs. 2.5%) (Gallo et al. 1993). Several studies have confirmed that visual impairments are more common among VLBWI than among normal birthweight infants and in ELBWI than in preterm infants with a birth weight of over 1000 g (Gallo et al. 1991; McGinnity et al. 1992; O’Connor et al. 2002a; Powls et al. 1997; Schalij-Delfos et al. 2000). Although the higher incidence of ROP in these groups may explain the higher incidence of later ophthalmic complications (Maly 1993), low birth weight itself has been associated with visual disabilities, such as myopia, strabismus, colour vision defects, and visual field defects, in both VLBWI and ELBWI with and without ROP (Darlow et al. 1997; Fledelius 1996; Hebbandi et al. 1997; Holmstrom et al. 1998b; O’Connor et al. 2002a).

In recent studies, blindness rates among surviving infants born extremely preterm have varied between 1.2% and 4% (Msall et al. 1991; Piecuch et al. 1997a; Wood et al. 2000), but rates as high as 9% and 18% have been reported from some centres (Battin et al. 1998; Emsley et al. 1998). Among ELBWI, the reported rate of blindness have been between 0% and 3.5% (Hack et al. 2000; Hebbandi et al. 1997; Lorenz et al. 1998; Robertson et al. 1994; Salokorpi et al. 2001; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000), and among those with a birth weight under 800 g between 2% and 7.8% (Hack et al. 1996; Lorenz et al. 1998). Definitions for populations studied, when the research was performed, and timing of data collection have all presumably had an effect on reported rates.
In VLBWI, the published rates of strabismus have varied from 9.9% to 19% (Gallo et al. 1993; McGinnity et al. 1992), myopia from 6.6% to 11% (Gallo et al. 1993; Holmstrom et al. 1998b; McGinnity et al. 1992), and astigmatism from 11% to 26% (Darlow et al. 1997; Holmstrom et al. 1998b). In ELBW1, the corresponding rates have been 14% (Hebbandi et al. 1997), 12% (Hebbandi et al. 1997), and 11% (Hebbandi et al. 1997). Reported rates of hypermetropia in VLBWI populations have ranged from 8% to 18% (Darlow et al. 1997; Hebbandi et al. 1997)

In the most preterm infants born at 23 to 25 GW, an increased disability rate (38% vs. 68%) was detected in infants born in 1990-1994 compared with those born in 1984-1989 (Emsley et al. 1998). The rise was mainly due to the higher incidence of visual impairments, as the rates of speech or developmental delays and motor impairments did not change. Besides the increased rate of blindness (4% vs. 18%), the rates of myopia (4% vs. 15%) and strabismus (8% vs. 13%) had also increased (Emsley et al. 1998). Other investigators detecting increased visual impairment rates in live-born infants, have supposed that these higher rates are related to improved survival of the most immature infants, who are at the greatest risk for visual impairments (Blohmke et al. 2000; Schalij-Delfos et al. 1997).

However, recently significantly decreased rates and severity of ROP have been detected among ELBW1 (Bullard et al. 1999; Fiedelius et al. 2000; Hussain et al. 1999; Keith et al. 1995; Kennedy et al. 1997). Blindness rates may also have declined due to better coverage of screening for the disease and use of efficient ROP treatments, i.e. laser- and cryotherapy (Javitt et al. 1993; Lappi 1993; McNamara et al. 1991; Multicenter Trial of Cryotherapy for Retinopathy of Prematurity 2001).

Severity of ROP has been found to be predictive of later developmental outcome. Powls et al. reported that poor contrast sensitivity and visual acuity were predictive of poor motor skills and lower IQ (Powls et al. 1997) and Msall demonstrated that infants with a birth weight below 1251 g severity of ROP was a marker for neurodevelopmental functional disability at the age of 5.5 years (Msall et al. 2000).

Developmental problems and visual impairments are assumed to share a common aetiology rather than visual impairment per se causing neurological disability. In an American study, blind ELBW1 had lower body weight, height, and head circumference,
and significantly more developmental problems at the age of four years than blind children born at term (Gosch et al. 1997). Swedish studies have confirmed that various disabilities are common in preterm infants who are blind or have poor vision due to ROP (Ek et al. 1998; Jacobson et al. 1998).

3.2.3. Cognitive impairment

In addition to neurosensory impairment, ELBW1 are also predisposed to intellectual disabilities. Intellectual disability rates with mean developmental test scores in studies performed in the late 1980s and 1990s, during the period when antenatal steroid and surfactant treatments were accepted to common use, are shown in Table 2.

The predominant test methods used during childhood are the Bayley scale, Griffiths Mental Developmental Scale, Stanford-Binet Intelligence Scale, and Wechsler Preschool and Primary Scale of Intelligence. Caution is recommended when comparing results between studies, as differences in test methods, study populations, assessment ages, definitions for exclusions, and limits for test scores may have a considerable effect on findings.

Intellectual disability is usually defined as test scores of more than 2SD below the mean value of the background population. As shown in Table 2, using the above-mentioned criterion for intellectual disability, rates vary in ELBW1 from 8% to 42%. In ELBW1 and extremely preterm infants, intellectual deficiency is also frequently associated with other problems, such as CP and visual impairments (Johnson et al. 1993; Kitchen et al. 1987; Msall et al. 1991; Salokorpi et al. 2001), but ELBW1 and even VLBW1 without any apparent disabling neurosensory disabilities have more impairments in language, fine and gross motor, personal-social, attention, and problem-solving skills than infants born at term (Collin et al. 1991; Fletcher et al. 1997; Liebhardt et al. 2000).
### Table 2. Intellectual disability (ID) rates in very / extremely low birth weight or extremely preterm infants.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Cohort</th>
<th>Definitions</th>
<th>Birth years</th>
<th>Method</th>
<th>Median/mean age or range</th>
<th>Mean score</th>
<th>Limit for ID*</th>
<th>ID rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victorian Infant Study Group (1991)</td>
<td>Regional</td>
<td>&lt;1000g</td>
<td>1985-87</td>
<td>B</td>
<td>2 years</td>
<td>99±18</td>
<td>&lt; -2 SD</td>
<td>10</td>
</tr>
<tr>
<td>Robertson et al. (1992)</td>
<td>Regional</td>
<td>500-1250g</td>
<td>1988-89</td>
<td>B / SB</td>
<td>24 months</td>
<td>NA</td>
<td>&lt; -3 SD</td>
<td>7</td>
</tr>
<tr>
<td>Johnson et al. (1993)</td>
<td>Regional</td>
<td>&lt;29 GW</td>
<td>1984-86</td>
<td>G</td>
<td>4 years</td>
<td>NA</td>
<td>&lt; 70</td>
<td>8</td>
</tr>
<tr>
<td>Synnes et al. (1994)</td>
<td>Hospital</td>
<td>23-25 GW</td>
<td>1983-89</td>
<td>B</td>
<td>18 months</td>
<td>NA</td>
<td>&lt; -2 SD</td>
<td>14</td>
</tr>
<tr>
<td>Robertson et al. (1994)</td>
<td>Regional</td>
<td>500-1249g</td>
<td>1990</td>
<td>B / SB</td>
<td>2-3 years</td>
<td>NA</td>
<td>&lt; -3 SD</td>
<td>2</td>
</tr>
<tr>
<td>French et al. (1995)</td>
<td>Regional</td>
<td>&lt;1000g</td>
<td>1984-87</td>
<td>G</td>
<td>43 months</td>
<td>NA</td>
<td>&lt; 85</td>
<td>9</td>
</tr>
<tr>
<td>Lefebvre et al. (1996)</td>
<td>Hospital</td>
<td>23-28 GW</td>
<td>1987-92</td>
<td>G</td>
<td>20 months</td>
<td>94±18</td>
<td>&lt; 80</td>
<td>16</td>
</tr>
<tr>
<td>Hack et al. (1996)</td>
<td>Hospital</td>
<td>&lt;1000g</td>
<td>1990-92</td>
<td>B</td>
<td>20 months</td>
<td>89.3±22</td>
<td>&lt; -2 SD</td>
<td>20</td>
</tr>
<tr>
<td>O’Shea et al. (1997)</td>
<td>2 NICUs</td>
<td>501-800g</td>
<td>1989-94</td>
<td>B</td>
<td>1 year</td>
<td>median:93</td>
<td>&lt; 68</td>
<td>13</td>
</tr>
<tr>
<td>Pincus et al. (1997)</td>
<td>Hospital</td>
<td>24-26 GW</td>
<td>1990-94</td>
<td>B/SB/McC</td>
<td>NA</td>
<td>NA</td>
<td>&lt; -2 SD</td>
<td>23</td>
</tr>
<tr>
<td>Battin et al. (1998)</td>
<td>Hospital</td>
<td>23-28 GW</td>
<td>1991-93</td>
<td>B</td>
<td>18 months</td>
<td>NA</td>
<td>&lt; -2 SD</td>
<td>18</td>
</tr>
<tr>
<td>Emsley et al. (1998)</td>
<td>Regional</td>
<td>23-25 GW</td>
<td>1990-94</td>
<td>G</td>
<td>3-4 years</td>
<td>NA</td>
<td>&lt; 70</td>
<td>15</td>
</tr>
<tr>
<td>Hack et al. (2000)</td>
<td>NICU</td>
<td>&lt;1000g</td>
<td>1992-95</td>
<td>B</td>
<td>20 months</td>
<td>75±1</td>
<td>&lt; -2 SD/ &lt; -1SD</td>
<td>42/ 68</td>
</tr>
<tr>
<td>Agustines et al. (2000)</td>
<td>Hospital</td>
<td>500-750g</td>
<td>1990-95</td>
<td>B</td>
<td>30 months</td>
<td>NA</td>
<td>&lt; -2 SD</td>
<td>28</td>
</tr>
<tr>
<td>Wood et al. (2000)</td>
<td>Regional</td>
<td>22-25 GW</td>
<td>1995</td>
<td>B</td>
<td>30 months</td>
<td>84±12</td>
<td>&lt; -2 SD</td>
<td>30</td>
</tr>
<tr>
<td>Vohr et al. (2000)</td>
<td>Multicenter</td>
<td>&lt;1000g</td>
<td>1993-94</td>
<td>B</td>
<td>20 months</td>
<td>76±17</td>
<td>&lt; -2 SD</td>
<td>37</td>
</tr>
<tr>
<td>Salokoripii et al. (2001)</td>
<td>Hospital</td>
<td>&lt;1000g</td>
<td>1990-94</td>
<td>W</td>
<td>4 years</td>
<td>NA</td>
<td>&lt; 71</td>
<td>14</td>
</tr>
</tbody>
</table>

* Limit for ID expressed as intelligence / developmental quotient below indicated scores or more than indicated SD below the mean value of the back-ground population

ID = Intellectual disability  
NA = Not available  
B = Bayley Mental Index  
SB = Stanford-Binet Intelligence Scale  
McC = McCarthy Scales  
G = Griffiths Mental Developmental Scale  
W = Wesler Preschool and Primary Scale of Intelligence
Bylund et al. found that infants with a birth weight under 1500 g had poorer results in all academic skill tests, but those with an IQ within the normal range did not differ significantly from normal birthweight controls (Bylund et al. 2000). However, in a study by Hille et al., 56% of non-disabled VLBWI needed extra help at school or were below age-appropriate level (Hille et al. 1994).

At pre-school and school age, ELBW on average seem to be more prone to school difficulties, needing special education, and repeating a grade than same-aged infants (Hack et al. 1994; Horwood et al. 1998; Whitfield et al. 1997). Halsey et al. revealed that prior to school entry the non-disabled ELBW had weaker performance in all measures of developmental assessment than their same-aged peers (Halsey et al. 1993). Klebanov et al. in turn found that ELBW were over three times more likely to fail a grade and that at school age, even for those ELBW with IQ scores within the normal range, math scores were significantly lower than those of their normal birthweight peers (Klebanov et al. 1994b). In the study of Stjernqvist et al., 92% of infants born extremely preterm had no major neurological deficit, but still their mean IQ was significantly lower than among full-term infants, and they also had significantly more visual-motor problems, behavioural, and attention deficit disorders (Stjernqvist et al. 1999).

4. Factors affecting outcome in ELBW

4.1 Factors affecting risk of death

Numerous studies show that low gestational age and birth weight are risk factors for perinatal and neonatal deaths in preterm infants (Allen et al. 1993; Ambalavanan et al. 2001; Bahado-Singh et al. 1998; Battin et al. 1998; Cartlidge et al. 1997; Cooke 1994; Copper et al. 1993; El-Metwally et al. 2000; Hagan et al. 1996; Horbar et al. 1997; Horbar et al. 1993; Lemons et al. 2001; Maier et al. 1997; Msall et al. 1993; Msall et al. 1991; O’Shea et al. 1997; Phelps et al. 1991; Roth et al. 1995; Salokorpi et al. 1999; Stevenson et al. 1998; Synnes et al. 1994; Whyte et al. 1993). However, the independent predictive role of both factors for neonatal morbidity has been questioned by some investigators. Although, in some studies the predictive role of birth weight in ELBW has been superior to gestational age (Ambalavanan et al. 2001), other studies,
have showed that prenatal estimations of femur length and gestational age have better predicted survival than an obstetric estimate of weight (Bahado-Singh et al. 1998; Bottoms et al. 1999), and that in infants born before 29 GW, low gestational age is an independent risk factor for neonatal death (Copper et al. 1993). Due to high correlation between birth weight and gestational age, these associations should, however, be interpreted with caution.

Meadow found that after the fourth day of life birth weight among ELBW1 had no effect on mortality (Meadow et al. 1996). Shankaran et al analysed risk factors for early death (<12 h) and found that besides low birth weight and gestational age, infants who died early had lower Apgar scores, were less often delivered by Caesarean section or intubated, and less often received mechanical ventilation, surfactant, or antenatal steroid treatment than infants who died later or survived. According to these authors, early deaths may reflect that these infants were considered non-viable by obstetricians and neonatologists (Shankaran et al. 2002).

A male disadvantage on survival among VLBWI and ELBW1 has been detected in earlier studies (Allen et al. 1993; Bottoms et al. 1997; Carllidge et al. 1997; Cooke 1994; Copper et al. 1993; El-Metwally et al. 2000; Ferrara et al. 1994; Finnstrom et al. 1997; Horbar et al. 1997; La Pine et al. 1995; Lemons et al. 2001; Msall et al. 1993; O’Shea et al. 1997; Phelps et al. 1991; Roth et al. 1995; Sauve et al. 1998; Stevenson et al. 1998; Synnes et al. 1994; Tyson et al. 1996). However, in a recent Canadian study, no gender differences were detected in the survival of infants born at 23-28 GW in 1991-1993 (Battin et al. 1998). Investigators assumed that the disappearance of the male survival disadvantage, which was still found in their previous study, might be due to the increased administration of exogenous surfactant and antenatal steroids to the later cohort. Both treatments are supposed to narrow the maturation differences caused by hormonal differences between the genders (Battin et al. 1998). However, despite of common use of surfactant and antenatal steroids, gender seem to continuously have an effect on survival. Stevenson et al. found that both in gestational age and birth weight-specific groups survival among male ELBW1 remained more unfavourable than that of females (Stevenson et al. 1998). Besides hormonal differences, female infants also have lower mean birth weight, and therefore, when comparing the survival of same-weighted female and male infants, females have an advantage being, on average, more mature.
Multiple pregnancy has been shown to be a disadvantage for survival in ELBW and in extremely preterm infants (Battin et al. 1998; Copper et al. 1993; Ferrara et al. 1994; Phelps et al. 1991; Sauve et al. 1998; Synnes et al. 1994). Synnes et al. found that twins had a survival disadvantage only before the gestational age of 28 GW (Synnes et al. 1994) and in other studies, no increased risk for survival was associated with multiple birth (Carlidge et al. 1997; Tyson et al. 1996). Similarly, controversial reports exist concerning the role of mode of delivery in survival of preterm infants. Caesarean section has been reported to confer protection in some studies (Bottoms et al. 1997; Holmgren et al. 2001; Horbar et al. 1997; Sauve et al. 1998), while in others, no effect or even a negative effect on mortality has been demonstrated (El-Metwally et al. 2000; Paul et al. 2002). In a Swedish population-based study, an increased risk for mortality was found after vaginal delivery in infants born at $\leq 27$ GW but not in more mature infants (Holmgren et al. 2001). Bottoms et al. also found a better survival and outcome in infants born by Caesarean section compared to those delivered vaginally but concluded that an active approach and willingness to treat immature infants might be more important than the actual mode of delivery (Bottoms et al. 1997).

In a Swedish study, level of care had significant effect on survival. The survival of infants born in tertiary (level III) hospitals was higher compared to those born in level II hospitals even in case these hospitals had full resources for neonatal intensive care (Finnstrom et al. 1997). Similar results have also been published elsewhere (Darlow et al. 2000).

Antenatal steroids have improved survival (Agustines et al. 2000; Crowley 1995; Doyle et al. 1989; Finnstrom et al. 1997; Horbar et al. 1997; Sauve et al. 1998; Tyson et al. 1996), decreased the incidence and severity of RDS and IVH (Agarwal et al. 2002; Cooke 1999; Costeloe et al. 2000; Crowley 1995; Heuchan et al. 2002; Leviton et al. 1993; Silver et al. 1996) and improved the neurodevelopmental outcome in various groups of VLBWI (Doyle et al. 2000; Salokorpi et al. 1997). However, as trials in animals have shown that repeated courses of antenatal steroids may have potential adverse effects on growth, brain growth and central nervous maturation (Aghajafari et al. 2002; Walfisch et al. 2001) potential side-effects related to repeated use of antenatal steroids need to be better evaluated in humans.
The effect of antenatal steroids might also be different in different study populations. Elimian et al. found a significant reduction in incidence of RDS, IVH, periventricular leukomalacia, NEC, and mortality in infants appropriate for gestational age and with a birth weight of under 1750 g born after labour with intact membranes, but in growth-restricted infants whose mothers suffered from hypertension, antenatal steroid had no beneficial effect (Elimian et al. 1999). In ELBW1 born to mothers with preterm rupture of membranes, neither the mortality nor morbidity rates have been shown to differ between groups which were either treated with antenatal steroids or left untreated (Chapman et al. 1999) and in a placebo controlled betamethasone trial, Garite et al. did not find, in any reduction in RDS or neonatal death rates related to antenatal steroid treatment in infants born extremely prematurely, at 24 to 28 weeks’ gestation, although in a steroid-treated group the rate of severe IVH was lower (Garite et al. 1992).

Surfactant treatment has decreased mortality, the severity of RDS, and serious pulmonary complications, such as pulmonary emphysema, pneumothorax, and pneumomediastinum, in VLBWI and ELBW1 (Agustines et al. 2000; El-Metwally et al. 2000; Ferrara et al. 1994; Hockstra et al. 1991; Long et al. 1991; O’Shea et al. 1997; Schwartz et al. 1994). Although surfactant has been shown to increase the survival of VLBWI by 30% to 50% (Jobe 1993; Long et al. 1991; Schwartz et al. 1994), the independent favourable effect of surfactant on survival of the most preterm infants born at 22 to 25 GW is still an open question. Very few randomised controlled studies with sufficiently large cohorts born at 22 to 25 GW exists. In a British study, surfactant did not increase the survival of infants born before GW 26 (Costeloe et al. 2000). Similar results have been reported in Canada (Jacobs et al. 2000; Smyth et al. 1995), while in a large American follow-up study including 310 infants born at 23 to 26 GW, significantly increased survival was found in infants treated with surfactant (Ferrara et al. 1994).

The synergistic effect of antenatal steroids and surfactant in decreasing severity of RDS or preventing death due to respiratory causes has been demonstrated in both animals and humans (Farrell et al. 1989; Kari et al. 1994; Robertson 1993). Jobe et al. reported that use of antenatal corticosteroids and postnatal surfactant in combination improved overall survival and decreased deaths related to RSD more than either treatment alone (Jobe et al. 1993).
4.2. Factors affecting risk of intraventricular haemorrhage

Extremely low birthweight infants are at increased risk for IVH, which is an obvious risk factor for death or later neurodevelopmental disability (Cooke 1994; O’Shea et al. 1997; Piecuch et al. 1997a; Piecuch et al. 1997b; Salokorpi et al. 2001; Vohr et al. 2000). Moreover, even mild IVH (grades I and II) may have long-term consequences on neurodevelopmental outcome (Collin et al. 1991). Ross et al. found that although preterm infants born between 28 and 32 weeks of gestation with mild IVH (grades I-II) had no significant differences in their global mental ability when compared with matched preterm infants without IVH at the age of two years, those with mild IVH had significantly worse performance on certain specific tasks (memory for location and ability to change response set) (Ross et al. 1996).

Vaginal delivery (Ment et al. 1992), foetal presentation (Ment et al. 1992), foetal distress (Heuchan et al. 2002), low gestational age (Heuchan et al. 2002), low Apgar scores (Heuchan et al. 2002), male gender (Heuchan et al. 2002), transfer after birth (Costeloe et al. 2000; Heuchan et al. 2002), and use of tocolysis (Costeloe et al. 2000) have also been shown to be risk factors for IVH among VLBWI and preterm infants. The incidence of IVH in infants born SGA before 30 GW has been demonstrated to be lower (Bardin et al. 1997; Heuchan et al. 2002), and antenatal steroid treatment to be protective against IVH or to decrease the severity of IVH in infants born before 30 GW or with a birth weight below 1750 g (Canterino et al. 2001; Costeloe et al. 2000; Elimian et al. 1999; Heuchan et al. 2002; Jobe et al. 1993; Leviton et al. 1993; Silver et al. 1996). Kari et al. found that the risk for IVH and periventricular leukomalasia was decreased in prenatally dexamethasone-treated infants (<32 GW) who postnatally received surfactant compared with placebo-treated infants. The blood pressure in the treatment group was more stable, which was considered to reduce haemorrhage to ventricles (Kari et al. 1994).

4.3. Factors affecting risk of bronchopulmonary dysplasia

Bronchopulmonary dysplasia is commonly defined as the need for supplementary oxygen at 28 days of age or at an age corresponding to 36 GW. Jobe has summarised the changing features of BPD in his recent papers (Jobe et al. 2001; Jobe 1999). The
definition of disease is difficult, unstandardised, and often simplified. The population at
greatest risk has changed and disease is nowadays rare in large preterm infants,
occurring mainly in infants weighing less than 1000 g at birth. Along with changes in
treatment and populations at risk, the pathology of the disease has changed, and the new
form is supposed to be primarily an aberration in lung development, such as
alveolarisation and vascularisation. Multiple factors have been suggested to be involved
in the changing aetiology of the disease (Bancalari et al. 2001; Jobe 1999; Van Marter
et al. 2002).

Kraybill et al. found an increased likelihood of BPD in males and in mechanically
ventilated ELBW with PaCO2 below 40 mmHg at 48 hours of age (Kraybill et al.
1989). Other proposed risk factors for BPD in preterm infants (born before 32 GW) are
intrauterine growth restriction (Bardin et al. 1997; Egreteau et al. 2001), low gestational
age (Costeloe et al. 2000; Egreteau et al. 2001), and higher CRIB scores reflecting
greater illness severity during the first hours after birth and/or quality of perinatal care
(Costeloe et al. 2000; Egreteau et al. 2001); in extremely preterm infants (born before
25 GW) male sex (Costeloe et al. 2000), use of tocolysis (Costeloe et al. 2000), low
maternal age (Costeloe et al. 2000), and neonatal hypothermia (Costeloe et al. 2000);
and in VLBWI and ELBW low birth weight (Rojas et al. 1995), sepsis (Rojas et al.
1995; Van Marter et al. 2002), patent ductus arteriosus (PDA) (Rojas et al. 1995), and
prolonged (>7 days) mechanical ventilation (Van Marter et al. 2002).

Antenatal steroid treatment has been shown to affect protectively development of BPD
by some investigators (Doyle et al. 1986; Van Marter et al. 1990), while the
effectiveness is questionable by others (Crowley 1995; Van Marter et al. 2001). Most
studies confirm no effect of surfactant on BPD (Merritt et al. 1991; Smyth et al. 1995)
while some have found that postnatally administered steroid treatment seems to be
beneficial in preventing the disease in VLBWI treated with surfactant (Rastogi et al.
1996).

4.4. Factors affecting risk of motor impairment

The risk factors for CP in preterm infants might differ from those in full-term infants.
Hagberg et al. estimated that in children born before 28 GW the origin of CP might be
ascribed to perinatal or neonatal factors in 80%, in term infants in 28% (Hagberg et al. 1996).

Results found for the effect of gestational age and birth weight on incidence of motor impairments in preterm infants are contradictory. In several studies, low gestational age and birth weight have not had an independent impact on motor impairment incidence in extremely preterm or ELBW infants (Doyle 1995; Hack et al. 2000; La Pine et al. 1995; Msall et al. 1991; Piecuch et al. 1997a; Piecuch et al. 1997b; The Victorian Infant Collaborative Study Group 1997a), while in a Swedish study, authors found an increasing incidence of CP in ELBWII with decreasing gestational age (Finnstrom et al. 1998).

Intraventricular haemorrhage grades III through IV, periventricular leukomalasia (PVL), and hydrocephalus have all been shown to be predictive of CP (Hagberg et al. 1996; Ikonen et al. 1992; Msall et al. 1991; O’Shea et al. 1998; Piecuch et al. 1997b; Salokorpi et al. 1999; Waugh et al. 1996; Vohr et al. 2000) and the predictive role of PVL to be superior to haemorrhage in ventricles (Dunin-Wasowicz et al. 2000; Levene 1990).

Salokorpi et al. found that hypoxia was more common in ELBWII with CP than in surviving ELBWII without CP (33% vs. 19%), although the difference between groups in their study was not statistically significant (Salokorpi et al. 1999). However, in other studies a significant associations have been detected between hypoxia and IVH/PVL (Calvert et al. 1987; Erickson et al. 2002; Fujimoto et al. 1994; Ikonen et al. 1992; Okumura et al. 2001; Wiswell et al. 1996) and hypoxia and CP in preterm infants (Graziani et al. 1992; Greisen et al. 1987).

Prolonged supplementary oxygen has been associated with increased rate of CP in extremely preterm infants (Msall et al. 1991), although all research groups have not confirmed the finding in ELBWII (Piecuch et al. 1997b). Such factors as birth asphyxia (Han et al. 2002; Msall et al. 1991), chorionamnionitis (Grether et al. 1996; Wu et al. 2000), multiple births (Grether et al. 1996), neonatal sepsis (Han et al. 2002), RDS (Han et al. 2002), intrauterine growth retardation (Finnstrom et al. 1998), NEC (Vohr et al. 2000), surfactant treatment (Vohr et al. 2000), hyponatremia (Murphy et al. 1997),
cardiovascular complications (PDA, hypotension, blood transfusion) (Murphy et al. 1997) have been reported as risk factors for CP in preterm infants.

The declined rate of CP in VLBWI found in Britain between 1982 and 1993 is assumed to be mainly due to the more common use of antenatal steroids (Cooke 1999). As antenatal steroids have been found to be protective against IVH and PLV, some researches have also assumed that with their increased use the neurologic outcome in preterm infants might be improved by decreasing the rate of CP (Canterino et al. 2001; Gray et al. 2001). On the contrary, however, in trials aimed at improving pulmonary function, postnatal steroid treatment has been associated with decreased cortical grey matter volume (Murphy et al. 2001) and an increased rate of CP (O’Shea et al. 1999; Shinwell et al. 2000).

4.5. Factors affecting risk of visual impairment

Retinopathy of prematurity is a risk factor for later visual impairment (Darlow et al. 1997; Hebbandi et al. 1997; Maly 1993). Incidence of visual impairments is also higher in ELBW infants without ROP than in normal birthweight infants. Visual impairments and ROP have been associated with several risk factors. Most of these factors are common to both conditions and are therefore reviewed here together.

Several investigators have found that Candida sepsis is associated with stage 3-4 ROP (Mittal et al. 1998; Noyola et al. 2002), even after controlling for gestational age, birth weight, days on supplementary oxygen, and five-minute Appgar scores (Mittal et al. 1998). However, although ROP was more common in infants with a history of candidemia in the study of Karlowicz et al., after controlling for other risk factors, such as gestational age, candidemia did not remain significant. The authors speculated that much of the detected association might have been mediated by low gestational age (Karlowicz et al. 2000).

Extremely preterm and low birthweight infants are at increased risk for both ROP and later visual impairment (Costeloe et al. 2000; Holmstrom et al. 1998a; Hussain et al. 1999; Karlowicz et al. 2000; Powls et al. 1997). Besides increased incidence of visual impairments in infants with ROP, ophthalmic abnormalities (e.g. strabismus and poor
visual acuity) have been detected at higher rates in VLBWI with IVH (especially grades III to IV) or PVL compared with VLBWI without such conditions (Lanzi et al. 1998; Phillips et al. 1997; Powls et al. 1997). An increased risk for ophthalmic problems has also been detected in white infants compared with black infants (Costeloe et al. 2000; Karłowicz et al. 2000), in infants with intrauterine growth restriction and those with low one-minute Apgar scores (Powls et al. 1997).

Tin et al. found that ROP requiring cryotherapy was four times more common in extremely preterm infants given supplementary oxygen for at least the first eight weeks to maintain oxygen saturation at 88% to 98% compared with those with a saturation target of 70% to 90% (Tin et al. 2001). Surfactant treatment has had no significant effect on severity or incidence of ROP (Kennedy et al. 1997; Repka et al. 1993), while in VLBWI, BPD and a prolonged supplementary oxygen requirement have been identified as a risk factors for the disease (Holmstrom et al. 1998a; Hussain et al. 1999).

4.6. Factors affecting risk of cognitive impairment

Cognitive impairments are common in preterm infants (Vohr et al. 1992). Several perinatal factors, such as male gender (Hack et al. 2000; Hindmarsh et al. 2000), BPD (Hack et al. 2000; Piecuch et al. 1997a), IVH/PVL (Leonard et al. 1990; Piecuch et al. 1997a), hydrocephalus (Msall et al. 1991), and maternal substance abuse (Piecuch et al. 1997a), have had a negative impact on cognitive development in study populations including ELBW or extremely preterm infants. In addition, ROP, even limited to one eye, seems to affect unfavourably cognitive development in VLBWI (Msall et al. 2000).

Msall detected no predictive impact of low gestational age or low birth weight on intellectual disability rates in infants born extremely preterm (Msall et al. 1991). Nor did Hack et al. find a significant difference in the rates of abnormal mental scores between infants with a birth weight of 750-999 g and those with a birth weight of 500-749 g (Hack et al. 2000). On the contrary, when Piecuch et al. followed infants born at 24 to 26 GW up to 32 months, normal cognitive development increased significantly with increasing gestational age, though no correlation was found between gestational age and neurological impairment rates (Piecuch et al. 1997a).
Low maternal education has been shown to be predictive of low intellectual scores (Ment et al. 1996; Sommerfelt et al. 1995), and low socio-economic status alone or together with parental distress predict unfavourable cognitive development and the need for special education in both extremely preterm and VLBW infants (Hack et al. 2000; Leonard et al. 1990; Msall et al. 1991; Piecuch et al. 1997a; Singer et al. 1997; Vohr et al. 1992).

Thompson et al. analysed risk factors for poor mental and motor development. The investigators compared four different groups of VLBWI classified according to neurobiological risk status (perinatal acidosis, need for mechanical ventilation, IVH, PVL, neonatal infections, hypoglycaemic episodes, seizures) and maternal distress level to high- and low-risk groups. Cognitive function was most favourable in the group with lowest maternal distress and lowest neurobiological risk scores and worst in the group which graded high in both measurements. Moreover, maternal distress was a more important risk factor for cognitive development than neurobiological risk factors (Thompson et al. 1994).

5. Predictive value of early neurological / developmental assessments

Koller et al. found that suspicious neurological status during infancy was not a predictor of subsequent neurological impairment; most subjects (73%) with a suspicious neurological status at the age of one year were considered to be neurologically normal at the age of 5 or 6 years (Koller et al. 1997). Among ELBWI, neurological findings at early assessments may be overly pessimistic. Kitchen et al. reported that 33% of children had a poorer diagnosis at the age of two years than at the age of five, and only 4% had a more severe handicap at five years of age (Kitchen et al. 1987).

However, Roth et al. found a significant correlation between neurodevelopmental outcome at the age of one year, eight years, and 14 to 15 years in infants born before 33 GW. Most of those classified as disabled at the age of one year, had major impairment also at the age of eight years and 14 to 15 years (91% and 86%, respectively). Most of the infants classified as normal at the age of one year were normally developed or had minor impairments and only 14% had disabling impairment at the age of 14 to 15 years. Infants who had minor impairments (e.g. abnormalities in tone, posture, and reflexes)
typically retained the impairment during teenage years, 31% had major impairment, and 12.5% were classified as normal. The authors hypothesised that the increasing number of mild impairments and the decreasing number of infants with normal development were related to the increasing range and complexity of skills required as the child grows older and that most deficits in these skills could not be detected in early childhood (Roth et al. 2001; Roth et al. 1994).

In comparison with normal weight children, ELBWI classified as non-disabled at an early age have significantly poorer performance on cognitive, verbal, perceptual, motor, and visual-motor measures at preschool-age (Halsey et al. 1993). Several other investigators have also confirmed the susceptibility of VLBWI and ELBWI, even those without major disabilities, to later developmental and behavioural problems, and thus, have suggested close long-term follow-up of these infants (Collin et al. 1991; Schendel et al. 1997).

Cognitive assessments at the early age have been found to be predictive of later cognitive development. Among ELBWI, Griffiths scores at three years of age predicted scores at the age of five years, but scores at the one year of age did not (Bowen et al. 1996), while Vohr et al. concluded that Bayley assessment in preterm infants at the age of one year correlated well with the McCarty General Cognitive Index and Perceptual Index at five years of age (Vohr et al. 1992).

Roth et al. showed that only 13% of preterm infants born before 33 GW who were classified as normal at infancy needed extra educational help as teenagers, which was below the national estimates in the United Kingdom (Roth et al. 2001). However, at the age of one year VLBWI without detected impairment had significant discrepancies between fine motor or language skills and problem-solving skills and scored lower in all behavioural field than same-aged full-term infants (Williamson et al. 1990). Koller et al. studied developmental patterns in cognitive development in VLBWI. A declining pattern was detected in 67%, and only 8% showed improvement in four assessments performed yearly up to the age of six years. A significant association was found between abnormal neurological status at the age of one year and low cognitive scores later (Koller et al. 1997).
6. Parental distress

The birth of a preterm infant is a stressful event for the parents (Cronin et al. 1995; Stjernqvist 1992; Trause et al. 1983). Owing to a prolonged, intensive initial hospitalisation period for ELBW1, parents and other family members may experience a lengthy physical separation from each other, increased need for external help and psychological support, changes in parental roles, and often increased economic concerns.

Neonatal intensive care is frightening for parents who are already worried about the infant’s survival and disablement (Benfield et al. 1976; Miles et al. 1992; Trause et al. 1983). Stjernqvist found that the birth of ELBW1 caused a crisis for 85% of mothers and 65% of fathers (Stjernqvist 1992). In the study of Yu et al., the most common grief feelings among parents with a critically ill infant admitted to NICU, were sadness, worry resulting in sleeping difficulties, loss of appetite, and disinterest in work (Yu et al. 1981). Parents may also feel confused because of changes in parenting roles during the long hospitalisation period (Miles et al. 1992). The severity of the infant’s illness may not be directly related to the degree of parental stress (Benfield et al. 1976; Spear et al. 2002); parents’ perception of the severity of illness has a greater impact on the experience (Catlett et al. 1994; Shields-Poe et al. 1997). The neonatal intensive care unit itself is also frightening. Jämsä et al. reported that parents found the audible signals and alarms of equipment to be most unpleasant. NICU’s high technology environment obscured the parenting role and delayed parents’ participation in child care (Jämsä et al. 1998). Most parents found it relieving to be able to unrestrictedly visit a NICU and to hear about other parent’s experiences with a critically ill infant who ultimately fared well (Yu et al. 1981).

After discharge, daily care of ELBW1 during the first years, is time-consuming and problematic, with common feeding difficulties and the infant’s need for special nourishment and medication. Uncertainties about the future may continue after the neonatal period as the child grows and is confronted with new demands. In an American study, behavioural problems in VLBWI were more frequent than in full-term infants and these behavioural characteristics seemed to have a significant impact on parents’ distress (Halpern et al. 2001). In a comparison made by Singer et al., distress of VLBWI
mothers was significantly higher than that of mothers with full-term infants when the child was one month old. The distress level was no longer elevated when the child was two years in mothers of infants without BPD. However, mothers of infants with BPD continued to experience more distress than control mothers. Parenting stress remained higher in families of infants with BPD up to the child’s age of three years (Singer et al. 1999). In families with a teenaged ELBW1, both positive and negative impacts have been observed, but mostly families coped well (Saigal et al. 2000a).

Ong et al. found that in VLBWI male gender, lower maternal education, mother’s role as primary caregiver, and high Child Behaviour Checklist scores indicating lower intelligence and adverse behaviour were associated with higher parenting stress scores when the child was aged one to five years. In addition, social environment seemed to have a marked impact on parenting stress (Ong et al. 2001).

In a Canadian study, families with a moderately handicapped VLBWI differed from those with children with no or only mild handicaps by having higher financial burdens, familial/social stress and personal strain (Cronin et al. 1995). Contrary findings do, however, exist: In another Canadian study, families with disabled VLBWI did not differ in family impact scores from families with healthy term infants (Lee et al. 1991) and in Sweden, no relationship between permanent neurological injuries and strength of reactions in family members was present during the first year of the ELBW1’s life (Stjernqvist 1992).

Although the long-term burden of disability in ELBW1 has been demonstrated to be greater on average than in an age-matched control population (Saigal et al. 1994), recent studies have shown that parents of ELBW1 rated the burden caused by the functional disability of their child less highly than did health care professionals (Saigal et al. 1999). Moreover, the majority of teenaged ELBW1, despite having more health problems, rated their health-related quality of life similarly to same-aged controls (Saigal et al. 1996). Saigal et al. and Lee et al. found that most parents of ELBW1 and VLBWI supported saving all infants regardless of prognosis (Lee et al. 1991; Saigal et al. 2000a); however, in Cronin et al., only half of the parents did so (Cronin et al. 1995). Parents of teenaged ELBW1 tended to view their child’s quality of life as high, indicating that disability does not always result in lower utility (Saigal et al. 2000c).
Bjerager et al. reported that VLBWI adults without disabilities had quality-of-life scores comparable with those of same-aged, normal birthweight controls. The scores of VLBW adults with disabilities did, however, differ significantly from those of controls (Bjerager et al. 1995).

In Sweden, when parenting stress was measured in parents seeking specialised medical assistance for their young child, fathers had lower total scores and lower scores in four subscales of SPSQ than mothers (Ostberg 1998). Only in social isolation did the scores of mothers and fathers not differ significantly. Many studies confirm that mothers experience more distress than fathers concerning preterm infants during the initial hospitalisation period and also later, after the first discharge (Benfield et al. 1976; Cronin et al. 1995; Miles et al. 1992; Trause et al. 1983). Early support of the husband might help mothers to adjust better to the birth of a preterm infant (Trause et al. 1983), whereas a rearing child primarily alone increases distress (Ong et al. 2001).

7. Costs of care

7.1. Neonatal care costs

Concurrently with the development of neonatal care, treatment costs of ELBWI have increased significantly (Boyle et al. 1983). When the costs of care in ELBWI were compared in Victoria state during the post-surfactant and pre-surfactant eras, the cost-utility and cost-effectiveness were lower during the initial hospitalisation in the post-surfactant era. However, when long-term costs of severely disabled infants were included, both ratios were higher in the post-surfactant era (The Victorian Infant Collaborative Study Group 1997b).

Stevenson et al. found that in a regional cohort of ELBWI, born in 1980 and 1981, neonatal care costs were 55 times the costs incurred by age- and sex-matched controls (Stevenson et al. 1996a). Neonatal intensive care costs per infant have been demonstrated to be independently related to gestational age, length of stay, and survival status, as well as to other factors such as need for ventilatory support, surgery, etc. In surviving infants, length of stay has been shown to increase with a decrease in
gestational age. Similarly, the costs of care increase with decreasing gestational age and birth weight (St John et al. 2000; Stahlman 1984). At the beginning of the 1990s, the overall costs of infants born at a gestational age of 24 to 26 GW accounted for 11.4%, those born at 27 to 32 GW 30.8%, and those born after 32 GW 57.8% of estimated annual neonatal care costs in USA (St John et al. 2000).

Severity of neonatal diseases is related to increased primary hospitalisation costs. Pikus et al. analysed costs during initial hospitalisation of infants born with a birth weight from 800 g to 2680 g (mean 1240 g) with massive IVH (grade IV). The costs of primary hospitalisation were high and majority had subsequent impaired intellectual function, motor deficit, and seizure disorders, which increased long-term costs (Pikus et al. 1997).

St. John et al. found no correlation in non-survivors between gestational age and costs of care (St John et al. 2000). As the majority of deaths occurred, regardless a gestational age, during the first days after birth, the overall costs in non-surviving ELBW1 remain moderate (St John et al. 2000). Stolz et al., report the costs of non-surviving VLBWI accounting for only 8.1% of overall NICU costs for the whole birthweight group (Stolz et al. 1998).

Parental costs during neonatal care have not been thoroughly investigated. A British study has shown that the costs related to visiting NICU can be considerable and may even restrict visiting at hospital (Stolz et al. 1998).

7.2. Costs after the initial hospitalisation period

The rehospitalisation rate was 34% during the first two years in a Dutch national cohort, including VLBWI and infants with gestational age of less than 32 GW. Respiratory tract disorders and surgical procedures, especially inguinal herniotomy, were the main causes for rehospitalisations (van Zeben-van der Aa et al. 1991). Similarly, the two-year rehospitalisation rate was high (72%) in ELBW1 in Taiwan, with respiratory problems cited as the main cause (Chien et al. 2002). In addition to higher hospital care costs, McCormick found nine times higher physician visit costs and costs originating from medication, equipment rental, diagnostic tests, and medical supplies during the first
post-discharge year in VLBWI compared with infants born at term (McCormick et al. 1991).

The rehospitalisation rate during childhood among VLBWI has been shown to remain higher than that of normal birthweight infants. Kitchen et al. reported that VLBWI were significantly more often hospitalised even at the age of five years than normal birthweight controls (1.7 vs. 0.5 admissions and 8.5 vs. 1.7 days in hospital) (Kitchen et al. 1990). Stevenson et al. found that even normally developed low birthweight infants (<2000g) followed up to the age of 8 to 9 years used more than twice the amount of health care services as compared with normal birthweight infants, resulting in significantly higher hospital and family practitioner service costs in a group of preterm infants (Stevenson et al. 1996a). Including the neonatal care costs, the mean total cost of medical care among low birthweight infants was 4.7-fold and among extremely low birthweight infants 16.2-fold the cost of care of control children (Stevenson et al. 1996a).

A recent study by Rogowski et al., which included costs until the age of one year, showed that medical treatment costs for first year survivors were related to birth weight. Decreasing costs with increasing birth weight were detected. The initial hospitalisation accounted for the major part of the costs; post-discharge medical costs were not separately analysed for different birth weight groups (Rogowski 1998). The study revealed that VLBWI who died during the initial hospitalisation had the lowest costs, and those who survived the initial hospitalisation but died during the first year had even higher costs than those who survived the first year (Rogowski 1998). This was mainly due to higher costs of rehospitalisations in infants dying after the initial hospitalisation. These costs were over five times higher than in non-survivors. In infants who survived the first year, the initial hospitalisation accounted for 89% of all medical costs, rehospitalisations for 9%, and outpatient care for 2% (Rogowski 1998).

School difficulties are common in infants born with low birth weight. Klebanov et al. showed that as birth weight decreased the prevalence of grade failure, placement in special classes, and disability rate increased (Klebanov et al. 1994b). Difficulties in reading and maths were considerable in ELBWI (Klebanov et al. 1994b). Chaikind et al. found that low birthweight infants (<2500g) were 50% more likely to attend special
education classes than their normal birthweight peers, resulting in US$ 370.8 million’s in annual additional costs of special education in USA (Chaikind et al. 1991).

In a regional study cohort from Great Britain, the estimated disability rate was 7.7% at the age of 8 to 9 years in infants with a birth weight of under 2000 g. The total costs of these infants, including health care and education, accounted for 38% of the cohort’s overall costs (Stevenson et al. 1996b). Although the costs of health care also included the costs of initial hospitalisation, special education in this school-aged study cohort accounted for the major proportion of overall costs (52%). The mean cost per disabled child was £19,593 compared with a mean cost of £4,197 among non-disabled infants and £2,038 among normal birthweight controls (Stevenson et al. 1996b).

The families of ELBW1 often confront notable economic losses, such as costs of special daily care, travelling, medication, private ambulatory visits, and loss of earnings. The burden of these costs on the families depends on the country’s insurance and social support systems. According to Gennaro, families of preterm infants (<37 GW or 2500 g) during the first six months of the infant’s life spend up to 2-4% of their total income on out-of-pocket expenses related to care of their child’s illnesses (Gennaro 1996). Travelling to health care providers comprised the majority of these costs (Gennaro 1996). McCormick estimated that medical costs during the first post-discharge year accrued to parents could in VLBWI families be two to seven times that in families with full-term infants (McCormick et al. 1991). Costs after the first discharge unrelated to rehospitalisations could account for up to 9% of total income in VLBWI families (McCormick et al. 1991). However, parental costs declined rapidly after the initial discharge; by the end of the first post-discharge year, the difference in parental costs between infants with a birth weight of under 1500 g and term infants had practically disappeared (McCormick et al. 1991).
8. **Summary of the literature**

The majority of studies have showed that the mortality rate of ELBW1 has continued to decline during the last decade, without a concomitant increase in rates of severe impairments (CP, severe visual impairment, hearing impairment, intellectual disability) in survivors.

Numerous and partly controversial perinatal and neonatal factors have been shown to affect unfavourably the outcome of ELBW1. However, strong evidence favours the use of antenatal steroids to mothers with threatening premature labour and surfactant treatment to ELBW1 with RDS, but long-term beneficial effects of repeated antenatal steroid doses and postnatal steroid treatment are controversial and a concern has arisen concerning the safety of these treatments.

Parental distress in families with a preterm infant, mainly evaluated during the NICU period, has been found to be initially high, but has, according to those few studies performed after initial hospitalisation, declined steadily during the child’s early childhood.

The costs of initial hospitalisation correlates well with a gestational age and a birth weight in ELBW1, but data concerning the overall costs of care after initial hospitalisation and the long-term costs of care accrued to parents are scarce.
AIMS OF THE STUDY

As the outcome of ELBWIs changes with advances in antenatal and neonatal care, continuous follow-up data of comprehensive population-based cohorts are needed to evaluate changes in prognosis and to update risk factors for unfavourable outcome. Moreover, as scarce data concerning the costs of care, especially after initial hospitalisation, and parental well-being during the child’s first years of life, after the critical neonatal period exist, we designed the present study with the following specific aims:

1. To establish birth rate, mortality, and morbidity in a comprehensive national cohort of extremely low birthweight infants born in Finland in 1996-1997 (I).

2. To establish neurosensory outcome at a corrected age of 18 months in a cohort of extremely low birthweight infants born in 1996-1997 (II).

3. To compare neurodevelopmental outcome at the age of two years in a subcohort of extremely low birthweight infants born in Helsinki University Hospital in 1996-1997 with the outcome in a control cohort of normal birthweight children (II).

4. To analyse risk and protective factors associated with neonatal mortality and morbidity (I) and unfavourable outcome at the age of 18-24 months (II) in a cohort of extremely low birthweight infants born in 1996-1997.

5. To compare parental distress in families of two-year-old extremely low birthweight infants with that of controls (III).

6. To assess health care-related costs to up to two years corrected age in extremely low birthweight infants in relation to birth weight and outcome, and to compare the costs with those of normal birthweight infants (IV).
SUBJECTS AND METHODS

1. Study design

This general population-based, nation-wide prospective cohort study of ELBW infants comprised 120,025 infants born in Finland over a two-year study period between 1996 and 1997. All 44 maternity hospitals participated. A subcohort of ELBWI and a control cohort born in Helsinki University Central Hospital were selected for additional evaluation to study parental distress (Study III) and costs of treatment (Study IV).

Figure 1 outlines the study design, defines study populations, and describes data briefly.

2. Study populations

2.1. Extremely low birthweight infant cohort and a regional subcohort

The study population consisted of all stillborn (gestational age of at least 22 full weeks or birth weight of 500 g or more) and live-born ELBWI born in Finland between 1 January 1996 and 31 December 1997. The entire national cohort was included in Study I. All 211 ELBWI surviving to an age corresponding to 40 GW were included in Study II. The infants (n=78) born and followed in Helsinki University Hospital formed the subcohort of Study II and all families (n=74) of the ELBWI in this subcohort, which included four twin pairs (n=74), were recruited to Study III.

Study IV, which examined costs of care, included all families of ELBWI (n=105) admitted during 1996-1997 to neonatal intensive care in the Hospital for Children and Adolescents, the paediatric department of Helsinki University Hospital.

2.2. Control cohort

Full-term infants born next to each ELBWI in Helsinki University Hospital (in 1996, one infant; in 1997 two infants) were eligible for the control group (Studies II and III). Inclusion criteria for control infants were gestational age ≥ 37 weeks, no need for specialised medical care during the first three days, and native language Finnish, Swedish, or English. A total of 75 out of 126 invited controls (60%) participated in
**Subjects and methods**

**Figure 1. Study design**

POPOPULATION
= All infants born in Finland in 1996 and 1997 (n= 120 025)

**EXPOSURE = ELBW**

Exposed = +

Unexposed = -

ALL ELBW
who survived until the age of 40 GW
n=211 (Study I, II)

ALL ELBW
who survived until the age of 2 years
n=208 (Study II)

ALL ELBW
stillborn and those who died before
the age of 40 GW
n=316 (Study I)

ELBW admitted to NICU of HUCH
n=105

Regional subsample = Control cohort
n=126

ELBW who survived until the age of 2 years
n=54 (Studies II, IV)

ELBW who died by the age of 2 years
n=21 (Study IV)

ELBW alive at 2 years of age born and followed in HUCH
n=78 (Studies II, III)

**STUDY I**

- Main outcome variables registered.
  - Mortality and causes of death up to an age corresponding to 40 GW
  - Neonatal morbidity (RDS, IVH, NEC, sepsis, PDA)
  - Rates of ROP, BPD, neurological status at an age corresponding to 36 GW

**STUDY II**

- Main outcome variables registered.
  - Mortality up to the age of 2 years
  - Hearing assessment
  - Ophthalmological assessment (12-18 mths)
  - Neurological and speech therapist’s assessment (18 mths)
  - Bayley Infant Scale (2 years)

**STUDY III**

- Parental stress at child’s age of 2 years
- PSQ

**STUDY IV**

- Costs related to medical care
  - during initial hospitalisation
  - during the first and second post-discharge years

GW = Gestational week
HUCH = Helsinki University Central Hospital
IVH = Intraventricular haemorrhag
NICU = Neonatal intensive care unit
PDA = Persistent ductus arteriosus
RDS = Respiratory distress syndrome
ROP = Retinopathy of prematurity
SPSQ = Swedish Parenthood Stress Questionnaire
Subjects and methods

Study II. Families of all 75 control infants participated in Study III and were invited in Study IV; 80% participated.

3. Definitions

3.1. Definitions of exposures

Gestational age was determined by obstetrical ultrasound examination before the end of GW 20 or by the last menstrual period. Infants with birth weight below -2SD according to Finnish intrauterine growth curves were defined as small for gestational age (SGA) (Pihkala et al. 1989).

Social class allocation with four categories was based on maternal occupation or education according to a classification used by the Central Statistical Office of Finland and the National Development and Research Centre for Welfare and Health (Central Statistical Office of Finland 1987; Gissler et al. 1998).

Maternity hospitals were classified according to the following four levels based on size, equipment, and staffing (Viisainen et al. 1994): Level III: University hospitals with a neonatal intensive care unit and a neonatologist available (n=5); Level II: All central hospitals and two local hospitals with an obstetrician available 24 hours a day and special wards for newborns with or without to provision of basic neonatal intensive care (n=18); Level I: Local hospitals with equipment and staff primarily for healthy newborns. Obstetricians and paediatricians are usually not at the hospital outside office hours (n=20); Level Ia: Small local hospitals with no equipment to care for sick newborns, usually run by a general practitioner or consultant obstetrician (n=1). Finland is geographically divided into five regional university hospital areas, each served by one level III hospital. The five university hospitals with their catchment areas were labelled from A to E for outcome analysis.

The clinical risk index scores for babies were calculated according to classification developed by The International Neonatal Network (The International Neonatal Network 1993).
3.2. Definitions of outcomes

Survival in Study I was defined as being alive at discharge or at an age corresponding to 40 GW. In Study II, survival rate was calculated from infants alive at the prematurity-corrected age of two years.

International criteria were used for defining respiratory distress syndrome (RDS) (Rudolph et al. 1960), necrotising enterocolitis (NEC) (Bell et al. 1978), intraventricular haemorrhage (IVH) (Papile et al. 1978), and retinopathy of prematurity (ROP) (The Committee for the Classification of Retinopathy of Prematurity 1984). The diagnostic criterion for sepsicaemia was a positive blood culture. Neurological abnormalities at an age corresponding to 36 GW were defined as seizures or muscular hypertonia or hypotonia. The definition for BPD was a need for supplementary oxygen at an age corresponding to 36 GW.

The same definitions were used when RDS, NEC, IVH, ROP, septicaemia, BPD, and neurological abnormalities at an age corresponding to 36 GW were used as exposures in Study II.

Cerebral palsy was defined as a non-progressive motor impairment with spastic or dystonic muscle tone, delayed motor development, brisk tendon reflexes, positive Babinski’s sign, and persistent primitive reflexes. Four categories, according to Hagberg et al., were used: 1) diplegia, 2) hemiplegia, 3) tetraplegia, and 4) ataxia or athetosis syndrome (Hagberg et al. 1996). Other motor impairments included delays in motor development (Sillanpää et al. 1996), variable abnormalities in muscle tone without other features of CP, and muscular hypotonia or hypertonia with specific cause (trisomy 21, central nervous system malformation). International criteria were used to define blindness (Steinkuller et al. 1999).

Impairment severity at the corrected age of 18 months was graded into three stages. Normal development was defined as no impairments in hearing, ophthalmic, motor, or speech assessment. Mild impairment included one to two impairments detected in the above-mentioned assessments but excluded blindness, hearing impairment necessitating a hearing aid, CP, and convulsions. Severe impairment consisted of three or four minor impairments in above mentioned assessments and/or one of the following four
Subjects and methods

disabilities: blindness, hearing impairment necessitating a hearing aid, CP, or convulsions.

4. Data collection procedures

All Finnish maternity hospitals (n=44) participated in the national follow-up. Perinatal and neonatal data were obtained from delivery rooms and neonatal care units by information forms designed for the study. The forms were returned to the National Research and Development Centre for Welfare and Health after the birth of each ELBW and when the infant’s age corresponded to 40 GW (alternatively, at discharge or when an infant died if that occurred before the age of 40 GW). The obtained data were registered in a national ELBW register established in 1996 (Study I).

A national follow-up programme included an ophthalmological assessment at the corrected age of 12 to 18 months, and examinations by a neurologist, psychologist, physiotherapist and speech therapist at the corrected age of 18 months (Study II).

In addition to the national follow-up programme, two psychologists performed developmental age assessments at the corrected age of 24 months on all infants in the subcohort. Control children were assessed at the age of two years with the same developmental methods as the ELBW children (Study II). During the visit parents of ELBW and control infants were invited to participate in Study III and were requested to complete the parental stress questionnaire (Study III).

The economic costs of care were calculated for three treatment periods extending from birth to the first discharge, from discharge to the corrected age of one year, and from the corrected age of one year to the corrected age of two years.

Costs of intensive care were obtained for all ELBW from the Helsinki University Hospital Patient Account Office. Hospital costs after intensive care for ELBW and costs for control infants up to the age of two years were obtained from the 18 hospitals responsible for follow-up and care.
Subjects and methods

Ancillary cost and the costs accrued to parents were obtained from the families by a mailed questionnaire.

5. Description of collected data

The forms used for data collection in Study I contained 101 variables with information concerning pregnancy, delivery, neonatal morbidity, treatment, and the infant’s short-term outcome at an age corresponding to 40 GW. The obtained data were cross-linked with the Finnish National Birth Register, which includes basic information on all newborns with a birth weight of at least 500 g or a gestational age of 22 full weeks as well as on their mothers. The death certificates from the Central Statistical Office of Finland were cross-checked to validate causes of death. Contradictory reports and complementary data were checked from patient records.

National outcome data of ELBWI at the corrected age of 18 months from all 23 hospitals responsible for follow-up were collected using prospectively designed form and then transferred to the same national ELBWI register (Study II). The form included the results of ophthalmological, motor, speech, and hearing assessments.

In developmental age assessment, the Bayley Infant Scale 2nd edition (mental section) was used (Bayley 1993).

The Swedish Parenthood Stress Questionnaire (SPSQ) (Ostberg et al. 2000; Ostberg et al. 1997) modified from the Parenting Stress Index designed by Richard Abidin (Abidin 1990), was used to measure parental distress in families of ELBWI and control infants. The method has been standardised and validated in Sweden, where the culture and social structure closely resemble those in Finland. The inquiry form, translated to Finnish, contains 34 items divided into five subscales designated as incompetence, role restriction, social isolation, spouse relationship problems, and health problems. Items are scored from 1 to 5 on the Likert scale, the highest score indicating problems or difficulties in a respective area of the parent-child relationship. The inquiry form was tested by calculating Cronbach’s alpha-coefficients for all subscales and for the total.
Subjects and methods

SPSQ score (Study III). All except one coefficient were above 0.65, showing that satisfactory internal consistency in most subscales had been achieved.

The costs of initial hospitalisation were determined by the level of care evaluated on a daily basis: intensive care (mechanical ventilation, total parenteral nutrition, exchange transfusions, surgical treatment, extensive diagnostic procedures), intermediate care (parenteral fluids, electronic monitoring, incubation treatment), and basic care (gavage feeding, phototherapy, minor laboratory, pulse-oxymetry follow-up). The treatment costs included average costs of staff, medicine, nutrition, hospital room, equipment, consumable items, and ancillary costs. Individually calculated costs of expensive drugs, such as surfactant and some antibiotics, blood products given, diagnostic costs including x-ray and laboratory costs, cost of surgery, and consultations fees were added to these costs.

Since no control infant needed specialised care during the initial hospitalisation, the pre-existing cost estimate of initial hospitalisation for healthy newborns was used in the analysis (personal communication, Järvenselkä 2002).

The costs originating from the period after intensive care included average costs of staff, medicine, nutrition, hospital room, equipment, consumable items, and ancillary costs, to which individual x-ray and laboratory costs, costs of surgery, and consultation fees were added. The number and length of hospitalisation periods were cross-checked with the national discharge register.

The costs of outpatient ambulatory visits were based on average costs which were separately calculated for each hospital and were dependent on visit type.

The estimation of outpatient care costs (public health centre or private polyclinics), ancillary costs (parent's accommodation, special day care, loss of earnings during the infant's first two years), and costs of medication, rehabilitation, and travelling were based on information obtained from parents via a mailed questionnaire. National averages were used in calculations. Pharmacotherapy costs were based on pharmacy fees.
Subjects and methods

Delivery costs and the costs originating from well baby clinic care were excluded from the analysis. No monetary value was assessed for loss of leisure time.

All costs were expressed in 1997 monetary values, and costs occurring before or after that year were converted to 1997 monetary values by applying the Consumer Price Index and the Medication Price Index. Finally, costs were converted into Euro.

6. Statistical analyses

Outcome data were mainly presented as proportions of infants with a particular outcome per of ELBWI, of all live-born ELBWI, of all ELBWI surviving the first 12 hours, or of all infants surviving the follow-up period (Studies I, II). The outcome results of each university hospital area were compared with the combined average value of the other areas (Study I).

As the inclusion criterion was based on birth weight, as 98% of infants born alive at 22 to 26 GW were included in the study population, and as most infants with a birth weight below 1000 g born after GW 27 were small for gestational age, the outcome comparisons between gestational age groups were performed mainly in infants born at 22-26 GW. Birth weight-based comparisons were made at 100-gram intervals.

Mantel-Haenzel, Pearson’s $\chi^2$-test, or Fisher’s exact test was used as appropriate to analyse outcome differences in categorical variables. Data for continuous variables (Studies I-IV) were presented as means and standard deviations (SD), with medians and ranges expressed in cases where distributions were skewed. Student’s t-test was used to test differences in continuous variables.

The correlations between categorical and continuous variables were analysed using Pearson’s correlation coefficient (Studies II, IV).

Total scores, and scores of each subscale in SPSQ were compared by using Student’s t-test. Single missing values were not replaced; only available values were used.
Subjects and methods

In Studies I and II, logistic regression analysis was used to detect risks or protective factors, independently of each other, for adverse neonatal or later outcome (death, IVH grades II-IV, oxygen dependency or retinopathy at an age corresponding to 36 GW, CP, other motor impairments). All variables included in analysis are listed in Table 3. The variables were entered stepwise both forwards and backwards. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

A linear regression model was used in Study II to identify risks for poor performance in Bayley assessment in the Helsinki ELBW1 subcohort and in the control cohort. The following variables were included in the analysis: preterm birth, intrauterine growth retardation, gender, primiparity, vaginal delivery, multiple birth, mother's age, social class, smoking any time during pregnancy, marital status, examiner, day of birth (i.e. number of days counted from 1 January 1996 to birth date to evaluate possible improvement over time), and assessment age. In addition, antenatal steroid treatment, maternal infection, pre-eclampsia, preterm rupture of membranes, gestational age, birth weight, anomalies, RDS, IVH grades II through IV, NEC with perforation, septicaemia, and examiner were included when the risks for poor scores in Bayley assessment were analysed separately in the ELBW1 subgroup. In linear regression analyses, variables were entered stepwise.

In Study IV, sensitivity analysis was performed on all measures based on average costs or on information obtained from parents (costs of local hospital, travelling, private doctor or general practitioner visit, rehabilitation, medication and loss of income). Each variable was varied independently ±10% to determine the impact of uncertainty related to these variables on final results.

For the majority of statistical analyses, a SPSS software package (versions 9.0 and 10.0 for Windows, Chicago, IL, USA) was used. P-values of less than 0.05 were considered to be significant.
**Subjects and methods**

**Table 3.** The variables included in logistic regression analysis when risk or potential protective factors for death, IVH, oxygen dependency at an age corresponding to 36 GW, and ROP were analysed. The definition of categories/units for each risk factor is indicated in the right column.

<table>
<thead>
<tr>
<th>Variables used in the analysis</th>
<th>Categories / units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy data:</strong></td>
<td></td>
</tr>
<tr>
<td># primiparity</td>
<td>Yes / No</td>
</tr>
<tr>
<td># multiple pregnancy</td>
<td>Yes / No</td>
</tr>
<tr>
<td># pre-eclampsia</td>
<td>Yes / No</td>
</tr>
<tr>
<td>diabetes</td>
<td>Yes / No</td>
</tr>
<tr>
<td># maternal infection</td>
<td>Yes / No</td>
</tr>
<tr>
<td>abruption of placenta</td>
<td>Yes / No</td>
</tr>
<tr>
<td># premature rupture of membranes</td>
<td>Yes / No</td>
</tr>
<tr>
<td># antenatal steroid treatment</td>
<td>Yes / No</td>
</tr>
<tr>
<td># hyperstimulation / <em>in vitro</em> fertilisation</td>
<td>Yes / No</td>
</tr>
<tr>
<td># maternal age &lt; 20 years</td>
<td>Yes / No</td>
</tr>
<tr>
<td># maternal age &gt; 40 years</td>
<td>Yes / No</td>
</tr>
<tr>
<td># social classes (1-4)</td>
<td>Yes / No</td>
</tr>
<tr>
<td># smoking during the pregnancy</td>
<td>Yes / No</td>
</tr>
<tr>
<td># married</td>
<td>Yes / No</td>
</tr>
<tr>
<td><strong>Birth data:</strong></td>
<td></td>
</tr>
<tr>
<td># birth in secondary or primary level hospital</td>
<td>Yes / No</td>
</tr>
<tr>
<td># birth in hospitals belonging to the catchment area of respective tertiary level hospitals</td>
<td>Yes / No</td>
</tr>
<tr>
<td>maternal transport before delivery</td>
<td>Yes / No</td>
</tr>
<tr>
<td># vaginal delivery</td>
<td>Yes / No</td>
</tr>
<tr>
<td>5-minute Apgar score &lt;4</td>
<td>Yes / No</td>
</tr>
<tr>
<td>gestational age &lt; 25 GW</td>
<td>Yes / No</td>
</tr>
<tr>
<td>*# gestational weeks</td>
<td>full weeks</td>
</tr>
<tr>
<td>birth weight weight &lt; 600 g</td>
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</tr>
<tr>
<td>*# birth weight</td>
<td>100g groups</td>
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<tr>
<td># intrauterine growth retardation (&lt;-2 SD)</td>
<td>Yes / No</td>
</tr>
<tr>
<td># male gender</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>
**Subjects and methods**

**Neonatal morbidity:**

<table>
<thead>
<tr>
<th></th>
<th>Yes / No</th>
</tr>
</thead>
<tbody>
<tr>
<td># anomalies</td>
<td></td>
</tr>
<tr>
<td># respiratory distress syndrome</td>
<td></td>
</tr>
<tr>
<td># septicaemia</td>
<td></td>
</tr>
<tr>
<td># necrotising enterocolitis</td>
<td></td>
</tr>
<tr>
<td># intraventricular haemorrhage (grade II-IV)</td>
<td></td>
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</table>

**Neonatal treatment:**

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<table>
<thead>
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<th></th>
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<tbody>
<tr>
<td>*duration of respirator support</td>
<td>days</td>
</tr>
<tr>
<td>*supplementary oxygen amount</td>
<td>per cents</td>
</tr>
<tr>
<td>*supplementary oxygen duration</td>
<td>days</td>
</tr>
<tr>
<td>surfactant treatment</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

**At the age corresponding to 36 GW:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen dependency</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Retinopathy of prematurity (stage III-V)</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

* The variables that were analysed in continuous / category form. Units used in the analysis are indicated in the right column.

# The variables included also in logistic regression analysis when risk factors for CP and for CP or death were analysed.

7. **Ethical considerations**

The study was approved by the ethics committees of the Hospital for Children and Adolescents, and the Departments of Obstetrics and Gynaecology, Helsinki University Hospital, by the National Research and Development Centre for Welfare and Health, by the national Data Protection Ombudsman, and by the Ministry of Social Affairs and Health. According to Finnish law, in addition to the above mentioned approvals, no parental consent from ELBWI families was needed in national Studies I and II. Informed consent was obtained from the parents of all control infants participating in Studies II, III, and IV and from the parents of ELBWI participating in Studies III and IV.
RESULTS

1. Short-term outcome (I)

During the two-year study period 529 ELBW1 (0.4% of the 120,025 newborns) were delivered to 480 mothers. The rate of pregnancy complications diagnosed before delivery was 58% (n=280): 19% (n=92) had pre-eclampsia, 19% (n=93) preterm rupture of membranes, 30% (n=143) infection at time of delivery, and 7% (n=33) precocious ablation of placenta. Two-thirds of the 316 mothers (66%, n=207) who delivered a live-born infant received some (complete or incomplete) antenatal steroid treatment, and 41% (n=130) received complete treatment of two doses at more than 24 hours and less than 7 days before delivery. The proportion of infants whose mothers received antenatal steroids increased with increasing gestational age and was 21% of live-born infants born at 22-23 GW, 72% of those born at 24-25 GW, 74% of those born at 26-27 BW, and 77% of those born at 28 GW or more.

Figure 2 shows the proportions of ELBW1 of all infants born in Finland during the two-year study period at different gestational weeks.

Figure 2. Percentages of ELBW1 of all infants born each gestational week in Finland during the two-year study period in 1996-1997
Results

ELBWIs were born in 77% (34/44) of all maternity hospitals. The majority (n=379; 72%) was born in tertiary-level, 24% (n=125) in secondary-level, and 5% in primary-level hospitals. Of live-born ELBWIs, 82% (n=288) were born in tertiary-level hospitals.

Perinatal mortality was 55% (293/529) accounting for 39% of all perinatal deaths in Finland during the study period. One-third of ELBWIs were stillborn (34%, n=178), and 26% (n=140) died before an age corresponding to 40 GW. Of the live-born ELBWIs who did not survive to the age corresponding to 40 GW, 49% (n=69) died during the first 12 hours, 79% during the first three days, and 82% during the first week. A total of 88% (n=309) of all live-born infants were admitted to neonatal intensive care.

The neonatal mortality rate was 38% (n=133): 18 infants died during the neonatal period after the first seven days. Seven infants died after the neonatal period but before the age corresponding to 40 GW. According to official death certificates, the reported leading causes for neonatal deaths were RDS (29%), immaturity (26%), and IVH grades III-IV (15%). Necrotising enterocolitis and bronchopulmonary dysplasia were the main causes of death in infants who died after the neonatal period.

Figure 3a presents mortality in relation to gestational age, and Figure 3b mortality in relation to birth weight.

Background characteristics of stillborn and live-born ELBWIs in relation to gestational age and birth weight, and all newborns delivered during the study period are presented in Tables 4a and 4b. The tables also show neonatal morbidity rates in relation to gestational age and birth weight in 283 ELBWIs surviving 12 hours.

A total of 211 ELBWIs (40% of all ELBWIs) survived until discharge or until an age corresponding to 40 GW. Figures 4a and 4b summarise the rates of ROP, oxygen dependency, and abnormal neurological status in surviving ELBWIs in relation to gestational age and birth weight.
Results

Figure 3. Percentages of stillborn ELBWIs, of ELBWIs who died on day 0-3, on day 4-27, or after the neonatal period before an age corresponding to 40 GW, and of those who survived in relation to gestational age and birth weight.

3a) 100 %
80 %
60 %
40 %
20 %
0 %
Gestational age (weeks)
22 (n=59) 23 (n=57) 24 (n=62) 25 (n=76) 26 (n=86)

= alive at an age corresponding to 40 GW

= infants who died after the neonatal period

= infants who died on day 4-27

3b) 100 %
80 %
60 %
40 %
20 %
0 %
Birth weight (g)
<400 (n=32) 400-499 (n=42) 500-599 (n=84) 600-699 (n=97) 700-799 (n=94) 800-899 (n=78) 900-999 (n=102)

= infants who died on day 0-3

= stillborn infants

Figure 4. Prevalence of retinopathy of prematurity (open circles), need for supplementary oxygen (crosses) and abnormal neurological status (filled triangles) among ELBWIs surviving until an age corresponding to 36 GW in relation to gestational age and birth weight.

Numbers of infants surviving at term are given, each percentage was calculated in those with data available.

4.a) 100 %
80 %
60 %
40 %
20 %
0 %
Gestational age (weeks)
22-23 (n=5) 24 (n=18) 25 (n=34) 26 (n=47)

4.b) 100 %
80 %
60 %
40 %
20 %
0 %
Birth weight (g)
<600 (n=10) 600-699 (n=50) 700-799 (n=38) 800-899 (n=53) 900-999 (n=64)
Table 4. Birth characteristics of extremely low birth weight infants (ELBW1) and all newborns born during the two-year study period.

n) in different gestational age groups

<table>
<thead>
<tr>
<th></th>
<th>Stillborn</th>
<th>ELBW1</th>
<th>Live-born</th>
<th>All infants born in 1996-1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>ALL</td>
<td>22-23GW</td>
<td>24-25GW</td>
</tr>
<tr>
<td>Male sex</td>
<td>178</td>
<td>351</td>
<td>57</td>
<td>95</td>
</tr>
<tr>
<td>SGA</td>
<td>92 (52)</td>
<td>173 (49)</td>
<td>33 (58)</td>
<td>56 (59)</td>
</tr>
<tr>
<td>Multiple birth infants</td>
<td>38 (21)</td>
<td>102 (29)</td>
<td>14 (25)</td>
<td>32 (34)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>10 (6)</td>
<td>185 (53)</td>
<td>2 (4)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Born in level III hospital</td>
<td>91 (51)</td>
<td>288 (82)</td>
<td>37 (65)</td>
<td>79 (83)</td>
</tr>
<tr>
<td>Mean birth weight ***</td>
<td>601 (±205)</td>
<td>750 (±159)</td>
<td>567 (±102)</td>
<td>715 (±132)</td>
</tr>
</tbody>
</table>

ELBW1 surviving 12 hours (each percent calculated from those data available)

<table>
<thead>
<tr>
<th>N</th>
<th>RDS</th>
<th>NEC (perforated)</th>
<th>Septicaemia #</th>
<th>PDA (operated)</th>
<th>IVH (gr I-II)</th>
<th>IVH (gr III-IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>601</td>
<td>216 (77)</td>
<td>24 (9)</td>
<td>68 (24)</td>
<td>26 (9)</td>
<td>34 (12)</td>
<td>43 (16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NA</th>
<th>NICU</th>
<th>Respiratory distress syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH</td>
<td>Intraventricular haemorrhage</td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>Necrotising enterocolitis</td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>Persistent ductus arteriosus</td>
<td></td>
</tr>
</tbody>
</table>

*** Mean birth weight in grams (SD)

NA “Not available”

# Blood culture positive
b) in different birth weight groups

<table>
<thead>
<tr>
<th></th>
<th>ELBW1</th>
<th>All infants born in 1996-1997</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stillborn</td>
<td>Live-born</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>ALL</td>
<td>&lt; 600 g</td>
</tr>
<tr>
<td>N</td>
<td>178</td>
<td>351</td>
</tr>
<tr>
<td>Male sex</td>
<td>92 (52)</td>
<td>173 (49)</td>
</tr>
<tr>
<td>SGA</td>
<td>88 (49)</td>
<td>121 (35)</td>
</tr>
<tr>
<td>Multiple birth infants</td>
<td>38 (21)</td>
<td>102 (29)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>10 (6)</td>
<td>185 (53)</td>
</tr>
<tr>
<td>Born in level III hospital</td>
<td>91 (51)</td>
<td>288 (82)</td>
</tr>
<tr>
<td>Mean gestational age**</td>
<td>26.0 (3.6)</td>
<td>26.4 (2.4)</td>
</tr>
</tbody>
</table>

** ELBW1 surviving 12 hours (each percent calculated from those data available)

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>RDS</th>
<th>NEC (perforated)</th>
<th>Septicaemia #</th>
<th>PDA (operated)</th>
<th>IVH (gr I-II)</th>
<th>IVH (gr III-IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL</td>
<td>283</td>
<td>35</td>
<td>55</td>
<td>54</td>
<td>62</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>216 (77)</td>
<td>33 (94)</td>
<td>49 (89)</td>
<td>43 (80)</td>
<td>41 (66)</td>
<td>50 (66)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>24 (9)</td>
<td>3 (9)</td>
<td>4 (7)</td>
<td>7 (13)</td>
<td>4 (7)</td>
<td>6 (8)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>68 (24)</td>
<td>7 (20)</td>
<td>21 (38)</td>
<td>15 (28)</td>
<td>14 (23)</td>
<td>11 (14)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>26 (9)</td>
<td>2 (6)</td>
<td>7 (13)</td>
<td>5 (9)</td>
<td>4 (7)</td>
<td>8 (10)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>34 (12)</td>
<td>3 (9)</td>
<td>10 (19)</td>
<td>8 (15)</td>
<td>5 (8)</td>
<td>8 (11)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>43 (16)</td>
<td>9 (26)</td>
<td>13 (25)</td>
<td>7 (13)</td>
<td>6 (10)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

** Mean gestational age in weeks (SD)
NA “Not available”
# Blood culture positive

IVH Intraventricular haemorrhage
RDS Respiratory distress syndrome
NEC Necrotising enterocolitis
SGA Small for gestational age
PDA Persistent ductus arteriosus
Results

2. Outcome at the corrected age of 18 months (II)

Follow-up data were obtained for all 211 ELBWI born during the two-year study period in Finland and who were alive at an age corresponding to 40 GW. Table 5 presents demographic data on all ELBW1 surviving two years, on the regional ELBW1 subcohort, and on the controls. According to the national birth register, the controls participating in the study did not significantly differ from those not participating with regard to the variables listed in Table 5.

Of the infants alive at term, three (1.4%) died before or at the corrected age of two years: one from BPD, one from pneumonia, and one accidentally.

Strabismus was the most common abnormality (n=23, 12%) detected in the ophthalmological assessment performed to 93% (n=197) of infants at the corrected age of 12-18 months. Myopia was found in 8% (n=15), and other abnormalities, such as astigmatism, hyperopia, or retinal scars, in 5% (n=10). Fourteen (8%) infants needed eye-glasses. One child was legally blind (0.5%), and two (1%) had lost vision in one eye. Ophthalmological status was considered normal in 77% (n=151) of ELBW1.

Neurological outcome was registered in 90.3% of ELBW1 at the corrected age of 18 ± 2 months, in 4.4% at 12-15 months, and in 5.3% at 20-24 months. Completely normal motor development was found in 76% (n=157). The rate of CP was 11% (23/208), and of other minor motor impairments 13% (27/208). Diplegia affected 7% (n=15), tetraplegia 2% (n=4), hemiplegia 1% (n=2), and ataxia or athetosis 1% (n=2) of infants. Of the infants with minor motor impairment, 59% (n=16) had delayed motor development when compared with age-specific averages in the Finnish population, 11% (n=3) had a congenital anomaly affecting the central nervous system (trisomy 21, meningomyelocele, or atrophy of the cerebellum), and 30% (n=8) had clumsiness, hypotonia, rigidity, or difficulties in movement regulation.

Verbal assessment was performed on 195 (94%) infants. Developmental speech delay was found in 42% (n=82) of cases. Hearing in 86% of infants was considered normal in oto-acoustic emission or brainstem auditory evoked potential assessments, 9% (n=18)
Table 5. Birth characteristics on surviving ELBW infants, the subcohort (ELBW infants born and followed in the Helsinki University Hospital), and the control cohort.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>All surviving ELBW (208 infants, 193 mothers)</th>
<th>Subcohort (78 infants, 74 mothers)</th>
<th>Control cohort (75 infants, 75 mothers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>104 (54)</td>
<td>42 (58) #</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Unmarried mother</td>
<td>67 (37)</td>
<td>31 (42) #</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Upper social classes 1-2</td>
<td>120 (65)</td>
<td>47 (64) #</td>
<td>62 (83)</td>
</tr>
<tr>
<td>Lower social classes 3-4</td>
<td>66 (36)</td>
<td>27 (36) #</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Mother’s smoking</td>
<td>37 (19)</td>
<td>14 (19)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Mother’s mean age, years (range)</td>
<td>31.5 (16.3-48.5)</td>
<td>32.5 (21.5-47.5)</td>
<td>32.0 (21.3-43.9)</td>
</tr>
<tr>
<td>Mean birth weight, g (range)</td>
<td>807 (447-995)</td>
<td>778 (447-995) #</td>
<td>3671 (2530-5250)</td>
</tr>
<tr>
<td>Mean gestational age, wk (range)</td>
<td>27.3 (22.3-34.9)</td>
<td>27.1 (23.7-32.6) #</td>
<td>39.9 (37.3-42.1)</td>
</tr>
<tr>
<td>Male sex</td>
<td>97 (47)</td>
<td>38 (49)</td>
<td>39 (52)</td>
</tr>
<tr>
<td>Multiple pregnancy infants</td>
<td>55 (26)</td>
<td>16 (21) #</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Antenatal steroid treatment</td>
<td>164 (79)</td>
<td>69 (88) #</td>
<td>0</td>
</tr>
<tr>
<td>Born in tertiary hospital</td>
<td>187 (90)</td>
<td>78 (100)</td>
<td>75 (100)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>68 (33)</td>
<td>23 (29) #</td>
<td>58 (77)</td>
</tr>
</tbody>
</table>

**Morbidity data**

<table>
<thead>
<tr>
<th></th>
<th>All surviving ELBW</th>
<th>Subcohort</th>
<th>Control cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational age</td>
<td>84 (40)</td>
<td>35 (45) #</td>
<td>1 (1)</td>
</tr>
<tr>
<td>RDS</td>
<td>144 (69)</td>
<td>54 (69)</td>
<td></td>
</tr>
<tr>
<td>Surfactant treatment</td>
<td>126 (61)</td>
<td>49 (63)</td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>12 (6)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Septicaemia</td>
<td>53 (26)</td>
<td>30 (38) *</td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>94 (45)</td>
<td>49 (63)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular haemorrhage gr I-II</td>
<td>25 (12)</td>
<td>7 (8)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular haemorrhage gr III-IV</td>
<td>15 (7)</td>
<td>7 (8)</td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity stages III-V</td>
<td>19 (9)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Oxygen dependency at an age corresponding to 36 GW</td>
<td>81 (39)</td>
<td>31 (40)</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05 (subcohort vs. entire cohort)  # p<0.05 (subcohort vs. control cohort)
had normal hearing in neurological examination, 3% (n=6) suffered from hearing impairment necessitating the use of a hearing aid or rehabilitation, and data for 3% (n=6) were missing.

Figure 5a shows motor impairment, CP, and ophthalmological abnormality rates in infants born at 22-26 weeks of gestation and Figure 5b shows these rates in different birthweight groups. In infants born after 26 GW, the prevalence of abnormalities in vision assessment was 15% (16/105), CP was found in 10%, and any motor abnormality in 23%. No infant born at 27 GW or more was blind or had a hearing impairment necessitating a hearing aid.

Of all infants with complete data available, 42% were normally developed, 40% mildly impaired, and 18% severely impaired. The severity of the impairments in most immature infants born at 22 to 26 GW is indicated in Figure 6a and severity in relation to birth weight is presented in Figure 6b.

The mean Bayley score in the regional ELBW1 subcohort was significantly lower than the mean score in the control cohort [95.1 (SD 12.9) vs. 106.3 (SD 9.6); p< 0.001]. Seventeen ELBW1 (22%) had Bayley scores below 85, one (1%) below 70, and one control infant (1%) below 85.

According to linear regression models, being an ELBW1 decreased the Bayley mental score by 10.4 points (SE 1.8, p<0.001) and male gender by 5.6 points (SE 1.8, p=0.002), but the scores seemed to improve 0.013 point (SE 0.004; p=0.004) each subsequent day of birth. Among ELBW1, the only factor significantly affecting Bayley scores was the number of days from 1 January 1996 to birth; scores seemed to improve 0.024 point per day (SE 0.007, p=0.001). Among controls, no such improvement over time was found, but male gender reduced scores by 6.3 points (SE 2.133, p=0.005).

Among ELBW1, the correlation coefficient between Bayley scores and day of birth was 0.388 (p=0.001); among controls, no correlation was present (r=0.072; p=0.537).
Results

Figure 5. Prevalence of abnormal ophthalmological status (open circles), any motor disability including cerebral palsy (filled triangles), and cerebral palsy (open triangles) at two years age among surviving ELBW in relation to a) gestational age and b) birth weight. Numbers of surviving infants are given, each percentage is calculated in those with data available.

5. a) Percentage

5. b) Percentage

Gestational age (weeks)

Birth weight (g)
Results

Figure 6. Percentages of non-surviving ELBW, normally developed ELBW, those with mild or severe disability, and those with incomplete data in relation to a) gestational age and b) birth weight.
Percentages were calculated per live-born ELBW in each group.

6. a)

6. b)
3. Risk factors for unfavourable outcome (I, II)

Low birth weight and gestational age were significant risks for early death and morbidity. Moreover, a statistically significant decline in ophthalmological abnormalities in infants born at 22 to 26 GW was found with increasing gestational age (p=0.040), and in all surviving infants with increasing birth weight (p=0.010). (Figures 5a and 5b. However, in the rates of CP, verbal impairment, or hearing impairment necessitating a hearing aid, no significant trends were found between the age groups from 22 to 26 GW or between birthweight groups.

Severe impairments did not increase significantly in our study population among surviving infants in relation to gestational age in infants born at 22 to 26 GW (p=0.109) or birth weight (p=0.653). In infants born at 22-26 GW, the rates of normal development were also comparable (p=0.356). However, survival without any impairment increased with increasing birth weight (p=0.021).

Table 6 summarises significant risk and protective factors for death, IVH, oxygen dependency at the age of 36 GW, ROP, and poor later outcome (CP, any motor impairment, or abnormalities in ophthalmological assessment) detected by logistic regression analysis.

In the logistic regression model, including ROP grades III-V, abnormal neurological status and need for extra oxygen at an age corresponding to 36 GW as explanatory factors, an abnormal neurological status (muscular hypotonia, hypertonia, or seizures) at an age corresponding to 40 GW was a risk for CP (OR 4.3, p=0.005) and for overall unfavourable motor development (OR 4.3, p=0.002). Oxygen dependency was a risk for motor impairments (OR 2.1, p=0.038) and ophthalmological abnormalities (OR 2.6, p=0.014), and ROP for ophthalmological abnormalities (OR 16.5, p< 0.001).
Results

Table 6. Significant risk factors for death and disabilities in extremely low birth weight infants (ELBW) expressed as odds ratios (OR), p-values (p), and 95% confidence intervals (95% CI). Variables listed in Table 3 were included in the multivariate logistic regression analyses.

Risk factors for death in live-born infants (n=351). Intraventricular haemorrhage (grade II-IV) associated mortality risk standardised by the risk factors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>CI 95% for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-minute Apgar score &lt;4</td>
<td>4.2</td>
<td>2.1-8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No antenatal steroid treatment</td>
<td>2.5</td>
<td>1.4-4.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Birth weight &lt; 600g</td>
<td>4.4</td>
<td>2.0-9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age &lt; 25 GW</td>
<td>3.4</td>
<td>1.7-6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>University hospital area B</td>
<td>4.0</td>
<td>2.0-7.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraventricular haemorrhage</td>
<td>2.7</td>
<td>1.3-5.5</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Risk factors for intraventricular haemorrhage (grade II-IV) in live-born infants (n=351).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>CI 95% for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>3.5</td>
<td>1.8-6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-minute Apgar score &lt;4</td>
<td>2.5</td>
<td>1.1-5.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>33.9</td>
<td>9.0-127.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No antenatal steroid treatment</td>
<td>2.2</td>
<td>1.2-5.0</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Risk factors for oxygen dependency at the age of 36 GW in surviving infants (n=211).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>CI 95% for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraventricular haemorrhage</td>
<td>3.6</td>
<td>1.1-11.7</td>
<td>0.035</td>
</tr>
<tr>
<td>Male sex</td>
<td>3.6</td>
<td>1.8-7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>4.1</td>
<td>1.9-8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight &lt;600g</td>
<td>3.7</td>
<td>1.01-13.5</td>
<td>0.049</td>
</tr>
<tr>
<td>University hospital area D</td>
<td>0.1</td>
<td>0.02-0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>University hospital area E</td>
<td>2.7</td>
<td>1.1-6.7</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Risk factors for retinopathy of prematurity (stage III-V) in surviving infants (n=211).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>CI 95% for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age &lt;25</td>
<td>26.1</td>
<td>7.8-87.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>University hospital area E</td>
<td>6.1</td>
<td>1.7-22.0</td>
<td>0.006</td>
</tr>
</tbody>
</table>
### Results

**Risk factors for cerebral palsy in surviving ELBW and for death or cerebral palsy in live-born ELBW**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antenatal steroid treatment</td>
<td>3.6</td>
<td>1.3-10.0</td>
<td>0.015</td>
<td>3.2</td>
<td>1.7-5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>4.3</td>
<td>1.5-12.2</td>
<td>0.006</td>
<td>2.7</td>
<td>1.4-5.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Birth in the university hospital area A</td>
<td>0.1</td>
<td>0.02-0.4</td>
<td>0.003</td>
<td>0.3</td>
<td>0.2-0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth in the university hospital area B</td>
<td>0.2</td>
<td>0.03-0.8</td>
<td>0.030</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (per 100 g increase)</td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>0.6-0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Gestational age (per one week increase)</td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>0.7-0.997</td>
<td>0.046</td>
</tr>
<tr>
<td>Anomalies</td>
<td></td>
<td></td>
<td></td>
<td>3.6</td>
<td>1.2-10.8</td>
<td>0.021</td>
</tr>
<tr>
<td>Intraventricular haemorrhage (gr. II-IV)</td>
<td>-</td>
<td></td>
<td></td>
<td>2.5</td>
<td>1.2-5.3</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Risk factors for any motor impairment in surviving ELBW and for any motor impairment or death in live-born ELBW.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antenatal steroid treatment</td>
<td>3.6</td>
<td>1.6-8.1</td>
<td>0.001</td>
<td>3.3</td>
<td>1.7-6.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Maternal infection</td>
<td>0.3</td>
<td>0.1-0.7</td>
<td>0.005</td>
<td>0.5</td>
<td>0.3-0.95</td>
<td>0.034</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.9</td>
<td>1.3-6.2</td>
<td>0.006</td>
<td>2.1</td>
<td>1.2-3.6</td>
<td>0.010</td>
</tr>
<tr>
<td>Intraventricular haemorrhage (gr. II-IV)</td>
<td>3.1</td>
<td>1.0-9.2</td>
<td>0.042</td>
<td>2.5</td>
<td>1.1-5.3</td>
<td>0.022</td>
</tr>
<tr>
<td>Birth in university hospital area A</td>
<td>-</td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.3-0.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>-</td>
<td></td>
<td></td>
<td>2.9</td>
<td>1.5-5.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Birth weight (per 100 g increase)</td>
<td>-</td>
<td></td>
<td></td>
<td>0.6</td>
<td>0.5-0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results

Figure 7 summarises the mortality and morbidity rates in five university hospital and in three groups of central hospitals classified according to the total number of ELBW1 births per hospital during the two-year study period. No infant born in a primary-level hospital survived. Significant differences were found in peri- (79% vs. 45%; p<0.001) and neonatal (59% vs. 32%; p<0.001) mortality between secondary- and tertiary-level hospitals, but a birth outside a tertiary care centre did not appear to be a risk for later morbidity (CP, any motor impairment, verbal impairment, hearing impairment necessitating a hearing aid, or abnormalities in ophthalmological assessment) in surviving ELBW1.

Differences in mortality and morbidity rates were found between the university hospital areas (A-E). Mortality among live-born infants in area B was significantly higher (58% vs. 35%; p=0.001), and in area A significantly lower (27% vs. 47%; p<0.001) than in the rest of the country. Bronchopulmonary dysplasia was rarer in area D (12% vs. 43%; p=0.002), and more common in area E (59% vs. 36%; p=0.021), which also had the highest incidence of ROP stages III-V (21% vs. 7%; p=0.010). The mean birth weight and gestational age were similar in different university hospital areas, but the mean CRIB score of infants born in area B was significantly higher than the mean score of infants born in other areas (10.0 vs. 7.0; p<0.001).

Regional differences were also detected in later outcome: In university hospital area A, the rate of CP was significantly lower (4% vs. 16%; p=0.004) and in university hospital area C higher (26% vs. 14%; p=0.002) than elsewhere in the country. No significant differences were found when the overall motor impairment rate in different university hospital areas was compared, although the rate was lowest in the university hospital area with the lowest CP rate (18% vs. 27% in other university hospital areas; p=0.068).
Figure 7. Percentages of stillborn ELBWIs, infants who died during the first week or after the first week, surviving ELBWIs with severe impairment, surviving infants without severe impairment, and surviving infants with incomplete information in relation to maternity hospital (university hospitals A-E, 17 central hospitals). Central hospitals are classified into three groups according to the total number of ELBWIs births during the study period: Group 1 (11-20 births/hospital during the study period); Group 2 (6-10 births/hospital during the study period); and Group 3 (less than 6 births/hospital during the study period).

The number of hospitals in each group are given in parenthesis. The total number of ELBWIs born in each hospital/hospital group are given over the bars.
4. Parental distress (III)

The Swedish Parental Stress Questionnaire scores of mothers in ELBW1 families did not significantly differ from the scores of control mothers. Nor did we find significant differences in fathers’ scores between the groups. In ELBW1 families, the scores of mothers did not statistically differ from the scores of fathers. However, control mothers had higher scores than control fathers in the role restriction subscale (p = 0.021).

When all mothers were compared with fathers, several significant differences were found. In the subscales of incompetence (2.20 vs. 1.95; p = 0.011), role restriction (3.37 vs. 3.04; p = 0.008), and spouse relationship (2.39 vs. 2.10; p = 0.018), mothers experienced more stress than fathers, who rated higher in the social isolation subscale (2.14 vs. 1.94; p = 0.040). No difference in the health problem scores was observed between the groups (2.23 vs. 2.23; p = 0.991).

Table 7 summarises the stress scale comparisons.

**Table 7.** Swedish Parenthood Stress Questionnaire (SPSQ) total and subscale scores in families of extremely low birth weight infants (ELBW1) and in control families

<table>
<thead>
<tr>
<th></th>
<th>Total SPSQ Scores</th>
<th>Subscales</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)</td>
<td>Incompetence</td>
<td>Role Restriction</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>ELBW1 mothers</td>
<td>56</td>
<td>2.41 (0.57)</td>
<td>2.19 (0.70)</td>
</tr>
<tr>
<td>Control mothers</td>
<td>66</td>
<td>2.43 (0.48)</td>
<td>2.20 (0.64)</td>
</tr>
<tr>
<td>p</td>
<td>0.852</td>
<td>0.933</td>
<td>0.473</td>
</tr>
</tbody>
</table>
### Results

**b) Comparison between ELBW1’s fathers and fathers from control families**

<table>
<thead>
<tr>
<th></th>
<th>Total SPSQ Scores</th>
<th>Subscales mean (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Incompetence</td>
<td>Role Restriction</td>
<td>Social Isolation</td>
<td>Spouse Relationship</td>
<td>Health Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELBW1 fathers</td>
<td>23</td>
<td>2.25 (0.51)</td>
<td>1.90 (0.62)</td>
<td>3.03 (0.84)</td>
<td>2.12 (0.66)</td>
<td>2.10 (0.67)</td>
<td>2.29 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control fathers</td>
<td>38</td>
<td>2.27 (0.40)</td>
<td>1.98 (0.44)</td>
<td>3.05 (0.79)</td>
<td>2.15 (0.54)</td>
<td>2.10 (0.60)</td>
<td>2.20 (0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.886</td>
<td>0.582</td>
<td>0.920</td>
<td>0.836</td>
<td>0.979</td>
<td>0.606</td>
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</tbody>
</table>

**c) Comparison between mothers and fathers in ELBW1 group**

<table>
<thead>
<tr>
<th></th>
<th>Total SPSQ Scores</th>
<th>Subscales mean (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Incompetence</td>
<td>Role Restriction</td>
<td>Social Isolation</td>
<td>Spouse Relationship</td>
<td>Health Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELBW1 mothers</td>
<td>56</td>
<td>2.41 (0.57)</td>
<td>2.19 (0.70)</td>
<td>3.32 (0.76)</td>
<td>1.97 (0.62)</td>
<td>2.46 (1.00)</td>
<td>2.10 (0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELBW1 fathers</td>
<td>23</td>
<td>2.25 (0.51)</td>
<td>1.90 (0.62)</td>
<td>3.03 (0.84)</td>
<td>2.12 (0.66)</td>
<td>2.10 (0.67)</td>
<td>2.29 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.259</td>
<td>0.081</td>
<td>0.146</td>
<td>0.361</td>
<td>0.074</td>
<td>0.307</td>
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</tr>
</tbody>
</table>

**d) Comparison between mothers and fathers in control group**

<table>
<thead>
<tr>
<th></th>
<th>Total SPSQ Scores</th>
<th>Subscales mean (SD)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Incompetence</td>
<td>Role Restriction</td>
<td>Social Isolation</td>
<td>Spouse Relationship</td>
<td>Health Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control mothers</td>
<td>66</td>
<td>2.43 (0.48)</td>
<td>2.20 (0.64)</td>
<td>3.41 (0.73)</td>
<td>1.91 (0.62)</td>
<td>2.32 (0.93)</td>
<td>2.34 (0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control fathers</td>
<td>38</td>
<td>2.27 (0.40)</td>
<td>1.98 (0.44)</td>
<td>3.05 (0.79)</td>
<td>2.15 (0.54)</td>
<td>2.10 (0.60)</td>
<td>2.20 (0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.099</td>
<td>0.059</td>
<td>0.021</td>
<td>0.052</td>
<td>0.142</td>
<td>0.395</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. Cost of care during the first two years (IV)

Complete cost data were available for 71 (68%) of the 105 ELBWIs admitted to NICU of Helsinki University Central Hospital (for all 21 infants who died and for 50 surviving infants) and for 60 (80%) of the 75 control infants. The participants did not differ significantly from those who did not participate in the study with respect to gestational age, birth weight, maternal age, social class, rates of multiple birth infants, neonatal morbidity, or two-year outcome.

Initial hospitalisation period

The mean total cost for each surviving ELBWIs at the first discharge was Euro 70 290 (SD 32 070, median Euro 66 535). The mean length of initial hospitalisation was 106 days (SD 40, median 97 days). Hospital costs (Euro 67 375, SD 28 390, median Euro 63 940) accounted for 96% of overall costs during initial hospitalisation and tertiary care costs for 84% of initial hospitalisation costs. The costs accrued to ELBWIs parents during this period were Euro 2755 (SD 3105, median Euro 1615), of which travelling costs accounted for the major part (64%), followed by loss of earnings (30%) and accommodation (6%).

Non-surviving ELBWIs had a mean initial hospitalisation period of 18.6 days (SD 32.7, median 3 days, range 0–124 days), with the mean cost being Euro 19 950 (SD 28 415, median Euro 6380, range Euro 1025-111 865). The overall resources used for care of non-surviving ELBWIs comprised 9.0% of all costs of ELBWIs care in Helsinki University Central Hospital.

The average estimated cost for healthy, normal-term newborns was Euro 515.

Figure 8 presents predischarge hospital costs in relation to birth weight in surviving and non-surviving ELBWIs. In infants born at 23 to 26 GW, a negative correlation was found between predischarge hospital costs and gestational age (r=–0.702; p<0.001).
Results

First and second year

A total of 49 (98%) ELBWI and 9 control infants (15%) were rehospitalised during the two-year study period. The ELBWI also needed hospital outpatient facilities during this period significantly more frequently than control infants (3.4 vs. 0.9 during the first year; p=0.001, and 2.6 vs. 0.8 during the second year; p=0.003), whereas controls had more outpatient visits to health centres and private doctors during the first year (3.7 vs. 2.0; p=0.020). During the second year (3.9 vs. 3.0; p=0.239) no such differences were found. The majority of infants in both groups needed regular or temporary medication during the study period [42 (84%) ELBWI and 54 (90%) control infants]. No control infants and three ELBWI were admitted to a special day care unit or had a personal assistant in a conventional day care group.

Among ELBWI, hospital costs accounted for the majority (60%) of all costs during the first post-discharge year, followed by parents’ loss of earnings (29%) and rehabilitation and medication costs (together 9%). Among control infants, the main cost items were parents’ loss of earnings (62%), outpatient care costs (19%), and hospital costs (16%). (For mean costs for both post-discharge years, see Study IV).

Parents’ loss of earnings were the main cost item during the second year in both groups, followed by hospital costs in ELBWI and outpatient care costs in the control group.

Despite a significant decrease in costs of ELBWI from the first to second post-discharge year, the overall costs of ELBWI throughout the study period remained higher than those of controls. However, no significant differences in total costs were found among ELBWI in relation to birth weight or gestational age during the first and second post-discharge years.

The mean health care cost per surviving ELBWI up to the corrected age of two years was Euro 104 635 (SD 55 140, median Euro 96 875), excluding travelling costs to hospitals during the first and second post-discharge years. The mean total cost per normal birthweight infant was Euro 3135 (SD 2060, median Euro 2315). The main cost item among ELBWI was hospital costs, accounting for 79% of total costs. Loss of income accounted for 14%, rehabilitation 2%, travelling 2%, and medication 1% of all
costs. Among controls, loss of income comprised 47%, hospital costs 30%, private doctor or health centre visits 18%, and home aid 3% of total costs.

The mean total cost increased significantly with the severity of disability. The total two-year costs of an ELBWI without any detected disability was 25 times, an ELBWI with mild disability 33 times, and an ELBWI with severe disability 68 times those of control infants.

Among ELBWI, the 10% change in loss of earnings altered the total cost estimate by 1.4%. Among control infants, the 10% change in loss of earnings altered total costs by 5.8%, and the 10% change in outpatient visit costs by 2.2%. In other sensitivity analyses, effects were even smaller.
DISCUSSION

1. Methodological considerations

By establishing a national ELBW1 research register, it was possible to prospectively collect a comprehensive population-based cohort of ELBW1, to obtain representative neonatal outcome data, and with detailed background and follow-up information to evaluate adequately the outcome of the cohort at 18 months of age. No infants fulfilling the criteria were excluded. Study population data were confirmed with several other sources such as the National Birth Register, death certificates, and patient records, as well as the Hospital Discharge Register when costs of care were assessed. It is thus reasonable to assume that the study gives an accurate picture of care and early outcome of ELBW1 born in our country during the late 1990s.

However, as the control infants needing specialised medical care during the first days after birth were excluded, a selection bias in the control cohort might be possible. The infants in the control cohort did not represent the average, contemporaneously born, full-term population since only healthy infants were included. This may have affected study results (especially in Studies II and IV), but as the number of excluded infants was small (n=5), we assume that this selection would have had only a minor effect.

Comprehensive data collection is essential for reliable study results. Tin et al. showed that generalisation could suffer if only those followed with ease are included. If results of their study were based only on those followed with ease, the disability rate would have been significantly lower (6.9% vs. 11.0%) than when all infants were included (Tin et al. 1998). In Study II, which examined 18-month outcome, no ELBW1 was lost in follow-up, but even in this situation, the gathered data was not fully comprehensive. Missing information resulted mainly from practical aspects; such as certain assessments not being performed on children with apparently normal development. We also preferred not to substitute for missing values due to obvious introduction of another type of bias.

In Studies III and IV, the non-responsiveness rate was relatively high and the direction of a possible bias more difficult to estimate. However, participants did not differ from
Discussion

non-participants with respect to demographic characteristics, neonatal features, or later outcome, and thus, we consider the samples to be sufficiently representative.

Data were gathered from the national health care system, which, in turn, created some restrictions. Since all maternity hospitals in the country (n=44) participated in neonatal data collection and all 23 hospitals responsible for follow-up in follow-up data collection, (although up to 75% of the data has been received from the university clinics) unavoidably several clinicians performed the physical and neurological assessments. We were unfortunately not able to conduct inter-rater reliability assessments, and consequently, cannot estimate the importance or magnitude of potential bias. The possible bias resulting from numerous investigators might have been avoided by performing a centralised study, but then the study would not presumably have extended to all-inclusive inclusion or follow-up rate.

The definition of stillbirth among ELBW1 is problematic. Although WHO's criteria for stillbirth is used in Finland, among these infants signs of life can be so subtle that even live-born infants born extremely immature might occasionally be deemed as stillborn; in the present study population, three infants with an one-minute Apgar-score of zero were resuscitated. Thus, including all stillborn and live-born infants in our study provided a more reliable basis for international epidemiological comparisons and also for evaluating the prognosis of most immature neonates.

A birthweight-based inclusion criterion is often criticised, since mortality and morbidity have been shown to be more related to gestational age than to weight. Nevertheless, the birthweight-based criterion was deemed as more applicable for a nation-wide study in tens of hospitals. It also facilitates comparisons with previous studies, in which the birthweight criterion has commonly been used. Our study population includes 98% of infants born at or before the 26th gestational week (all surviving infants) in addition to those growth-restricted infants born after the 26th week. Thus, gestational age-based outcome comparisons could be performed between infants born at these lowest weeks of gestation (at 22 to 26 GW).

The accurate measurement of gestational age and birth weight are crucial when analysing outcome results. Gestational age, primarily assessed according to the last
menstrual period, is confirmed in Finland by one or two ultrasound examinations performed before the end of GW 20. In case of more than two weeks discrepancy between the expected dates, the ultrasound-based estimation of the expectancy is chosen. More than 95% of pregnant women in Finland participate in community maternal care, which includes ultrasound examinations. Since antenatal ultrasound examination has been shown to be superior to postnatal gestational age assessment in very preterm infants (Wariyar et al. 1997), the estimation of gestational age was based primarily on these antenatal ultrasound assessments.

The definitions of diseases used in this study were either internationally approved (IVH, RDS, NEC, ROP, blindness, intellectual disability), nationally applicable and commonly used (CP, the diagnosis of which need to be confirmed by clinician and physiotherapists), or explicitly specified to include particular disease states or impairments such as sepsis (only when blood culture was possible). Despite this, the definition of several states or impairments, such as BPD (need for supplementary oxygen at an age corresponding to 36 GW) depends on requirements for optimal saturation, which can vary between units. This should be kept in mind when study results are compared.

Only a few validated methods have been used to measure parenting stress. The Swedish instrument, SPSQ, developed from Parenting Stress Index (PSI) designed by Richard Abidin (Abidin 1990), has been considered to be a reliable method for measuring the parental stress in risk populations (Ostberg 1998). The method has been validated and standardised in Sweden (Ostberg 1998; Ostberg et al. 2000; Ostberg et al. 1997). As the population in Finland closely resembles that in Sweden, SPSQ was also considered to be a valid method in our parenting stress assessment. The internal consistency of the full scale and of the five subscales in our study population was acceptable (Study IV) and comparable with the Swedish validation samples.

Most previous economic studies have concentrated on the neonatal intensive care period and included only hospital costs, disregarding costs accrued to parents (Petrou et al. 2001). As extremely preterm birth may have long-lasting consequences, our aims were to include all costs related to health care during the infant's first two years. Costs were
Discussion

included irrespective of payer, which was considered reasonable as the majority of occurred costs are at least partly covered by Finnish social security.

Since economic data was obtained from parents, hospitals, and institutions retrospectively, the role of recall bias could not be ignored. To minimise this, parents were not required to recall actual costs, but were asked detailed information on medication, travelling distances, etc. Some cost items, such as number and length of hospitalisation periods, could be confirmed from the national Hospital Discharge Register and costs obtained directly from hospitals. Furthermore, the sensitivity analyses performed on all estimated components revealed that the final cost figures were relatively insensitive up to 10% changes in the estimated variables. The cost data of the control group, obtained concurrently and using the same methods as for ELBWI data give an adequate reference for costs.

2. Birth rate

The proportion of ELBWI of all newborns in Finland during the two-year study period was comparable with that in a previously published Swedish study (Finnstrom et al. 1997). However, comparison of birth rates in ELBWI between countries should be done cautiously. Wide variation exists between the definitions for abortion and stillbirth even in Nordic countries possibly causing differences in perinatal statistics. In Norway, all deliveries after 16 GW are registered as births; in Sweden and Denmark, infants without any signs of life born at 28 GW or more are regarded as stillborn; in Finland the limit is a birth weight of 500 g or gestational age of 22 full weeks; and in Iceland, a birth weight of 1000 g or more is the limit, but if a weight is not available, gestational age of 28 full weeks is used (Nordic Medical Statistical Committee 1993). The proportion of live-born VLBWI in England showed an increasing trend during the 1980s (Alberman et al. 1991). Besides the real increase in VLBWI births, e.g. due to increased numbers of multiple births related to infertility treatments, several other factors could have increased the rates, such as more detailed registration, a decreased number of infants without birth weight registered, and changes in recording of stillbirths and life births. In Uusimaa, the southern part of Finland, the number of live-born ELBWI increased

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Discussion

significantly between 1978 and 1989. During the same period the number of surviving ELBWIs in Helsinki University Hospital increased from less than 20 to more than 40 per year (Jarvenpaa et al. 1991). However, since 1987, the overall birth rate of ELBWIs in the whole country according to the National Birth Register has remained relatively stable varying from 0.364% to 0.481% with no statistically significant trends (National Birth Register; National Centre for Welfare and Health).

3. Mortality

In agreement with previously published studies, ELBWIs deaths in Finland accounted for a notable proportion of all perinatal deaths during 1996-1997 (Amon 1988; Finnstrom et al. 1997; Jarvenpaa et al. 1991). Intramuterine deaths were common and the rate increased with increasing immaturity as shown by Battin et al., who reported that a high stillbirth rate (43%) at 23 GW decreased with increasing maturity to 6% in infants born at 27-28 GW. The authors suggested that possible differences in obstetric practise might explain high stillbirth rates at the limit of viability (Battin et al. 1998).

In the present study, the neonatal mortality rate is comparable with other population-based studies but is higher than that in NICU-based studies (Table 1). As in previous studies have shown, the survival at 22 to 23 GW was still rare and has not improved significantly over time (Allen et al. 1993; Battin et al. 1998; Emsley et al. 1998; Finnstrom et al. 1997; Whyte et al. 1993). The majority (79%) of postnatal deaths, in the present study, occurred during the first three days. Several investigators have confirmed that early deaths in ELBWIs are common and correlate negatively with birth weight and gestational age (Agustines et al. 2000; Battin et al. 1998; Cartlidge et al. 1997; El-Metwally et al. 2000; Hack et al. 1991; Hagan et al. 1996; Synnes et al. 1994; Whyte et al. 1993). However, Meadow et al. found that after the fourth day the correlation between death rate and birth weight had disappeared (Meadow et al. 1996).

When Hack et al. compared the time to death in two cohorts of infants with a birth weight of less than 750 g born in 1988-1989 and 1990-1992, they observed that significantly fewer infants died during the first day (81% vs. 68%) and more after the neonatal period (6% vs. 17%)(Hack et al. 1996). Our findings do not confirm that the
Discussion

present antenatal and neonatal care in Finland would excessively prolong the suffering of those ELBW1 who eventually died as the rate of all post-neonatal deaths in our study was relatively low (7% of all deaths occurring after birth).

As also shown by other investigators, RDS was the main cause of neonatal deaths in ELBW1 admitted to NICU (Hack et al. 1996). Other primary causes of death detected in recent studies have been infections and immaturity. Barton et al. found that up to 50% of the neonatal deaths of ELBW1 were ascribed to infections (Barton et al. 1999), considerably more than the 9% in our study. However, some infections in the present study could have been masked by other diagnosis, such as immaturity, and thus gone undetected. Prematurity has previously been reported to be the main cause of neonatal death in 0-84% (Barton et al. 1999; Cartlidge et al. 1997; Doyle et al. 1999b; Erkkola et al. 1991; Finnstrom et al. 1997; Hack et al. 1996; Msall et al. 2000; Philip 1995). This wide range in prevalence reflects that, as a cause of death, prematurity is a poorly specified entity and may also include some specific but unrecognised causes of death.

On the basis of survival and outcome results, in countries, such as Sweden, Norway, and Canada, recommendations have been made about the treatment of extremely immature infants born at 22-25 GW (Committee for Consensus Conference Programme 1999; Fetus and Newborn Committee 1994; Finnstrom et al. 1997). The national advice usually justifies active ante- and perinatal treatment of infants born at 25 GW. However, the treatment of infants born at 23-24 GW is recommended on a case-by-case basis, and treating infants born at 22 GW is not typically advised, although possible inaccuracies in gestational age estimation should be kept in mind. Based on our findings, the general opinion regarding treatment of infants born at 22-23 GW was conservative, as seen in only a few mothers of these infants receiving antenatal steroids or delivering by Caesarean section. The attitudes towards active treatment of infants born at 24 GW differed to some degree between hospitals, but infants born at 25 GW were actively treated in the whole country.

Our post-discharge mortality rate in ELBW children up to the age of two years was comparable with recent studies (Dezoete et al. 1997; Vohr et al. 2000). However, unlike in many follow-up studies, in the present study, no post-discharge death could not be ascribed to SIDS.
4. Neurosensory outcome at the corrected age of 18 months

4.1. Cerebral palsy and motor impairments

The rate of CP in our study is comparable to previously published studies in which CP rates in ELBW infants at the age of one to three years has varied between 7% and 17% (Finnström et al. 1997; Hack et al. 2000; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000). When the mortality and CP morbidity of the present subcohort were compared with the results of an earlier regional cohort born in 1991-1994 in the same area, the neonatal mortality rate seemed to have decreased from 31% to 21% (p=0.046), and the prevalence of CP from 17% to 4% (p=0.002) (Salokorpi et al. 2001). Thus, despite the increased survival rate of ELBW infants, the prevalence of CP has apparently not increased in the Southern Finland.

The rates of the other motor impairments are more difficult to compare between studies. Definitions and inclusion criteria for motor impairment vary considerably and timing of the assessment may influence results. Hack et al. classified hypotonia and hypertonia in addition to CP and shunted hydrocephalus as major neurological abnormalities, assuming that these might be variants of CP. The overall rate of these abnormalities in their study was 20% (Hack et al. 2000). In the present cohort, the combined rate of motor delay, tone disorders, and motor impairments not classified as CP was relatively high (13%). This rate was similar to that found by Dezoete et al. (15.2%), but higher than the rates reported in other studies (6 to 8%) (Dezoete et al. 1997; Piecuch et al. 1997a; Vohr et al. 2000; Wood et al. 2000). Differences might be explained by variation in inclusion criteria, assessment methods, and study populations. As the overall rate of motor impairments was relatively similar in the different studies (ranging from 20% to 25%, vs. 24% in the present study) (Hack et al. 2000; Piecuch et al. 1997a; Vohr et al. 2000; Wood et al. 2000), classification of motor impairments to CP or to other motor impairments presumably may also vary between the studies.

Consistent with earlier reports, a delay in motor development was fairly common (8%) in our study population. Wolf et al. described 60% of VLBWI as having below average psychomotor test scores at the age of six months. Hediger et al. showed that low birth weight and gestational age were independently associated with a delay in motor
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development through early childhood (Hediger et al. 2002; Wolf et al. 2002). Relying on unpublished findings by the Child Development Unit, Dezoete et al. assumed that approximately half of the ELBWI with motor delay or tone disorder at the age of 18 months would have normal motor development if assessed at the age of 2.5 to 3 years (Dezoete et al. 1997). Similarly, we conclude that the majority of infants with delayed motor development in our study are likely normal variants with no permanent motor impairment, but we cannot exclude the possibility that some might have mild CP that went undetected at early age.

4.2. Visual impairment

Ophthalmological problems are common in ELBW children. Compared with previous studies reporting a visual impairment rate of 6% to 9% (Cooke 1994; Vohr et al. 2000), the total ophthalmological abnormality rate in our study was higher (23%), but similar as reported rate by Pennefather et al. (Pennefather et al. 1995). Inclusion of mild cases, such as mild strabismus and mild refractive errors without visual impairment or need for any treatment, might partly explain the high rate in our study. A total of 8% of infants in the present study cohort needed correction of refractive errors or treatment of strabismus with eye-glasses which compares with detected rates in previous studies.

The prevalence of blindness in the present study was comparable with numerous follow-up studies (0.5-4%) (Hack et al. 1996; Hack et al. 2000; Msall et al. 1991; Piecuch et al. 1997a; Robertson et al. 1994; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000; Wood et al. 2000), as were the rates of strabismus and myopia (Emsley et al. 1998; Fledeius 1996; Gallo et al. 1991; Hebbandi et al. 1997; Holmstrom et al. 1998b; McGinnity et al. 1992; O'Connor et al. 2002b; Pennefather et al. 1995; Quinn et al. 1998; Wood et al. 2000). By contrast, we found less astigmatism and hyperopia than in previously published studies (Darlow et al. 1997; Hebbandi et al. 1997).

Blindness is commonly detected in ophthalmologic assessments even during the early infancy. Significant changes in distribution of myopia and other refractive errors occur before 12 months of age; the percentage of eyes with high myopia, for instance, may double. After one year of age, only marginal changes occurred in distribution of
refractive errors (Quinn et al. 1998). Based on these findings, we can suppose that most serious disabilities in visual acuity were detected in our study.

4.3. Intellectual impairment

Poorer cognitive skills in ELBW children compared with full-term controls have been detected in earlier studies (Hack et al. 1994; Halsey et al. 1993; Johnson et al. 1993; Klebanov et al. 1994a; Saigal et al. 2000b; Stjernqvist et al. 1999). Stjernqvist et al. found a decrease of approximately 1SD in IQ of infants born before 29 GW compared with term controls, although the majority of those born preterm had a low-risk environment and no severe health problems (Stjernqvist et al. 1999). The significant difference between mental Bayley scores of ELBW children and full-term controls found in our study is in accord with these studies.

The improvement of Bayley scores in the ELBW cohort over time was an unexpected finding. No improvement was found among the controls, confirming the stability of the method. The neonatal mortality rate during the study period remained stable, thus selective deaths could not either explain the results. Improved peri-, neo-, and post-neonatal care might have had an effect on improved scores by the end of the study period. However, owing to the short follow-up, the stability of the finding remains to be confirmed, and the factors responsible for the improvement, to be uncovered.

4.4. Overall outcome

Compared with previous studies, the rate of normal development in our study (42%) seems to be lower (Cooke 1994; Dezoete et al. 1997; Finnstrom et al. 1998; The Victorian Infant Collaborative Study Group 1997a; Vohr et al. 2000). In most studies, however, only major impairments were reported. Thus, our inclusion of minor abnormalities without evident disability may partly explain this difference. As the range of normal development at 18 months of age is wide, some ELBW1 in our study population with mild abnormalities may subsequently develop normally with no permanent deficit, but some might have an increased risk for impairments detected later, possibly not detected until school age. Determining the predictive value of these
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common minor impairments on later development and behaviour is an important subject for future studies, and also warrants continuous follow-up of all these children.

5. Risk factors for unfavourable outcome

With advances in perinatal and neonatal care, the prognosis and clinical picture of diseases in ELBW have changed. As risk factors detected in earlier cohorts may not be fully valid in new cohorts, continuous updating of factors predictive of unfavourable outcome is needed.

Extremely low birth weight (< 600 g) and gestational age (< 25 GW) were independent risk factors for death and short-term morbidity in surviving infants as confirmed in earlier studies (Allen et al. 1993; Ambalavanan et al. 2001; Bahado-Singh et al. 1998; Battrin et al. 1998; Cartlidge et al. 1997; Cooke 1994; Copper et al. 1993; El-Metwally et al. 2000; Lemons et al. 2001; Maier et al. 1997; Msall et al. 1993; Msall et al. 1991; Oshea et al. 1997; Phelps et al. 1991; Roth et al. 1995; Salokorpi et al. 1999; Stevenson et al. 1998; Synnes et al. 1994; Whyte et al. 1993). The survival rate and neurological outcome of infants born at the limit of viability, at 22-23 GW, remain unsatisfactory and no significant improvements have occurred over time (Allen et al. 1993; Emsley et al. 1998; Finnstrom et al. 1997; Hack et al. 1989; Tin et al. 1997; Whyte et al. 1993; Wood et al. 2000). In studies from the 1990s, neonatal survival rates of infants born at 22–23 GW have varied from 0% to 25%. In our study, these infants had significantly lower (9%) neonatal survival rates than those born at 24-25 GW (60%), and early outcome of the five survivors was not favourable, as no infant had completely normal follow-up results at an age corresponding to 40 GW. Infants born at 25-29 GW had no statistically significant differences in neonatal survival rates, but owing to birthweight-based inclusion criterion, most of infants born after 26 GW were not included in the study and the majority of those who were included were SGA. Thus, outcome results can not be generalised in infants born after 27 full weeks.

The effect of gestational age on later neurological outcome in ELBW is contradictory. In a study by Piecuch et al. cognitive development was significantly correlated with gestational age but neurological development was not (Piecuch et al. 1997a). In our
study population, neither gestational age nor birth weight were significant independent risk factors for later motor impairments in multivariate logistic regression analysis (CP, any motor impairment). Abnormalities in ophthalmological status increased as gestational age and birth weight decreased. The rates of CP, speech delays, and hearing impairments did not show any significant trend in different birthweight or gestational age groups; however, in the rate of other motor impairments, a decreasing but statistically non-significant trend could be seen with increasing birth weight. Early cognitive development in the ELBW1 subcohort did not seem to be related to low birth weight, but being a ELBW1 was highly significant when these infants were compared with controls.

As gestational age and birth weight are risks for death, we assumed that the majority of the most immature infants might have died, and the infants who survived had a neurosensory prognosis as favourable as the more mature ones concerning occurrence of CP, hearing impairment, speech delay, and cognitive development.

Low maternal education and social class have been associated with poor cognitive development of low birthweight children (Hack et al. 2000; Msall et al. 1991; Piecuch et al. 1997a; Singer et al. 1997; Vohr et al. 1992). Although the mothers of ELBW1 in the subcohort had a lower average educational level, low maternal education was not a risk factor for poor mental Bayley scores. However, in Finland, mothers are relatively well educated, and even in the lowest social class, no mother had an education of less than nine years.

Antenatal steroid treatment might have reduced the risk for death and IVH in live-born infants. Vaginal delivery was not independently associated with increased risk of death but was significantly associated with IVH, the difference persisting even after adjustment for low Apgar score, RDS, and lack of antenatal steroid treatment. We did not find the increased risks for death associated with male gender or twin pregnancy, that have been described in previous studies (Copper et al. 1993; Finnstrom et al. 1997; Synnes et al. 1994; Tyson et al. 1996). Male gender was, however, a significant risk for poor pulmonary outcome, as also described previously (Costeloe et al. 2000).

In agreement with previous studies, the survival of ELBW1 born at level III hospitals was better than at level II and I hospitals (Finnstrom et al. 1997; Holmgren et al. 2001;
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Phibbs et al. 1996). There are several explanations for this outcome difference. Some infants might have been born unexpectedly with no time to transfer the mother to a tertiary care centre. Long distances, especially in the northern parts of Finland can sometimes make a safe transport of the mother to a high-level centre impossible. Attitudes towards referral of mothers and active treatment of infants born at 22-24 GW may also vary at different level hospitals and in different parts of the country. Antenatal treatment may have been unavailable and the infant’s primary situation may therefore have been worse. As centres with larger ELBW1 populations have more experience in caring for this special needs group and likely have develop standardised treatment practices, and as the annual birth rate of ELBW1 in Finland is only about 180 live births, it seems reasonable to centralise these births to tertiary care centres whenever possible.

Of the university hospital areas with the lowest prevalence of CP, area A had the lowest and area B the highest mortality rate. Among surviving ELBW1, birth in either area seemed to have a protective effect. However, when analysis included all live-born infants with outcome variables defined as survival without CP and survival with CP or death, the lower rate of CP in area B was found to be associated with increased mortality. As area A remained a statistically significant protective factor, regional factors seem to influence outcome even in a country with a rather homogenous health care system and population. It is also noteworthy that both morbidity and mortality should be included when risk factors for poor outcome are analysed.

6. Parental coping

According to previous studies, the birth of an extremely low birthweight infant is a crisis for both parents (Cronin et al. 1995; Stjernqvist 1992; Trause et al. 1983). However, most parents in our regional subcohort seemed to have recovered well by the infant’s age of two years and were no more distressed than parents of same-aged, full-term infants. Although this finding contradicts the results of a few previous investigations (Stjernqvist 1992; Taylor et al. 2001), it does find support in some studies (Lee et al. 1991). Supportive therapy, such as the services of a family therapist and weekly group meetings, offered routinely to parents during the neonatal intensive care and follow-up periods may have decreased parents’ anxiety in our study population.
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Infants’ age at the time of assessment might also have had an effect on results. By the age of two years, the life-threatening intensive care period has passed and possible minor developmental problems, common in ELBWIs, do not yet cause everyday strain. Great variation in development exists, even among normal birthweight infants, and therefore minor developmental delays might not cause distress in families. However, at school-age, the child confronts new demands and minor impairments may become more distinguishable, cause difficulties at school, and lead to an increase in distress in some ELBWIs. Since obvious impairments were rare (n=5) in our subcohort, the effect of severe impairments on parental distress during the child’s infancy could not be reliably estimated.

An association between maternal education and the level of maternal stress have been described in previous studies, where higher maternal education has been associated with lower parental distress (Cronin et al. 1995; Ostberg 1998). As the average educational level in control mothers was higher than among ELBWIs mothers, more pronounced differences between SPSQ scores were expected, but no such differences were found.

In agreement with earlier studies (Benfield et al. 1976; Cronin et al. 1995; Miles et al. 1992; Trause et al. 1983) mothers seemed to express more distress than fathers, although the difference was not significant. Mothers had significantly more incompetence, role restriction, and spouse relationship problems, whereas fathers felt more distress in social isolation. Presumably, owing to smaller group sizes, these differences were no longer significant at group level. Fathers who accompanied their child to hospital and participated in the study may have felt a greater responsibility for their child, and thus, these fathers might have had reduced opportunities for social activities. The results might also reflect the traditional, but still existing role differentiation in which fathers fulfil their main duties outside the home.
7. Economic Costs

Initial hospital care costs significantly increased with decreasing gestational age and birth weight, in agreement with previous findings (Pikus et al. 1997; St John et al. 2000; Stahlman 1984). By contrast, no differences were found in annual costs after the first discharge in relation to gestational age or birth weight. The neurological disability rate in our study cohort was unrelated to birth weight, which might partly explain post-discharge costs not increasing with decreasing birth weight. Stevenson et al. included hospital costs up to the age of four years as well as estimates of life-time costs of education and social services. They found birth weight to poorly predict costs, and up to 30% of variance in life-time costs to be explained by neonatal clinical factors, such as RDS, IVH, septicaemia, and NEC (Stevenson et al. 1991).

The overall costs in ELBW I increased significantly with aggravation of disabilities. Throughout the study period, even costs in normally developed ELBW I remained significantly higher than costs among control infants, as also shown in previous studies (McCormick et al. 1991; Stevenson et al. 1996a). The reason for higher costs in ELBW I with normal neurological development in our study might be explained by a higher frequency of rehospitalisations, and by current treatment practices of frequent neurological and paediatric assessments in early childhood of all ELBW I regardless of whether they have disabilities or not. Scarce evidence exists as to whether the costs remain higher in later childhood and adolescence.

Since most mothers in ELBW I families took child-care leave and only a few infants needed special day care services, costs of special day care remained low in our study population. However, among those who needed special day care, the cost per child was high. Costs related to special education in ELBW I may account for a notable proportion of overall costs at school-age (Chaikind et al. 1991). Thus, although costs of care were shown to significantly decline over time, future costs of special day care and education will likely have an increasing effect on average annual costs in ELBW I as the children grow.

Late deaths with prolonged suffering were rare, which could explain the relatively low costs of non-surviving ELBW I. In agreement with Stolz et al. the costs of non-surviving
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ELBWI accounted for only a minor portion of overall NICU costs of ELBWI (Stolz et al. 1998).

Studies on health care costs accrued to parents of preterm infants have shown that these costs account for a notable proportion of family income at least during the initial hospitalisation and shortly after discharge (Gennaro 1996; McCormick et al. 1991), and that these costs decline promptly during the first year and by the end of first year did not differ from costs of term infants (McCormick et al. 1991). In our study population, however, parental costs of ELBWI remained significantly higher than costs in control families throughout the study period. Differences in study populations, insurance, and health care organisation, and especially regional treatment and follow-up practices might explain this discrepancy.

Despite health care costs in ELBWI being fairly high, our findings indicate that they are be comparable with other life-saving treatments (Harma et al. 1996; Leijala et al. 1992). Although neonatal costs per survivor increased with decreasing birth weight, denying care from the infants born most preterm leads to only moderate savings. Stolz et al have reported that total savings related to denying care from infants born with a birth weight of less than 700 g amount to merely 10.3% of total neonatal intensive care unit costs (Stolz et al. 1998).

Generalisation of these results should be done with caution, as differences in hospital and post-discharge costs are to be expected between countries and even between hospitals within a single country, depending on differences in national health services, salaries, treatment strategies, and general cost levels. Moreover, the regional differences detected in mortality and morbidity rates might cause additional variability to the costs. Caution is also warranted since a relatively large number of families refused to participate in the study, although the birth characteristics and outcome results of these infants did not significantly differ from those of participants.
CONCLUSIONS

With regard to outcome, costs of care, and parental coping with extremely low birth weight infants, we conclude:

1. Intrauterine and early deaths of ELBWIs were common. Low gestational age and birth weight were independent risk factors for mortality, and both mortality and morbidity of infants born at the limit of viability (22-23 GW) remained high. With increasing maturity, the survival rate improved rapidly. Most postnatal deaths occurred during the first days of life, and thus current antenatal treatment and neonatal intensive care in Finland do not seem to excessively prolong the suffering of those infants who eventually died. As regional- and hospital-level differences in survival rates and short-term outcome were detected, the mortality and morbidity of ELBWIs need to be continuously followed and the differences evaluated.

2. Among the surviving ELBW, ophthalmological abnormalities at the corrected age of 18 months decreased significantly with increasing gestational age (22 to 26 GW) and with increasing birth weight, but the rates of CP, hearing impairments, and speech delay did not. The rate of minor neurological deficits and developmental delays in ELBWIs was high, necessitating long-term follow-up of these infants. Moreover, regional differences detected in early neurological outcome of ELBWIs warrants continuous quality control. In Helsinki University Hospital, the developmental scores (Bayley mental test) appeared to improve over time but owing to the short study period, the stability of this finding remains to be confirmed in subsequent studies.

3. In a regional subcohort, no significant differences were found in parental distress at the child’s age of two years between parents of ELBWIs and parents of full-term controls, suggesting that parents of ELBWIs have emerged from the initial shock well. However, the group of severe handicapped infants in our study population was too small to detect possible problems in these families.

4. Hospital costs from the initial NICU period accounted for most of the overall costs among ELBWIs up to the age of two years. The costs of the initial hospitalisation
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period increased significantly with decreasing gestational age and birth weight, but after the initial discharge, no significant differences in annual costs were detected in relation to either birth weight or gestational age. While overall costs increased with increasing severity of disability, even among ELBWIs without disabilities, cost remained higher than among normal birthweight control infants.

5. As cognitive impairments and behavioural problems may not become evident before a child grows older, continuous follow-up of the comprehensive population-based cohorts is needed. This will also provide valuable information about the predictive role of minor impairments, which are commonly detected in early childhood, on later development. Another goal is the continued detection of risk factors and protective factors, which might be influenced by properly targeted treatments. Besides biological factors, rearing environment also has a prominent role in development among ELBWIs, particularly in cognitive development. Taking the family’s wellbeing into account is an important challenge for modern neonatal care.
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