School-age Outcomes of Children Born at the Limit of Viability

A Swedish National Prospective Follow-up Study at 10 to 12 years

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At first glance
You were so small
I hardly saw a baby at all,
with tubes and wires
a frightening sight
but you were in for a
big fight.

Not even pound and a half
just skin and bones,
Your body so small
with problems so big,
but you fought hard
and continued to grow.

So many fears
So many tears

You are home now
and growing big
I love you dear
more than words can say.
A miracle baby
A gift from God.

You showed the world
You showed us all.

By Dianne, Autumn’s (expremie) Grandmother

Dedicated to my family
ABSTRACT

**Background/Aim:** During the past two decades, major advances in maternal-fetal medicine, neonatology, and the development of regionalized perinatal care have resulted in dramatic increases in survival rates, by more than 60%, of extremely immature (EI) infants born at less than 26 completed weeks of gestation, creating a new infant population. Studies of school-age outcomes in children with an extremely low birth weight of < 1000 g, born in the 1980s, indicated that these children had a substantially high prevalence of low-severity neuropsychological deficits, behavioral problems, and difficulties at school. Information on school-age outcomes of extremely preterm children born in the 1990s is sparse, and mainly restricted to the neurobehavioral and developmental outcome. The aim of this research was to investigate the comprehensive neurological, developmental, functional, and mental health status and health care needs of children born at 23-25 weeks of gestation in the 1990s, allowing a total view of the child in the context of the family, his peers, school, and the health care system. The ultimate aim was to obtain a clearer understanding of the functional capacities of these vulnerable children and the possibilities of ameliorative interventions, as a basis for planning and provision of services for this growing population.

**Methods:** We studied 11-year-old children born from 1990 through 1992 before 26 completed weeks of gestation in all of Sweden. All had been evaluated at a corrected age of 36 months. Of 89 eligible children, 86 (97%) were studied at a mean age of 11 years. An equal number of children born at term served as controls. The following methods were used: 1) well validated, mailed questionnaires filled out by the parents, class teachers and the children themselves; 2) structured interviews were conducted with a parent or a primary caregiver; 3) review of pediatric case records and records from other specialist health care services; and 4) anthropometric measurements (length, weight, head circumference and body mass index) from birth to 11 years of age. The following domains were explored: current health status, growth attainment, mental health assessment, emotional well-being, adaptive functioning and social competencies, school performance, executive functions, and learning and language skills. Relations of socioeconomic background and of environmental and perinatal risk factors to the long-term outcome were evaluated.

**Results:** EI children compared with the controls had significantly higher rates of specific diagnoses or disabilities including neurosensory impairment (15% vs 2%, respectively), asthma (20% vs 6%), poor motor skills (26% vs 3%), poor visual perception (21% vs 4%), poor learning skills (27% vs 3%), poor adaptive functioning (42% vs 9%), and poor academic performance (49% vs 7%). As a consequence of these disabilities, significantly more EI children than controls had chronic conditions, which included functional limitations (64% vs 11%), compensatory dependency needs (59% vs 25%), and services above those routinely required by children in general (67% vs 22%).

Regarding growth attainment, EI children had significantly lower values for all three growth parameters (length, weight and head circumference) than the controls at 11 years. They showed a sharp decline in weight and height z scores up to 3 months’ corrected age, followed by good catch-up growth in both weight and height up to 11 years. EI children did not exhibit catch-up growth in head circumference after the first 6 months of life. Preterm birth and parental height were significant predictors of 11-year height, and group status (prematurity) correlated strongly with head circumference.
Our results also suggest that the EI children had a significantly greater risk for poorer mental health and poorer emotional well-being than the control participants, including internalizing (anxiety/depression, withdrawn behavior and somatic complaints), and attention, social, and thought problems. No differences in externalizing problems were found between the EI cohort and controls. Multivariable analyses disclosed a number of significant predictors of behavioral adjustment: group status (EI vs control), family function, social risk, male gender, and presence of a chronic medical condition.

Concerning school performance, more than half (58%) of our EI cohort were experiencing school difficulties and 15%, compared with 5% of the control children were attending special schools or having full-time special education. Despite fewer adaptive skills in the EI cohort these children were not different from the controls in respect to being happy and being positively adjusted in their day-to-day life.

Compared with controls, EI children had a significantly increased risk for executive dysfunctions in most of the areas assessed (Attention control and Attention switching, Hypoactivity, Planning/organizing, and Working memory). EI children were also at increased risk for deficient skills in language tasks (comprehension, communication, and expression) and in the four standard measures of learning skills (reading/writing, math, general learning, and coping in learning). However, only a relatively small number of EI children exhibited severe impairments in executive or non-executive skills. Multivariate analyses revealed that prematurity, executive dysfunction and male gender were associated with poor learning skills.

**Conclusions and implications:** Children born extremely immature have significantly greater health problems and special health care needs that require ongoing services through the school years. However, it is notable that very few children have severe impairments that curtail major activities of daily living. The overall results of this study are reassuring. Despite having an increased risk for mental health problems, executive dysfunctions and school difficulties, 85% of the EI children were in the mainstream schools and a majority were not having major adjustment difficulties. In terms of growth, most of our EI children showed good catch-up in late childhood and were within 2SD of their mean midparental height at 11 years of age. Although biological immaturity is associated with an increased risk for a substantial number of behavioral/emotional problems, improvement of the modifiable environmental factors will benefit the outcome in EI children. We also believe that knowledge of the course of development of psychopathological conditions from early childhood to adolescence and beyond is crucial for identifying the need for intervention and prevention strategies. Thus when there is evidence to suggest neuropsychological and behavioral or emotional problems, early identification and preventive measures might help families to manage these from an early stage. Our findings further suggest that current preterm follow-up programs might benefit from the addition of psychological and family services to traditional neurodevelopmental assessments, especially in the neonatal period and first years of life.

**Key words:** School-age outcome, extremely immature, functional limitations, growth, special health care needs, mental health, executive functions
Abbreviations

ADHD, Attention Deficit/Hyperactivity Disorder
ANCOVA, univariate analysis of covariance
ANCS, antenatal corticosteroids
BMI, body mass index
BPD, bronchopulmonary dysplasia
BW, birth weight
C, control
CBCL, Child Behavior Check List
CI, confidence interval
CLD, chronic lung disease
CP, cerebral palsy
DSM - IV-R, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised
DSRS, Depression Self-Rating Scale
EDD, expected date of delivery
EDF, executive dysfunction
EF, executive function
EI, extremely immature (< 26 weeks’ gestation)
ELBW, extremely low birth weight (< 1000 g BW)
EPT, extremely preterm (< 28 weeks’ gestation)
ES, effect size
FTF, “Five to Fifteen”
GECS, global executive composite score
HC, head circumference
IQ, intelligence quotient
IVH, intraventricular hemorrhage
LBW, low birth weight (BW < 2500 g)
MANCOVA, multivariate analysis of covariance
MDI, mental development index
NEC, necrotizing enterocolitis
NICHD, National Institute of Child Health and Human Development
NSI, neurosensory impairment
OR, odds ratio
PCA, post-conceptional age
PVL, periventricular leukomalacia
QuICCC, Questionnaire for Identifying Chronic Conditions in Children
ROP, retinopathy of prematurity
SD, standard deviation
SES, socioeconomic status
SGA, small for gestational age
TPS, total problem score
TRF, Teacher Report Form
VPT, very preterm, (< 32 weeks’ gestation)
VLBW, very low birth weight (BW < 1500 g BW)
Original Papers

The present thesis is based on the following papers, which will be referred by their Roman numerals:


The original papers have been reprinted with kind permission of the publishers
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During the past three decades, major advances made in maternal-fetal medicine and neonatal intensive care, and regionalization of high risk deliveries, have resulted in a significant increase, by more than 90-95 %, in the survival rates of children born with very low birth weights (VLBW) of 1000-1500 g. In the 1990s, a number of factors resulted in dramatic increases in the survival of extremely low birth weight infants (ELBW, < 1000 g): use of antenatal corticosteroids (ANCS); active surveillance in high risk pregnancies and a change in the perception of viability among obstetricians, with provision of active care in threatened deliveries after very short gestational periods, enhanced collaboration between obstetricians and neonatologists; and continued advances in neonatal care. According to recent reports, in Sweden approximately 140-150 infants are born alive annually at gestational ages of < 26 weeks (extremely immature, EI), and of these EI infants 60-65% survive (increased survival with increasing gestational ages). Similar results have been reported elsewhere. While there has been success in improving the survival of these EI infants, prevention of adverse neurodevelopmental outcomes has been a major challenge. There is increasing concern that among the extremely preterm infants, especially those born between 22-26 weeks of gestation, current management is unable to significantly reduce the unacceptably high rates (30%) of both significant neurosensory disability (i.e., cerebral palsy, blindness, and deafness) and developmental cognitive disability (Bayley mental index < 70). The primary goals of perinatal care are not only to reduce infant mortality, but also to lower the rates of neurodevelopmental disability, optimize developmental functioning, and enhance health-related quality of life in high risk infants. Furthermore, studies of school-age outcomes in infants with an ELBW, who were born in the 1980s, indicated that these children had a substantially high prevalence of low-severity neuropsychological deficits, behavioral problems, and school difficulties. Information on school-age outcomes of extremely preterm (EPT, < 28 weeks’ gestation) or EI children born in the 1990s is sparse, and mainly restricted to neurobehavioral and developmental outcomes. These EI children are reaching school-age in increasing numbers and there is an urgent need to determine how they function in their daily life, to analyze their special health needs, and to find out to what extent their needs are met. Long-term follow-up is also necessary to address the question whether the documented increase in short-term gains translates into long-term benefits and a good quality of life, and to evaluate the impact of treatment on these growing children who a few decades ago would rarely have survived.
This thesis presents the findings from a long-term prospective investigation of a Swedish national cohort of school-age children (10-12 years of age) who were born at fewer than 26 weeks gestation in the early 1990s.

**Historical trends in the treatment of preterm infants**

The treatment of preterm infants has changed dramatically over the past century. These changes fall into three major eras. In the first era, which covers the period from the early 20th century to the 1940s, special life-sustaining methods were as yet unavailable, treatment at the most was conservative, and few VLBW infants survived. In his review of the existing literature in 1940, Benton concluded that low birth weight (LBW) children showed early developmental retardation compared with children born at term, and that there was little evidence of developmental catch-up with age. He emphasized, however, that “nervous traits” or behavioral difficulties were observed even in studies that failed to report differences in intelligence between LBW and term groups. These difficulties included fatigability, irritability, emotional outbursts, attention problems, and forgetfulness.

In the second era, which extended from the 1940s to 1960s, studies of LBW children born during this period revealed high rates of neurological and developmental morbidity associated with iatrogenic effects of treatments instituted at that time, such as overuse of oxygen leading to blindness, antibiotic treatments leading to deafness, and inadvertent deprivation of nutrition. Lubchenco et al, for example, showed that only one third of the VLBW children in their sample, born in the years 1947 through 1950, had intelligence quotients (IQ) greater than 89 and were free of neurological impairments. Similar observations were made by Drillen, who found that two thirds of a follow-up sample, born between 1948 and 1960 with birth weight less than 3 lb (1160 g), were either undercapable in normal schools or not performing appropriately for their age. Subtle learning difficulties and behavior problems continued to be observed and the outcomes differed in relation to the degree of maturity at birth.

The modern era of neonatal intensive care, which I would prefer to call dawn in the golden era of neonatology, began in the 1960s and has been characterized by a reduction in morbidity among VLBW children and increases in the survival of the tiniest infants. Paneth estimated that survival of infants with birth weight (BW) < 1000 g in the US increased 70-fold between 1960 and 1985. Similar observations were made in Sweden. Factors initially responsible for these changes included
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provision of assisted ventilation, improved obstetric and delivery room care, cardiovascular monitoring, provision of parenteral nutrition, and treatment of specific complications of prematurity such as apnea and patent ductus arteriosus. Since the 1990s, an increase in survival of the lowest gestational age infants has resulted from active delivery room resuscitation, the use of ANCS and surfactant therapy, maternal and neonatal transport to specialized perinatal centers and enhanced collaboration between neonatologists and obstetricians.9,10,25

Survival, morbidity, and early childhood outcomes in extreme prematurity

Survival

Geographically based population studies that include all births (stillbirths, and intrapartum and delivery deaths) will produce accurate and reliable estimates of gestational age-specific survival. According to a review by Hack and Fanaroff,10 in most of the population-based studies survival rates at 23 weeks gestation have ranged from 2% (95% confidence interval [CI] 1-11) to 35% (95% CI 13-34). A remarkable increase in survival rates at 24 weeks gestation was evident, with ranges from 17% (95% CI 9-27) to 62% (95 % CI 48-75). At 25 weeks, survival ranged from 35% (95% CI 26-44) to 72% (95% CI 57-84%). Much higher survival rates of extremely preterm infants are reported from studies conducted in single tertiary centers that have aggressive perinatal practices; however, those results should be viewed with caution on account of small numbers of infants, exclusion of stillbirths and delivery room deaths, and selective referral patterns. These survival rates range from 5 to 50% at 23 weeks of gestation, 33% to 90% at 24 weeks and 50% to 85% at 25 weeks.9,10,23-25 According to the Swedish Birth Registry,2 the survival rates among infants born at 23-24 weeks doubled from the period 1989-91 to 1999-2001. In infants born at 25 weeks gestation the survival rate increased from 54% to 80% between the corresponding time periods. The gestational age at which a liveborn infant has a 50% chance of survival decreased from 30 weeks of gestation in 1960 to 24 weeks in the 1990s.9 It has been apparent from all analyses that neonatal mortality is influenced by birth weight, gestational age, gender, race, intrauterine growth, and site of delivery.42-44 The attitude of the obstetrician45,46 and variations in the philosophies of care may also determine the outcome.47,48 Some centers selectively treat EI infants in the delivery room, whereas in others infants may be treated above a certain specific birth weight or gestational age. In such instances decisions on the later continuation of care are based on the response of the infants to the treatment. Variations in the initiation or withdrawal of treatment thus influence the mortality, its timing and the rate of
morbidity, and alter the outcome for the survivors. These aspects of treatment are seldom described. In a recent Swedish study Håkansson et al compared two different regional strategies for the perinatal management of extreme prematurity, one in northern Sweden that adhered to an aggressive protocol, and the other in southern regions of Sweden that adhered to a more restrictive policy regarding cesarean sections and resuscitation of the newborn. They reported that significantly more infants born at 23-25 weeks in the northern regions were alive at 24 hours and at 1 year of life.

Neonatal morbidity

Despite the remarkable decrease in the mortality of extremely preterm infants since the 1990s the rates of major neonatal morbidity, have not changed and have remained stable. The neonatal diseases that have an influence on later development include chronic lung disease (CLD), severe brain injury, necrotizing enterocolitis (NEC), nosocomial infections, and severe retinopathy of prematurity (ROP). In addition, other less well studied factors such as transient hypothyroxinemia and breast milk feeding, and demographic and clinical management practices, are associated with the outcome. The majority of the survivors born at 23-25 weeks gestation seem to have one or more neonatal complications, and a half of those with a birth weight (BW) of less than 750 g.

Chronic lung disease, defined as oxygen dependency at a postconceptional age (PCA) of 36 weeks, occurs in 57% (95% CI 11-88) to 86% (95% CI 67-96) of infants born at 23 weeks gestation, 33% (95% CI 13-59) to 89% (95% CI 52-100) at 24 weeks, and 16% (95% CI 5-34) to 71% (95% CI 49-87) at 25 weeks. It occurs in 41% (95% CI 27-50) to 61% (53-70) of infants with a BW of 500-800 g. CLD is associated with poor nutrition and growth, poor feeding skills, and episodes of nosocomial infection. All of these factors contribute to prolonged hospitalization and a poorer long-term outcome. The current rates of CLD are similar to those among infants born prior to the use of surfactant and postnatal steroid (PNS) therapy, or in some instances are increased. A Danish national study in the mid 1990s, in which 65% of all infants born alive at < 25 weeks gestation were actively treated, showed a remarkably low prevalence of CLD at a postconceptional age of 36 or 40 weeks. The authors claim that the very low incidence of CLD in this cohort of 24-25 weekers was a result of early use of nasal continuous positive airway pressure.
**Infection/Sepsis** remains a major cause of neonatal morbidity in extremely preterm infants. Forty to 45% of infants with a birth weight of < 750 g or a gestational age of < 25 weeks have one or more episodes of septicemia in their neonatal period. Of particular importance is the twofold increase in mechanical ventilation among infected infants – a significant risk factor for CLD. Necrotizing enterocolitis, which is usually complicated by sepsis and poor growth, occurs reportedly in 11% of infants at 23 weeks gestation, 3% at 24 weeks, and 9% to 16% of infants with a birth weight of < 750 g. The risk of late onset infection was inversely related to birth weight or gestational age. Infection seems to affect growth, especially weight and head circumference, both at a PCA of 36 weeks and later at 18 months of age. It is of great concern that infants with neonatal infections are significantly likely to have poor head growth. The impact of neonatal infection on growth in extremely preterm infants, both during the infection and in the long term, is not known.

**Brain injury** is usually identified by abnormal cerebral ultrasound findings. Lesions associated with an adverse neurodevelopmental outcome include grade 3 or 4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and periventricular hemorrhagic infarction, periventricular cysts, and/ or persistent ventriculomegaly. The rates of severe ultrasound abnormality range from 10% (95% CI 0.3-45) to 83% (95% CI 36-100) at 23 weeks of gestation, from 9% (95% CI 2-21) to 64% (95% CI 38-84) at 24 weeks and from 7% (95% CI 2-17) to 22% (95% CI 10-41) at 25 weeks. In contrast to other abnormalities, the rates of severe IVH (grade 3-4) have decreased with time. The US National Institute of Child Health and Human Development (NICHD) network reported a decline in the incidence of severe IVH from 18% in 1993-94 to 11% in 1999-2001 in a population of VLBW infants (500-1499 g); PVL was reduced to 8% from 3% between the same time periods. A recent study has also documented a significant reduction in cystic PVL among infants born at 23-27 weeks gestation between approximately the same periods (from 5.3% in 1993-94 to 0 in 2000-2002). Inter-rater variations in reading cerebral ultrasound, the postnatal age at which the scan is performed and the question of how the lesions are classified influence the reported frequencies of cerebral ultrasound abnormalities.

**Retinopathy of prematurity.** The rates of ROP similarly vary between centers according to the criteria used for diagnosis and therapy. Severe ROP is classified as either stage 3-4 retinopathy or retinopathy that requires laser or cryotherapy, and may include blindness. The reported incidence of severe retinopathy
ranges from 25% to 50% at 23 weeks gestation, from 13% to 33% at 24 weeks, and from 10% to 17% at 25 weeks.\textsuperscript{10, 23,24,61} Although the rates of blindness may have decreased since the introduction of cryotherapy or laser treatment, children receiving such therapies may still have severe residual myopia and peripheral vision defects.\textsuperscript{69} Although uncommon, cerebral visual impairment or cortical blindness associated with a cerebral insult, particularly PVL, may also occur.\textsuperscript{70} The majority of survivors at 23-25 weeks have one or more neonatal complications, and half of those that weigh < 750 g at birth.\textsuperscript{10} Of the survivors in the EPICure study,\textsuperscript{22} comprising all infants born at < 26 weeks gestation in all of the United Kingdom and Northern Ireland, 38% had no major complications, and in a similar study (EPIBEL)\textsuperscript{71} from Belgium 37% of infants born at less than 26 weeks survived with a major morbidity. Of survivors in the Canadian network, 24%, 36% and 38% of infants born at 23 weeks, 24 weeks and 25 weeks, respectively, survived without a major morbidity.\textsuperscript{24} From a recent Swedish study from two tertiary perinatal centers,\textsuperscript{61} the outcome in all infants (including stillbirths) born at less than 26 weeks gestation was reported. In that study aggressive treatment was offered to mothers and the infants. Eighty-one percent of the survivors were discharged home without a major morbidity, i.e., without severe ROP, IVH grade 3-4, PVL or NEC and 54% of the infants were free from any major morbidity. The study demonstrated that increased survival was not achieved at the expense of an increased neonatal morbidity.

**Early Childhood Outcome**

When the survival is assured in these tiny fragile infants, there is focus on growth and development. Health care professionals, families, and the educators are concerned about the long-term development of these children, as increasing survival of EI infants will possibly increase the percentage of disabled children in the society.

It is noteworthy that chronic health conditions occur in 15 to 20% of the general population in Sweden and elsewhere.\textsuperscript{72-75} Rates of disabilities have continued to rise during the past 20 years in the general population of children, as reported from the majority of studies in Scandinavian countries and elsewhere.\textsuperscript{72-76} In the majority of studies reporting on early childhood outcomes of extreme prematurity, children are considered to be severely disabled or impaired either if they have a major neurological abnormality such as cerebral palsy (CP), unilateral or bilateral blindness, or deafness requiring a hearing aid, or if their cognitive functioning is less than 2 SD below the mean for the normative population or controls (Mental Development Index (MDI) < 68 or < 70), or both.\textsuperscript{77} For many
years, there has been a tendency to investigate the health and abilities of children by using measures of impairment and disability. Although these measures have been criticized, few measures of functional ability, disability, or quality of life have been validated for use during early childhood. These measures of impairment, however, do not fully capture the scope of functional limitations. For example, a child with cerebral palsy may have an abnormal gait but be independent in daily mobility and have normal cognitive ability, whereas another child who has mild to moderate difficulties with attention control, visual perception, and learning skills and behavior might suffer from a substantial handicap and be significantly disadvantaged at school. More than a decade ago, McCormick proposed that the framework of neonatal follow-up should be expanded to place wider focus on health status, functional development, behavior, and family outcomes.

Families and the community professionals very often request practical information about outcomes that have an impact on daily activities in locomotion, communication, learning, and becoming independent in self-care.

In general, rates of disability increase with decreasing gestational age and birth weight, but these relationships vary, possibly on account of the selected survival of lower risk infants born at 23 or 24 weeks and of the poor reliability in determining gestational age. In their review, Hack and Fanaroff reported rates of severe disability that ranged from 18 to 40% among infants born at 23 to 25 weeks gestation. The overall rates of severe disability in infants born at these gestational ages are remarkably similar, at about 30-32%. At 23 weeks gestation, outcome reports are sparse and there is much variation between centers because of small numbers of infants. The rate of severe disability for this gestational age is reported to be around 34%. At 24 weeks gestation, the rates of severe disability ranged from 22% to 45%, with rates of cerebral palsy ranging from 11% (95% CI 1-35) to 15% (95% CI 5-32). Subnormal cognition was noted in 14% (95% CI 2-43) to 39% (95% CI 17-64) and blindness in 0% to 9% (95% CI 2-24). At 25 weeks the rates of severe disability ranged from 12% (95% CI 2-37) to 35% (95% CI 15-59), with the incidence of cerebral palsy ranging from 3% (95% CI 0-17) to 20% (95% CI 8-39) and that of subnormal cognition from 10% (95% CI 2-26) to 30% (95% CI 23-37). Most of the studies showed that many of the severely disabled children had multiple impairments. Wood et al reported follow-up data on the EPICure study and found similarly poor neurodevelopmental outcomes among the survivors at 30 months of corrected age. In their report, the rates of severe disability were 35%, 27% and 24%, respectively, among the surviving children born at 23 weeks (n=26), 24 weeks (n = 90) and 25 weeks of gestation.
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(n = 167). In these children the most common form of severe disability was mental delay. In a large NICHD multicenter study in the USA, the neurodevelopmental outcome in ELBW infants was evaluated. In their subgroup of infants born at or below 26 weeks gestation, 50.2%, 47.2 %, and 44.6%, respectively, had MDI < 70, during the three time epochs, 1993-1994, 1995-96, and 1997-98. Furthermore, they reported a significant decrease in the rate of MDI < 70 from 42% to 37% between the first and second time epoch, i.e., from 1993-94 to 1997-98; in addition a decrease in bilateral or unilateral blindness was observed during the same periods. Some recent studies have shown a trend toward an increase in neurodevelopmental impairments in children born at 23-25 weeks during the past decade. On the other hand, in a few studies improvements in disability rates have been found among preterm children born at 23-27 weeks gestation in the 1990s.

The infant weighing < 500 gram

The World Health Organization (WHO) has suggested that infants with a birth weight of < 500 g should be excluded from analyses of perinatal outcomes, but stillbirth and livebirths infants with this birth weight are included in the perinatal mortality statistics of some countries. In Sweden only liveborn infants with BW < 500 g are included in the mortality statistics. In the largest study by far of infants weighing < 500 g at birth, the outcome of 4172 infants from 374 participating centers in the Vermont Oxford network was investigated. The overall survival rate was 17% and the majority of those who survived were females (67%) and small for gestational age (SGA)(78%). Vohr et al reported on a large cohort of extremely low birth weight infants, 15 of whom weighed <500 g at birth, who were evaluated at 18 months. They found that 43% of the infants with BWs <500 g showed abnormalities at neurological examination and 29% had cerebral palsy. More than half of the infants who were born at <500 g required early intervention services and occupational and physical therapy at home. From a population based study of infants weighing < 500 g at birth, born at > 20 weeks of gestation during the years 1983-94, it was reported that 113 of 382 liveborn infants of this cohort (30%) received intensive care and 18 of the 113 (15%) survived. At 3 years of age, 13 were alive and 9 of these (69%) had one or more disabilities including mental retardation, blindness, deafness and cerebral palsy. A recent Swedish study addressed the outcome of infants born at 23-25 weeks gestation in two perinatal tertiary centers during the years 1992-1998. The survival rate among those who were < 500 g at birth was 32% (6 of 19) and the majority of those six infants had more than one major neonatal morbidity.
reports from most of the studies, the majority of infants with a BW of less than 500 g are extremely preterm, mostly SGA, and predominantly female. They seem to have poor early neurodevelopmental outcomes, probably reflecting the effect of both prematurity and intrauterine growth failure. Reports from Japan have been more optimistic. There have been anecdotal reports of children with a BW < 500 g birth weight who have had normal development.

**Risk factors for disability**

It is reasonable to assume that major morbidities during the neonatal period may have a significant impact on subsequent health and development. In an international multicenter study, Schmidt et al. analyzed the individual and combined prognostic effects of bronchopulmonary dysplasia (BPD), ultrasonographic signs of brain injury (grade 3-4 IVH, PVL, and ventriculomegaly) and severe ROP on the 18-month outcome of children with birth weights of 500-999 g who had survived to a PCA of 36 weeks. The three neonatal morbidities were similarly and independently correlated with a poor 18-month outcome. In children free of bronchopulmonary dysplasia (BPD), brain injury, or severe ROP, the rate of poor outcome was 18%. With any one, any two, and any three of the morbidities the rates of poor outcome were 42%, 62% and 88%, respectively. The study also showed that neonatal morbidity more directly affected the causal pathways leading to a poor long-term outcome than did birth weight or gestational age per se. Others have shown similar results. Hoekstra et al. found that not only male gender, but also CLD and abnormal ultrasound were risk factors for poor early childhood outcome in children born at 23-26 weeks, whereas the effect of birth weight barely reached significance. Significant risk factors for a poor 18-month outcome in the NIHCD study of infants with birth weights of 401-1000 g were CLD, grade 3 to 4 IVH/PVL, PNS administration for chronic lung disease, NEC, and male gender. Although abnormal ultrasounds were predictive of later CP in two large multicenter studies on ELBW infants, the majority of children with CP in these studies had normal scans in the neonatal period. Risk factors for a poor functional outcome include parenchymal brain injury, PNS administration, and CLD. In addition to neonatal complications, functional outcome has also been correlated to socioeconomic and family status. A number of additional perinatal and neonatal variables may constitute risk factors for later disability. In a recently reported study comprising infants weighing 401-1000 g at birth and enrolled in the NIHCD neonatal network, 65% of the infants had at least one bout of infection during their hospitalization after birth. Compared with uninfected children, infected children were more likely to have CP, impaired
mental development or impaired vision. Additional predictors of later disability include PNS use for CLD, an inadequate supply of long-chain polyunsaturated fatty acids, poor postnatal growth, and stressful factors in the nursery environment. Among the important factors in improving the long-term outcome are prevention of severe IVH and PVL, reduction of CLD by improved ventilatory techniques, combating nosocomial infection and avoiding iatrogenic complications, improving the nursery environment, and providing individualized neonatal care. Although several neonatal complications and other factors have been associated with later morbidity, none of these has been shown to predict disability in survivors with reliability that is clinically satisfactory for informed decisions regarding withholding or withdrawing neonatal intensive care. As discussed by Lorenz, the positive predictive value of reported studies is no greater than 85%, indicating that a significant proportion of infants (> 14%) with predicted disability will not become disabled.

A brief review of school-age outcomes in extremely low birth weight or extremely preterm children born during the 1980s

When a child born with ELBW reaches school age, some of the hurdles have been cleared. Physical handicaps and severe neurodisabilities are usually identified in the early years of life. For many of these children who make it to school age without significant neurological or sensory disability, there are usually other subtle (mild to moderate) conditions that may affect school performance, social competence, and quality of life. In addition, late or latent conditions are usually revealed when the child enters a formal academic environment. These mild to moderate dysfunctions include learning disabilities, school difficulties, behavioral problems, borderline mental retardation, executive dysfunctions, and other neuropsychological impairments. These problems occur reportedly in 50-70% of ELBW or EPT infants, and an inverse relation to birth weight is again found.

Differences in intelligence between preterm infants and their term peers have been widely reported from a number of studies. Learning problems at school persist into adolescence in ELBW children and are apparent even in those who seem to have normal intelligence and no neurological impairment.

In contrast to the major disabilities, behavioral problems and cognitive and executive dysfunctions are influenced by socioeconomic and environmental factors such as the socioeconomic status, educational background, and physical
Background

and mental health of the caretakers.\textsuperscript{111,112} There is growing consensus about school-age outcomes of VLBW and ELBW infants, but much of the evidence comes from research data that are subject to potential selection bias.\textsuperscript{105,111,112} Methodological differences between follow-up studies make generalizations regarding the outcome difficult. Furthermore, care of the infants in a neonatal intensive care unit (NICU) is evolving rapidly so that reports on school-age outcomes may reflect practices that are not necessarily used today. Inclusion of controls from the same era with preferably complete cohorts of consecutive births and larger sample sizes would provide a reliable basis for comparisons. Complete follow-up at later ages, longitudinal designs and population-based studies provide a better understanding and unbiased approach, allowing outcomes to be determined with certainty.

Neurosensory disability

The rates of major disability, including moderate/severe mental retardation, cerebral palsy, and sensorineural hearing loss/blindness or severe visual impairment, in school-age children born with ELBW in the 1980s are reported to range from 17 to 27\%.\textsuperscript{29,83} In a multinational population-based study of school-age children with ELBW, the rates of neurosensory impairments were remarkably similar (22-27\%) in three cohorts, but significantly lower (11\%) in a fourth (Dutch) cohort. This was attributed to the less aggressive management in the Dutch cohort. These rates of handicap have remained constant during the past decade.\textsuperscript{10} There are only few reports on school-age outcomes regarding rates of sensorineural disabilities in hospital-based, regional, or national cohorts of ELBW or EPT infants born in the 1990s.\textsuperscript{33-35} In the two studies reporting on incidence rates of severe disability in children born at < 26 weeks gestation, these rates were similar, i.e., 23\% (53 of 241)\textsuperscript{35} and 29\% (22 of 77).\textsuperscript{113}

Growth

VLBW and ELBW children experience significant growth failure in their early childhood.\textsuperscript{114-118} Reports on growth outcomes of ELBW infants born in the 1980s document compensatory catch-up in growth parameters up to adolescence.\textsuperscript{119-122} However, ELBW adolescents remained significantly shorter and lighter than their control peers in the majority of these studies. In most reports growth outcomes are presented in relation to birth weight rather than to gestational age. This raises a possibility of introducing bias, as more mature
children with fetal growth restriction are included. There are concerns that disturbances of growth in intrauterine and postnatal life of preterm infants may have long-term implications for their adult health. It has been hypothesized that adaptations made by the fetus or infant when undernourished induce alterations in metabolism and hormonal output, possibly increasing the risk for diabetes and for cardiovascular disease (CVD) later in life. Furthermore, there is accumulating evidence of a risk for future development of CVD in growth-restricted infants who exhibit an accelerated weight gain in childhood.

Many studies have identified significant correlates to growth and catch-up among VLBW or ELBW infants in childhood and adolescence. These are intrauterine growth failure, neonatal complications, parental height, and postnatal steroids for treatment of CLD. Influence of gender on catch-up growth in ELBW/VLBW adolescents has been documented. With the exception of one population-based study in the United Kingdom, information is lacking on growth outcomes of infants born at < 26 weeks’ gestation in the 1990s.

**Functional limitations and special health care needs**

Children with special health care needs are defined as those who have, or are at increased risk for a chronic physical, developmental, behavioral or emotional condition and who require health and related services of a type or amount beyond those required by children generally. It is clearly evident from multiple reports that children born at a very early gestational age or with a birth weight < 1000 g have significantly higher rates of functional limitations and needs for increased services beyond routine care compared to children born at term. Major functional limitations include mental or emotional deficiencies, physical growth delay, visual difficulties, inability to participate in sports, and impaired social skills. Special health care needs include special education, occupational and physical therapy, and counseling. However, very few children seem to have such severe functional limitations as to limit their activities in daily life, as documented by a few studies.

Information on school-age outcomes in ELBW or EPT infants, born in the 1990s is sparse and mainly restricted to the neurobehavioral and developmental status. There is little information on the daily functioning of these children or on their health care needs.
Background

Respiratory outcome

Since the availability of surfactant, few reports have been published on the respiratory health of ELBW or very preterm (VPT, < 32 weeks’ gestation) school-age children born in the 1990s. The respiratory function in ELBW or VPT born before surfactant became available was not as good as in normal birth weight children, specifically with reduction reflecting airflow. Among ELBW /very preterm survivors, those with CLD had more abnormal respiratory function than those without CLD. Since the introduction of surfactant for the treatment of respiratory distress syndrome, its effect on respiratory function in the small number of children enrolled in clinical trials has been found to be minimal or possibly beneficial. The nature of CLD has also changed in recent times, consistently with the survival of tinier infants and with the advent of “new BPD”. In a recent population-based study of ELBW or EPT children at 8-9 years of age, born in the 1990s, it was concluded that abnormalities in respiratory function in such children, compared with normal birth weight (NBW) controls, described in the presurfactant era persisted in the 1990s. In the ELBW children born in the 1980s, there seemed to be a tendency toward reduction of respiratory ill health after the early childhood years, with a significant improvement in lung function; this including those who had had chronic lung diseases in the neonatal period. However, many other studies have demonstrated that pulmonary function abnormalities consistent with subtle obstructive lung disease are present in VLBW /ELBW or very preterm children compared with controls. The respiratory status of extremely premature children at school age surviving the “new BPD”, which is characterized predominantly by alveolar arrest, remains to be seen. What also remain to be determined are the effects of newer therapeutic approaches such as ANCS, surfactant, better ventilation techniques, optimizing nutritional strategies, combating of neonatal infections, and postnatal steroids on the respiratory health.

Behavioral effects of Prematurity

Follow-up studies of school-age outcomes in infants born in the 1980s with an ELBW have shown that these infants have a significantly high prevalence of low-severity neuropsychological, behavioral and school problems. In a meta-analysis of case-control studies reported from 1980 to 2001 in which cognitive and behavioral outcomes were examined, it was found that school-age children who were born very preterm exhibited more internalizing, attention and externalizing problems, although these difficulties were not encountered in all studies. The
Background

vast research on behavioral outcomes in children with a very low or extremely low birth has revealed that these children are particularly vulnerable to inattention and hyperactivity problems and social difficulties.\textsuperscript{110,158-167} Symptoms suggestive of attention deficit/hyperactivity disorder (ADHD) are reported to occur two to four times more frequently in VLBW/ELBW infants than in controls.\textsuperscript{160,163,168-173} Preterm children with ADHD have significantly worse performance on cognitive tasks and a higher rate of school failure than the controls.\textsuperscript{110,174,175} Interestingly there are fewer comorbid disruptive behavior problems in ELBW/VLBW children, suggesting a more biologically determined ADHD in those born preterm compared with ADHD found in the general population.\textsuperscript{32,176} Furthermore, there is some evidence to suggest that compared with the controls, VLBW or ELBW adolescents\textsuperscript{110,161,163} and VLBW young adults\textsuperscript{177} have a high prevalence of anxiety and depression. Gender and environment play an important contributory role in behavioral disorders of prematurity.\textsuperscript{111,112}

Apart from one report from Australia\textsuperscript{34} and an abstract from the USA,\textsuperscript{178} we are unaware of any other reports of behavioral outcomes at school age in ELBW or extremely preterm children who were born in the 1990s.

Cognitive Functions

Cognitive deficits are consistently observed among children born very preterm or with ELBW even when sociodemographic and environmental factors are taken into consideration.\textsuperscript{29,105,107,111} In the above mentioned meta-analysis\textsuperscript{107} of case-control studies reported from 1980 to 2001 in which cognitive and behavioral outcomes were examined, it was found that school-age children who were born very preterm had an overall mean IQ that was two thirds of SD below that of the healthy controls. The studies in their review involved cohorts born before 1989. Also, in the few studies in the meta-analysis, that comprised cohorts of ELBW children, the mean overall IQ difference between the ELBW and control children was mostly larger than the overall mean difference reported. Moreover, in most of the studies children with NSIs were excluded. There is a gradient or linear trend whereby preterm children with higher birth weights and preterms who are more mature at birth are associated with higher IQ scores. The same gradient is evident in the ELBW population at school age.\textsuperscript{31,179,180} In one study, the likelihood of an IQ $< 70$ was 9.5 times greater in a $< 750$ g birth weight group and 2.15 times greater in those weighing 750-1499 g at birth than in the term controls.\textsuperscript{181}

There are a few studies on the cognitive outcome in school age children at 8-10 years of age born extremely preterm or with ELBW in the 1990s. In these reports,
the mean decrease in the overall IQ scores in the ELBW or EPT cohort ranged from 9.4 to 12.1 points. In a recent population-based (EPICure) study of 6-year-old children who were born before 26 weeks, the mean decrease in overall cognitive score in the Kaufman assessment battery test was 24 points. In that study, girls performed significantly better than boys. Furthermore, the percentage of children with IQs < 70 ranged from 15% in the ELBW school-age cohort to 43% in 6-year-old children in the EPICure study. In contrast to the major disabilities, behavioral and developmental outcomes are affected by the social and environmental risks measured in terms of maternal education, social class and race. However, it seems that the socioeconomic status (SES) has a lower impact on IQs in extremely preterm children, suggesting that biological risk overrides moderating environmental influences.

**Executive functions**

Executive functions (EF) refer to a combination of a host of interrelated processes that are responsible for purposeful, goal-directed behavior that is instrumental in cognitive, behavioral, emotional, and social functions. The principal cognitive processes that are associated with EF include deployment of attention, anticipation, planning, organizing, initiation of activity, self-regulation, working memory, utilization of feedback, and cognitive flexibility. Executive dysfunction (EDF) is not a unitary disorder but represents a range of impairment profiles such as decreased conceptual reasoning, verbal working memory, planning, attention control, inhibition and spatial conceptualization. Research addressing the EF problems in preterm children has been limited. Nevertheless, EF difficulties are lately being consistently reported in preterm children. EF influence academic and behavioral competencies and have therefore become central area of investigation in preterm children with or without neurodevelopmental disorders. Studies on ELBW children with normal intelligence have shown deficits in executive functions, and it has been postulated that these EF deficits might be responsible for the increased likelihood of learning difficulty. EDF will also have generalized effects on the child’s ability to acquire knowledge. This may also explain findings of subsequent impairments in social competence and adaptive behavior skills in VLBW or ELBW middle-school-age children. So far there is only one report on EF in a large cohort of school-age children born very preterm or with ELBW in the 1990s. The authors found that these children had EDF on a range of measures, compared to normal birth weight controls. Another, recent investigation on preterm children at a preschool age of 51/2 years,
showed that these children had subnormal levels of executive functioning, even though their general IQ was normal.194

**School performance**

More than half of former ELBW children require special assistance in school.29,31 Fifteen to 22% of former ELBW children are receiving full-time special education.29,136,141 By middle-school age, ELBW children are 3-5 times more likely to have a learning problem in reading, writing, spelling and mathematics,103 with math and reading being most disrupted.29,103,179,199 These rates are independent of IQ. The grade of prematurity is strongly related to math181 and one study suggested that the effect of prematurity accounted for a 0.4 standard deviation (SD) decrease in math and a 0.25 SD decrease in reading.200 By adolescence there is an 8-10-fold increase in the use of special remedial education resources or the need for special arrangements at school.31,137,179 It is estimated that almost 30% of ELBW children are in the main stream school without services.29 As with most other areas of function, an inverse gradient of learning difficulty is found.109 Many children born preterm also display later nonverbal learning disability, in which verbal cognitive skills are better developed than the nonverbal abilities.169-171 As in the case of IQ, environmental factors have a moderating effect on learning disorders. Recent reports suggest that both biomedical and environmental risks are associated with educable mental handicap and specific learning disorders (mild cognitive and adaptive difficulties).142 It is likely that the combined effect of lower cognitive abilities, a lower socioeconomic status (SES) and behavioral issues inhibit adjustment to the formal education in which complex concepts require problem solving at a more advanced level.172 Academic achievements seem to be determined by multiple factors.176 The gender-mediated effect on school function has been well documented. Boys have a higher odds ratio for special education, indicating a 2-5 times higher likelihood of problems in math, reading, spelling, and writing and a 2-fold increase in the risk of being in full-time special education.29,103,179,180 It should be kept in mind that heredity plays a part in the prevalence of learning disorders. In a recent study in Sweden, 23% of school children who had required neonatal intensive care had strong heredity for deficits in reading and/or writing skills.201 It seems that the potential combination of learning disorder, low-average IQs, executive dysfunctions, and other neuropsychological deficits found at school age place the child born prematurely at a significant disadvantage.
Background

Language skills

Many language functions, particularly complex and perhaps subtle verbal processes such as understanding of syntax, abstract verbal skills, verb production, mean length of utterance, auditory discrimination, imitation of articulatory patterns, difficulty following complex instructions, poor organization, and language processing and reasoning have been found to be deficient in children born preterm as compared with their controls.\(^{175,193,202,203}\) This is particularly true for children born at a gestational age of \(< 32\) weeks, and in males. These types of problems may not be obvious, but they are critically important in social and academic endeavors. It is also known that many of the language functions fall in the average range, especially receptive language, verbal fluency, and memory for prose.\(^{173,176,201,204}\) Language seems to be particularly susceptible to negative environmental influences. Despite the importance of biological immaturity and perinatal factors, strong emphasis has been placed on environmental factors as predictors of language and speech development.\(^{205,206}\)
1. The Study

1.1 Rationale for this investigation

Dramatic increases in the survival of EI infants during the past decade have created a new population of infants who previously would rarely have survived. A substantial number of these children have already reached school age in Sweden and elsewhere. These successes in saving lives among the tiniest infants require that we assess the impact of the treatment itself on this population of children and address the question whether the short-term gains have translated into long-term benefits. There is continuous debate regarding the limits of viability and the ethics of resuscitating EI infants, in view of the increasing evidence that these infants face significant neurological and developmental handicaps as they grow older. A number of earlier studies have indicated that ELBW children seem to have very high rates of mild to moderate dysfunctions in behavior, attention, social competence, and school functions. Our knowledge is poor concerning the health, daily functioning, special health care needs, and school achievement of these EI children. Information on school-age outcomes in ELBW or EI infants born in the 1990s is very limited and mainly restricted to the neurobehavioral and developmental status.

A comprehensive and systematic long-term follow-up at school age is imperative in order to establish the basis for planning and provision of care and support for these children who were born extremely immature.

1.2 Aims and hypotheses

Aim
The principal aim of this prospective, case-controlled Swedish national investigation was to characterize the overall neurological, developmental (growth), functional, mental health and health care status of 10-12 year old EI children born at less than 26 weeks’ gestation in the 1990s, in order to obtain a total view of the child within the context of the family, his peers, the school and the health care system.
Aims & Hypotheses

The specific aims were:

1) To estimate the rates of chronic conditions, functional limitations and special health care needs of EI children (born at < 26 weeks) and to compare them with those of full-term normal controls at 11 years of age;

2) To examine changes in growth from birth to 11 years and to analyze correlates of growth attainment;

3) To evaluate the mental health and emotional well-being of EI children and to identify sociodemographic and environmental factors associated with mental and emotional well-being in these children;

4) To assess the social competencies, adaptive functioning, and school performance in EI children;

5) To investigate the nature, frequency and severity of executive dysfunctions in EI children;

6) To investigate the nature, frequency and severity of learning and language skills in EI children.

The ultimate aim was to obtain a clearer understanding of the functional capacities in the daily lives of these vulnerable children and to assess the possibilities of ameliorative interventions, as a basis for planning and provision of services for this growing population.

Hypotheses

Based on the available literature, we hypothesized

1) that EI children will have high rates of developmental problems, functional limitations and special health care needs as compared with normal controls born at term, and that these limitations and needs will remain significantly high in those EI children who are free from neurosensory disabilities; further that after adjustments are made for social risk and gender, the differences in these problems and limitations will persist between the groups;

2) that EI children will have significant growth failure in infancy and that they may continue to show failure to thrive during early childhood years;
3) that EI children will have high rates of attention deficit and of social and possibly anxiety/depression problems; that there will be no significant difference in aggressive and delinquent behaviors between EI and controls, and that the relationship between EI and behavioral problems might be partially explained by psychosocial risk factors;

4) that EI children will show deficits in executive functions and that these deficits will have a negative impact on the learning abilities of these children.

1.3. Population

1.3a. EI cohort

The children assessed in the study represent a subpopulation of survivors in the Swedish national study on all children with birth weights < 1001 g ("the 1000 g study"), i.e., all the 89 surviving children born at 23-25 weeks gestation. For the Swedish national study, data were collected prospectively on all ELBW infants (gestational age ≥ 23 weeks and birth weight < 1000 g) who were born from March 1990 through April 1992 in the whole of Sweden. A total of 633 ELBW infants were born alive and 370 (63%) survived to time of discharge home (Fig. 1B). The short-term outcome and 3-year follow-up in these children have been described previously.\textsuperscript{17,211} Of these 633 ELBW infants, 247 were born at less than 26 completed weeks (extremely immature, EI), of whom 89 (36%) survived through the neonatal period and all were known to be alive at 3 years of age. All of these 89 EI children were identified and alive at the age of 11 years and were eligible for the present study.

The database generated from the previous studies in this longitudinal investigation was established at the national epidemiological centre of the Swedish National Board of Health and Welfare. Permission was obtained to access the database. The names and addresses of the EI children and their families, including those that had moved abroad, were traced from the Swedish national tax board, where we also confirmed that the child was alive at the time of the present assessment. A letter was then sent to the pediatrician caring for the EI child, asking if he or she thought it appropriate for the family to be contacted. Three families that had moved to other countries were traced and approached.
The study Population

Figure 1A. Map of Sweden showing places of residence of the study children; red dots = EI children and blue dots = controls

Figure 1B. Flow chart showing the selection of the study sample and the numbers and proportions successfully followed up and assessed

<table>
<thead>
<tr>
<th>Total livebirths in Sweden (March 1990 - April 1992)</th>
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<tbody>
<tr>
<td>n = 245,850</td>
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<table>
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<tr>
<th>Birth weight ≤ 1000g</th>
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<tr>
<td>n = 931</td>
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<table>
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<tr>
<th>Livebirths with birth weight ≤ 1000g</th>
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<td>n = 633</td>
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<tr>
<th>Total births at 23-25 weeks’ gestation</th>
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<td>n = 420 (0.17% of all births)</td>
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<table>
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<tr>
<th>Livebirths at 23-25 weeks’ gestation</th>
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<tr>
<td>n = 247 (0.1% of all livebirths)</td>
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<tr>
<th>Alive and assessed</th>
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<tr>
<td>At discharge home (neonatally)</td>
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<td>n = 89</td>
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<th>At 3 years of age</th>
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<tr>
<td>n = 89</td>
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<tr>
<th>Assessed with equal number of controls at age 11</th>
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<tr>
<td>n = 86 (97% of all survivors)</td>
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<tr>
<th>Not assessed (refused, abroad)</th>
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<tr>
<td>n = 3</td>
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</table>
Population

Once the family was located and with the pediatrician’s permission, the research nurse wrote to the parents asking for their participation in the study and requesting their written permission to send questionnaires to the child’s school teacher, the parents and the children themselves. Once the EI and control families had given their written agreement to participate in the study, they were contacted by the research nurse, who explained the procedures in filling out the questionnaires. With the permission of the parents, questionnaires were sent to the children’s class teachers and the children themselves, enclosing a letter with relevant instructions for filling out the questionnaires. If the children needed assistance in understanding the questions, this was provided by their teachers. Questionnaires from all respondents were returned to the study coordinator at the University of Umeå. Two reminders were sent to non-respondents and when possible an approach was also made by telephone. Missing data from the returned questionnaire were followed up in the same way. Parents of EI children were also asked for permission to review the pediatric case records, child health records, and records from the other specialist health services in order to identify any neurosensory impairment. In the case of the controls, if the parents reported that their child had been seen by specialist services we asked for their permission to approach these services for further information.

1.3b. Comparison group

The control group was recruited at the present assessment (10-12 years of age) from the national birth register, by selecting a full term, normal birth weight child born at the same hospital, of the same gender and nearest in birth date (± 7 days) to the EI child. We identified three control participants for every index child. As we aimed to have one control for every EI child, we initially contacted the first of the control families. If the family did not respond or refused to participate, we then approached the second family and if necessary the third. Recruiting the control families was a slow process and this resulted in a control group which was on average 8 months older than the EI children. The control group was approached and examined in the same way as the study population.
2. Methods

The following domains were explored:
- Current health status, i.e., prevalence of neurosensory handicaps (impairments) and of other medical and psychiatric illnesses
- Functional limitations and special health care needs imposed by these chronic conditions
- Assessment of growth development and analyses of the correlates of growth from birth up to the age of 11 years.
- Mental health: behavioral problems and emotional well-being.
- Executive functions, learning and language skills.
- Social competencies, adaptive functioning.
- School achievement and school performance.

Measures

2.1. Health status:

2.1.1. Categorical measures

Specific medical diagnoses and disabilities were identified by reviewing case records and by measuring responses to a standard and validated parental questionnaire, Nordic Child Health and Family Questionnaire\textsuperscript{212}

2.1.1a. Neurosensory impairments (NSI)

NSIs at the present assessment were identified and characterized by reviewing pediatric and school health records of all EI children and of those control participants whose parents reported that their child had been seen at services for such impairments. Records from other specialist health services such as habilitation or eye rehabilitation centers were reviewed for those EI and control participants whose parents reported at the present assessment that their child had received care from these health services. \textit{Cerebral palsy} was classified as hemiplegia, diplegia, or quadriplegia. CP was also categorized functionally as mild (no evidence of clinically important functional difficulty related to gait or use of hands), moderate (independent walking but with an abnormal gait), or disabling (not walking, severe motor disability). \textit{Severe visual impairment} was defined as unilateral or bilateral blindness or visual acuity < 20/200 without glasses in at least one eye, and
hearing disability as sensorineural hearing defects requiring hearing aids. Formal psychometric tests were not carried out, but had been performed in all children who were receiving full-time special education (EI: 13; and Control: 4). Major disability was defined as moderate or disabling CP, severe visual impairment including unilateral or bilateral blindness, sensorineural hearing disability requiring a hearing aid, or need for full-time special education in a special school as a measure of severe mental retardation.

2.1.1b. Chronic medical and psychiatric illnesses
The Nordic health and family questionnaire\textsuperscript{212} includes items that identify and measure the severity of children’s chronic medical, behavioral, or other psychiatric conditions. There are 14 items which identify specific health conditions, diagnosed by a medical specialist or a child psychologist. There is also an open question about any other specific health condition. Respondents were instructed to tick the answer only if the condition had persisted or was expected to last for a period of 12 months or more. A positive response was categorized as mild, moderate or severe.

2.1.1c. Developmental disabilities
Developmental disabilities such as poor motor skills, poor visual perception and poor learning skills were assessed with “Five to Fifteen” (FTF), a parent questionnaire for the assessment of ADHD and comorbid conditions.\textsuperscript{213} FTF comprises 181 items that are organized into eight domains (motor skills, executive functions, memory, learning, language, perception, social skills, and emotional/behavioral problems). This questionnaire has been validated and norms for the Swedish population have been established.\textsuperscript{213, 214} Impairments in motor skills, visual perception, and learning skills were defined in terms of standard deviation scores that were either 2 or 3 SD above the normative mean, corresponding to moderate (92\textsuperscript{nd}- 95\textsuperscript{th} percentile) and severe difficulties (> 98\textsuperscript{th} percentile), respectively.

2.2. Non-categorical measures

A Questionnaire for Identifying Children with Chronic Conditions (QuICCC)\textsuperscript{215,216} was administered to a parent or primary caregiver, usually the mother. Sixty-two percent of the parents of the EI children and 24\% of those of the control participants were interviewed in their homes, while 23\% and 21\%, respectively, were interviewed at the pediatric research center of Umeå University.
Hospital. The interviews with the remaining parents in the two groups were conducted on the telephone. QuICCC incorporates the consequences of chronic health conditions that have a physical, psychological, or cognitive basis and have lasted or are expected to last for 12 months or more. It has 39 question sequences divided into 3 domains: functional limitations, with 16 items concerning physical, emotional, cognitive, and social development; dependence on compensatory aids, which has 12 items, including use of medications, special diet, assistive devices at home or at school, and personal assistance; and need for services above those routinely needed by children, which has 11 items including medical, psychological, and educational services and special treatments and arrangements at school or at home. Most questions in QuICCC have multiple parts. The first part of each question sequence concerns one or more specific consequences of having a chronic health condition. If the respondent reports that a child experiences the consequence, the interviewer moves to the second level of the sequence, which asks whether the consequence is the result of a medical, behavioral, or other health condition. If the answer to the second part of the question is affirmative, the interviewer proceeds to the final part of the question, which applies to the duration (or expected duration) criterion of 12 months or longer. To be identified as having a chronic condition, a child must qualify in each component of at least one question sequence.215 We asked the parents about further details of the reported conditions and therapies that were provided. Detailed interviews were conducted and if the need arose we had one or more follow-up interviews with the families during the study period. We did not use the item pertaining to an individual educational plan in the domain of service above routine, since it was not applicable to the Swedish school system. However, all children with special educational arrangements were encompassed by other relevant items in the QuICCC, such as “special arrangements in school” and “Full-time special class instructions or special schools”. In the functional limitation domain, we added one sequence in the final part of the item “physical delay” by asking whether the children had ever had serious growth delay; however, we also maintained the original algorithm of the item. In the domain of compensatory dependency we added an item by asking whether the child uses prescription glasses. QuICCC was not validated before use.

2.3. Growth (Anthropometric measurements)

2.3a. Growth data collection
Growth development from birth to the age of 11 years was examined prospectively and correlates of growth attainment were analyzed. Weight, height,
and head circumference (HC) measurements and body mass index (BMI, kg/m\(^2\)) from birth to the present assessment were reviewed from the pediatric case records and from records in the child health care center and at school. The method of data collection in the perinatal period in the EI children has been described previously.\textsuperscript{17} Fetal ultrasonography performed at 16-17 weeks of gestation was used to determine the gestational age at birth in 97% of the EI children. Trained nurses at the neonatal intensive care unit measured the weight at birth in all EI children. Thereafter, weight was measured at repeated intervals up to discharge from the hospital. Measurements of HC and length in the EI children were postponed at birth on many occasions, but between the 2\textsuperscript{nd} and 4\textsuperscript{th} weeks of postnatal age all surviving EI children had their length and HC measurements performed and subsequently the three growth parameters (weight, length, and HC) were measured at regular intervals up to discharge from the hospital. Data concerning the child’s condition at birth, birth weight, birth length, and HC are recorded on a special form, which is sent to the child care center where the child is seen at regular intervals up to the age of 6 years. All children are registered at the child health care center. After the hospital period in the EI children and from birth in the control participants, the length, weight, and HC were measured during health checks either at the hospital or at child health care center up to the age of 6 years. After that age, measurements of length and weight were taken at school by a school nurse at regular intervals, once or more often every year. Growth data were collected from the child health care units, hospital records and school health services until the children reached 11-12 years of age. At the present assessment (11-12 years), the weight, length and HC were measured in all the EI and control participants by a trained nurse in a standardized way. The ages at the time of measurement were corrected for gestational age up to the age of 3 years.

\textit{Length} was measured supine until the child could stand up by itself, which is generally at about 2 years of age. After that age, height was measured with a stadiometer attached to the wall. All height measurements were made to the last completed 0.5 cm.

\textit{Weight} in the first 2 years of life was measured naked to the last completed 0.1 kg on a balance scale or with an electronic scale. Children from ages 2 to 11 years were weighed wearing minimal clothing on a digital scale with an accuracy of 0.1 kg.

\textit{Head circumference} was measured in the maximum fronto-occipital plane a using non-extensible plastic coated tape measure. After 4 years of age, HC is not usually measured at routine health check-ups and HC records were therefore not available from the age of 4 to the time of the present assessment at 11 years.
The average numbers of measurements of weight and height from birth to 11 years in EI and control participants were 34 (range 15-45) and 18 (range 10-36), respectively. The corresponding numbers of HC measurements from birth to 3 years in the two groups were 17 (10-32) and 6 (4-9), respectively. Data on parental anthropometry (height and weight), obtained by self-reports, were available in 97% of the study population.

2.3b. Growth data analysis
The growth data for each child were examined before they were combined with the data sets of the two previous studies for analysis.\textsuperscript{17,211} Before the statistical analysis was performed, the raw growth data were inspected for recording errors. This was done in two stages. First, non-positive age increments were listed and scrutinized. Second, tentative standard deviation scores were established to look for extreme values in either direction. For determining weight/height at exact predefined ages, fourth-degree polynomial regression\textsuperscript{217} curves were fitted for each child and variable. Interpolated values were then calculated for the predefined ages in EI and control children. Z scores for weight, height, BMI and HC were computed relative to the Swedish population norms currently being used in Sweden.\textsuperscript{218,219} Swedish reference values for calculation of HC Z scores were unavailable from age 4 years onwards, and we therefore used the UK growth chart for computing HC Z scores at 11 years of age.\textsuperscript{220} In EI children z scores for the growth variables from birth to expected date of delivery (EDD) corresponding to 40 weeks of gestation were computed relative to the Swedish reference data based on estimated fetal weight.\textsuperscript{221} A Z score is calculated by subtracting the expected value for the measurement (weight, height, BMI, or HC) from the child’s actual measurement and dividing by the standard deviation (SD) for the measurement. The cut-offs for overweight at different ages in boys and girls were defined as proposed by Cole et al.\textsuperscript{222} When data were available for both parents, z scores were averaged to obtain a mid-parental height z score. Otherwise, the measurement from the sole parent was assumed to represent mid-parental height. Multiple regression analysis was performed to identify correlates of growth at 11 years of age (see below).
2.4. Mental health

*In the assessment of the children’s mental health we have explored the following domains:*

a. Behavioral profile (internalizing behaviors, externalizing behaviors (aggressive and delinquent behaviors), social, attention and other behavioral problems)

b. Emotional well-being /status (depression, anxiety and withdrawn behaviors)

The above-mentioned behavioral/ emotional profiles were assessed by responses to 3 standardized and validated questionnaires concerning mental and emotional well-being filled out by the parents, school teachers and the children themselves, which were sent to them by mail. These scales are as follows:

a. Achenbach Child Behavior Checklist, Parent report (CBCL), 1991\(^{223}\) (Behavior rating scale, rated by parents in the home environment).

b. Achenbach Teacher Report Form (TRF), 1991\(^{224}\) (behavior rating scale analogous to the CBCL, rated by class teacher in the school environment).

c. Five to Fifteen’’ (FTF): a parent and teacher version of questionnaire for the assessment of ADHD and co-morbid conditions.\(^{213}\)

d. Depression Symptoms Rating Scale (DSRS).\(^{225}\)

All of the aforementioned behavior assessment rating scales are standardized and validated. Swedish gender- and age-specific norms have been established in most of these scales, e.g. CBCL,\(^{223}\) DSRS,\(^{225}\) FTF.\(^{213}\)

2.4a. Behavior – dimensional profile

To assess the parents’ and the teachers’ perception of the children’s behavior, the parents completed the CBCL\(^{223}\), and the teachers completed the analogous TRF.\(^{224}\) Both forms include 118 items for scoring particular behavior/ emotional problems, plus two open-ended problem items. The CBCL and TRF differ somewhat according to the home vs school context in which the child is seen, but the scoring profiles enable both instruments to be scored in terms of a common set of eight problem behaviors. The list contains 118 items of difficult behaviors, all scored 0 (not true), one (somewhat or sometimes true), or two (very true or often true). Principal components analyses reveal 8 sets of behaviors: withdrawn, somatic complaints, anxious or depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. Principal factor analyses of the 8 categories produce two broad-band groupings, namely: internalizing derived from the sum of the items in the first three groupings, and externalizing, namely: from the last two (delinquent behaviour and aggressive behavior). The
remaining three categories (social, thought, and attention problems) comprise problems fitting either broad-band dimension. The CBCL and TRF scales are also constructed in terms of items that measure 6 sets of behavioral syndromes based on the criteria of the *Diagnostic and the Statistical Manual of the Mental Disorders, fourth edition, revised (DSM-IV-R)*\(^\text{226}\): affective disorder, anxiety, somatic problems, ADHD, conduct disorder, and oppositional defiant disorder. Respondents were asked to base their answers on the preceding 6 months. To provide a common metric across the different tests, the raw scores in the CBCL and TRF problem subscales and the scores in the competence scales of CBCL (activity, social, and school scale) were converted to Z scores (standard deviation scores, SDS). Z scores for problem and competence scales in the CBCL were computed relative to the Swedish norms being used in Sweden at the time.\(^\text{227}\) Swedish reference norms for calculation of Z scores in TRF problem scales were not available, and we therefore computed Z scores for TRF problem scales relative to the mean scores of the controls of the same sex. On all behavioral scales higher scores indicated more problematic behavior. For all problem subscales of TRF and CBCL, a score higher than the 90th percentile for the controls of the same sex was classified as being in the abnormal range. The percentile distribution of the total problem score (TPS) in the CBCL scale in our control group was similar to that of a Swedish reference population.\(^\text{227}\)

### 2.4b. Attention-hyperactivity

was assessed by 4 standardized measures (questionnaires rated by parents and teachers)

1. Attention difficulties subscales of CBCL and TRF\(^\text{223,224}\)
2. Five to Fifteen” (FTF): A parent and an analogous teacher version of the questionnaire for the assessment of ADHD and comorbid conditions.\(^\text{213}\)

### 2.4c. Emotional well-being

of children was assessed by the internalizing scales of TRF and CBCL which measure anxiety, depression, and withdrawn behaviors in the school and home environment, respectively. Children also completed a self-report on a depression self-rating scale (DSRS).\(^\text{225}\) DSRS is an 18-item self-report questionnaire, consisting of a psychiatric symptom checklist which measures anxiety and depression. The child is asked to rate his/her own situation during the last month on a 3-point scale. Scores of 2, 1, and 0 refer to “most of the time”, “sometimes” and “never”, respectively. In DSRS, a score higher than the 90\(^{th}\) percentile for the controls of the same sex was classified as being in the abnormal range. The items of the DSRS were developed after an extensive evaluation in the population and have been tested against an operational clinical definition of depressive disorder.\(^\text{225}\)
2.5. Assessment of Executive Functions, Language skills, and Learning skills

Executive function is a broad term that describes the psychological processes defined by the control of thought and behavior. EF incorporates strategy use, inhibitory control, planning, cognitive ability, sequencing and monitoring of thoughts and behavior and is critical in the integration of information. Attention control and working memory are inextricably intertwined with these functions. Executive control of attention requires active management of attentional resources to avoid distraction and interference. The interplay between the monitoring, manipulation and storage of stimuli is thought to be coordinated by the executive influence within memory and attention. Attention can be further divided into three components, namely, sustained attention, selective attention, and ability to switch attention.

To assess the parents’ and the teachers’ perception of the children’s EF, language and learning skills, the parents completed the FTF and the teachers completed an identical questionnaire. FTF comprises 181 items that are organized into 8 domains (motor skills, executive functions, working memory, learning, language, perception, social skills, and emotional/behavioral and obsessive-compulsive problems). Each of the 181 items consists of a statement that the child has difficulties with a certain task compared with the other children of the same age. The parts of parent or teacher FTF that assess executive function, working memory, language and learning skills were used for this study.

To assess the executive functions in our study cohort we used Attention, Hypoactivity, Hyperactivity/Impulsivity, Planning/Organizing subdomains and Working memory domain from parent or teacher FTF: 1) Attention assesses the ability to pay attention to and concentrate on various tasks and activities, and the ability to select and switch attention when needed or desirable; 2) Hypoactivity refers to a tendency to become too passive, and difficulty initiating of activity; 3) Hyperactivity/impulsivity concerns impulse control and regulation of activity (tendency to become too active); 4) Planning /organizing assesses items related to the ability to plan and organize, e.g., “difficulty understanding consequences of own actions”, “difficulty planning and preparing for tasks” and “difficulty completing sequential tasks”; and 5) Working memory domain contained statements mostly pertaining to short-term memory. For example: “difficulty remembering what has occurred recently, such as who has phoned or, what he/she ate a few hours ago”; “difficulty remembering where he/she has put things”; “difficulty remembering appointments with peers or what homework he/she has”; “difficulty acquiring new skills, such as rules of new play or games”; “difficulty
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learning rhymes, songs, multiplication tables, etc. by heart”; “difficulty remembering long or multiple-step instructions”. All items from above mentioned subdomains and the working memory domain of the parent or teacher FTF were collapsed into a domain broader than that in the original FTF, named Global Executive Composite Score (GECS).

The language skills domain consists of 21 items; 5 assessing the comprehension of spoken language, 13 assessing expressive language skills, and 3 assessing skills in conversation and communication with others.

The learning skills domain assesses responses to 28 items related to the child’s learning ability in school subjects such as math, reading and writing, and responses to the items assessing daily learning ability and coping in learning. The learning skills domain is further organized into 4 subdomains: reading/writing (8 items), math (5 items), general learning (5 items), and coping in learning (10 items). All items are scored as 0, 1 or 2, representing: “does not apply” (0), “applies sometimes / to some extent” (1), or “definitely applies” (2). For each domain or subdomain a mean score of 0 to 2 was calculated.

We converted mean domain/subdomain scores of the parent-FTF to Z scores in relation to the Swedish age- and gender-specific reference population. The parent-FTF has been validated and norms for the Swedish population have been established. Swedish reference norms for calculation of Z scores in the analogous teacher-FTF were not available, and we therefore we computed Z scores for teacher-FTF domains and subdomains, relative to the mean scores of the controls of the same sex. A substantial correlation has been reported between the parent-FTF domains and the corresponding domains in the Achenbach’s Child Behavior Checklist (CBCL) scale. The FTF domains have also shown a significant correlation with the corresponding domains in NEPSY, a neuropsychological assessment instrument. FTF was initially intended only for parents, but the items have been formulated so that they are equally suitable for teachers. The teacher-FTF was not validated before use. Impairments in individual components of EF, language skills and learning skills were defined in terms of standard deviation scores that were 2 SD above the normative mean, corresponding to clinically significant difficulties.
2.6. Measurement of adaptive functioning and social competence

Parents provided responses regarding the following items from the competence scales of the CBCL: general activities (activity scale), which measures the amount and the quality of the child’s participation in sports, hobbies, and organized activities; social activities (social scale), which measures participation in organizations and clubs, number of friends, and frequency of contacts with friends, how well the child gets along with the parents, siblings and other children; and school performance (school scale), which measures performance in academic subjects on a standard scale, grade retentions, any academic or other problems at school, and special education services received by the child at school. Assessments of adaptive functioning at school were based on the Achenbach’s TRF. Teachers provided responses for the five items on adaptive functioning that measured the child’s performance in academic subjects and four adaptive characteristics: How hard is he/she working? How appropriate is he/she behaving? How much is he/she learning daily? How happy is the pupil?

2.7. School performance

School performance was assessed by the Teacher’s academic Report Form (TRF), "Five to Fifteen” (FTF) and by competence scale of CBCL. The TRF includes information on the adaptive functioning, child’s grade, special assistance in education, referrals to special education programs, grade retention, and school achievements in different subjects like math, reading and language competence. School difficulties were defined as the child repeating a grade and / or using special educational resources (part-time or full-time). FTF taps information on the academic skills in different subjects from the two sources, namely the class teacher and the parents. Parents also rated their children’s school performance in the school subscale of adaptive functioning (competence scale) of CBCL.

2.8. Perinatal and other risk factors.

All outcome data were related to perinatal factors pertaining to pregnancy, and neonatal period including mode of delivery, plurality, birth order, birth weight, and length of neonatal stay, severity of illness, intervening health variables, and health problems emerging since the neonatal period, in order to test and focus on the
specific hypotheses about factors causing disability. The data for each child were combined with the data sets of the two previous studies for analysis.17,211

2.9. Socioeconomic background and environmental factors

We evaluated the relation of SES and other environmental factors to the outcome, such as chronic conditions, growth, mental health, emotional adjustment, executive functions, learning and language skills, adaptive functioning, social competencies, and school performance.

2.9.1. Socioeconomic status

Sociodemographic characteristics, including variables such as the parents’ educational level, the family’s disposable income, and the family structure, were assessed by The Nordic Health and Family Questionnaire.212 The mother’s education was classified into 3 groups: 1) more than 12 years, 2) 10-12 years, 3) 9 years or less. The cut-off point for high/low education was defined as the last group against the others. The family’s disposable income was classified into 6 groups, and the cut-off point for high/low income groups was between the two highest groups and the others. The family structure was defined as a single-parent or two-parent family. Any social risk was defined as single-parent family or mother’s educational level ≤ 9 years or low family income. The composite social risk index included maternal education (0 for high school or above and 1 for 9 or less than 9 years of schooling), family structure (0 for 2-parent family and 1 for single-parent family), and family income (0 for high and 1 for low income). The composite scale ranged from 0 for the lowest social risk index to 3 for the highest social risk. SES was also measured on the basis of the Swedish socioeconomic classification system.232 In its most aggregated form the classification consists of 6 groups. For the purpose of this study we further categorized SES into 3 main groups: laborers (unskilled and semiskilled workers), non-manual employees (assistant and intermediate non- manual employees), and professional employees.

2.9.2. Environmental risk

Information on family factors was obtained from the parents through the Nordic Child Health and Family Questionnaire212 and from the responses to a brief 12-item maternal mental health scale.

2.9.2a. Family function

Family function was measured by a 12-item general functioning scale derived from the Nordic Child Health and Family Questionnaire.212 This instrument
assesses family functioning in 5 dimensions: affective responsiveness, problem solving, affective involvement, communication and roles, and behavior control. The items concerning family function have five alternatives graded from strongly agree to strongly disagree. The total score ranges from 0 to 60, with higher scores indicating disturbance.

2.9.2b. Maternal mental health
Maternal mood and maternal psychological health were measured by a 12-item brief inventory devised by a research group at the division of psychiatry of Umeå University. In this scale there are 6 items that measure maternal mood; 3 items measuring positive affect (scores range from 0-18), and 3 items measuring negative affect (scores also range from 0-18). Low maternal mood was identified when the negative mood score was greater than the positive mood score. The positive mood affect was scored as 0 and the negative affect as 1. The remaining 6 items measure categorical responses to questions on the psychological health of the mother (visiting a psychiatrist or a psychologist; suicidal ideation; use of psychopharmacological drugs; phobias and fears). Maternal health risk scores included all categorical responses from the maternal mood scale (0 for positive and 1 for negative maternal mood) and the psychological health scale (0 for not true and 1 for true). These scores were summed to obtain a composite maternal mental health risk index (range 0-12). Higher scores indicate disturbance.

2.10. Statistical analyses
Data were collected on standardized forms and encoded for computerized analysis with the use of Windows SPSS version 13.0 (SPSS inc. Chicago, Ill). The assessment data for each EI child were examined before they were combined with the data set from two previous main studies\textsuperscript{17,211} for analysis. Descriptive statistics such as frequency distributions, means and SDs were used. Differences in dichotomous outcomes between the groups were analyzed with the $\chi^2$ or Fisher’s exact test, when appropriate. Continuous outcome measures were compared by unpaired or paired student-$t$ tests to test the differences between the means. Various statistical models (see below) were used to examine the differences in outcomes between the groups and also to analyze the relationship of explanatory factors such as socioeconomic, family function and maternal mental health status to the outcome.
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**Study I**

In the assessment of chronic conditions and special health care needs, multivariate logistic regression analyses were performed to examine the differences in dichotomous outcomes between the groups for all measures of functional limitations, compensatory dependency, and service use above routine, when appropriate. Social risk and gender were included as covariates. As measures of socioeconomic status, we analyzed social risk factors such as single-parent family, low income or mother’s education ≤ 9 years separately and as a single categorical variable, i.e., any social risk versus none. We repeated the analyses to compare the outcomes of the EI children and controls with no neurosensory impairment.

**Study II**

To compare the growth of children relative to the reference population at each age, and to compare rates of change in Z scores between the consecutive ages, data were analyzed by the single-group t test. Children’s heights were compared with their mid-parental height by using paired t tests. Data were compared between the groups by non-paired t tests. Multiple regression analysis was performed to identify correlates of growth at 11 years of age. Two regression models were constructed. In the first model, stepwise regression analyses were carried out to determine whether preterm birth was a factor associated with growth at 11 years after controlling for other explanatory variables such as gender, having a chronic condition at 11 years, parental height and weight, and SES. In the other model, analyses were repeated in the EI children only, to determine whether growth was predicted by major neonatal complications (IVH grade 3-4 or PVL, ROP ≥ stage 3, BPD, and necrotizing enterocolitis), birth weight, or gestational age after controlling for other explanatory variables such as SES, parental anthropometric measures, and having a chronic condition at the present assessment.

We had a large number of measurements of length, weight, and head circumferences throughout the study period in both EI and control children. As the measurements were not taken at exact ages, we performed a polynomial regression analysis in order to reduce the fluctuation in the sample size at various ages. We fitted fourth-degree polynomial-regression analysis\(^{217}\) curves for each child and variable. Interpolated values were then calculated for predefined ages in EI and control children.
Studies III and IV

Behavioral/emotional problems and competencies are likely to be related to stresses in a child’s life as well to factors such as social risk. In the analyses of the CBCL and TRF competence and problem scale scores, we therefore, adjusted for social risk factors, family function, maternal mental health risk, and presence of a chronic medical condition in the child. Multivariate analysis of covariance (MANCOVA) was performed to test the differences between the groups. The independent variables were group status (EI vs control) and gender, and the dependent variables were each of the 6 DSM-oriented syndrome scales of CBCL or analogous scales of TRF tested as multivariable dependent variables. The following variables were included as covariates/factors in the model: composite social risk index, family function, maternal mental health risk score, and presence of a chronic medical condition. MANCOVAs of CBCL and TRF syndrome scales were performed in two separate analyses. Follow-up analyses of covariance (ANCOVA) were carried out on each of the 6 DSM-oriented behavioral syndrome subscales of CBCL and TRF, with the same covariates as in the MANCOVAs of CBCL and TRF syndrome scale scores. ANCOVA was also performed on the 5 TRF adaptive functioning scales (academic performance, daily learning, hard work, classroom behavior, and being happy), on 3 competence scales of CBCL (social, activity, and school scale), and on the DSRS, with the same covariates/factors as in the ANCOVAs of the CBCL and TRF syndrome scale scores.

ANCOVA was performed to test differences between the groups regarding the 5 individual EF components/subdomains (attention, hyperactivity-impulsivity, hypoactivity, planning/organizing, and working memory), and 3 subdomains assessing language skills (comprehension, expression, and communication). The independent variables were group status (EI vs control) and gender. Composite social risk score and family function were entered as covariates.

We also performed multivariate analysis of covariance (MANCOVA) to test differences between the groups in learning skills. The independent variables were group status (EI vs control) and gender; the dependent variables were each of the 4 subdomains of the learning skills (i.e., reading and writing, math, general learning, and coping in learning) in the parent-FTF and the analogous scales of the teacher-FTF questionnaire, tested as multivariable dependent variables. The covariates included in the model were global executive composite score (GECS), composite social risk index, and family function. MANCOVAs of parent- and teacher-reported learning skills were carried out in two separate analyses. The effect size
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(ES) is given by the partial eta-squared statistic which describes the proportion of total variability attributable to a factor or covariate (the proportion which if multiplied by 100 is the percentage of total variability due to the group differences). All significant MANCOVA and ANCOVA effects were interpreted using Cohen’s criteria for ES, where effects are deemed small, medium, and large if they account for 1% to 5.8%, 5.9% to 13.8%, and > 13.8% of variance, respectively.233

Multivariate logistic regression analyses were also performed to test differences in dichotomous outcomes regarding behavioral problems, executive dysfunctions, and language and learning skills between the groups. Social risk, family function, gender, maternal mental health risk score, and presence of a chronic medical condition were entered as covariates. P values < .05 were considered significant.

2.11. Sample Power

The assumptions for the calculation of sample size are as follows: More than one quarter (25-28%) of the extremely low birth weight children show neuropsychological disorders of some type as compared to the children born at term, in which the prevalence of these disorders does not exceed 6-8%.163 Many studies have reported that attention-deficit disorder in its varying forms is prevalent in 15% -23% of ELBW infants compared to 4- 6% of their peers, with more than twice the relative risk (RR) for developing ADHD (pooled RR, 2.64; 95% CI 1.85-3.78).107 More than a quarter of ELBW children have been found to have significant cognitive impairment, compared with the expected 2.3-2.5 % in the normal population.29 Thus with 80% power, and an α error of .05 in detecting an increase in the number of children with cognitive and hyperactivity disorders from 5% in the control population to 20% in the ELBW group, a sample size of 140 children (70 per group) will be required. Our sample size of 86 children in each group (EI and controls) was well above the target for enabling us to detect these clinically important differences.
3. Findings
The main findings in this longitudinal investigation are as follows.

3.1. Sociodemographic and birth data

All of the 89 surviving children in the EI cohort had been assessed in their neonatal period and at 3 years of age.\(^ {17,211}\) At the time of the present study one child had emigrated and was lost to follow-up, and two families refused to participate. Thus 86 children (97%) remained for assessment (mean age 10.9 years; SD 0.76) (Fig 1B). Of the 3 non-participating children, one had a significant neurosensory impairment and the other two had no disability, with a normal neurosensory and growth outcome at 3 years of age.\(^ {211}\)

Three EI children with severe motor disability were excluded from the present growth study, which thus comprised 83 children (94% of all survivors). Another 3 were on growth hormone (GH) treatment and were included in the study only until the start of that treatment (at 4 years and 10 months; 3 years and 8 months; and 4 years and 9 months). Thus, in the growth study 83 EI children (94% of all survivors) were assessed up to 4 years of age and 80 (90%) were assessed from age 4 up to 11 years.

In the studies of mental health, executive functions, and learning and language skills, the assessment of the behavioral/emotional and neuropsychological status could not be carried out in 3 EI children as they were severely retarded. Thus in assessing these outcomes, 83 EI children were studied.

*Sociodemographic characteristics* collected at the time of the present assessment, including years of maternal education, single-parent families and social class, were similar in the EI and control groups (Table 1). One child in each group was in foster care. In the EI cohort, 80 infants (93%) were born at tertiary care centers; 26 (32%) of their mothers received antenatal corticosteroids and 22 infants (26%) were treated with surfactant. The EI children had a mean (SD) birth weight of 765 (111) g and a mean gestational age of 24.6 (0.7) weeks. Eight percent of the EI children were small for gestational age\(^ {221}\) and 17% were from multiple births. Thirty-three children (38%) were oxygen dependent at 36 weeks of PCA, 22 (27%) had severe (stage ≥ 3) ROP and 12 (14%) had either grade 3 or 4 IVH, or PVL or both, at discharge home. The control participants were on average 8 months older than the EI cohort. The assessment regarding functioning and special health care needs would not be expected to change in relation to this small age difference.
3.2. Developmental disabilities and specific diagnosis (Study I)

Table 2 summarizes the findings regarding abnormal neurosensory outcomes and other medical or psychiatric conditions. At 11 years of age, 13 children (15%) in the EI cohort exhibited one or more NSI: 5 had CP, 10 had severe visual impairment, and 5 required hearing aids. In contrast, 2 children in the control group had NSI. Of the five children (6%) diagnosed with CP, 3 were not walking (disabling CP) and another 2 were walking independently. These 3 children with disabling CP were severely handicapped and they had profound mental retardation (IQ < 50). In the remaining 2 children with ambulatory CP, one had diplegia and the other had hemiplegia. Ten children (12%) in the EI group had either unilateral blindness or severe visual impairment. Four of these had unilateral blindness. The overall prevalence of at least one major disability (moderate or disabling CP, severe visual impairment, hearing disability requiring aids, or receiving full-time special education) was 21% (18 of 86) in the EI children and 6% (5 of 86) in the control participants (\(P = 0.006\)).

The EI children had a significantly higher rate of NSI and medical and psychiatric disorders, overall, than the control participants (EI 45%, controls 22%; \(P = 0.002\)) (Table 2). The difference was mainly attributable to NSI, asthma, and chronic constipation. Significantly higher rates were found in the EI cohort than in the controls for poor motor skills (26% vs 3%; \(P < 0.001\)), impaired visual perception (21% vs 4%; \(P < 0.001\)), poor learning skills (27% vs 3%; \(P < 0.001\)), poor adaptive functioning at school (42% vs 9%; \(P < 0.001\)) and poor academic performance (49% vs 7%, \(P < 0.001\)). These group differences remained significant in children without NSI (data not shown). A significantly higher proportion of the families of EI children expressed their dissatisfaction with the professional support and/or reported out of pocket expenditures incurred upon the parents by reason of their child’s health problem (EI 23%, control 5%; \(P < 0.05\)).
Table 1. Infant Birth, Neonatal Data, and Sociodemographic Characteristics

<table>
<thead>
<tr>
<th>Birth and Neonatal Data</th>
<th>EI (n=86)</th>
<th>Control (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age, wk, mean (SD)</strong></td>
<td>24.6 (0.7)</td>
<td>39.2 (2.7)²</td>
</tr>
<tr>
<td>23-24 wk, n</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>25 wk, n</td>
<td>58</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Birth weight, g, mean (SD)</strong></td>
<td>765 (110)</td>
<td>3520 (601)²</td>
</tr>
<tr>
<td>SGA (&lt; -2SD)</td>
<td>7 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>46 (53)</td>
<td>46 (53)</td>
</tr>
<tr>
<td>Multiple births</td>
<td>15 (17)</td>
<td>NA</td>
</tr>
<tr>
<td>In vitro fertilization</td>
<td>7 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Born at tertiary care center</td>
<td>80 (93)</td>
<td>80 (93)</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>3 (4)</td>
<td>NA</td>
</tr>
<tr>
<td>Antenatal corticosteroids</td>
<td>26 (32)</td>
<td>NA</td>
</tr>
<tr>
<td>Surfactant treatment</td>
<td>22 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>Neonatal hospital stay, days, mean (SD)</td>
<td>108 (27.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>83 (95)</td>
<td>NA</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>33 (38)</td>
<td>NA</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (grade 3 or 4) / Periventricular Leukomalacia</td>
<td>12 (14)</td>
<td>NA</td>
</tr>
<tr>
<td>Retinopathy of prematurity ≥ stage 3</td>
<td>22 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>2 (2)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Sociodemographic data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age, mean (SD), y</td>
<td>30.1 (4.9)</td>
<td>31.3 (5.2)</td>
</tr>
<tr>
<td>Adults in home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-parent family</td>
<td>75 (87)</td>
<td>75 (87)</td>
</tr>
<tr>
<td>Both biological parents</td>
<td>57 (66)</td>
<td>62 (71)</td>
</tr>
<tr>
<td>Single-parent family</td>
<td>11 (13)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>No siblings</td>
<td>17 (22)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Number of children in the family, mean (SD)</td>
<td>2.3 (2.1-3.6)</td>
<td>2.4 (2.2-2.6)</td>
</tr>
</tbody>
</table>
Table 1 continued.

<table>
<thead>
<tr>
<th>Maternal education</th>
<th>10 (12)</th>
<th>9 (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤9 y</td>
<td>10 (12)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>10-12 y</td>
<td>51 (59)</td>
<td>41 (48)</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>25 (29)</td>
<td>36 (42)</td>
</tr>
<tr>
<td>Family income, monthly, mean (SD), US dollars</td>
<td>3729 (1544)</td>
<td>4067 (1580)</td>
</tr>
<tr>
<td>Low income</td>
<td>24 (28)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Composite social risk score&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>56 (65)</td>
<td>62 (72)</td>
</tr>
<tr>
<td>1</td>
<td>12 (14)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>2</td>
<td>14 (16)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>3</td>
<td>4 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Social risk (any)</td>
<td>30 (35)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>Socioeconomic status&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laborers</td>
<td>39 (45)</td>
<td>27 (31)</td>
</tr>
<tr>
<td>Assistant and intermediate non-manual employees</td>
<td>28 (33)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Professionals</td>
<td>19 (22)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Family function score, mean (SD)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>20.9 (7.02)</td>
<td>19.4 (6.18)</td>
</tr>
<tr>
<td>Age of child at present assessment, mean (SD), y</td>
<td>10.9 (0.76)</td>
<td>11.6 (0.85)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are given as numbers (percentages) unless otherwise stated; <sup>a</sup> P < 0.001; <sup>b</sup> derived from Swedish reference population<sup>221</sup>; <sup>c</sup> Defined as need for supplemental oxygen at 36 weeks’ postmenstrual age; <sup>d</sup> Mother’s age at birth of EI child or control; <sup>e</sup> In the calculation of composite social risk score, 1 point was assigned for each of the following: Single status, mother’s education ≤ 9 years, and low income; <sup>f</sup> Socioeconomic status classification<sup>232</sup>; <sup>g</sup> See methods for description of family function; NA, not applicable.
<table>
<thead>
<tr>
<th>Variable</th>
<th>EI n = 86</th>
<th>Control n = 86</th>
<th>P value for group difference</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory impairment£</td>
<td>13 (15)</td>
<td>2 (2)</td>
<td>0.003</td>
<td>7.7 (1.7-34.6)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild *</td>
<td>5 (6)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate**</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling***</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Visual Impairment</td>
<td>10 (12)</td>
<td>1 (1)</td>
<td>0.005</td>
<td>11.3 (1.4-90.5)</td>
</tr>
<tr>
<td>Unilateral blindness</td>
<td>4 (5)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual impairment (&lt; 20/200)£</td>
<td>6 (7)</td>
<td>1 (1)</td>
<td>0.014</td>
<td>2.3 (1.3-5.2)</td>
</tr>
<tr>
<td>Medical or psychiatric disorderµ</td>
<td>36 (42)</td>
<td>18 (21)</td>
<td>0.005</td>
<td>2.6 (1.3-5.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>17 (20)</td>
<td>5 (6)</td>
<td>0.006</td>
<td>2.3 (1.3-5.2)</td>
</tr>
<tr>
<td>Allergic disorders (atopic eczema, allergic rhino-</td>
<td>4 (5)</td>
<td>7 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>conjunctivitis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation (moderate to severe)</td>
<td>11 (13)</td>
<td>1 (1)</td>
<td>0.002</td>
<td>12.8 (1.6-101.4)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precordious puberty</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosis</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention deficit/ hyperactivité disorder</td>
<td>6 (7)</td>
<td>3 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslexia</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total with at least one disorder (NSI or medical or</td>
<td>38 (45)</td>
<td>19 (22)</td>
<td>0.002</td>
<td>2.8 (1.5-5.5)</td>
</tr>
<tr>
<td>psychiatric disorder)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are numbers (percentages) of children unless otherwise stated; £ See “Methods” section for classification of neurosensory impairments at 11 years. Medical and psychiatric disorders are adapted from the Nordic health and family questionnaire and include those with duration of 12 months or more at 11 years of age; ‘ Derived from the Mantel-Haenszel estimate; ¥ Data for the neurosensory impairments and medical or psychiatric disorders are the numbers and percentages of children with at least one condition in that category; * No evidence of clinically important functional difficulty related to gait or to hand use. ** Independent walking but with abnormal gait; *** Not walking, severe motor disability (wheelchair dependency). ¥ One EI child was legally blind, vision of < 0.1 (could see only light in the better eye).
3.3. Consequences of Chronic Conditions

3.3a. Functional Limitations
Compared with the full-term controls, the EI cohort had significantly higher rates of functional limitations (Table 3). These limitations included mental or emotional delay, blindness or difficulty in seeing, need to reduce time and effort in physical activities, physical delay, restriction in activities, and trouble understanding simple instructions. Except for the restriction in activities, these differences remained significant when children with neurosensory impairment were excluded. The overall rate of one or more functional limitation was significantly higher in the EI cohort (EI 64%, control 11%; \( P < 0.001 \)). After exclusion of children with NSI in the two cohorts, the corresponding rate in the EI children was still significantly higher than in the controls (58% vs 9%; \( P < 0.001 \)). The most common functional limitation in EI children with or without NSI was mental or emotional delay. Severe functional limitations such as difficulty with feeding, dressing, washing, being blind or unable to walk were restricted to 4 EI children with neurosensory impairment.

3.3b. Compensatory dependency needs
Compared with the control cohort, the EI children had a significantly greater need for assistive devices or personal help to minimize or compensate for their functional limitations (Table 4). The most common compensatory need in EI children was the use of prescription glasses. The rates of medication use in the EI and control cohorts, respectively, were: 17% vs 6% for asthma; 7% vs 4% for ADHD; 4% vs 8% for allergic disorders; 4% vs 1% for epilepsy and 5% vs 1% for constipation. The use of a wheelchair and a need for other special equipment to help with walking, feeding, toileting or bathing were restricted to 4 EI children with NSI. Overall 59% of the total EI children, 52% of the NSI-free EI subgroup and 25% of the total control participants had one or more compensatory dependence needs.

3.3c. Service use above routine
Compared with the control children, the EI children had a significantly greater need for services above the routine (Table 5). These services included visiting a physician regularly for a chronic condition, physical or occupational therapy, nursing care and medical procedures, full-time special education in special schools or in special classes attached to the mainstream schools, and a need for special arrangements at school. When the NSI-free children in the two groups were analyzed separately, the difference remained significant in only two outcomes, i.e., receiving physical or occupational therapy and special arrangements at school. Fifty EI children (58%) had special arrangements at
school and 13 (15%) received full-time special education in special schools or classes, whereas the corresponding rates among the control participants were 10% (n=9) and 5 % (n = 4), respectively. Of the 13 EI children (15%) receiving full-time special education, 8 (62%) had one or more neurosensory impairment. Of the remaining 5 EI children receiving full-time special education who had no NSI, all were in special schools because of severe learning and behavioral problems. Five percent (n = 4) of the children in the control group were placed in the special school because of severe learning and behavioral problems.

Logistic regression analyses adjusting for social risk factors and gender showed that, EI children had significantly more chronic conditions in all three domains of QuICCC than control participants. These differences remained significant when the 13 EI children and 2 control participants with NSI were excluded from the analyses (see Tables 3, 4, and 5). In the analyses of the total population including children with NSI, boys showed an increased risk for any functional limitation (odds ratio [OR] 2.3; 95% CI 1.1- 4.7) and mental delay (OR 2.4; 95% CI 1.05- 5.5). Social risk was significantly related to three outcomes, namely any functional limitation: OR 2.7 (95% CI 1.2-6.2); mental delay: OR 3.1 (95% CI 1.3-7.1); and receiving full-time special education: OR 4.6 (95% CI 1.6-13.4).

3.3d. Rates of chronic conditions in multiple domains
Overall, 81% of the EI children and 33% of the control participants were identified as having a chronic condition in one of the 3 domains of QuICCC (Figure 2). These rates in the groups without NSI were 80% vs 32% respectively (P < 0.001). Thirty percent of the EI children and 3 % of the controls had a chronic condition in all 3 domains of QuICCC (P < 0.001). In the NSI-free children these rates were 16% and 1% respectively (P < 0.001). In a subanalysis in which the outcomes in EI children were compared with respect to gestational age category, no significant differences in rates were found in an any of the three QuICCC domains between children born at 23-24 weeks (n=28) and those born at 25 weeks (n=58) (93 % vs 78 % respectively; P = 0.1).
Table 3. Functional limitations associated with a chronic condition of 12 months or more *

<table>
<thead>
<tr>
<th></th>
<th>Total population (n = 86)</th>
<th>NSI-free EI (n = 73)</th>
<th>EI vs Control</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P value*</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical delay</td>
<td>18 (21)</td>
<td>12 (16)</td>
<td>1 (1)</td>
<td>24.4 (3.1-188.3)</td>
<td>0.002</td>
<td>17.8 (2.2-142.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mental or emotional delay</td>
<td>31 (36)</td>
<td>22 (30)</td>
<td>6 (7)</td>
<td>7.8 (3.0-20.5)</td>
<td>&lt;0.001</td>
<td>7.1 (2.5-20.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restricted in certain activities</td>
<td>14 (16)</td>
<td>6 (8)</td>
<td>2 (2)</td>
<td>7.9 (1.7-36.0)</td>
<td>0.008</td>
<td>6.5 (2.1-20.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Reduced time or effort in activity</td>
<td>21 (24)</td>
<td>13 (18)</td>
<td>4 (5)</td>
<td>30.6 (4.0-233.0)</td>
<td>0.001</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Unable to participate in sports or other physical activities</td>
<td>8 (9)</td>
<td>2 (3)</td>
<td>2 (2)</td>
<td>4.1 (0.8-20.8)</td>
<td>0.08</td>
<td>17.8 (2.2-142.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Blind or difficulty seeing (uncorrected by glasses)</td>
<td>23 (27)</td>
<td>11 (15)</td>
<td>1 (1)</td>
<td>30.6 (4.0-233.0)</td>
<td>0.001</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Deaf or difficulty hearing</td>
<td>5 (6)</td>
<td>0</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.029</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Difficulty eating</td>
<td>5 (6)</td>
<td>1 (1)</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.09</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Trouble understanding simple instructions</td>
<td>19 (22)</td>
<td>14 (19)</td>
<td>3 (3)</td>
<td>30.6 (4.0-233.0)</td>
<td>0.001</td>
<td>9.7 (2.1-44.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Unable to walk without help</td>
<td>3 (4)</td>
<td>0</td>
<td>1 (1)</td>
<td>2.7 (0.3-27.4)</td>
<td>0.39</td>
<td>2.7 (0.3-27.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Unable to play or socialize with others</td>
<td>8 (9)</td>
<td>3 (4)</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.003</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Trouble speaking/communicating</td>
<td>20 (23)</td>
<td>12 (16)</td>
<td>4 (5)</td>
<td>30.6 (4.0-233.0)</td>
<td>0.002</td>
<td>5.2 (1.4-19.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Severe limitations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty feeding him/herself</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.12</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Difficulty dressing</td>
<td>5 (6)</td>
<td>2 (3)</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.029</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Difficulty washing/bathing</td>
<td>5 (6)</td>
<td>1 (1)</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.029</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Difficulty using toilet</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
<td>30.6 (4.0-233.0)</td>
<td>0.12</td>
<td>4.3 (1.3-13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Any functional limitation</td>
<td>55 (64)</td>
<td>42 (58)</td>
<td>10 (11)</td>
<td>30.6 (4.0-233.0)</td>
<td>&lt;0.001</td>
<td>16.5 (6.4-42.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) of children unless otherwise stated; * Adapted from QuICC.215,216 Σ Derived from the logistic regression adjusting for social risk (single-parent family, maternal education, or low income) and sex; Comparing proportions with the control group with Fisher’s exact test or testing that the odds ratio is unity, whichever is applicable.
<table>
<thead>
<tr>
<th>Compensatory Need</th>
<th>EI Total population (n = 86)</th>
<th>NSI-Free EI (n = 73)</th>
<th>Control Total population (n = 86)</th>
<th>NSI-Free Control (n = 84)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P valueφ</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P valueφ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takes regular prescribed medication</td>
<td>23 (27)</td>
<td>16 (22)</td>
<td>12 (14)</td>
<td>2.3 (1.04 - 4.9)</td>
<td>0.039</td>
<td></td>
<td>1.85 (0.8 - 4.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Life-threatening allergic reactions</td>
<td>1</td>
<td>1(1)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follows physician-ordered special diet</td>
<td>6 (7)</td>
<td>1(1)</td>
<td>5 (6)</td>
<td>1.2 (0.35-4.1)</td>
<td>0.76</td>
<td></td>
<td>1.85 (0.8- 4.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Needs glasses</td>
<td>42 (49)</td>
<td>31 (43)</td>
<td>7 (8)</td>
<td>11.0 (4.5-26.7)</td>
<td>&lt; 0.001</td>
<td></td>
<td>9.9 (3.8-26.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Needs special equipment to see (other than glasses)</td>
<td>4 (5)</td>
<td>0</td>
<td>1 (1)</td>
<td>4.1 (0.5-37.9)</td>
<td>0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs special equipment to communicate</td>
<td>5 (6)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>&lt; .005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs special equipment to walk</td>
<td>4 (5)</td>
<td>0</td>
<td>1 (1)</td>
<td>3.5 (0.34-33.2)</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs help or equipment to feed him/herself</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs help or equipment to dress</td>
<td>6 (7)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>3.1 (0.6-16.1)</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs help or equipment to wash</td>
<td>7 (8)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>6.9 (0.8-57.8)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs help or equipment for toileting</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs equipment to eat</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs equipment for other functions</td>
<td>8 (9)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>2.7 (0.7-10.5)</td>
<td>0.16</td>
<td></td>
<td>3.5 (1.8-7.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Any compensatory dependency need</td>
<td>51 (59)</td>
<td>38 (52)</td>
<td>22 (25)</td>
<td>4.3 (2.2-8.3)</td>
<td>&lt; 0.001</td>
<td></td>
<td>3.5 (1.8-7.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Any compensatory dependency need other than glasses</td>
<td>30 (35)</td>
<td>20 (27)</td>
<td>16 (18)</td>
<td>2.3 (1.1-4.7)</td>
<td>0.02</td>
<td></td>
<td>1.9 (0.86 – 4.1)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) of children unless otherwise stated. * Adapted from QuICC215,216; Σ Derived from the logistic regression adjusting for socioeconomic status (single-parent family, maternal education, or low income) and sex; φ Comparing proportions with the control group with Fisher’s exact test or testing that the odds ratio is unity, whichever is applicable.
Table 5. Services needed above routine for a chronic condition of 12 months or more*

<table>
<thead>
<tr>
<th>Service</th>
<th>Total population (n = 86)</th>
<th>NSI-free (n = 73)</th>
<th>Total population (n = 86)</th>
<th>NSI-free (n = 73)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P value</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits physician or specialist on a regular basis</td>
<td>20 (23)</td>
<td>14 (19)</td>
<td>9 (10)</td>
<td>2.5 (1.1-6.0)</td>
<td></td>
<td>0.036</td>
<td>2.3 (0.9-5.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Visits counselor, psychologist or a social worker</td>
<td>11 (13)</td>
<td>6 (8)</td>
<td>5 (6)</td>
<td>2.3 (0.7-6.8)</td>
<td></td>
<td>0.15</td>
<td>1.7 (0.5-6.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Receives physical/occupational or other therapy</td>
<td>17 (20)</td>
<td>9 (12)</td>
<td>2 (2)</td>
<td>10.2 (2.3-45.8)</td>
<td></td>
<td>0.002</td>
<td>12.0 (1.5-97.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Receives nursing care or has undergone medical procedures</td>
<td>6 (7)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>5.9 (0.7-50.9)</td>
<td></td>
<td>0.10</td>
<td>2.4 (0.21-26.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hospitalized for a chronic condition</td>
<td>7 (8)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>7.2 (0.8-60.0)</td>
<td></td>
<td>0.07</td>
<td>3.6 (0.4-36.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Individualized rehabilitation plan</td>
<td>12 (14)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>6.5 (1.4-30.3)</td>
<td></td>
<td>0.01</td>
<td>3.7 (0.4-36.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Receives fulltime separate class instructions or attends special schools</td>
<td>13 (15)</td>
<td>5 (7)</td>
<td>4 (5)</td>
<td>3.4 (1.0-11.1)</td>
<td></td>
<td>0.04</td>
<td>1.9 (0.4-8.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Has special arrangements at school</td>
<td>50 (58)</td>
<td>39 (53)</td>
<td>9 (10)</td>
<td>11.9 (5.3-26.8)</td>
<td></td>
<td>&lt; 0.001</td>
<td>12.8 (5.2-31.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Unable to get a needed medical service</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any services needed above routine</td>
<td>58 (67)</td>
<td>46 (63)</td>
<td>19 (22)</td>
<td>7.4 (3.7-14.7)</td>
<td></td>
<td>&lt; 0.001</td>
<td>6.9 (3.3-14.1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) of children unless otherwise stated; * Adapted from QuICCC; 215,216; Σ Derived from the logistic regression adjusting for socioeconomic status (single-parent family, maternal education, or low income) and sex; φ Attending special school or training school for the physically disabled and severely mentally retarded or receiving full-time special education attached to the mainstream school; * Special arrangements at school include modified schedule (modification of class schedule, curriculum, or gym classes), tutoring by a teacher or by other professionals (special teachers) or resource room, classroom made accessible with special equipment, provision of special transportation, and special diets at school.
The differences remained significant between the groups when the children with neurosensory impairment were excluded.

Figure 2. *Adapted from QuICCC215,216
The differences remained significant between the groups when the children with neurosensory impairment were excluded.
Findings

3.4. Growth (Study II)

Raw data on weight, length, HC and BMI at various ages are shown in table 6.

3.4a. Weight
EI children showed a marked drop in weight Z scores in the neonatal period and the scores continued to decline up to 3 months of corrected age. After that age, these scores in the EI children began to increase and continued to do so, reaching the mean of the reference Swedish population at approximately 11 years of age. The mean difference in weight Z scores between the EI and control participants was significant at all ages, but, it decreased from –2.32 at 3 months of corrected age to -0.39 at 11 years of age (data not shown). The proportion of EI children with subnormal weight (<2SD below the mean) increased from 7% at birth to 60% at 3 months of corrected age, after which it decreased at later ages (Fig 3A). Compared with their male controls, EI boys had significantly lower mean weight Z scores at all ages from birth to 11 years, whereas between the girls of the two groups this difference disappeared from 7 years of age onwards (Fig 4a, 4b). At 11 years of age, the EI boys were 5 kg lighter in weight than their control participants (difference in means: EI boys, -4.9 [95% CI -8.2 to -1.6], P = 0.003).

3.4b. Height
There were not enough length Z scores at birth in EI children to make statistical comparisons worthwhile. Compared with their controls and the reference population, the EI children had significantly lower height Z scores at all ages. Like the Z scores for weight, the height Z scores increased after 3 months of corrected age. EI children showed a significant increase in height Z scores between the ages of 3 months (corrected for prematurity) and 3 years (mean increase 1.44, 95% CI 1.18 to 1.71) and between ages 7 and 11 years (mean increase 0.28, 95% CI 0.20 to 0.36). Between the ages of 3 and 7 years, the height Z scores did not change in the EI children, but remained fairly constant and significantly below zero. In the control participants the height Z scores did not change significantly from 0 between any consecutive ages. At the present assessment, the mean (SD) height Z scores were significantly lower in the EI children than in the control participants (EI: -0.53 [1.08] vs control: 0.10 [0.93]; P < 0.001). The proportion of EI children with a subnormal height increased from 37% at EDD to 62% at 3 months of corrected age, and was subsequently reduced at later ages (Fig 3B). At 11 years, a small and non-significant proportion of EI children (EI: 6%; control: 1%, P = 0.2) remained subnormal in height. A similar pattern of catch-up growth in height Z scores was observed in EI boys and girls (Fig 4c, 4d).
Table 6. Raw Growth Data at Each Age

<table>
<thead>
<tr>
<th>Age (n)</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Head circumference, cm</th>
<th>Body mass index kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EI</td>
<td>Control</td>
<td>EI</td>
<td>Control</td>
</tr>
<tr>
<td>Birth (EI: 83)*</td>
<td>0.765 (0.11)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EDD/birth** (EI: 83; C: 83)</td>
<td>2.7 (0.4)</td>
<td>3.52 (0.6)</td>
<td>46.7 (1.8)</td>
<td>50 (2.6)</td>
</tr>
<tr>
<td>3 mo (EI: 83; C: 83)</td>
<td>4.7 (0.8)</td>
<td>6.0 (0.8)</td>
<td>56 (2.9)</td>
<td>60.8 (2.5)</td>
</tr>
<tr>
<td>6 mo (EI: 83; C: 83)</td>
<td>6.4 (0.9)</td>
<td>7.7 (0.9)</td>
<td>63.2 (2.8)</td>
<td>66.9 (2.4)</td>
</tr>
<tr>
<td>9 mo (EI: 83; C: 83)</td>
<td>7.6 (0.98)</td>
<td>8.9 (1.1)</td>
<td>68.3 (2.8)</td>
<td>71.5 (2.7)</td>
</tr>
<tr>
<td>12 mo (EI: 83; C: 83)</td>
<td>8.6 (1)</td>
<td>9.9 (1.2)</td>
<td>72.7 (2.9)</td>
<td>75.3 (2.6)</td>
</tr>
<tr>
<td>2 yr (EI: 83; C: 83)</td>
<td>11.3 (1.5)</td>
<td>12.7 (1.6)</td>
<td>84.8 (3.6)</td>
<td>87.3 (3.2)</td>
</tr>
<tr>
<td>3 yr (EI: 83; C: 83)</td>
<td>13.5 (2)</td>
<td>15.0 (1.9)</td>
<td>93.6 (4.1)</td>
<td>96.2 (3.9)</td>
</tr>
<tr>
<td>4 yr (EI: 80; C: 80)</td>
<td>15.3 (2.6)</td>
<td>17.2 (2.4)</td>
<td>100.2 (4.9)</td>
<td>103.9 (4.3)</td>
</tr>
<tr>
<td>5 yr (EI: 80; C: 80)</td>
<td>17.6 (3.1)</td>
<td>19.6 (2.9)</td>
<td>107.2 (5.2)</td>
<td>111.0 (4.5)</td>
</tr>
<tr>
<td>7 yr (EI: 80; C: 80)</td>
<td>22.7 (4.7)</td>
<td>24.6 (4.1)</td>
<td>119.9 (6.0)</td>
<td>123.7 (5.4)</td>
</tr>
<tr>
<td>9 yr (EI: 80; C: 80)</td>
<td>28.9 (6.6)</td>
<td>31.3 (6.1)</td>
<td>131.2 (6.5)</td>
<td>135.5 (5.8)</td>
</tr>
<tr>
<td>11 yr (EI: 80; C: 80)</td>
<td>36.4 (8.8)</td>
<td>39 (7.6)</td>
<td>142.5 (7.5)</td>
<td>146.9 (6.3)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) unless otherwise stated; Age is corrected for preterm birth up to 3 years of age; * Indicates birth weight in EI infants; ** Indicates raw data at the expected date of delivery (EDD) in EI children and at birth in control participants; -, not available.
Findings

11 years of age, the EI girls were 3.1 cm and the EI boys 5.7 cm shorter than their contemporary control participants (difference in means: girls, -3.1 [95% CI -6.2 to -0.09; \( P = 0.04 \)]; boys, -5.7 [ 95% CI -8.71 to -2.7, \( P < 0.001 \)].

3.4c. BMI

Compared with their controls the EI children had significantly lower BMI Z scores up to 5 years of age, but by 7 years this difference had disappeared (data not shown). There was a significant increase in the mean BMI Z scores between ages 1 and 11 years in both groups (mean increase [SD]; EI 1.5 [1.15] and control: 0.85 [1.4]). The mean gain in BMI between 1 and 11 years of age was significantly greater in the EI cohort than in the control participants (difference in mean gain 0.64; 95% CI 0.25 to 1.03, \( P = .002 \)). At age 11 years, EI children as a group were relatively heavy for their height, but their mean BMI Z score was not significantly different from 0 (mean difference 0.29; 95% CI -0.005 to 0.59) or from the controls (mean difference -0.09; 95% CI; -0.5 to 0.31). Fifteen percent of the EI cohort compared with 17 % of the control participants were overweight according to the cut-offs for BMI proposed by Cole et al.\(^{222}\) In an analysis for gender differences in BMI, the mean BMI Z scores for EI girls were found to be comparable to those for their controls from age 2 to 11 years, whereas the mean BMI Z scores for EI boys were significantly lower than those for their control participants up to 7 years of age, reaching the mean of the reference at approximately 9 years (Fig. 4e, 4f).

3.4d. Head Circumference

There were not enough HC measurements at birth in EI children to allow comparisons. At EDD, the mean HC Z scores in EI children were significantly lower than those in their control participants (mean difference -1.1; 95% CI -1.33 to -0.87, \( P < 0.001 \)). These remained significantly lower than the control scores and the reference mean at all ages at which comparison was possible (data not shown, see study II). The control participants did not change their Z scores from the reference mean between any consecutive ages. A significantly higher proportion of the EI cohort compared with controls had subnormal HC (< 2 SD below the mean) at 11 years of age (EI 22% ; control 1%, \( P < 0.001 \)) (Fig 3C). In addition, there were significant differences between EI and control children by gender at 11 years of age: The mean HC of EI boys was 2 cm lower than that of their
Figure 3. Percentage of EL (<26 week’s gestation) children with subnormal weight for age (A; weight below -2SD), height for age (B; height below -2SD), and HC for age (C; HC below -2SD) at different ages218-221: A comparison with controls (number of children assessed, birth to 4 years: EL, 83 and Controls, 83; 5-11 years: EL, 80 and Controls, 80); Age is corrected for preterm birth up to 3 years of age. *Indicates proportion of EI infants with subnormal weight at birth; **Indicates proportion of EI children at EDD and control participants at birth with subnormal weight, length, or HC.
control participants and it was 1.2 cm lower in EI girls than in their controls \((P < 0.001)\). Unlike the increases in height and weight, the EI children did not show any catch-up growth in HC after the age of 6 months (Fig. 4g, 4h).

### 3.4e. SGA, growth deficiency and chronic condition
At 11 years of age, the mean Z scores of weight, height and HC for 6 EI children who were born SGA were -0.48, -0.96, and -2.6 respectively. The corresponding values in the EI children who were born appropriate for gestational age (AGA) \((n=74)\) were -0.12, -0.5, and -0.99, respectively. Of the 6 EI children who were born SGA, at 11 years of age none had a weight Z score less than -2SD, one child had a height Z scores less than -2 SD and 5 had a HC Z scores less than -2SD. The mean Z scores in height, weight and HC in EI children with \((n = 33)\) and without \((n= 47)\) any chronic condition did not differ significantly at age 11 years: height Z scores -0.47 (1.03) vs -0.6 (1.1); weight z scores -0.13 (1.1) vs -0.17 (1.3), and HC Z scores -1.36 (1.0) vs -1.1 (1.1), respectively. Three children had been investigated earlier in childhood for short stature and had been started on growth hormone therapy at 4-5 years of age, although none of them had growth hormone deficiency. Before starting growth hormone therapy these children had a mean height Z score of -3.1 (SD 0.6) at 4 years of age.

### 3.4f. Parental Anthropometry
Mid-parental height Z scores were available for parents of 81 children (98%) in each group, i.e., in the EI and control cohorts. There were no differences in maternal or paternal height or weight between the two groups. The difference in mean height Z scores between the EI children and their parents (mid-parental height Z score) was significantly below 0 at age 11 years \((\text{paired t test, } t = - 4.99; P < 0.001; \text{mean difference in height Z scores -0.56; 95% CI -0.79 to -0.34})\). The corresponding values in the control participants were not different from 0 \((\text{mean difference -0.09, 95% CI -0.28 to 0.09})\). A majority of the EI children (94%) were within 2 SD of their mean mid-parental height Z scores.

### 3.4g. Correlates of Growth
Stepwise multiple regression analyses revealed that the Z scores for height and HC at age 11 years continued to be significantly lower in the EI children than in the control participants after adjustment for mid-parental height, sex, SES, and having a chronic condition. Mid-parental height \((Z \text{ score})\) was a significant predictor of the children’s height, explaining 22% of the variance \((\beta = .545, P < 0.001)\), followed by group status (prematurity),
Findings

which explained 8% of the variance (beta= .528, \( P < 0.001 \)). Group status was the major determinant of HC (Z score) (\( R^2 = 0.24 \), beta = 1.0, \( P < 0.001 \)), and mid-parental height (Z score) showed a weak but significant correlation with HC, explaining 3% of the variance (beta = 0.25, \( P = .01 \)). Maternal weight was the only variable that correlated with weight or BMI Z scores (for weight Z score, \( R^2 = .26 \), beta = .042, \( P < 0.001 \) and for BMI Z score, \( R^2 = .17 \), beta = .047, \( P < 0.001 \)). In the separate analyses of boys and girls, preterm birth was a significant predictor of weight in boys but not in girls. In the subanalysis of the EI cohort only, mid-parental height and birth weight Z scores correlated with height at 11 years of age (data not shown). As observed in the analyses of both groups, the only variable that correlated with weight and BMI Z scores was mother’s weight. Birth weight Z scores predicted head size. Sex, gestational age, SES, and presence of a chronic condition did not correlate with any of the anthropometric measurements at the present assessment.
Figure 4 a-h, Graphs illustrating mean Z scores of weight, height, BMI and HC at each age, in EI (< 26 weeks’ gestation) boys (number of boys assessed, birth to 4 yr: EI, 38; Control, 38; 5 to 11 yr: EI, 36; Control, 36) and girls (number of girls assessed, birth to 4 years: EI, 45; Control, 45; 5 to 11 yr: EI, 44; Controls, 44): comparison with control participants. Age is corrected for preterm birth up to 3 years of age. * Z scores at birth in EI children; ** Z scores at EDD in EI children and birth Z scores in control participant; The null line is the Z score for the reference group.
3.5. Adaptive functioning and Social competence (Study III)

EI and control cohorts were compared regarding a number of items that assessed adaptive functioning and social competence. On the TRF scale that assesses academic performance in the mainstream school, EI children had significantly poorer scores than the control participants ($P < .001$). ANCOVA revealed that prematurity was strongly associated with poor academic performance, as indicated by teacher ratings (data not shown). None of the other covariates were associated with the academic performance of either EI or control children. Furthermore, the EI children had significantly poorer scores than the controls with respect to TRF ratings of how much the child was learning ($P < .001$) and to total adaptive function computed by summing ratings on four adaptive characteristics ($P < .001$). There were no statistically significant interactions between gender and group regarding these variables. On the CBCL school and social scale, the EI children obtained poorer scores than the control participants (data not shown). Social risk was associated with activity scale of CBCL ($F (1,162) = 11.29$, $P = .001$, ES = 6.5%). Although social risk was also associated with the social scale of CBCL, it represented only a small effect (4% of the variance) compared with the medium effect (8%) observed for group status (prematurity vs control). Compared with the controls, a significantly higher proportion of EI children had failed a grade (15% vs 5%; $P < .05$), or had school difficulties (59% vs 12%; $P < .001$) (Table 7). Thirteen EI children compared with 4 children in the control group were receiving full-time special education in a special school or special class ($P = .023$). A significantly lower proportion of EI than of control children participated in any sports at school or at home (76% vs 92%; $P = .004$) and significantly more EI children were rated below average in sports (29% vs 5%; $P < .001$). However, no differences were found in the proportion of children who participated in activities and games other than sports. Furthermore, the proportion of children with impaired family relationships or relationships with peers or of those who had few friends did not differ between the two groups (Table 7).

3.6. Mental Health Measures by group and by Evaluation Source (Study III)

3.6a. Behavioral scores by parent and teacher report

Parents and teachers reported significantly higher scores in EI children compared with controls for internalizing problems (anxious/depressed, withdrawn, somatic problems) and attention, thought, and social problem scales. The mean Z scores in EI versus control children according to the parent
Findings

reports were: 0.44 vs -0.17, respectively, \( P = .002 \), for withdrawn behavior; 0.70 vs -0.14, \( P < .001 \), for anxious/depressed behaviors; 1.17 vs 0.15, \( P < .001 \), for attention difficulties; 1.3 vs 0.39, \( P = .001 \), for social problems; 0.75 vs 0.1, \( P = .024 \), for thought problems (Fig. 5A). The pattern of findings was closely similar for the teachers (Fig. 5B). Based on both parents’ and teachers’ ratings, the mean raw total problem score (TPS) was significantly higher in EI children than in controls (EI vs control 23.1 vs 13.72, mean difference 9.36, \( P = .001 \), on the CBCL scale; and EI vs control 25.89 vs 15.05, mean difference 10.84, \( P = .001 \), on the TRF scale). Compared with those of the controls, parents and teachers of EI children were more likely to rate their child as scoring in the abnormal range for a number of behaviors (defined as CBCL and TRF problem scale scores higher than the 90th percentile for the reference and controls, respectively) (Table 8). The parent-reported rate of abnormal behavior among EI children for the anxious/depressed problem subscale was 27% (adjusted odds ratio [OR] 2.56; \( P = .036 \)); for withdrawn problems it was 36% (OR 2.9; \( P = .011 \)); and for attention problems it was 30% (OR 3.5; \( P = .007 \)). Similar to the EI parents, teachers reported significantly higher rates of abnormal scores for internalizing (anxiety/depressed and withdrawn) and attention problems in the EI children compared with controls. Teachers also reported significantly higher rates of abnormal scores for EI children for somatic, thought, and social problems (Table 8).

3.6b. Depression symptoms according to children’s self-report (DSRS) (Study III)

The mean scores in the children’s self-reports (DSRS) were significantly higher in EI children, indicating a trend toward increased depression symptoms compared with the control group (EI 7.04, control 5.45; mean difference 1.58 95% CI 0.29 -2.86, \( P = .017 \)). Five out of 18 of the DSRS items were significantly more likely to be reported by EI children than by the control participants, these being “haven’t lots of energy” (\( P = .003 \); “horrible dreams” (\( P = .01 \); “can’t stick up for myself” (\( P = .001 \); “feeling very sad” (\( P = .04 \)) and “feeling very bored” (\( P = .02 \). The proportion of EI children in the abnormal range (defined as a DSRS score higher than the 90th percentile for the controls) was not significantly different from that of corresponding controls (Table 8). Univariate analysis revealed that prematurity had a small but significant effect on depression symptoms as reported by the children, suggesting that the trend toward increased depression symptoms persisted among EI children after adjustment for the socioeconomic and other environmental factors. None of the other covariates were associated with children’s depression symptoms.

<table>
<thead>
<tr>
<th></th>
<th>EI n (%)</th>
<th>Control n (%)</th>
<th>P value for difference between EI and Controls&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent report (CBCL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation in one or more sports (EI 86; C 86)</td>
<td>65 (76)</td>
<td>80 (92)</td>
<td>.004</td>
</tr>
<tr>
<td>Competence in sports (EI, 65; C, 79)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below average</td>
<td>19 (29)</td>
<td>4 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Average</td>
<td>38 (59)</td>
<td>55 (69)</td>
<td></td>
</tr>
<tr>
<td>Above average</td>
<td>8 (12)</td>
<td>21 (26)</td>
<td></td>
</tr>
<tr>
<td>Participation in hobbies, activities and games other than sports (EI, 86; C, 86)</td>
<td>73 (85)</td>
<td>77 (89)</td>
<td>.51</td>
</tr>
<tr>
<td>Participation in jobs or chores, one or more (EI, 86; C, 86)</td>
<td>59 (69)</td>
<td>67 (77)</td>
<td>.23</td>
</tr>
<tr>
<td>Belongs to organizations, clubs and teams, one or more (EI, 86; C, 86)</td>
<td>53 (62)</td>
<td>70 (81)</td>
<td>.007</td>
</tr>
<tr>
<td>Few friends (EI, 86; C, 86)</td>
<td>11 (13)</td>
<td>4 (5)</td>
<td>.06</td>
</tr>
<tr>
<td>Impaired family relationship (EI, 84; C, 86)</td>
<td>10 (12)</td>
<td>5 (6)</td>
<td>.18</td>
</tr>
<tr>
<td>Impaired relationship with peers (EI, 83; C, 86)</td>
<td>11 (13)</td>
<td>4 (5)</td>
<td>.06</td>
</tr>
<tr>
<td>Cannot work or play alone (EI, 83; C, 86)</td>
<td>12 (14)</td>
<td>7 (8)</td>
<td>.22</td>
</tr>
<tr>
<td><strong>School performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special class or special school (EI, 86; C, 86)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13 (15)</td>
<td>4 (5)</td>
<td>.023</td>
</tr>
<tr>
<td>Grade repetition (EI, 83; C, 86)</td>
<td>13 (15)</td>
<td>4 (5)</td>
<td>.027</td>
</tr>
<tr>
<td>School difficulties (EI, 86; C, 86)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>51 (59)</td>
<td>10 (12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data were adapted from competence scores of CBCL.<sup>222</sup> C indicates control; <sup>a</sup> P value by Fisher’s exact test; <sup>b</sup> For rating of competence in sports number is based only on those who participated in sports; <sup>c</sup> Attending special school or training school for the physically disabled and severely mentally retarded or receiving full-time special education attached to the mainstream school; <sup>d</sup> Defined as repetition of a grade and/or use of special educational resources (part time or full-time).
Figure 5 A-B. Graphs illustrating mean Z scores for eight behavior problem scales in EI children obtained from parent report CBCL (A) or from teacher report TRF (B). The null line is the Z score for the reference Swedish population in graph A and it represents the Z score for the controls in graph B; * P < .05; **P < .005; ns, not significant
Table 8. Frequencies of Abnormal Behaviors Above 90\textsuperscript{th} Percentile Cut-offs\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>EI (n=83)</th>
<th>Control (n=86)</th>
<th>Adjusted OR \textsuperscript{b} (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent report (CBCL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious /Depressed</td>
<td>22 (27)</td>
<td>9 (10)</td>
<td>2.56 (1.06-6.18)</td>
<td>.036</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>30 (36)</td>
<td>12 (14)</td>
<td>2.9 (1.27- 6.63)</td>
<td>.011</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>11 (13)</td>
<td>7 (8)</td>
<td>1.26 (0.42-3.72)</td>
<td>.68</td>
</tr>
<tr>
<td>Social problems</td>
<td>21 (25)</td>
<td>10 (12)</td>
<td>1.92 (0.79-4.63)</td>
<td>.14</td>
</tr>
<tr>
<td>Thought problems</td>
<td>16 (20)</td>
<td>9 (10)</td>
<td>1.78 (0.71-4.5)</td>
<td>.22</td>
</tr>
<tr>
<td>Attention problems</td>
<td>25 (30)</td>
<td>8 (9)</td>
<td>3.46 (1.40- 8.54)</td>
<td>.007</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>11 (13)</td>
<td>10 (12)</td>
<td>0.99 (0.36-2.73)</td>
<td>.98</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>9 (11)</td>
<td>9 (10)</td>
<td>0.87 (0.31- 2.49)</td>
<td>.80</td>
</tr>
<tr>
<td>Internalizing</td>
<td>27 (33)</td>
<td>9 (10)</td>
<td>3.35 (1.38- 8.11)</td>
<td>.007</td>
</tr>
<tr>
<td>Externalizing</td>
<td>8 (10)</td>
<td>7 (8)</td>
<td>0.76 (0.22-2.61)</td>
<td>.66</td>
</tr>
<tr>
<td>Total Problems</td>
<td>24 (29)</td>
<td>9 (10)</td>
<td>2.86 (1.17- 7.0)</td>
<td>.021</td>
</tr>
<tr>
<td><strong>Teacher report (TRF)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious /Depressed</td>
<td>19 (23)</td>
<td>8 (9)</td>
<td>3.54 (1.39- 9.03)</td>
<td>.008</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>19 (23)</td>
<td>8 (9)</td>
<td>3.15 (1.25-8.0)</td>
<td>.015</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>17 (21)</td>
<td>6 (7)</td>
<td>3.94 (1.37-11.32)</td>
<td>.011</td>
</tr>
<tr>
<td>Social problems</td>
<td>17 (21)</td>
<td>7 (8)</td>
<td>2.86 (1.08- 7.58)</td>
<td>.035</td>
</tr>
<tr>
<td>Thought problems</td>
<td>25 (30)</td>
<td>7 (8)</td>
<td>5.04 (1.87-13.61)</td>
<td>.001</td>
</tr>
<tr>
<td>Attention problems</td>
<td>20 (24)</td>
<td>6 (7)</td>
<td>3.43 (1.26-9.35)</td>
<td>.016</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>17 (21)</td>
<td>11 (13)</td>
<td>1.33 (0.53-3.33)</td>
<td>.53</td>
</tr>
<tr>
<td>Delinquent behavior</td>
<td>19 (23)</td>
<td>9 (10)</td>
<td>2.20 (0.89-5.45)</td>
<td>.08</td>
</tr>
<tr>
<td>Internalizing</td>
<td>21(25)</td>
<td>8 (9)</td>
<td>3.51 (1.41-8.78)</td>
<td>.007</td>
</tr>
<tr>
<td>Externalizing</td>
<td>15 (18)</td>
<td>9 (10)</td>
<td>1.76 (0.65-4.76)</td>
<td>.27</td>
</tr>
<tr>
<td>Total Problems</td>
<td>20 (24)</td>
<td>8 (9)</td>
<td>3.1 (1.19-8.07)</td>
<td>.021</td>
</tr>
<tr>
<td><strong>Children’s self-report\textsuperscript{c}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression Self-Rating scale (DSRS)</td>
<td>10 (12)</td>
<td>8 (9)</td>
<td>1.27 (0.46-3.54)</td>
<td>.64</td>
</tr>
</tbody>
</table>

Values are n (%) of children unless otherwise stated. Data were adapted from the problem scales of CBCL\textsuperscript{223} and TRF\textsuperscript{224} and from the children’s self-report (Depression Self-Rating Scale, DSRS)\textsuperscript{225}. \textsuperscript{a}Cut-off for all scales are > 90\textsuperscript{th} percentile for the controls of the same gender; OR = odds ratio; CI = confidence interval; \textsuperscript{b}Derived from the logistic regression adjusted for gender, social risk, family function, maternal mental health, and presence of a chronic medical condition; \textsuperscript{c}81 EI children and 86 controls had complete data on DSRS.
3.7. Statistical analyses of behavioral outcomes

MANCOVA effects by parent report (CBCL)

MANCOVA of 6 DSM-oriented CBCL syndrome scales revealed significant multivariate main effects for group status, i.e., prematurity vs control (\(P = .003, \text{ES} = 12\%\)); social risk (\(P = .014, \text{ES} = 10\%\)); family function (\(P = .036, \text{ES} = 8.2\%\)); and presence of a chronic medical condition (\(P = .042, \text{ES} = 7.9\%\)). No interactions emerged, indicating that prematurity, gender, family function, social risk, and presence of a chronic medical condition were independently associated with the multivariate measure of CBCL syndrome scales.

MANCOVA effects by teacher report (TRF)

As with the parent reports (CBCL), MANCOVA of DSM-oriented analogous TRF syndrome scales revealed a significant multivariate effect for prematurity (\(P =.003, \text{ES} = 13\%\)), indicating that across the 6 problem scales there was a significant difference between the EI and control children. There was also a significant multivariate main effect for gender (\(P <.001, \text{ES} = 15\%\)). No interactions emerged, indicating that prematurity and gender were associated independently with the multivariate measure of TRF syndrome scales.

Univariate effects by parent report

*Group status (prematurity vs controls)*

In the follow-up univariate analyses, all the categorical independent variables and covariates/factors were the same, as were used in the MANCOVAs of DSM–oriented syndrome scales in CBCL and TRF. The analyses revealed significant effects for prematurity on 3 (affective problems, anxiety, and attention difficulties) of the 6 DSM-oriented syndrome scales of CBCL, suggesting that the significant behavior problems persisted in these domains among the EI children after controlling for psychosocial risk factors, gender, and presence of a chronic medical illness (data not shown). The analyses also demonstrated that besides prematurity, the number of other variables was significantly associated with the number of behavior problems as described below.
Findings

*Family function, Gender, and presence of a Chronic Medical Condition*

Significant effects of family function emerged for the following domains: anxiety problems \( (P = .003, \text{ES} = 5.2\%) \); somatic problems \( (P = .03, \text{ES} = 2.8\%) \), and attention problems \( (P = .046, \text{ES} = 2.4\%) \). Boys had higher ADHD scores than girls \( (P = .014, \text{ES} = 3.7\%) \). However, there was no interaction between status and gender \( (F (1,161) = .541, P = \text{ns}) \), suggesting that relatively, EI boys and girls differed to a similar extent from their respective controls. Presence of a chronic medical condition was associated with affective problems \( (P = .002, \text{ES} = 5.8\%) \) and anxiety problems, \( (P = .013, \text{ES} = 3.8\%) \).

**Univariate effects by teacher report**

ANCOVAs of 6 DSM–oriented syndrome scales of TRF revealed significant effects of prematurity on 4 disorders: affective, anxiety, somatic, and attention difficulties (data not shown). As in the CBCL scale, the significant effect of gender on the ADHD problems emerged \( (P < .001, \text{ES} = 11.4\%) \) and again there was no interaction of group status with gender \( (F (1,158) = 1.835, P = \text{ns}) \). No other covariates were associated with any of the DSM–oriented syndrome scales of TRF.

Logistic regression analyses based on parent- and teacher-reported abnormal behavioral outcomes (CBCL and TRF), showed that controlling for demographic variables (social risk, family function, maternal mental health, presence of a chronic medical condition, and gender) made no statistical difference to the results, which remained significantly high in the EI cohort (Table 8).

**Measures of Executive Functions, Language and Learning Skills by Group and by Evaluation Source (Study IV)**

**3.8. Executive functions**

Compared with those of controls, parents of EI children reported significantly higher scores for the individual EF components/subdomains and the GECS, indicating an increased risk for executive dysfunctions. The mean z scores calculated from the parent reports in the EI and control groups were 0.21 vs -0.45, \( P < .001 \) for attention; 0.31 vs -0.19, \( P < .001 \) for hyperactivity/ impulsivity; 0.29 vs -0.30, \( P < .001 \) for Hypoactivity; 0.63 vs -0.20, \( P < .001 \) for planning/ organizing; and 0.52 vs -0.23, \( P < .001 \) for working memory (Fig.6A). A similar pattern was revealed by the teacher.
Figure 6 A,B. Graphs illustrating mean Z scores for 5 executive function subdomains and 3 language skill subscales in EI children and controls, obtained from parent-FTF (A) or from teacher-FTF (B); The null line is the Z score for the reference Swedish population in graph A and it represents the Z score for the controls in graph B; * P < .05; **P < .005

reports (Fig 6B) except for the scores in the hyperactivity/impulsivity subdomain, which did not differ between the two groups. Compared with those of the controls, parents and teachers of EI children were more likely to rate their child as scoring in the clinical range (> 2SD) for a number of individual executive function problems (Table 9). The parent-reported rates of clinically significant problems for planning/organizing in the
total and NSI-free EI cohorts were 27% and 21%, respectively, and for memory the corresponding rates were 17% and 14%. In addition, teachers reported a significantly higher rate of clinically significant problems in the attention and hypoactivity subdomains in both the total and NSI-free EI cohorts compared with the control children (Table 9). The rates of clinically significant problems in the hyperactivity/impulsivity subdomain (> 2SD) did not differ between the groups, according to both the parent and teacher rating. Although reductions in the rates of clinically significant EF problems (inattention, Hypoactivity, planning/organization, and working memory) were noted when the children without significant NSI were analyzed, the statistical conclusions were unaffected (Table 9).

Within the univariate models (ANCOVA), significant differences persisted between EI and control groups in the GECS and in the individual components of EF when adjustments were made for social risk factors, family function, and gender (data not shown). Similar results were obtained in the ANCOVAs of the analogous teacher-FTF scales. According to the parent FTF, family function and gender were associated with the GECS domain, representing only small effects (5% and 4% of the variance, respectively) as compared with the medium effect of the group status (prematurity) (12% of the variance), according to the criteria for effect sizes in ANCOVA. According to the teacher FTF, besides the group status, gender was associated with GECS, in that boys were at higher risk than girls for executive dysfunctions (representing a medium effect accounting for 11% of the variance). These results were not altered when the children without NSI in the two groups were analyzed on the basis of parent and teacher ratings (data not shown). Furthermore, no statistically significant interaction effects were found in any of the ANCOVA models.

3.9. Language skills (study IV)

According to both the parents’ and the teachers’ ratings, the EI cohort scored significantly higher than the control children across the parameters of language skills, indicating an increased risk of language problems in the comprehension, expression, and communicative subdomains of language skills. According to the parent FTF, the mean z scores of the comprehension, expression and communication subdomains were raised by 0.6, 0.65, and 0.38, respectively, compared with the controls (all \( P \text{ values} < .001 \)) (Fig 6A). The reports by teachers followed a similar pattern (Fig 6B). ANCOVA revealed that the significant differences between the EI and control groups in the overall language skills domain and its three subdomains (comprehension, expression, and communication) persisted when adjustments were made for social risk
findings, family function, and gender (data not shown). Similar results were obtained in the ANCOVAs of the teacher reports on FTF language skills. According to the parent report family function was associated with the expressive and communicative subdomains of language skills however, it represented only a minor effect (4% of the variance in each of them) compared with the medium effect (7% of the variance) of group status (EI vs control). In the teacher FTF, none of the explanatory covariates were associated with the overall language skills domain or its 3 subdomains. Furthermore, none of the ANCOVA models showed any significant interaction effects (data not shown).

Most of the items (4 of the 5) in the comprehension subdomain of language skills were significantly more likely to be reported by both parents and teachers of EI children than of control participants, namely “difficulty in understanding explanations and instructions”, “difficulty in perceiving what others say”, “difficulty with abstract concepts” and “tends to misinterpret what is said” (all $P < .005$ by parent or teacher ratings). Parents and teachers of the EI cohort, compared with those of the controls, were significantly more likely to report 2 of the 3 items of communicative language skills, these being “difficulty in keeping on track while describing something”, and “problems in shifting from listening to talking” (all $P < .005$ in parent and teacher ratings). In addition, parents reported the third item of communicative language skills significantly more often in the EI children than in the controls, i.e., “difficulty in telling about situations and experiences” ($P < .005$). In the domain of expressive language skills, only 4 of the 13 items were reported significantly more often in the EI children than in the controls; these were: “difficulty in explaining what she/he wants” “difficulty in speaking fluently without breaks”; “difficulty in speaking whole sentences grammatically correct”, and “difficulty in pronouncing complex words” (all $P$ values < .05). Additionally, the parents of EI children were more likely than those of controls to endorse 2 particular items in expressive language skills, i.e., “rapid and incomprehensible speech at times” and “muddled speech” (all $P$ values <.05).

The parent-reported rates of poor linguistic skills in the clinical range in all 3 parameters (> 2SD above the normative mean) were significantly higher in the EI cohort than in the controls (Table 9). Again, teachers reported a similar rate of poor linguistic skills in the EI and control children. The statistical conclusion regarding the rates of poor linguistic skills did not change either when the groups without NSI were analyzed (Table 9) or when the mainstream school children in the 2 groups were analyzed (data not shown). The majority of the EI children had not clinically significant problems in language skills, either overall or in the individual components (expression, communication, and comprehension).
3.10. Learning Skills (study IV)

The EI and control children who were placed in the mainstream schools (EI, 73; C, 82) were compared regarding the 4 subdomains of learning skills. According to the parent and teacher FTF, the mainstream EI cohort scored significantly higher than the corresponding control children in all subdomains of learning skills, indicating an increased risk of problems in reading/writing, math, general learning, and coping in learning. The mean z scores in the mainstream EI cohort and controls, respectively, were 0.34 vs -0.26, P < .001 for reading/writing; 1.03 vs -0.3, P < .001 for math; 0.56 vs -0.3, P < .001 for general learning; and 0.74 vs -0.37, P < .001 for coping in learning skills. A similar pattern was obtained from the teachers’ reports (Fig. 7). ANCOVA revealed that the difference between the mainstream EI children and controls persisted regarding the overall learning skills and the 4 subdomains (reading/writing, math, general learning, and coping in learning) after adjustments for social risk, family function, and gender. These results did not change when the mainstream children without NSI were analyzed (data not shown).

As shown in Table 10, according to the parent and teacher FTF the mainstream EI children were at increased risk for having clinically significant problems in math (P < .005), general learning (P < .005), and coping in learning (P < .05). The logistic regression analyses showed that the results were not affected by adjustments for socioeconomic risk factors and family function, nor were they altered when the mainstream children without NSI in the two groups were analyzed (data not shown).

![Figure 7. Graph illustrating mean Z scores for learning skill subscales in EI children and controls, obtained from parent –FTF (A) or from teacher –FTF (B). The null line is the Z score for the reference Swedish population in graph A and it represents the Z score for the controls in graph B; * P < .05; **P < .005](image-url)
Multivariate analysis of covariance of learning skills based on parent and teacher reports

MANCOVA of four parent–FTF learning skill subdomains revealed significant multivariate effects of group status (prematurity vs control) ($P < .001$, ES = 18%); GECS ($P < .001$, ES = 66%); and gender ($P < .001$, ES = 16%). As with the parent report, MANCOVA of the teacher-FTF learning skill subdomains revealed significant multivariate effects of prematurity ($P = .003$, ES = 14%), GECS ($P < .001$, ES = 63%), and gender ($P < .001$, ES = 16%) (for detailed data on MANCOVA analyses see paper IV). No interactions emerged in the MANCOVAs of parent or teacher reports, indicating that prematurity, GECS, and gender were independently associated with the multivariate measure of FTF-learning skill subdomains (reading/writing, math, and general learning, and coping in learning).
Table 9. Proportions of Children in each Group scoring in the clinical range (> 2 SD above the mean) in Executive Functions and Language Skills

<table>
<thead>
<tr>
<th></th>
<th>EI</th>
<th>control</th>
<th>Total population</th>
<th>Adjusted OR (95% CI)(^a)</th>
<th>NSI-free (n = 73)</th>
<th>NSI-free (n = 84)</th>
<th>Adjusted OR (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population (n = 83)</td>
<td>Total population (n = 86)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent report (FTF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>EI</td>
<td>control</td>
<td>Total population</td>
<td>Adjusted OR (95% CI)(^a)</td>
<td>NSI-free (n = 73)</td>
<td>NSI-free (n = 84)</td>
<td>Adjusted OR (95% CI)(^b)</td>
</tr>
<tr>
<td>Hyperactivity / impulsivity</td>
<td>12 (14)</td>
<td>5 (6)</td>
<td>2.3 (0.72-7.2)</td>
<td>7 (10)</td>
<td>4 (5)</td>
<td>1.8 (0.48-6.9)</td>
<td></td>
</tr>
<tr>
<td>Hypoactivity</td>
<td>9 (11)</td>
<td>6 (7)</td>
<td>1.5 (0.54-4.5)</td>
<td>7 (10)</td>
<td>5 (6)</td>
<td>1.6 (0.47-5.3)</td>
<td></td>
</tr>
<tr>
<td>Planning / organizing</td>
<td>23 (27)</td>
<td>5 (6)</td>
<td>5.9 (2.1-16.9)(^b)</td>
<td>15 (21)</td>
<td>4 (5)</td>
<td>5.03 (1.6-16.2)(^b)</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>14 (17)</td>
<td>2 (3)</td>
<td>8.6 (1.8-39.7)(^b)</td>
<td>10 (14)</td>
<td>1 (1)</td>
<td>14.2 (1.7-116.2)(^b)</td>
<td></td>
</tr>
<tr>
<td>Language skills, overall</td>
<td>15 (18)</td>
<td>2 (2)</td>
<td>9.2 (2.0-42.1)(^b)</td>
<td>11 (15)</td>
<td>1 (1)</td>
<td>15.6 (1.9-126.8)(^b)</td>
<td></td>
</tr>
<tr>
<td>Comprehension</td>
<td>12 (14)</td>
<td>3 (3)</td>
<td>4.6 (1.2-17.1)(^b)</td>
<td>9 (12)</td>
<td>2 (2)</td>
<td>5.9 (1.2-28.4)(^b)</td>
<td></td>
</tr>
<tr>
<td>Expressive language</td>
<td>14 (17)</td>
<td>3 (3)</td>
<td>5.4 (1.4-20.3)(^b)</td>
<td>9 (12)</td>
<td>2 (2)</td>
<td>5.5 (1.1-27.6)(^b)</td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>15 (18)</td>
<td>2 (2)</td>
<td>8.4 (1.8-39)(^b)</td>
<td>11 (15)</td>
<td>2 (2)</td>
<td>6.9 (1.4-33.5)(^b)</td>
<td></td>
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<tr>
<td>Teacher report (FTF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>15 (18)</td>
<td>4 (5)</td>
<td>4.2 (1.3-13.5)(^b)</td>
<td>12 (16)</td>
<td>3 (4)</td>
<td>5.2 (1.4-19.7)(^b)</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity / impulsivity</td>
<td>8 (10)</td>
<td>3 (4)</td>
<td>2.7 (0.7-10.9)</td>
<td>5 (7)</td>
<td>3 (4)</td>
<td>2.0 (0.5-9.1)</td>
<td></td>
</tr>
<tr>
<td>Hypoactivity</td>
<td>14 (17)</td>
<td>4 (5)</td>
<td>3.8 (1.2-12.2)(^b)</td>
<td>12 (16)</td>
<td>3 (4)</td>
<td>5.1 (1.3-19.1)(^b)</td>
<td></td>
</tr>
<tr>
<td>Planning/ organizing</td>
<td>19 (23)</td>
<td>5 (6)</td>
<td>4.7 (1.6-13.4)(^b)</td>
<td>16 (22)</td>
<td>4 (5)</td>
<td>5.9 (1.8-18.8)(^b)</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>25 (30)</td>
<td>6 (7)</td>
<td>5.5 (2.1-14.5)(^c)</td>
<td>22 (30)</td>
<td>5 (6)</td>
<td>6.6 (2.4-18.8)(^c)</td>
<td></td>
</tr>
<tr>
<td>Language skills, overall</td>
<td>15 (18)</td>
<td>5 (6)</td>
<td>3.4 (1.2-10.1)(^b)</td>
<td>13 (18)</td>
<td>4 (5)</td>
<td>4.4 (1.3-14.4)(^b)</td>
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</tr>
<tr>
<td>Comprehension</td>
<td>14 (17)</td>
<td>5 (6)</td>
<td>3.1 (1.0-9.2)(^b)</td>
<td>12 (16)</td>
<td>4 (5)</td>
<td>3.9 (1.18-12.8)(^b)</td>
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</tr>
<tr>
<td>Expressive language</td>
<td>14 (17)</td>
<td>5 (6)</td>
<td>3.3 (1.1-10.1)(^b)</td>
<td>12 (16)</td>
<td>4 (5)</td>
<td>4.4 (1.3-14.9)(^b)</td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>13 (16)</td>
<td>5 (6)</td>
<td>2.9 (0.96-8.7)</td>
<td>11 (15)</td>
<td>4 (5)</td>
<td>3.5 (1.1-11.8)(^b)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) of children unless otherwise stated. Data are obtained from the FTF Parent and Teacher questionnaires\(^{21}\). \(^{a}\)Derived from the logistic regression analyses adjusted for gender, social risk, and family function; OR = odds ratio; CI = confidence interval; \(^{b}\)P < .05; \(^{c}\)P < .001
Table 10. Proportion of Mainstream Children in each Group Scoring in the Clinical Range (> 2 SD) in Learning Skills

<table>
<thead>
<tr>
<th></th>
<th>EI</th>
<th>Control</th>
<th>Adjusted OR (95% CI)(^a)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>(n = 73)</td>
<td>(n = 82)</td>
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**Parent report (FTF)**
- Reading/ writing: 7 (10) vs 2 (2), OR 4.1 (0.8-20.9), \(P = .085\)
- Math\(^b\): 17 (23) vs 0, na, \(P < .001\)
- General learning: 11 (15) vs 1 (1), OR 13.2 (1.6-106.5), \(P = .016\)
- Coping in learning: 10 (14) vs 1 (1), OR 10.9 (1.3-90.9), \(P = .027\)

**Teacher report (FTF)**
- Reading/ writing: 10 (14) vs 4 (5), OR 3.4 (0.9-11.4), \(P = .052\)
- Math: 19 (26) vs 2 (2), OR 15.1 (3.3-68.6), \(P < .001\)
- General learning: 18 (25) vs 5 (6), OR 5.8 (2.0-16.8), \(P = .001\)
- Coping in learning: 15 (21) vs 2 (2), OR 11.2 (2.4-51.7), \(P = .002\)

Values are \(n\) (%), unless otherwise stated; na, not appropriate for calculation, i.e., wide confidence intervals for exponents. Data are adapted from the learning skills domains of parent and teacher FTF\(^{211}\). \(^a\)Derived from the logistic regression analyses adjusted for gender, social risk, and family function; \(^b\)P value by Fisher’s exact test for mainstream EI children (< 26 weeks’ gestation) vs control.
4. Discussion

This thesis addresses the impact of extreme prematurity on subsequent childhood health and well-being seen comprehensively as the ability to participate in developmentally appropriate physical, behavioral and social tasks, the school achievement of the children, and their need for special health care as compared with normal peers. To our knowledge this is the first study concerning school age outcomes in children born in the 1990s at extremely low gestational ages (< 26 weeks).

4.1. Strengths of the Study

This prospective follow-up study is based on a combination of the parents’, teachers’ and children’s perception of the children’s health, and information obtained from school and health records and records from other specialist health services. We have used validated yet relatively inexpensive methods of assessing outcomes, with a focus on the views of parents, teachers, and the children themselves regarding the functional level and integration of the children at school, and their family and social life. The findings probably represent the true state of the child’s overall functioning and health care needs. Additional notable features that strengthen the validity of our study are the national composition of the cohort, the prospective follow-up, a high follow-up rate of 97%, and inclusion of a matched group of children who were born in the same hospital and nearest in time to the EI children. The issue of selection of an appropriate comparison group has not been fully resolved. Many studies have used classroom control groups from mainstream schools to represent a relatively healthy group. The nature of such control groups may, however, overestimate the differences in preterm children, especially in the frequency of cognitive deficits and school difficulties. Further strengths of our study are that we have used well validated instruments to measure a wide range of behavioral problems and impairments in adaptive functioning. The Achenbach CBCL and TRF have been used for both clinical and research purposes for many years across different cultures. The FTF-parent questionnaire has been validated in Scandinavian countries. This questionnaire has been used both in clinical screening and for research purposes for the last few years in Sweden, Finland, and other Scandinavian countries. A significant correlation has been reported between the parent-FTF domains and the corresponding domains in the CBCL. The five FTF domains that assess motor skills, executive functions, perception, memory, and language skills have been shown to have a significant correlation with the corresponding domains in NEPSY, a neuropsychological assessment instrument. We obtained reports on the children’s school functioning, behavior, and social competence from
teachers and parents and from the children themselves. For children at risk of having developmental and educational problems, it might be especially crucial to obtain ratings from different adults in different settings, for example school and home. Each rater can provide important and different information on a child’s behavior, as perceptions and interpretations of behavior vary, and the ratings may be a valid reflection of the child’s behavior under different contexts.\textsuperscript{164,237,238}

### 4.2. Limitations

One of the main weaknesses of the study is a lack of an in-depth psychiatric interview, which would have allowed categorization of DSM diagnoses of psychopathology. Psychometric testing would have been useful in understanding the pathophysiological causes related to specific defects, and in identifying patterns of strengths and weaknesses of the children. However, a particular aim of this study was to use relatively inexpensive yet validated ways of assessing outcomes with a focus on the views of parents, teachers and the children themselves, and on the children’s functional level and special health care needs in day-to-day life. Another limitation is the relatively small size of our study population. Furthermore, the behavioral data were not obtained by direct observations of the children. But on the other hand no satisfactory standardized observational methods are available for assessment of behavioral/emotional problems, and also it would have been logistically difficult to carry out such observational assessments in our study children, who live in places scattered all over Sweden. We consider, however, that our methods with a multi-informant assessment approach in different situations in the children’s daily life were sufficiently reliable and valid to measure the behavioral/emotional profiles of the study participants.

Our outcome data reflect perinatal practices of more than a decade ago and the results may not be relevant to the preterm babies born at present. The majority of our EI children were not beneficiaries of the more recent innovations of neonatal intensive care, such as administration of ANCS to the mothers and surfactant replacement in the infants. The management practices have now changed considerably. Currently most mothers delivering extremely immature babies receive antenatal steroids, and surfactant is administered to most of the EI infants in Sweden and elsewhere.\textsuperscript{10,24,25} However, it should be noted that 92% of our EI infants were cared for in well-developed regionalized tertiary perinatal care facilities. Our study probably provides the most accurate and up-to-date data available on the likely rates of an adverse long-term outcome until superseded by more recent information.
4.3. Chronic conditions, disabilities and special health care needs

Information on functional outcomes at school age among children born extremely preterm in the 1990s is sparse. With the exception of one study in the USA, the outcomes of extremely preterm children born in the 1990s and studied at school age pertain mainly to behavioral and neurodevelopmental disabilities. Our knowledge is poor concerning other aspects of health such as daily functioning and special health care needs. In conformity with our findings, these studies report highly significant differences between children born at extremely preterm gestational ages and control populations. The rate of major disability (one or more) in our EI cohort was significantly higher than that in the control participants. Few investigators have reported rates of sensorineural disabilities in regional or national cohorts of very preterm infants born in the 1990s. Doyle et al found that 29% (22 of 77) of survivors who were born at 23-25 weeks gestation had a major disability, a rate similar to that of 21% (18/86) in our study. More recently Marlow et al (EPICure study) reported that 22% of such survivors (53 of 241) had a severe disability at 6 years of age, a rate again similar to the rate of major disability in our study. Direct comparisons are rendered difficult, however, by the fact that the disabilities are not defined identically in all studies and that the ages at assessment vary. Another important limitation in comparing our data with those in other studies, as mentioned earlier, is the lack of psychometric testing on all children in our EI cohort. Instead we used the need for full-time special education as a measure of significant cognitive deficits.

Asthma played a significant role in determining special health care needs in our EI children. Similar findings have been reported by others, but in those studies more mature children with a higher median gestational age were assessed. Studies on the respiratory outcome in school-age children born extremely preterm in the postsurfactant era have begun to appear. Doyle et al recently reported the respiratory outcome at 8-9 years of age in a large cohort of ELBW or EPT, born in the 1990s. They found that abnormalities in respiratory function in ELBW/EPT cohort compared with normal birth weight (NBW) controls, described in the presurfactant era, persisted in the 1990s, and that treatment with surfactant was not associated with any substantial differences in respiratory function. Similar results were reported from a small randomized surfactant trial in children at the ages of 6-7 years. However, the respiratory outcome of EI children at school age and beyond, in the post-surfactant era with better techniques of ventilation and improvement in nutritional strategies, particularly since the emergence of “new BPD” remains to be seen.
We administered QuICCC to the parents with the aim of identifying children with special health care needs. The use of the non-categorical approach (independent of diagnosis) is important when studying the outcomes in survivors of neonatal intensive care, as it allows assessment of the impact of multiple chronic morbidities on day-to-day [functioning and evaluation of special health] care needs. Children identified in QuICCC fit the definition of children with health care needs (have, or are at risk of having, physical, developmental, behavioral or emotional conditions, requiring health care services of a type or amount beyond that required by children in general). QuICCC comprises most of the elements of the World Health Organization’s international classification of functioning and disability, which includes limitations in body/structure, personal activity, participation in society and environmental facilitation.\(^{239-241}\)

Few studies have addressed the functional limitations and special health care needs of preterm or ELBW children.\(^{33,122,136,137}\) In conformity with those studies we found that compared with the control participants our EI children as a group had a significantly higher prevalence of functional limitations such as mental or emotional delay, visual difficulties, restriction in daily activities, and reduced self-care abilities. Our findings regarding functional limitations and special health care needs in the EI cohort are comparable to the results of a recent study by Hack et al\(^{33}\) of an ELBW cohort born in the mid 1990s. They used the same instrument as in our study (QuICCC). Very similar observations were made by the same group in an earlier study,\(^{137}\) using the same QuICCC instrument, concerning chronic conditions in 11-year-old children born in the mid 1980s with birth weights below 750 g. In our EI cohort the prevalence of a chronic condition in any of the domains of QuICCC was 81% in the total population and 80% in the subgroup free from neurosensory impairment (Fig 2). Again, these findings are comparable to those in the study by Hack et al, who reported rates of 76% and 72% in their total ELBW cohort and their cohort without neurosensory impairment, respectively.\(^{33}\)

In our control children the rate of chronic conditions identified by QuICCC was slightly higher than the 15-30 % rate found in other studies either in the USA with use of the same instrument\(^{215,242,243}\) or in Scandinavian countries with use of different methods and definitions.\(^{72,73,76}\) One plausible reason for the difference could be the inclusion, in our study, of children with borderline consequences of a chronic condition such as need for a special diet, prescription of glasses for correction of vision, or allergy medication, and life-threatening allergy reactions. Moreover, during the past 20 years rates of disabilities have continued to rise, as reported from the majority of studies in Scandinavian countries\(^{72,73,76}\) and elsewhere.\(^{75}\) All these factors could have contributed to the high rates of chronic conditions in our control population.
It is notable that although the rates of functional limitations and special needs in the EI cohort were significantly higher than those in the control group, very few children had impairments so severe as to prevent them from carrying out their major daily activities such as eating, bathing and dressing, and from school attendance. This finding is in line with those in other two studies that have addressed the health status and special health care needs in school-age ELBW children.\textsuperscript{122,137} It has been demonstrated that although adolescents born at extremely low gestational ages accurately characterize themselves as having more health problems and learning difficulties than their normal birth weight peers, their self-rating of their health-related quality of life is the same or even higher than that of such peers.\textsuperscript{244,245}

4.4. Growth attainment in the first 11 years of life and analyses of correlates

Our EI children who were born at the limit of viability attained poor growth in their postnatal period and early childhood. This was followed by catch-up growth up to the age of 11 years, but nevertheless the children remained smaller than their term-born peers. With regard to growth, this is the first study (based on gestational age) of long-term growth outcomes in children born extremely immature in the 1990s. We have presented our data on the basis of gestational age, thereby avoiding the confounding bias associated with reporting outcomes in terms of birth weight categories.\textsuperscript{123} The data are presented in Z scores which provide a more sensitive estimate of deviation of growth than the use of percentiles or cut-off levels for growth deficiency.\textsuperscript{246,247} One strength of our study is the large number of measurements at various time points throughout the study period in both EI and control participants. Since the measurements were not made at exact ages, we performed a polynomial regression analysis in order to reduce the fluctuation in sample size over various ages,\textsuperscript{217} and the interpolated values could be used for predefined ages.

Our results reveal that EI children have growth failure in early extrauterine life in comparison with the normal intrauterine growth during the third trimester. The relative decline in growth parameters continued up to 3 months of corrected age. Growth data are available from a report on a large population-based EPICure study of 283 infants born at less than 26 weeks gestation in 1995 in the United Kingdom.\textsuperscript{129} At EDD, their mean Z scores for weight, height and HC were -1.72, -2.49, and -0.86, respectively, compared with -1.6, -1.8, and -1.3 at EDD in our study. These data reveal the similar distributions of growth failure in weight, height and HC in early extrauterine life. High rates of growth failure have also been observed in a
recent, large retrospective study from the United States, concerning growth outcomes at discharge in 24,317 infants who were born between 23 and 34 weeks of gestation in 1997-2001.

At 24 months of corrected age, the rates of subnormal growth regarding weight, height, and head circumference in our study were 20%, 13% and 17%, respectively, compared with 13%, 25% and 38% in the EPICure study at 30 months of corrected age. Thus the findings in our study were similar for weight, but the proportions of infants with subnormal length and head sizes were considerably higher in the EPICure study. A possible explanation for the lower disability rate in our cohort of EI children could be the better results for growth of head circumference and height. However, our relatively small sample size limits the comparison of data. Others have also reported increased rates of growth deficiencies in early childhood among VLBW or ELBW children.

At age 11 years, the EI children were lighter and shorter than the control participants and the difference was more marked in boys than in girls. It is worthy of note that, a majority of these children (> 90%) were within 2SD of the reference mean for age. Our EI cohort displayed fast catch-up growth in weight and length from 3 months of corrected age to 3 years, after which there was a period of late catch-up which continued up to the present assessment. Catch-up growth in weight was more rapid than the increase in height Z scores. A number of other investigators have reported late catch-up growth in weight and height of ELBW or VLBW children in their early teens and in adolescence. Moreover, In all of these aforementioned studies, preterm children had significantly lower Z scores for all anthropometric measures during adolescence compared to their normal birth weight peers, and in some of these cohorts where outcomes have been reported at a young adult age, the differences in growth parameters continued to remain significant.

At the present assessment, 15% of our EI cohort would be considered overweight according to age- and gender-specific cut-offs for BMI. Moreover, there were significantly larger childhood gains of BMI in EI children than in the control participants. There are reports that low birth weight in combination with accelerated weight gain during childhood is associated with an increased risk of cardiovascular disease in adult life. Those studies did not, however, specifically address children born extremely preterm, a group with a dramatic increase in survival in the past decade, who exhibit substantial growth failure in early infancy. There is some evidence suggesting that the risk of cardiovascular disease is more strongly related to the speed of childhood
gain in BMI than to the BMI attained at any particular age.\textsuperscript{252} Thus it is reasonable to speculate that the pronounced growth restriction in the postnatal period and in early infancy, with an accelerated catch-up in childhood, may put these immature babies at risk of metabolic and cardiovascular morbidity in later life, a concern which is shared by others.\textsuperscript{249,250}

Our EI girls showed more pronounced catch-up growth in weight than EI boys, which is compatible with the greater change in BMI in EI girls than in EI boys. Furthermore, we observed a trend toward an increased prevalence of overweight in the EI girls compared to the EI boys at different ages. A greater increase in BMI in preterm girls at adolescence\textsuperscript{122} and in young adult VLBW girls\textsuperscript{249} has also been reported. As speculated by others, the sex differences in growth probably have multifactorial causes. The greater susceptibility of VLBW boys to neonatal complications and the length of neonatal hospital stay were similar in the EI boys and EI girls. However, EI girls had lower rates of chronic conditions than EI boys (33\% vs. 51\%; \textit{P} = 0.11), but the difference was not significant.

At the present assessment, the mean head circumference Z scores in EI boys and girls were 1.3 and 0.89 SD lower than those in their contemporary control participants, respectively. These reductions amount to 2 cm and 1.3 cm in EI boys and EI girls, respectively. In contrast to the increase in weight and height, our EI cohort did not show any catch-up growth in HC after the first 6 months of life. Our findings are in agreement with other results\textsuperscript{184,253,254} strengthening the evidence that the HC catch-up growth mostly occurs during the first year of life. Furthermore, 21\% of the EI children had a subnormal HC at 3 years of corrected age, and in a similar proportion (22\%) HC remained subnormal at 11 years of age. Similar reductions in head growth attainment have been reported from studies of adolescent growth outcomes in VLBW or ELBW children.\textsuperscript{118,121,122,134} As in the studies by Peralta-Carcelen et al\textsuperscript{121} and Peterson et al,\textsuperscript{255} we found that HC was significantly lower in EI children who were born SGA than in those who were AGA. Subnormal head size has been associated with poor developmental outcomes in preterm children.\textsuperscript{134,184,255-257}

Although the EI children had significantly lower height z scores compared to their mid-parental height by age 11 (mean difference 0.57 SD), a majority of them (> 90\%) were within 2 SD of their mean mid-parental height. The proportion of children with subnormal height decreased from 15\% to 6\% within a period of 2 years, i.e., from 9 to 11 years of age. It is likely that some of our EI children had entered puberty. However, we did not collect
Discussion

Data on pubertal development, and bone ages were not measured. Some investigators have found no differences in sexual maturation rates by gender in children who were ELBW\textsuperscript{118,121} or VLBW,\textsuperscript{134} in comparison with term control children. A few studies have shown an advanced bone age in VLBW\textsuperscript{134} and ELBW adolescents\textsuperscript{121} with reference to their chronological age and it was speculated that this may contribute to a shorter height in adulthood in preterm children.

\textit{Multivariate analyses} revealed that the differences in height and head size between EI and control participants persisted when adjustments were made for other explanatory variables. Of all the tested variables, mid-parental height and group status were the only ones to predict height at age 11 years, whereas the major correlate of HC was group status. In the subanalysis of EI children only, parental height was the major determinant of height, emphasizing the strong genetic influence on growth, and birth weight for age correlated with height but the association was weak. Head size was influenced by the birth weight scores in EI children. In fact in the majority of the EI children (83\%) who were born SGA the head size remained subnormal at 11 years of age. However, our study does not provide useful data on long-term growth after intrauterine growth impairment, since only 7\% of the EI children were SGA at birth. A number of studies have identified significant correlates of growth and catch-up among VLBW or ELBW infants in childhood and adolescence. Intrauterine growth restriction has a negative effect on the growth and catch-up during childhood and into adolescence.\textsuperscript{117,121,127,128} Neonatal complications have been shown to bear a negative relation to growth during early infancy and childhood,\textsuperscript{129-131} and parental size is positively related to growth parameters in childhood and adolescence.\textsuperscript{117,120-122,127,132}

The negative effect of long courses of PNS on linear growth has become evident from the published reports on this subject.\textsuperscript{129,133} Administration of PNS for treatment of chronic lung disease of prematurity was not considered to be an important predictor of the long-term outcome with regard to growth and neurosensory impairment in the early 1990s, and information on PNS was therefore not collected prospectively in our longitudinal investigation of preterm infants born from 1990 through 1992. Furthermore, 92\% of our immature cohorts (survivors) were born in the seven Swedish tertiary perinatal care facilities of Sweden. In my personal communication with the co-authors of the studies on the neonatal and 3-year follow-up of our EI cohort,\textsuperscript{17,211} it was brought to my knowledge that PNS treatment of chronic lung disease in preterm babies was not a common practice in Sweden in the beginning of the 1990s. However, we do not have the exact information on this matter.
Growth outcomes reported for our EI children born in early 1990s may not be relevant for current survivors, in view of the significant advances in intensive care of extremely preterm babies in the past 15 years, which have included greater awareness to ensure optimal nutrition in the neonatal period and during infancy. At present, we do not really know whether the children born extremely preterm are expected to follow growth trajectories similar to those of their full term peers, but the severe growth failure exhibited by the children of our EI cohort in their early postnatal life is unequivocal. We believe that by optimizing nutrition in the neonatal period and in infancy, health and growth outcomes may be improved.

4.5. Mental health, Emotional well-being, and Environment

According to the parents’ and teachers’ ratings, the EI children had significantly higher problem scores in internalizing behaviors (anxiety/depression, withdrawn and somatic problems), and attention, social and thought problems. The children’s self-report also pointed to an increased trend toward depression symptoms in the EI cohort. No differences in externalizing problems were indicated by either the parent or teacher report.

Reports on prematurity-related behavioral outcomes during adolescence in children born before the 1990s disclosed a wide array of emotional problems and behavioral disturbances. Attention-deficit/ hyperactivity disorder, as well as internalizing, externalizing, social, and thought problems have been linked with prematurity. In a meta-analysis, 227 studies reporting behavioral and cognitive data published between 1980 and 2001 were reviewed. Among 16 of these studies, presenting behavioral data that were considered worthy of review and involving children born before the 1990s, 69% revealed a significant increase in internalizing problems, 75% a significant increase in externalizing problems, and 67% higher rates of attention problems. In a recent and the only population-based study on neurobehavioral outcomes of 8-year-old ELBW children who were born in the 1990s, these children were found to have attentional difficulties and internalizing problems and fewer adaptive skills compared to the normal birth weight cohort. In agreement with the results of the aforementioned study, in our study both the parents and teachers reported increased internalizing and attention difficulties and significantly lower scores for adaptive functioning in EI children compared to their controls.
Discussion

In an international study of 408 ELBW children aged 8-10 years from four countries, behavioral problems were compared in a cross-cultural perspective; behavioral data for all the survivors from four large prospective studies of preterm children were obtained with the same instrument, namely Achenbach’s CBCL. It was found that despite cross-cultural differences, some of the behavioral problems and characteristics were strikingly similar in all the cohorts; for example the mean scores of social, thought, and attention difficulty scales were 0.5 -1.2 standard deviations higher than their country-specific norms or controls. Further, in none of these cohorts were there any significant differences in the aggressive or delinquent behaviors between the ELBW children and their controls or country-specific norms/reference population. These findings are strikingly similar to our results (Fig 8). Moreover, similar ratings were reported by teachers (TRF) in our EI children. Furthermore, our EI children did not display externalizing (aggressive or delinquent) behavior problems as judged by the parent or teacher report. Others have reported an increase in attentional/hyperactivity problems but not in conduct disorder or aggressive behaviors in ELBW or VLBW children investigated at 8-12 years of age, in adolescence, or at a young adult age. It is particularly surprising that these children, despite having many risk factors for externalizing and risk-taking behavior (ADHD problems, social problems, and learning difficulties) do not, according to teachers or parents, have high rates of conduct disorder. Furthermore, these results are not in agreement with those of

Figure 8. A comparison of problem scales of parent reports (CBCL) in ELBW or EI children from the five population cohorts of five countries; the null line represents the country-specific reference group. Statistically significant difference between each ELBW cohort and its country-specific norm.
the follow-up studies of children with ADHD problems in the general pediatric population that have shown high rates of continued psychopathology and comorbidity of conduct and oppositional defiant disorders. It has been postulated that the low risk-taking may be attributable to increased parental monitoring and protection. An increased risk of anxious/ depressed and withdrawn behaviors as seen in our EI children might possibly lead to behavioral inhibition as well as to decreased antisocial behaviors. There is some evidence that the ADHD symptoms reported among VLBW children are more of the inattention than of the hyperactivity type and are less associated with comorbidity and conduct disorder. This might probably also explain why ADHD symptoms in preterm children do not seem to have negative implications for the persistence of major sequelae into adulthood. However, it should be noted that the ADHD profile seen in our EI cohort and in many other VLBW or ELBW populations does not represent a clinical diagnosis of ADHD.

We found an increase in anxious/depressed and withdrawn symptoms in EI children as based on parent and teacher reports, and a significant increase in a trend toward depression symptoms according to the children’s self-report. Increased rates of depression, anxiety, and overall internalizing behaviors, which include shy and withdrawn behaviors have been reported among VLBW or ELBW children. In our EI cohort more than one fourth had poor motor skills, one fourth were restricted in their activities because of one or more handicaps and almost one half had moderate to severe learning difficulties. These rates did not alter when children without NSI were analyzed. Like others, we believe that these difficulties might have imposed upon our EI children functional limitations in social situations, leading to more cautious, even anxious and withdrawn behaviors during interactions with peers. However, in-depth psychiatric interviews and direct behavioral observations are needed to understand the extent to which these limitations create a handicap that leads these children to withdraw from their social group. Our findings are similar to those of others who reported that children with chronic medical illnesses were at increased risk for emotional problems, particularly depression/anxiety and peer conflict/social withdrawal. Furthermore, in our study differences in behavioral problems persisted whether or not the children with NSIs were excluded, as has also been documented by others.

Sociodemographic and environmental factors also significantly influence the long-term outcome and quality of life of children born preterm. McCormick et al pointed out the greater importance of environmental factors compared to the birth status and proposed interventions aimed at reducing the environmental risks. In our study, boys showed a significantly increased risk for
attention problems. Family function, social risk, and presence of a chronic medical condition predicted behavioral adjustment in our study population. Although we did not measure exactly the same constructs, our findings are similar to those of Levi-Schiff, Saigal et al, and Klebanov et al with respect to the importance of family environment and social risk in predicting the behavioral adjustment of preterm children. Furthermore, in accordance with previous studies, we did not find any interactions between group status (EI and controls) and other covariates, indicating that the correlates of behavioral outcome did not differ between our EI children and the controls.

4.6. School performance, adaptive functioning

More than half of our EI cohort were experiencing school problems. However, a notable observation was that 85% of the EI children were attending mainstream schools and that the majority of them were not having major adjustment difficulties. Despite fewer adaptive skills in our EI cohort, these children did not differ from the controls in respect to being happy and being positively adjusted in their day-to-day life. According to the parent report, the presence of a chronic medical condition was associated with poor school performance. However, it represented only a small effect (3 %) compared with the large effect (16%) of extreme prematurity. No other environmental variables were associated with the school problems, according to both parent and teacher reports. ADHD problems were a significant predictor of school difficulties as reported by parents and teachers. Our findings are in agreement with previous reports of a higher rate of school failure and of grade retentions in ELBW teens compared to controls. Furthermore, our results are similar to those in a number of other reports that demonstrate a significant association between ADHD and poor academic performance, high rates of school failures including lower grades at school, and receiving full-time special education. Our EI children were seen by their parents as being less well-adjusted in extracurricular activities, as judged from parent reports. These differences remained when the children with NSIs were excluded from the analysis, suggesting that these findings could not be explained on the basis of more disabled EI children who were unable to participate. Others have reported a similar finding of poorer social adjustment, mainly involving social functioning as judged by social attainments and global evaluations of competence, especially in activities such as sports. However, no difference was found between the groups regarding the question of having few friends or in teacher and peer relationships, and more than two thirds (76%) of our EI cohort were participating in coached sports.
4.7. Executive Functions

Executive function is a broad term that refers to an assemblage of higher order cognitive abilities such as strategy use, cognitive flexibility, and inhibition, sequencing and monitoring of thoughts and behavior. Attention and working memory are inextricably entwined with these functions. Executive abilities are important for cognitive and adaptive functions. Our knowledge of the prevalence, nature, and severity of executive dysfunctions in school-age children who were born extremely preterm is sparse.

In our population-based investigation, relying on parents and teachers’ ratings, the EI children displayed significant EDF in areas such as attention and impulse control, hypoactivity or initiation of activity, planning/organizing, and working memory. Recently, Anderson et al. reported executive dysfunctions in a large cohort of ELBW children when compared with normal birth weight controls. ELBW children were shown to have more problem scores on the initiation, working memory, planning/organizing, and monitoring subscales – suggesting difficulties in metacognition. Problems with behavioral regulation were not as pronounced in their ELBW or preterm cohort. Furthermore, they showed that ELBW children in general, compared with normal birth controls, were two to three times more likely to have trouble in starting activities, displaying flexibility in generating ideas and strategies for problem solving, holding information in short-term (working) memory, planning a sequence of action in advance, and organizing information. They also found that children born at 23 to 25 weeks gestation had more problems than those born at 26 to 27 weeks. In a very recent study, Taylor et al. reported outcome on neuropsychological skills including EF, adaptive functioning and achievement in a cohort of 204 ELBW children born from 1992 to 1995 at 8 years of age. They found that these children had worse outcome than the NBW controls on all measures. Furthermore, within the ELBW group lower scores on EF and memory were related to BW < 750 g, cranial ultrasound abnormality, PNS therapy and NEC. Harvey et al. reported that in comparison with controls, children with ELBW were at risk for deficits in executive behaviors including planning, sequencing, and inhibition, which could have implications for later learning. They also found limited correlations between tests of executive functions and previous IQ tests in children with ELBW, and none in the control group. Furthermore, they reported that the poor EF performance was associated with degree of prematurity and chronic lung disease. Although we have not used same methods and have not measured the same constructs, our results are consistent with those of aforementioned studies or of a number of other studies showing impairments across a range of executive functions including planning ability, impulse control, working memory, spatial organization and mental flexibility, or with the findings by other investigators.
who have reported attention outcomes in population of preterm infants.\textsuperscript{32,163,167} However in all of these studies except two,\textsuperscript{190,274} the investigated children were more mature at birth and born about 10 years earlier than our cohort.

The magnitude of the mean differences between the EI and control cohorts averaged 0.66 SD (95\% CI 0.50-0.82) and 0.82 SD (95\% CI 0.33-1.31) for the executive function subdomains, according to the parent- and teacher- FTF, respectively (Fig 6 A and B). Significantly more EI children than controls displayed clinically significant problems in planning/organizing and working memory domains, according to both parent and teacher reports. In addition, as calculated from the teachers’ ratings, significantly more EI children had clinically significant problems in the inattention subdomain. However, the proportions of EI children who displayed clinically significant problems in the individual components of EF were relatively small (10-30\%). We can reasonably assume that our EI children were also at greater risk for “low virulent” or subtle executive dysfunctional problems that affect their learning ability and educational progress (see later discussion). What is more worrisome is that the children who exhibit mild problems and who do not display more clinically significant problems in hyperactivity/impulsivity than their controls, are less likely to arouse parental or teachers’ concerns, to be referred for assessment and to receive specialist assistance at the appropriate time.

We have recently reported an increased prevalence of poor motor skills, poor visual perception, poor adaptive functioning at school, and poor academic performance in our EI cohort compared with their control participants at 11 years of age.\textsuperscript{267} We also found that compared with their controls our EI cohort had a significantly increased risk of having emotional/behavioral problems, including social, thought, and attention problems.\textsuperscript{277} These differences were significant whether or not children with NSI were excluded. Thus, in consistency with the findings in a number of previous neuropsychological studies, our EI cohort was at risk for impairment across a range of neuropsychological outcomes,\textsuperscript{104,160,175,278-280} including EDF.\textsuperscript{190-194,274} It is not known whether EDF in our EI cohort is a cause or effect of impairments in other neuropsychological faculties. Studies with neuroimaging of the brain in preterm children should elucidate the issue of whether EDF in our EI children is the primary complication or is secondary to other neuropsychological impairments.
4.8. Language skills

There is very little information about the linguistic and speech abilities in school-age children who were born extremely preterm in the 1990s. In view of the fact that psychologists, psychiatrists and mental health clinicians have little training in speech and language impairments, the important role of these functions in academic, social and vocational difficulties may often be overlooked. In our study, according to both teachers´ and parents´ ratings, EL children were at increased risk for difficulties in following complex instructions, abstract concepts, language processing (difficulty perceiving what others say and misinterpreting what is said), and in reasoning, and had muddled speech. They were also at increased risk for difficulties in conversational and communicative language skills, such as keeping on track when narrating something and conversational difficulties, e.g., problems with shifting from listening to talking. Our findings are in agreement with a number of reports on deficiencies in language skills in preterm children, such as understanding of syntax, abstract verbal skills, verb production, following instructions, and language processing and reasoning. However, as reported by others, vocabulary and articulatory defects such as auditory discrimination and imitation of articulatory patterns did not differ significantly between the groups. A few studies on functional magnetic resonance imaging and event-related potentials have indicated that there could be actual differences in the way auditory and language potentials are carried out in those born prematurely. Executive function may mediate strategies for verbal memory and semantic clustering, and speech and language disabilities are often associated with hearing and cognitive disabilities. In our correlation analyses (data not shown), we found that problems in comprehensive and communicative language skills were strongly correlated to deficits in working memory, according to both parent and teacher ratings. This finding is in line with other results showing that more subtle language-based problems are related to the neuropsychological substrate such as working memory in preterm children. It may reasonably be assumed that children with moderately severe difficulty in using language and in understanding what others say to them are more likely to have significant behavioral problems, and are therefore likely to have poorer social skills. Communicative problems may thus contribute to failure in school or at work.
4.9. Learning skills

We also examined the relationship between extreme immaturity and learning skills at this assessment (11 years of age). In MANCOVAs, the multivariate general linear models, we controlled for important explanatory covariates such as social risk factors, family function, GECS, and gender. The key findings based on both teacher and parent ratings were as follows: 1) Group status (EI vs control) was associated with an increased risk for poor learning skills; 2) Compared with the control participants, the EI children were at increased risk for impairments in all the four measures/subdomains of learning skills, i.e., reading/writing, math, general learning, and coping in learning; 3) GECS was strongly associated with learning skills; and 4) boys, compared with girls, had significantly poorer learning skills across the four learning skill measures. Although being extremely immature or being a male was independently associated with an increased risk for problems in the learning skills with large effect sizes, GECS, which is a composite measure of executive function, represented a much larger effect size, explaining 66% and 63% of the variance according to the parent and teacher ratings, respectively. Furthermore, a significantly higher proportion of mainstream EI children than of children in the control group were exhibiting impairments in the clinical range (> 2SD) in math, general learning, and coping in learning. The highest rates of clinical problems according to the parent and teacher ratings were identified in math (23% and 26%) and general learning (15% and 25%), respectively. EI children in our study performed particularly poorly in math, with a mean Z score above 1 SD (both teacher and parent ratings). These differences were not only statistically significant but also clinically relevant. Difficulties in math have been reported from several recent investigations and were independent of IQ scores. However, it is noteworthy that many of the mainstream EI children in our study (74-90%) did not have severe clinical impairments in learning skills.

Our analyses generally failed to indicate moderating influences of background and family factors on the studied effects of extreme prematurity. The two exceptions were that group differences in GECS (a composite measure of executive function) and in expressive and communicative language skills were more pronounced in children from families with high family function scores, an indication of risk for family dysfunction. However, these executive and non-executive outcomes were affected to a minor extent by family function. One possible explanation for this, as suggested by others, is that children at higher neonatal risk are less able to benefit from an environmental advantage. Another possibility is that the negative effects of extreme prematurity obscure or override the more subtle influences of the home environment; or
alternatively, that the effect of neonatal risk is smaller in the presence of greater environmental risk factors.\textsuperscript{287} Previous studies, including ours, have shown that more advantaged family environments can attenuate some of the adverse behavioral and developmental consequences of low birth weight.\textsuperscript{277,289-291} It may reasonably be assumed from these results that the observed degree of effect of the environment may depend on the type of outcome assessed. Furthermore, our results are in good accordance with some earlier reports suggesting that preterm girls perform consistently better than preterm boys.\textsuperscript{30,85,199} The lower achievement scores of boys compared to girls in the normal birth weight group has been reported.\textsuperscript{292} This may suggest that the factors other than male vulnerability to extreme prematurity or ELBW may contribute to the sex differences.

Finally the potential combination of learning disorders, low-average IQs, and other neuropsychological deficits found at school-age place children born extremely immature at a significant disadvantage.
Conclusions

5. Conclusions

In this long-term, prospective, longitudinal, case-controlled national follow up investigation of children who were born extremely immature (EI; < 26 weeks’ gestation) at the threshold of viability, we have shown the following:

1) These children had significantly greater health problems and special health care needs which would require continued attention through the school health services.

2) EI children attained poor growth in their postnatal period and early childhood. This was followed by catch-up growth up to the age of 11 years, but nevertheless the children remained smaller than their term-born peers.

3) EI children, in particular EI boys, were less well adjusted to the school environment, with poorer school performance and learning problems. More than twice as many boys as girls had school difficulties.

4) EI children had an increased risk for mental health problems, particularly attention, social, and anxiety/depression difficulties. Family dysfunction, gender, and presence of a chronic medical illness were associated with some of the behavioral problems. Differences in behavioral problems persisted even in non-impaired EI children.

5) EI children had a significantly increased risk for executive dysfunction in most of the areas assessed (Attention, Initiation of activity, Planning/organizing, and Working memory). These children also showed an increased risk for deficient skills in certain language tasks and learning skills (reading/writing, math, coping in learning, and general learning). Executive dysfunctions and male gender were associated with poor learning skills in these children.

6) Although biological immaturity is associated with an increased risk for a substantial number of behavioral/emotional problems, improvement of the modifiable environmental factors will benefit the outcome in EI children.
Conclusions

On the positive side

1. Very few EI children were impaired to such an extent as not to be able to perform ADL (activities in daily life).

2. In terms of growth, the majority of our EI children displayed good catch-up in their late childhood and were within 2 SD of their mid-parental height at 11 years of age.

3. Despite having an increased risk for mental health problems, executive dysfunctions and school difficulties, 85% of the EI children were in the mainstream schools and the majority of them did not have any major adjustment problems. EI children did not exhibit out-acting behaviors to a greater extent than their controls. The absence of externalizing behaviors (anti-social problems) would probably imply a good prognosis.
6. Implications

We, like many others believe that research into therapies that prevent neonatal complications will contribute to improving the future outcomes of extremely immature infants. Although we have come a long way, we still have far to go.

The overall findings in our study are reassuring. A majority of the EI children attend mainstream school without having major adjustment problems. However, this should not obscure the fact that these children have very high special health care needs, which include the use of school-based services. I would like to reiterate that despite the universal health care in Sweden, almost one fourth of EI parents expressed their dissatisfaction and unmet needs related to the special health care and other supportive services, especially at school.

Knowledge of the course of psychopathology from early childhood to adolescence and beyond is crucial for identifying the need for intervention and prevention strategies. Thus when there is evidence to suggest neuropsychological and behavioral or emotional problems, early identification and preventive interventions, including family support, might help families to manage these at an early stage. Findings in our study suggest that current preterm follow-up programs might benefit from the addition of psychological and family services to traditional neurodevelopmental assessments, especially in the neonatal period and first years of life.

With regard to growth development, it is not clear whether children born extremely preterm are expected to follow growth trajectories similar to those of their full term peers, but the severe growth failure exhibited by the children of our EI cohort in their early postnatal life is unequivocal. We believe that by optimizing nutrition in the neonatal period and in infancy, health and growth outcomes may be improved.

Finally I would like to end the discussion with the following words from a distinguished expert in the field of follow-up of preterm children, Marie McCormick.

“While those of us who are doing follow-up of extremely preterm children have our share of tragic cases of severely impaired children, we also have much larger numbers of children who may have differing combinations of milder difficulties or dysfunctions and who will do well with adequate educational & family support. Identifying effective ways to intervene with these families should be a priority”.
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9. Populärvetenskaplig Sammanfattning

Bakgrund/syfte

Överlevnad av mycket för tidigt födda barn (barn födda vid 23-25 graviditetsveckor, extrem prematura barn, EPB) har ökat 4-faldigt under 1990-talet. EPB tillhör med säkerhet en riskgrupp men kunskapen om dessa barns hälsa i skolåldern och hur de fungerar i sin dagliga miljö (hemmet, i skolan, och med sina jämnåriga) är ofullständig. Studier i andra länder av barn med extremt låg födelsevikt, <1000g, födda på 80-talet, har visat att en betydande andel av för tidigt födda barn har skolsvårigheter, motoriska problem och beteenderubningar, sociala problem och ökade hälsobehov. Syftet med denna forskning var att undersöka det omfattande neurologiska, utvecklingsmässiga, funktionella, psykiska samt hälsobehovrelaterade behovet hos barn födda vid 23-25 veckors gestationsålder på 90-talet, och att därigenom få en helhets bild av barnet i sitt sammanhang med sin familj, sina jämnåriga, i skol- och hälsovårdssituationen.

Metoder


Resultat

EPB hade jämfört med kontrollgruppen signifikant högre förekomst av specifika diagnoser eller handikapp inkluderande neurosensoriska handikapp (15% respektive 2%), astma (20% resp 6%), nedsatt motorisk förmåga (26% resp 3%), nedsatt syn (21% resp 4%), nedsatt inlärningsförmåga (27 resp 3%), nedsatt anpassningsförmåga (42% resp 9%) och nedsatta prestationer i skolan (49% resp 7%). Som en följd av dessa svårigheter hade extremt prematura barn i jämförelse med kontrollgruppen signifikant mer funktionsbegränsningar (64% resp 11%), och hälsobehov (professionell omsorg i skolan och samhället) utöver vad barn generellt behöver (67% resp 22%).
Vad gäller tillväxt hade EPB otillfredsställande/dålig tillväxt under framförallt det första levnadsåret, efterföljt av bra återväxt (catch-up) gällande både längd och vikt till 11 års ålder. EPB uppvisade ingen catch-up vad gäller skalltillväxt efter de första 6 levnadsmånaderna. Vid 11 år var EPB fortfarande något (4,5 cm) kortare och tunnare (3 kg) än kontrollbarn. Prematuritet och äftlighet (föräldrarnas längd) var signifikanta prediktorer av kroppslängden vid 11 års ålder. Prematuritet korrelerade starkt till huvudomfåget.

Våra resultat tyder också på att EPB jämfört med kontrollgruppen har signifikant ökad risk för sämre psykisk hälsa i form av internaliserade symtom (ångest/depression, tillbakaderad beteende, somatiska symtom), uppmärksamhetsbrist, sociala problem och tankestörningar. Inga skillnader avseende aggressivt beteende påvisades mellan EPB och kontrollgruppen. Signifikanta prediktorer för psykiska symptomer var: grupptillhörighet (EPB respektive kontrollgrupp), familjefunktion, social risk, manligt kön och kroniskt medicinsk tillstånd.

Gällande skolprestationer hade fler än hälften (58 %) av EPB skolsvårigheter, och 15 % hade heltids specialundervisning, vilket kan jämföras med 5% i kontrollgruppen. Jämfört med kontrollerna hade de EPB ökad risk för exekutiv dysfunktion inom de flesta områden som bedömdes (uppmärksamhet, hypoaktivitet, planering/organiseringsförmåga och arbetsminne). EPB hade också risk för brister i språklig förmåga (språkbrist, kommunikation, och expressiv förmåga). Större risk för brister fanns också i de fyra standardmåttet av inlärningsförmåga (läsning/skrivning, matematik, intellektuella färdigheter). Dock visade endast ett relativt litet antal av de EPB allvarlig nedsättning i exekutiva och icke-exekutiva färdigheter. Statistiska analyser avslöjade att prematuritet, exekutiv dysfunktion och manligt kön var associerade med försämrad inlärningsförmåga.

**Slutsats**

Extremt prematura barn har signifikant större hälsoproblem och högre behov av speciella återkommande hälsosårgärder under skolåren. Dock är det påfallande att mycket få barn har allvarliga nedsättningar som innebär hinder i ADL. De sammanvägda resultaten från denna studie är uppmuntrande. Trots ökad risk för problem med psykisk hälsa, exekutiv dysfunktion och skolsvårigheter gick 85% av de extremt prematura barnen i vanliga skolor och majoriteten hade inga allvarliga anpassningssårgärder. Vad gäller tillväxt uppvisade de flesta EPB god catch-up senare i barndomen och var vid 11 års ålder inom 2 standard deviationer från deras mållängd.
beräknat från föräldrarnas längd. Trots att vara född mycket för tidigt (biologisk omognad) är associerad med en ökad risk för beteende/emotionella problem kan förbättring av de modifierbara miljöfaktorerna gagna EPB. Våra fynd tyder också på att aktuella uppföljningsprogram av prematura barn skulle kunna förbättras genom införandet av psykologiska och sociala hälsovårdsinsatser integrerat i den medicinska uppföljningen speciellt under neonatalperioden och under de första levnadsåren.