

Linköping University Medical Dissertations
No. 1076

Long-term follow-up of very low birthweight children

A prospective study from the southeast region of Sweden

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Linköping 2008

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ISBN 978-91-7393-812-9

ISSN 0345-0082

Printed in Sweden by LiU-Tryck, Linköping, 2008

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Distributed by

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I would like to dedicate this thesis to all the children with very low birthweight who were enrolled in the follow-up assessments, together with the normal weight children, and their families.

If we knew what it was
we were doing, it would
not be called research,
would it?
Albert Einstein

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LIST OF PUBLICATIONS

This thesis is based on the following articles, which will be referred to in the text by their Roman numerals:

- I. Gäddlin PO, Finnström O, Hellgren K, Leijon I.
Hospital readmissions and morbidity in a fifteen-year follow-up of very low birthweight children in Southeast Sweden.
Acta Paediatr 2007;96:499-505
- II. Gäddlin PO, Finnström O, Wang C, Leijon I.
A fifteen-year follow-up of neurological conditions in VLBW children without overt disability: Relation to gender, neonatal risk factors, and end stage MRI findings.
Early Hum Dev 2008;84:343-349
- III. Gäddlin PO, Finnström O, Samuelsson S, Wadsby M, Wang C, Leijon I.
Academic achievements, behavioural outcomes and MRI findings at 15 years of age in very low birthweight children.
Acta Paediatr 2008;97:1426-32
- IV. Gäddlin PO, Finnström O, Sydsjö G, Leijon I.
Health, quality of life, educational level, and occupation in early adulthood in very low birthweight subjects in south-east Sweden.
Submitted

ABSTRACT

Background: The survival rates for very low birthweight (VLBW; birthweight ≤ 1500 g) children are increasing, but they run a greater risk than controls of developing neurosensory disabilities and other functional problems during childhood. However, there is a great need for more knowledge regarding long-term outcome to adulthood in VLBW subjects.

Aims: To evaluate long-term outcomes in a regional cohort of VLBW children born in 1987-88 regarding hospital readmissions, morbidity, neurological conditions, cognitive function, reading skills, school achievements, behaviour, growth, general health, and social functioning in relation to gender, neonatal risk factors, disability and Magnetic Resonance Imaging (MRI) findings.

Study design: Prospective longitudinal case-controlled long-term regional follow-up.

Material and Methods: A total of 86 (80.4%) children (47 boys out of 60 and 39 girls out of 47 live-borns) survived the neonatal period and were recruited to the follow-up study. A total of 86 term controls (45 boys and 41 girls) were included from the newborn period. Readmissions, hospital diagnoses, need of habilitation and child psychiatric care were checked in registers to 15 years of age. The VLBW children were enrolled in the follow-up study at 40 weeks gestational age and at 4, 9, and 15 years of age in assessing neurological conditions. At 15 years of age, the groups were assessed in cognition (WISC III), reading skills, school outcome, behaviour, vision and growth. Fifty-nine (69%) VLBW children were examined using cerebral MRI. Physical and mental health, weight and height, education, and socio-economic situation were assessed at 20 years of age in 77/85 VLBW and 69/84 control subjects by means of postal questionnaires.

Results: VLBW boys had three times more readmissions compared with control boys ($p=0.003$). Gestational age below 30 weeks, birthweight less than 1000 g, and mechanical ventilation were neonatal risk factors for readmissions. Five (5.8%) children had moderate/severe cerebral palsy, 5 (5.8%) had attention deficit hyperactivity disorder, and 1 was blind due to retinopathy of prematurity.

VLBW children were inferior in neurological function in comparison with controls at 40 weeks of gestational age and 4 and 15 years of age. Fourteen of 56 (25%) VLBW children without overt disability had abnormal MRI findings. Mechanical and/or intraventricular haemorrhages (IVH) were significantly related to less favourable neurological outcome. VLBW children performed significantly lower than their controls on a few reading variables and on WISC III. Half of them had IQ lower than 85. Ten VLBW children with IQ < 70 had not been clinically identified earlier and a majority of these children attended mainstream school. Small head circumference correlated with low IQ. Mechanical ventilation and IVH correlated with lower IQ and poorer reading skills. At 20 years of age, the VLBW subjects did not differ significantly from the controls in self-perceived health, education, occupation and way of living.

Conclusions: Most VLBW subjects were without major health problems up to 20 years of age and had attended mainstream schools. The presence of IVH and mechanical ventilation during the neonatal period negatively influenced health outcomes. VLBW children without overt neurological disability performed somewhat less well in neurological examinations in comparison with controls. VLBW children achieved poorer results in cognitive tests, but reading skills made a catch-up to 15 years of age. A majority of VLBW subjects managed transition to adulthood similar to that of controls.

SAMMANFATTNING

Bakgrund: Överlevnaden för nyfödda barn med mycket låg födelsevikt (1500 g eller lägre; VLBW) har ökat avsevärt under de senaste årtionden och man finner nu att ca 90 % av barnen skrivs ut från neonatalavdelningar. Risken för cerebral pares (CP) har visat sig vara ökad jämfört med barn födda i fullgången tid. Studier visade att VLBW-barn som kommit upp i skolåldern hade högre frekvens av läs- och skrivsvårigheter, oftare behövde specialundervisning, samt hade högre grad av beteendeproblem jämfört med klasskamrater.

Uppföljningsstudier var tidigare mestadels gjorda på populationer från större sjukhus, kontrollgrupp saknades eller inlemdes efter flera år, uppföljningstiden var kort och flera viktiga områden av barnets utveckling var ofullständigt undersökta. I Sverige saknades en studie med långtidsuppföljning av VLBW-barn födda under en tidsperiod då alltför många barn hade börjat erhålla andningshjälp med respirator. Socioekonomiska förhållanden i Sverige kan inte heller helt och hållet jämföras med flertalet andra länder.

Syfte: Den här avhandlingens syfte var att studera hur det går för VLBW-barn upp till 15 års ålder avseende sjuklighet, motoriska funktioner, kognitiva funktioner, skolprestationer och beteende, samt vid 20 års ålder avseende hälsotillstånd, sysselsättning och boende. Undersökningsresultaten relaterades till nyföddhetsfaktorer och fynd vid magnet resonans-undersökning (MRI) av hjärnan vid 15 års ålder.

Material och metoder: 86 överlevande VLBW-barn samt 86 barn födda i fullgången tid från 1/2 1987 till 30/4 1988 i sydöstra sjukvårdsregionen (Jönköpings, Kalmar och Östergötlands län) har ingått i studien. Uppgift om antalet sjukhusinläggningar och huvuddiagnos inhämtades från Slutenvårdsregistret, Epidemiologiskt centrum, Socialstyrelsen. Uppgifter om antalet barn med CP, ADHD, mental retardation och barnpsykiatrisk vårdbehov inhämtades från habiliteringscentraler och barnpsykiatriska kliniker i regionen. Information om skolbetyg från 9:e årskursen och skolgång inhämtades från kommunerna. Neurologiska och motoriska undersökningar utfördes på barn utan synligt handikapp enligt särskilda protokoll såväl neonatalt som vid 4, 9 och 15 års ålder. Vikt och längd, kognitiv test (WISC III), lästester och MRI undersökning (enbart VLBW-barn) gjordes vid 15 års ålder. Barn och föräldrar fick fylla i formulär om beteende. Vid 20 års ålder (december 2007) fick deltagarna tre frågeformulär: ett studiespecifikt med frågor om hälsa, vikt och längd, användning av tobak och alkohol, gymnasiestudier, nuvarande sysselsättning och boende; SF-36, som belyser fysisk kapacitet, allmän hälsa, vitalitet och psykiskt välbefinnande; samt KASAM (känsla av sammanhang), som belyser hur man upplever sitt eget sätt att fungera, uppdelat i begriplighet, hanterbarhet och meningsfullhet.

Resultat: VLBW-barn (mest pojkar) vårdades oftare på sjukhus under första levnadsåren jämfört med kontroller. Infektioner och neurologiska sjukdomar dominerade för både VLBW-pojkar och -flickor. Fem (5,8 %) VLBW-barn hade måttlig/svår CP och fem hade ADHD. Hjärnblödning eller respiratorbehandling under nyföddhetsperioden var de faktorer som oftast var relaterade till sämre hälsotillstånd. Det var ingen skillnad i antal barn med behov av barnpsykiatrisk vård mellan grupperna. Det var ingen skillnad i summering av 9 slutbetyg mellan grupperna, men VLBW-pojkar hade lägre betyg i matematik och teknologi jämfört med sina kontroller. VLBW-barnen var lättare och kortare, men skillnaderna var störst mellan VLBW-flickor och deras kontroller. VLBW-barnen (fr.a. pojkarna) presterade lägre i neurologiska undersökningar, samt i kognitiva test. Tio av tolv av barnen som hade IQ under 70 var tidigare inte kända. Det fanns skillnader mellan grupperna i lästester, men signifikant enbart i ett test. Jämfört med lästester vid 9 års ålder hade VLBW-barnen gjort en upphämtning. Det framkom inga skillnader i beteende mellan grupperna, men VLBW-flickor uppgav färre beteendeproblem än sina kontroller. Vid 20 års ålder framkom inga skillnader i självuppskattad hälsa eller behov av vårdkontakter och läkemedel mellan grupperna. Tobaksanvändning var lika i grupperna, men fler i VLBW-gruppen var icke-användare av alkohol. Det var ingen signifikant skillnad i andel som gått ut gymnasiet, nuvarande sysselsättning eller boendeform mellan grupperna. Det var inga signifikanta skillnader i resultat på SF-36 och KASAM mellan grupperna.

Konklusion: Hjärnblödning och respiratoranvändning under nyföddhetsperioden var de faktorer som hade störst inverkan på VLBW-barnens hälsotillstånd upp till 20 års ålder. CP och ADHD förekom hos relativt få, men lågt IQ var vanligt. VLBW-pojkar hade större sjukvårdsbehov, presterade lägre i neurologiska test och hade lägre skolbetyg än sina kontroller. VLBW-gruppen skilde sig inte från kontrollgruppen avseende beteendeproblem. Självuppskattad hälsa vid 20 år skilde sig inte mellan grupperna. Särskilda uppföljningsprogram för VLBW-barn är nödvändigt där kognitiva tester ingår vilka bör utföras före skolstart.

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
AGA	appropriate for gestational age
BMI	body mass index
BPD	bronchopulmonary dysplasia
BW	birthweight
CBCL	Child Behaviour Check List
CI	confidence interval
CP	cerebral palsy
ELBW	extremely low birthweight
GA	gestational age
HD	hospital days
ICD	international classification of diseases
IVH	intraventricular haemorrhage
LBW	low birthweight
MCS	mental health score
MR	mental retardation
MRI	magnetic resonance imaging
OFC	occipito-frontal circumference
OR	odds ratio
PCS	physical health score
PVL	periventricular leucomalacia
QoL	quality of life
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SD	standard deviation
SOC	sense of coherence
SGA	small for gestational age
WISC	Wechsler Intelligence Scale for Children
VLBW	very low birthweight
WMD	white matter damage
YSR	Youth Self-Report

BACKGROUND

Introduction

Research on long-term outcome in children with very low birthweight (VLBW; ≤ 1500 g) has been more and more evident due to increasing survival rate in very immature human beings in recent decades [1-6]. The improved survival rates of preterm and especially very preterm babies is an effect of major advances in medical care, i.e. maternal-fetal, obstetrical, and neonatal intensive care [3].

Successful ante-, peri- and neonatal management depends on active surveillance of high risk pregnancies, antenatal corticosteroid and neonatal surfactant treatment, growing knowledge in assisted ventilation, and better non-invasive technical equipment for monitoring sick newborn. The limit of viability has gradually declined to levels that could not be imagined thirty years ago [7-9]. In a review article in March 1980 entitled “For the 1980s: How small is too small?”, Schechner concluded that intensive care for newborns with birthweight below 750 g or gestational age (GA) less than 26 weeks was questionable [10]. However, among professionals and lay public discussions have continued during these decades about ethical conflicts concerning conceivable higher risk of neurodevelopmental disabilities following increased survival rates in extremely preterm neonates [11-14].

Outcome data in VLBW children are of interest not only for care professionals, but also for parents and members of the family, schoolteachers, and society. In every country, the mortality rates reflect the standards of perinatal care, especially for extremely low birthweight infants (ELBW; ≤ 1000 g). In well developed countries the mortality rate for infants with BW more than 1000 g is no longer a useful measure of quality of care [15,16]. Other outcome data based on regular follow-up examinations with standardized methods in high-risk groups, such as VLBW children, are more essential in order to identify changes in long-term outcomes. In modern healthcare monitoring of health status and wellbeing in the population is a core principle in public health activity.

Traditionally, neonatologists have mainly focused on rates of neonatal morbidities with probable impacts on developmental outcome. Besides low GA and low BW [1], respiratory distress syndrome (RDS) [17,18], bronchopulmonary dysplasia (BPD) [19], small for gestational age (SGA) [20,21], intraventricular haemorrhage (IVH) [22,23], retinopathy of prematurity (ROP) [19], sepsis and necrotizing enterocolitis [24], and male sex [25] have a major impact on later outcome.

Several studies have reported high frequency of rehospitalization [26-28], neurosensory and neurological disabilities as cerebral palsy (CP) and impaired function in motor skills [1,29-34], low cognitive and academic ability [30,35-37], behavioural problems [38-41], and poor growth [42-45] in VLBW children during childhood and adolescence.

Many earlier studies were based on data of VLBW populations from university hospitals and with short follow-up terms, lack of control children or inclusion of controls after the neonatal period, lack of consideration to gender and neonatal risk factors, or lack of a comprehensive view of general health outcome. In addition, these deficiencies restrict the ability to generalize the results. In research concerning follow-up outcomes, population-based studies are preferable, as hospital-based cohorts may be subject to selection bias [46,47].

Due to socio-economic inequalities, results from international studies are not entirely applicable in Sweden. Socio-economic characteristics in Sweden are often satisfactory or good, problems with alcohol and drugs during pregnancy are rare and there are few teenage pregnancies, but older mothers and prenatal care are more frequent compared to many other countries [48].

Of importance in follow-up studies concerning high-risk infants is the definition of inclusion criteria. In general, birthweight rather than gestational age have been more common as the crucial criterion for inclusion, a tradition probably depending on the simple fact that measuring BW is more reliable than calculating GA. Fetal ultrasonography before 20 weeks of gestation has replaced first day of last menstrual period in calculating estimated date of birth with a continuous shift during the 1980s.

Traditionally, studies have been based on birthweight, i.e. low BW (LBW; ≤ 2500 g), very low BW (VLBW; ≤ 1500 g), and extremely low BW (ELBW; ≤ 1000 g) implying the possibility of comparing results. However, by using BW as the specific inclusion criterion, a high frequency of children with growth deviation will be eligible. These populations will therefore comprise children with a more extensive range of gestational ages, which may influence outcome. As the accuracy in predicting estimated date of birth with ultrasonography has increased over the last decade, more and more studies based on GA as the inclusion criterion have been published.

The characterizations of follow-up studies in short-term and long-term studies are not entirely uniform and may be confusing. Follow-up examinations at 2-3 years of age were originally defined as long-term studies. In my opinion, prospective longitudinal follow-up studies with outcome assessments during infancy and childhood are preferably defined as short-term studies, assessments during school-ages ought to be defined as long-term studies, during late adolescence and early adulthood defined as very long-term, and outcome studies regarding adults as extremely long-term.

According to official statistics from 1973 through 2006, the frequency of VLBW births in Sweden was on average 0.76%, a rate which has remained fairly stable lasting recent decades

(range 0.59-0.85%), although there are regional differences [49]. This means that approximately 765 VLBW infants were born alive each year in Sweden (range 565-1043). By comparison, in the USA approximately 60,000 VLBW infants (1.5% of all live births) are born each year [48].

Lagercrantz, Svenningsen and Tunell reported a mortality rate of 28% in VLBW infants born in the early 1980s included in a Swedish multi-centre study [50]. In the late 1980s and early 1990s, according to results from the Stockholm Neonatal Project, the mortality rate was 17.5% [51]. Recent reports from Sweden are sparse regarding studies on VLBW children and mortality rates. In addition, official statistics show a decline in neonatal mortality from 38.2% in 1973 to 10.0% in 2006. In 2005, mortality was 7.8%, the lowest rate hitherto [49] (Figure 1).

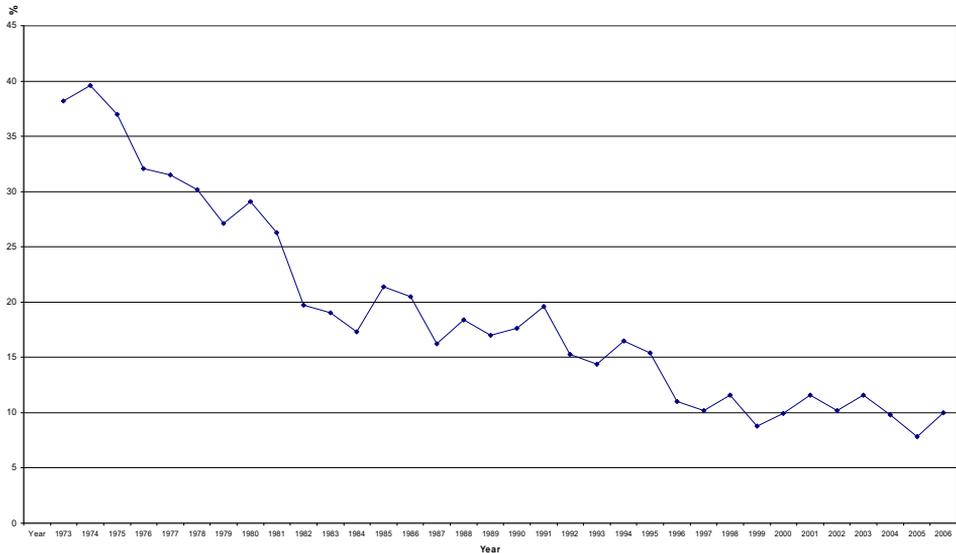


Figure 1. Neonatal mortality (0-28 days) in VLBW children 1973 – 2006 in Sweden [49].

Follow-up studies

International follow-up studies

Originally, reports of outcomes in VLBW children were mainly based on university hospital populations and thus only representative for selected populations. Survival and discharge from the neonatal care units were considered successful outcomes. The majority of the early follow-up studies extended to the first years of life and few studies included controls in examinations.

In a hospital based study of VLBW children born in 1974, 66% survived and were eligible for follow-up examination. In the subgroup with BW below 1000 g, 30% had a significant handicap and in the subgroup of SGA infants 53% were significantly handicapped at 2 years of age [20]. A survival rate of 45% was reported for infants with BW 1250 g or less born 1974-77. At follow-up examinations between 18 months and 4 years of age, 14% had major handicaps [52].

Mortality and morbidity in VLBW children born before and after introduction of neonatal intensive care were studied in a geographic region in Canada [1]. Between 1964-1969 and 1973-1977 mortality decreased significantly from 60% to 43%, whereas the incidence of major sequelae at follow-up assessments was not significantly affected. In 1966-70, the survival rate for VLBW children born in a tertiary perinatal centre was 37%, but had increased to 68% by 1980-82 [2]. The latter cohort had a significantly increased prevalence of CP compared with the earlier cohort. In a hospital study from California, ELBW infants born from 1961 through 1980 had an overall neonatal mortality of 63%, whereas there was a decline in mortality rate with time. Twenty-eight percent had significant morbidity, of which 12% had severe handicaps and 16% had moderate handicaps [53]. Furthermore, data from this long-term study indicated an improved prognosis for ELBW children, results that were confirmed by another contemporary study [54].

In some follow-up studies from the 1970s, 80-90% of VLBW children were reported to be free from serious handicap during early childhood. However, during the preschool and school age and adolescent years poorer cognitive functions and academic achievements became evident when comparisons with term control children were performed [55-57]. Around 50% of VLBW children required special education or resource help at early school age compared with 24% in the general population [56,57]. Behavioural problems, including attention deficit hyperactivity disorder (ADHD), anxiety and depression, were reported in higher frequencies compared to classmates [38,58,59]. Subnormal growth and chronic health problems were prevalent [42-44,60].

In the mid-1990s, survivors from the 1970s reached early adulthood, with increasing numbers of follow-up reports concerning general health outcome, which to some part contributed to an encouraging assessment [61-72].

Follow-up studies in Sweden

Follow-up studies in Sweden principally reflect patterns in international follow-up studies with originally hospital based cohorts of LBW children, followed by studies of VLBW and ELBW children. These studies were followed by population-based and/or participants eligible regarding GA. However, no very long-term follow-up studies of ELBW/VLBW subjects exist.

In the 1960s, Bjerre et al studied a hospital based cohort of 188 LBW children born 1966 in Malmö [73]. At 5 years of age, 139 (60%) had normal neurological status, 5% had CP and 27% had delayed motor maturation. CP was found in the children with very low BW and short GA [74]. In another hospital based study of 72 live-born VLBW infants born in the late 1970s, neonatal mortality was 27% [75]. At a follow-up examination at 2 years of age, 12% of the infants had abnormal neurological outcome. In a hospital based multi-centre study of VLBW children followed to 2 years of age, Lagercrantz et al reported that frequency of severe neurodevelopmental impairment was low, 4% [76].

In a national register study of males listed in the National Service Enrolment Register at 19 years of age, VLBW males were found to be shorter and lighter, having increased frequency of impaired vision and hearing and lower intelligence scores compared to controls. CP, mental retardation (MR), or epilepsy was found in 10% of the participants [77]. Forslund and Bjerre conducted a prospective hospital based study of 46 preterm children born before 35 weeks of GA and 26 full term controls [78]. These children were followed up at 18 months and at 4 and 8 years of age [79]. At 19 years of age, 39 preterm children were assessed and had significant more somatic problems than the controls, but there were no significant differences between the groups in cognitive function or in length and weight [64].

During the 1980s, five prospective follow-up studies of ELBW/VLBW or very preterm children were designed; a hospital based study of infants born 1984-86 with BW below 901 g [80], a hospital based study of infants born 1985-86 with GA less than 29 weeks [81], a regionally based study of VLBW infants born 1987-88 [82,83], a population based study of infants born 1988-91 with GA less than 29 weeks [84,85], and a mixed hospital and population based study of VLBW children born 1988-93 (The Stockholm Neonatal Project) [51,86-88].

Stjernqvist and Svenningsen assessed 20 ELBW children and 20 controls at 4 years of age as regards growth, health and quality of life (QoL), development and behaviour [80]. Major neurological disorders were found in 4 (20%) children, all with IVH grade III-IV and/or periventricular leucomalacia (PVL). Cognitive development was within the normal range by 85% of the children, although mean scores were lower than for full-term controls. Another study by these authors concerned 61 very preterm children who were examined at age 10 [81]. Shorter height, lower weight, and smaller head circumference were found in the preterm

children, but also significantly lower IQ scores, and more general behavioural problems than controls.

A study of very preterm infants from Gothenburg was initially focused on ophthalmological outcomes and these results have previously been published [84]. At 8-11 years of age, 43 out of 51 participated in psychological evaluation [85]. Thirty percent of the children performed below average for Full Scale IQ (< 80). Discrepancies between Verbal IQ and Performance IQ of more than 15 IQ units were found in 42% of the children.

In the Stockholm Neonatal Project, motor skills were assessed with 165 VLBW children participating at 5.5 years of age [86]. The majority of the VLBW children performed within the normal range, but less well than control children. Cognitive function was also assessed at 5.5 years of age in 182 of the VLBW children with significant differences in full-scale IQ, verbal subscale IQ and performance subscale IQ compared to controls [87]. Worth noting was that the VLBW children fell well within the normal range results on Wechsler Preschool and Primary Scale of Intelligence-Revised. Controls performed significantly better than the VLBW children on tests of executive function, even after controlling for IQ [88]. In both groups, girls achieved significantly higher results.

One national prospective follow-up study of ELBW children was conducted in the early 1990s [89]. At a median age of 36 months of corrected age, 362 (98%) surviving infants were assessed, using a special designed protocol. Mean height, weight and head circumference were significantly lower than the reference values. The incidence of CP was 7% among all children. More than 90% of the ELBW children born at 25 or more completed gestational weeks were without neurosensory handicaps, whereas in infants born at 23-24 weeks of gestation outcomes were less favourable.

Recently, results from long-term follow-up studies of a subpopulation of the survivors in the Swedish national ELBW study have been published, i.e. all 89 surviving children born at 23-25 weeks of gestation and thus representing children born at the limit of viability [90-92]. Farooqi et al found that extremely immature children had significantly greater health problems and special health care needs than controls at 11 years of age, but few were impaired to such an extent as not to be able to perform activities in daily life [90]. Five children had CP, 10 had severe visual impairment and 5 required hearing aids. The overall prevalence of at least one major disability was 21% in the extremely preterm group and 6% in the control group. Furthermore, extremely preterm children attained poor growth in early childhood, followed by catch-up growth to the age of 11 years and were within 2 SD of their mid-parental height, but nevertheless remained smaller than their controls [91]. Compared with control subjects, parents of extremely immature children reported significantly more problems with internalizing behaviour (anxiety/depression, withdrawn, somatic problems) and attention, thought and social problems [92]. Teachers reported similar patterns. On the other hand, 85% of the extremely immature children were in mainstream schools.

Outcomes

What will be the optimal outcome variable in follow-up studies of VLBW children?

Hitherto, there is no simple answer and the golden standard has varied as follow-up studies have become more and more long-term and extensive. Survival rate, rehospitalization, neurodevelopmental impairments, cognitive deficits, and growth attainment have historically been of major interest. Other critical areas of outcomes have been recognized and more and more data is recommending outcomes in behaviour, school performance, general health status and QoL, social functioning and transition to adulthood [93,94].

It also seems to be important that new ways of reporting findings be found to reflect a more complex picture. Profiles of outcomes may be more informative, preferably in terms that provide some notion of the level of dysfunction associated with specific findings or scores [95].

Rehospitalization

Rehospitalization during infancy, childhood and school-age up to adolescence reflects health status and severity of illness. Increased frequency of readmissions in VLBW children, especially during infancy and for boys have been reported [27,28,43,96-99]. VLBW children with chronic conditions and/or those with poor neurodevelopmental outcomes were at highest risk of rehospitalization [26]. Data have mainly been obtained retrospectively by means of questionnaires, interviews or from medical records [27,60,100].

Changes over decades in readmitting frequencies are influenced by improved survival rate, severity of illness and chronic conditions, but also organization of health care systems, resulting in more outpatients [97,101,102]. Leijon et al found in a recent study, that a large proportion of premature children had more outpatient attendances (OR 5.6, 95% CI 2.1-15.0) and received specialist care during the first years of life to a higher degree than controls [99]. In another recent Swedish study, utilization of healthcare by VLBW infants was found to be higher in paediatric and ophthalmic outpatient clinics than for the control group [103].

Infectious and respiratory diseases were the main reasons for rehospitalization during infancy and childhood, for both boys and girls [43,96,97,104]. In addition, neurological disorders and surgical procedures represented a fairly high proportion of causes of readmission in VLBW children compared to controls [43,97].

Male sex, ELBW, very low GA, BPD, IVH, and length of stay in the neonatal unit increased the risk of rehospitalization [96-98,104], while others did not find such associations [27,28].

Asthma

Preterm birth and VLBW seem to be related to increased risk of asthma, both as clinical diagnosis and in lung function tests [105,106]. Preterm girls were found to have more current asthma (OR 2.6; 95% CI 1.4-4.7; $p<0.05$) and recurrent wheezing (OR 1.7; 95% CI 1.1-2.7; $p<0.001$), than term control girls, especially if they required mechanical ventilation after birth [105]. Halvorsen et al reported that 56% of very preterm subjects had a positive methacholine provocation test compared to 26% of controls at 17 years of age [106]. Genetic causes and a family history of asthma may predispose premature children to more severe respiratory disease [105]. Maternal smoking during pregnancy increases the risk of readmission for asthma and acute bronchitis [107]. However, respiratory healths in VLBW children were comparable with term controls at 14 years of age with rates of asthma in 21% of VLBW children and 21% in controls [108].

In order to study the impact of very low BW on the risk of developing asthma, bronchial hyper-responsiveness and atopy, the VLBW children and controls in our regional cohort from south-east Sweden were included in assessments at 12 years of age [109]. A history of asthma was more frequent in the VLBW children, as compared to the controls (22% vs. 9%; $p=0.046$). In univariate analyses, very preterm birth (GA below 30 weeks) (risk ratio (RR) 2.5, 95% CI 1.1-5.8; $p=0.04$), mechanical ventilation in the neonatal period (RR 2.8, 95% CI 1.2-6.4; $p=0.03$), and neonatal oxygen supplementation more than 1 day (RR 4.3, 95% CI 1.3-14.0; $p<0.01$) were significantly associated with a history of asthma by the age of 12 years. In multivariate logistic regression, oxygen supplementation seemed to be the only independent factor for a history of asthma (adjusted OR 4.2, 95% CI 0.95-19) and was particularly evident in the case of oxygen supplementation more than 9 days (adjusted OR 6.7, 95% CI 1.0-44). In addition, oxygen supplementation more than 9 days seemed to be associated with current asthma (adjusted OR 8.1, 95% CI 0.98-68). Thus, prematurity per se was not the most important risk factor for asthma developing. A history of maternal asthma was not significantly associated with a history of asthma up to 12 years of age in this study.

Children in the VLBW group who needed mechanical ventilation during the neonatal period were more likely to have bronchial hyper-responsiveness at 12 years of age than the VLBW children who did not require mechanical ventilation. The increased risk of bronchial hyper-responsiveness was evident in the VLBW infants who needed mechanical ventilation five days or more (RR 2.9, 95% CI 1.5-5.4). Neither preterm birth, SGA, nor neonatal respiratory support had any impact on the spirometric values at 12 years of age.

No significant relationship between VLBW and atopic manifestations could be confirmed in this study, since prevalence of allergic rhino-conjunctivitis, eczema and positive skin prick tests were similar in the VLBW and term children. In addition, the levels of immunoglobulin E in serum and interleukin-4 and -5, and interferon-gamma in vitro did not differ significantly between the two groups.

Neurodevelopmental outcome

In a majority of follow-up studies of VLBW children, neurological outcome has been of interest, especially the incidence of CP, but also visual and hearing impairments.

Neurological outcome: Cerebral palsy

Low BW or low GA were correlated with CP in several studies [33,110,111]. The incidence rates vary from 5% to 11% regarding moderate and severe CP [34,86,112,113]. Escobar et al reported from a meta-analysis of 85 different VLBW cohorts, a median incidence of CP among all the cohorts of 7.7% [32]. In a Swedish nationwide follow-up study of ELBW children at 36 months of age, the incidence of CP was 7% in the whole group with increasing rates in lower gestational ages [89]. Comparison between studies of outcomes related to CP diagnoses in VLBW children have been uncertain regarding heterogeneous study-populations, criteria of diagnoses, and non-classification of functional status [114,115]. Real differences in incidence between hospitals and countries have also been reported by some authors [32,46,114]. Of great importance is the geographical population based survey of CP in western Sweden where changes over decades in frequency of CP in VLBW children have been shown with increased incidence during the 1980s [33,111,116]. The collaboration of European Cerebral Palsy Registers has recently reported a fall in CP rates in the most immature groups [110]. Between 1980 and 1996, CP rates dropped from a mean of 61/1000 live-born VLBW infants to 40, a fall related to a decline in frequency of bilateral spastic CP among infants with BW 1000-1499 g. In this group, boys had a higher prevalence of CP than girls (61 vs. 50/1000). Also in several other studies, a greater risk of CP in boys has been reported [34,111,117,118].

CP is caused by white matter damage (WMD), as a consequence of PVL and/or IVH [119-122]. WMD shown as focal necrotic lesions of PVL deep in the cerebral white matter near the vascular end-zones have been found in children with CP [121,122]. WMD occurs predominantly between the 24th and 34th weeks of gestation, and in the diffuse WMD death from preoligodendrocytes and a marked prominence of activated microglia have been found [119,123]. In addition to the previously mentioned perinatal factors, neonatal hypoxia-ischemia, mechanical ventilation, inotropic support, pro-inflammation at birth with increased levels of cytokines, and neonatal sepsis have all been described to be related to WMD [119,123-126].

The ultrasonographic technique was introduced during the 1980s, bringing with it with the possibility to repeat non-invasive brain examinations on newborn children in the neonatal care units, although technical deficiencies made precise identification of IVH and PVL incomplete [127-129]. Nowadays, technical improvements in ultrasonography and the introduction of magnetic resonance imaging (MRI) have further increased the capability to image the newborn brain with the possibility to also diagnose subtle brain lesions [130-133].

Neurological outcome: Neurological function and motor skills

Gross motor function is considered an important component of neurological examination. Assessments of VLBW children without disability, i.e. CP, have shown inferior neurological function and motor skills compared with term controls [30,134]. During infancy and childhood, variation in motor performance is common. Stable motor behaviour, i.e. either poor or normal motor performance at several follow-up examinations, was reported in 53% of the VLBW infants from 5 months to 5.5 years, and 47% thus had a variation in motor performance [86]. Improvements in motor skills during infancy and childhood indicating catch-up have been described [134]. Increasing neurological impairments between 8 and 15 years of age have been found [135], but also persistent impaired motor skills into adolescence in neurologically intact VLBW children, and poorer results for girls [29].

Delayed development or inferior motor function is more common in VLBW boys than VLBW girls [25,118]. The causes of gender differences leading to a disadvantage in neurodevelopmental outcome for boys are still unknown, although a need for more initial ventilatory and circulatory support for preterm boys has been reported [136].

Motor skills correlate to BW and GA, the lower the BW and the GA, the poorer the motor performance [86,137]. IVH, BPD, ROP, and mechanical ventilation has also been reported to be associated with poorer neurological outcome [31,36,86,130].

Visual function

Retrolental fibroplasia was described during the 1940s as a cause of visual impairments in VLBW children and was subsequently defined as adverse end-stage grade of ROP. Knowledge of correlation between elevated oxygen saturation and ROP, and possibility to monitor oxygen pressure and saturation has resulted in decreasing frequency of severe grades of ROP. ROP grade III or more was found in 6% of infants with BW 1250 g or less in a hospital based study from 1974-77 [52]. There are still reports of high frequencies (21-40%) of ROP in VLBW populations born during the last decades [138,139]. In a population based study from New Zealand, ROP was present in 21% of the children, of whom 4% had ROP grade III or more [138]. Total ROP incidence of 40% was described in a study from Sweden [139]. Severe ROP, i.e. grade III or more, was observed in 20% and cryotherapy was performed in 11%. In the mid-1980s, an international classification of ROP was published, leading to routinely early screening during the neonatal period [140]. However, one single examination at discharge or a postmenstrual age of 40 weeks was performed in several hospitals up to the late 1980s.

Higher incidences of strabismus, impaired visual acuity, and more frequent need for eye glasses are other findings in several follow-up studies [84,138,141]. In the New Zealand study, strabismus was found in 33% of the children with previous ROP findings and in 19% of the children with no previous ROP findings at 7 years of age [138]. Fourteen percent of

VLBW children attending mainstream schools had strabismus at 7 years of age, almost the same frequency of manifest and latent strabismus [141]. Visual acuity was significantly poorer in the VLBW children compared to controls, and 13% of the VLBW subjects and 4% of the controls wore glasses [141].

Hellgren et al assessed participants of our VLBW sample at 15 years of age and found that median visual acuity in the best eye was better in the control group (1.6) than in the VLBW group (1.3) ($p=0.009$) and observed manifest strabismus in 6.8% of the VLBW children compared to 1.8% in the controls (ns) [142]. Visual dysfunction, according to predefined criteria, was demonstrated in 20 VLBW subjects and 8 controls ($p=0.02$).

Hearing function

Hearing impairments in VLBW infants are frequent at term [143]. Brainstem auditory evoked response and/or otoacoustic emissions have been used in testing preterm children. Neonatal hearing impairment can be sensorineural where the highest risk appears to be in children who require more intensive care in the neonatal period and are often associated with other neurological morbidity, or conductive hearing loss, which is more common [144,145]. Severe hearing impairments during childhood have been reported in a prevalence ranging from 0.8% to 6% [115]. Data on long-term outcome in hearing function are sparse. Farooqi et al reported that 6% of extremely preterm children needed hearing aids at 11 years of age [90].

Growth

Data on growth in VLBW children were reported from early follow-up studies [52,146,147]. The growth pattern was characterized by a decline in weight, length and head circumference from birth to discharge from hospital, followed by partial recovery in all three measures of growth by two to eight years of age. Suboptimal weight gain was more marked in SGA children and children with disabilities. VLBW children with weight or height below the 10th centile at two years of age usually remained in this category at five years and had no evidence of catch-up [42].

Several follow-up studies published in the last few decades account growth attainment as a fundamental part of outcomes variables. Growth is influenced by medical complications and nutritional management and is thus also an indicator of quality of care. Furthermore, a Scandinavian study has reported that a large proportion of children born premature are growth retarded, more than earlier data have shown [148]. Intrauterine growth restriction and growth failure with poor postnatal growth, especially small head circumference, have been found to correlate to increased rates of motor and cognitive impairments at 2 and 7 years of age, respectively [45,149].

In early adolescence, growth divergences persisted between controls and VLBW children, who had smaller head circumferences than expected from their short heights [44,150]. In the VLBW group, smaller head size was associated with lower IQ and mathematics and reading scores [44]. SGA children have an increased risk of performing less well in cognitive tests and academic achievements, but consideration to postnatal growth is important and may influence outcome [149,151-153].

Long-term growth to early adulthood showed persistent differences in weight and height, though not significant in all studies [65,66]. Knowledge of growth in VLBW children up to adulthood is still imperfect.

During the last decade a growing epidemiological interest has emerged as regards associations between early-life growth patterns and later risk of diseases in adulthood. Low BW, especially in intrauterine growth restricted children, and a high weight gain early in life have been suggested as constituting risk factors for diseases, such as cardiovascular disease and metabolic syndrome [154-158]

Cognitive function

Several studies of cognitive function have reported significantly lower test results for VLBW children compared with normative data or control groups, although mean IQ has been within the normal range [39,159]. Mean IQ has varied between studies, to some extent due to differences in including all surviving infants or only those attending mainstream schools or without any major handicap. Impaired intellectual outcome, which may affect academic functioning during school age, has also been found among neurologically intact VLBW children [35].

The difference in mean IQ between preterm children and controls has been shown to be about 11, with no significant gender differences [81,85,160,161]. A recent meta-analysis of pooled data from 15 studies of VLBW children aged 5-14 found that weighted mean differences ranged from 7 to 23 IQ points with 95% CI 9.2-12.5, and an aggregate difference of 10.9 between VLBW children and controls [161]. Existing test norms have been used to compare with the results from study groups, but these data might be old or demographically irrelevant [162]. Examinations of cognitive function in younger ages are more unreliable in predicting future outcomes, although low scores are substantial in predicting a higher risk of impairments in learning, attention and behaviour [162,163]. In addition, secular trends of an increase in IQ have been found.

Of main interest is whether there is any change in cognitive function over time: whether early examined cognitive function improves, remains stable, or deteriorates over time is not yet clear [164]. Greater impairments with increasing age have been found in VLBW children [35,135,165], but also persistent deficits in cognitive and academic achievement over time

[67,166]. Longitudinal follow-up studies have demonstrated some catch-up in cognitive functions [167,168].

Reports concerning gender differences in cognitive function in VLBW children are sparse. Gabrielson et al reported no gender differences regarding Full Scale IQ, Verbal IQ and Performance IQ in very preterm children with GA less than 29 weeks [85], whereas Böhm et al found significantly better results in executive functions for VLBW girls [88].

Perinatal risk factors associated with adverse cognitive function are low BW, low GA, parenchymal lesions in the brain, and days on mechanical ventilation [35,85,137,161]. In a meta-analysis, Bhutta et al identified a linear relationship between GA and IQ from 25 to 40 weeks with a predicted decrease of 1.7 IQ units per week (95% CI 0.81-2.55) [161].

Maternal chorio-amnionitis and pro-inflammation at birth in preterm children may have lasting negative consequences resulting in long-term cognitive and developmental impairments [126,169]. Socio-economic factors have significant impact on cognitive function in preterm children [170,171]. Despite the strong correlation between socio-economic factors and IQ, differences in IQ between VLBW children and controls remain after controlling for socio-economic factors [35].

Academic achievement

VLBW children show poorer academic performance than normal BW controls [60,172,173]. Significant differences in learning disabilities persist when subjects with neurosensory disorders or low IQ are excluded [174]. Teachers have been asked to rate the child's level of performance in relation to peers. 25-40% of VLBW children at 7 to 8 years of age performed poorly in reading, written expression, spelling, mathematics, and physical education [39]. Stjernqvist and Svenningsen reported that 38% of preterm children with GA below 29 weeks and 12% of controls performed below grade level at 10 years of age [81].

Assessments of academic achievements, mostly in reading comprehension and mathematics, differ between VLBW children and controls [35,165]. Longitudinal follow-up studies on educational outcome in VLBW cohorts did not find any catch-up at higher ages, if anything, increased divergences [35,165,166]. Samuelsson et al found significant differences in reading skill tests at 9 years of age between VLBW children and controls participating in a follow-up study of our VLBW population [175]. At 15 years of age, 56 VLBW subjects and 52 controls were re-examined on word decoding, word recognition, and reading comprehension [176]. Most group differences in reading skills did not reach significance, and VLBW children showed improved reading comprehension between 9 and 15 years of age. The results suggest that VLBW children display positive changes over time in reading skills.

Studies including results from school reports seem to be very rare. Pharoah et al found significant differences in total point score and in mean point score per examination subject

between VLBW subjects and matched controls attending mainstream schools and without disability [177].

Gender differences have been small, or are not reported in some studies, but others have documented a higher likelihood of problems in reading, spelling, writing, and mathematics for boys [39,178]. In a large national study, no gender differences were found in academic achievements [39].

Neonatal variables, such as BW, GA, Apgar score at 5 minutes, number of days on mechanical ventilation, and presence and grade of IVH and PVL, were not found to predict either outcome in reading comprehension or mathematics [35]. Considerations of socioeconomic background factors are important in evaluating developmental outcome and academic achievement. Higher socio-demographic risks were associated with less improvement over time in reading and mathematics [165].

Educational attainment

VLBW children have a greater need of special education or grade retention compared to normal weight controls. About three times as many premature children (48%) required special educational interventions compared with full-term children (15%) at 7 to 8 years of age [171]. In a national cohort of VLBW children, 25% received some form of special education assistance compared with 9% in normal weight controls at 7 to 8 years of age [39]. OR for being enrolled in special school, class or unit was 6.3 for ELBW children and 5.6 for children with BW 1000-1500 g. VLBW boys seemed to have the same risk of poor educational outcome as VLBW girls. Sixty-six percent of very preterm children vs. 95% of term controls were in mainstream education at an age-appropriate level without extra support and 30% vs. 2% received special education at 10 years of age in a Swedish study [81].

At 18 to 19 years of age, VLBW men from the Swedish National Service Enrolment Register had left school earlier than normal weight controls (OR 1.6; 95% CI 1.2-2.2) [77]. A Danish study could not demonstrate any significant differences between VLBW subjects and their controls in number of individuals who had a high school/university level of education [179]. The authors of an American study found that 40% of VLBW subjects had repeated a grade in school compared with 27% of controls, 74% vs. 83% had graduated from high school and those who graduated did so at a significantly higher mean age [62]. Gender differences were apparent with fewer VLBW men enrolled in postsecondary studies. Differences in grade repetition and educational attainment remained significant when subjects with neurosensory impairment or very low IQ were excluded. An assessment from the UK regarding young adults previously attending mainstream schools found that VLBW subjects left school at a significantly younger age than controls (16.4 vs. 17.1 years) and fewer had university degrees (23% vs. 58%) [66].

Behaviour

During the last decades increasing number of studies have been published regarding behavioural problems in preschool- and school-aged VLBW children [30,38,39,41,134,160,173]. Hyperactivity and impulsivity, reduced ability to pay attention and to concentrate, withdrawal, anxiety, and depression behaviour are more common in VLBW children.

Psychiatric symptoms were evident in 28% of VLBW children compared to 9% in controls, with ADHD as the main risk [173]. In a Norwegian population based study, 40% of LBW children had behavioural problems and 27% had a psychiatric disorder compared to 7% and 9%, respectively, in normal weight controls at 11 years of age [180]. Four percent of the LBW children and 2% of controls had ADHD according to clinical diagnosis, but 10% and 1%, respectively, had ADHD according to specific screening. These screening results have been confirmed by other authors [30]. A meta-analysis showed that children born preterm had a 2.6-fold (95% CI 1.9-3.8) relative risk for developing ADHD and frequently manifest externalizing or internalizing behaviours during school-age [161].

Self-reports on behavioural problems in VLBW children, however, are to some extent conflicting. VLBW adolescents stated fewer problems than their parents [37], and no differences in self-reporting of inattention, hyper-impulsivity or subtypes of ADHD behaviour was found between VLBW subjects and their controls in young adults [40]. A significant excess of total behavioural problems was found in 81% of 16 case-controlled studies of VLBW/very preterm children aged 5-14 years [161].

Gender differences in behaviour have been reported by some authors. Boys were more susceptible to externalizing behavioural problems, whilst girls were more susceptible to internalizing problems at pre-school ages [41]. VLBW girls reported more emotional and behavioural problems than their parents and compared to VLBW adolescent boys [37]. Withdrawal and internalizing behaviour were more common in VLBW females and delinquent behaviour were less occurring in VLBW males than in controls in young adulthood [40]. However, some authors have noted similar findings for males and females in behavioural outcomes [180,181].

VLBW or preterm children are at increased risk of behavioural and emotional problems, though the perinatal risk factors seem to be more unclear. Behavioural, attention and language problems exhibited in school classroom increased in relation to decreased birth weight [58]. SGA was of significant importance in the parent reported results of behaviour, except for internalizing behaviour [37]. In addition, socio-economic factors have an impact on behavioural outcomes, though these results do not completely diminish when controlling for the effects of socio-demographic and familial variables [58].

Health status, chronic illness, quality of life

Most follow-up studies of VLBW subjects have focused chiefly on disabilities and diseases and consequently expressed the frequencies of deviant physical and psychic conditions compared with term controls. Short-term follow-up studies are limited to examinations or observations by health professionals or parents, whereas long-term studies provide the opportunity to include self-perceived data about health and QoL.

The World Health Organization (WHO) defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity [182]. A holistic approach to health also contains social, cultural and socio-economic considerations, best summarized as QoL. In such an approach, a person is completely healthy if he or she has the ability to reach vital goals, such as education, profession, way of living, relations, and recreational activities [183]. Health and well-being could also be reflected in a sense of coherence (SOC) according to the salutogenic health theory [184].

Over the past decade, growing interest in the holistic definition of health has resulted in reports that supplement earlier studies from a biostatistical point of view [61,63,66,70,179,185]. In a Norwegian study, VLBW adolescents perceived their own functional health and well-being to be comparable to controls' according to results on the Child Health Questionnaire [185]. However, parents reported lower psychosocial health and QoL measures for VLBW subjects than for controls.

In a Danish study, QoL defined as four basic human needs was assessed in VLBW subjects and controls aged between 18 and 20 years [179]. No differences in subjective and objective mean QoL scores were found between VLBW subjects without handicap and controls. However, handicapped subjects scored significantly lower on subjective and objective QoL. In a similar Danish population assessed 10 years later, Dinesen and Greisen reported that there was no significant difference in subjective QoL between VLBW subjects and controls [63]. Objective QoL in non-handicapped VLBW subjects was significantly lower than in the reference group. VLBW subjects, previously in mainstream school, showed no differences in health status on the Medical Outcomes Study, Short Form (SF-36) instrument, with the exception of poorer performance in physical functioning in VLBW subjects [66]. Significant differences were found between VLBW males and their controls in physical functioning and general health [66]. In a Swedish study, former preterm individuals did not differ from controls in self-rated QoL score at 19 years of age [64]. VLBW subjects assessed with a self-reporting instrument at 20 years of age reported similar proportions of excellent, average and poor health profiles as normal-weight subjects [70].

However, the effects of preterm birth and/or VLBW on health related QoL seem to diminish over time [186]. BW and GA had the greatest impact in younger years, although their impact extended into adolescence and adulthood.

Social functioning

Important aspects of life to young adults are relationships with friends and family members, romantic relationships, participating in sports and clubs, test drinking, living independently and getting a job, all aspects of social functioning and part of transition to adulthood. Recently, some studies have reported results of social functioning in ELBW and VLBW subjects [37,66,68,70,93].

VLBW subjects assessed at age 19-22 years did not differ from controls in frequencies of intimate relationships and social activities [66]. In this study, more preterm individuals, both VLBW males and females, were in paid work, fewer were full time students and more were likely to be living at home with parents than controls. VLBW subjects reported significantly more risk avoidance, but also significantly better scores on “Work Performance” [70]. A Canadian study found no significant differences at young adulthood (22-25 years) between ELBW subjects and controls in employment/school status or in proportion of individuals living independently or married/cohabiting [68].

Magnetic Resonance Imaging and white matter damage

Brain damage in the preterm infant, when it occurs, is chiefly composed of subependymal or germinal matrix-intraventricular haemorrhage, PVL, or posthaemorrhagic hydrocephalus. CP correlates with focal necrotic PVL in the cerebral white matter and cognitive and behavioural deficits may correlate to more diffuse white matter injury [119,121,132,187].

Cranial MRI has proven to be an effective technique in clinical practice in order to understand the relation between structural defects of the brain and neurodevelopmental sequelae [121,122]. Recent studies of neonatal cranial ultrasound and MRI in preterm children have demonstrated, that ultrasound had poorer sensitivity for detection of subtle white matter injury [130,131,188]. Due to difficulties in transporting the tiny preterm child to the scanner, MRI or computer tomography do not play a mayor role in early diagnosis of PVL. Thus, ultrasonography of the brain remains the modality of choice in the neonatal period.

During the 1990s several studies were published of preterm and VLBW children examined with MRI. Olsén et al assessed preterm children representing a geographically defined region of northern Finland with MRI at 8 years of age [120]. The prevalence of PVL in this population was 32% and observed in all children with CP, in 25% with minor neurological dysfunction, and in 25% of children without neurological abnormality. Non-disabled VLBW children examined with MRI at age 6 had periventricular gliosis in 50% [189], and of 29 high-risk preterm children, 19 had MRI abnormalities, especially PVL (n=17, 59%) at the age of 5.5-7 years [124].

A few studies with MRI scans in adolescents who were born preterm have been performed [190-192]. Abnormal MRI findings were found in 56% of preterm subjects born before 33 weeks of gestation at age 14-15 years and 90% of these had white matter lesions [191]. VLBW children attending mainstream schools and examined with MRI scans at 15-17 years of age showed abnormalities in 43% of the children, and PVL occurred in 32% [190]. Skranes et al reported that white matter reduction was found in 53% of VLBW children at 15 years of age [192].

Technical improvements in MRI equipment have facilitated examinations of preterm children closer and closer to birth. Children with GA below 34 weeks were examined at term with MRI in a study by Valkama et al [193]. Parenchymal lesions, defined as haemorrhages, PVL, infarctions and reduction of white matter were found in 38% of the infants. Maalouf et al studied 41 extremely preterm children born at a GA of less than 30 weeks with a neonatal MRI scanner close to birth and then repeated examination in 29 children at term [194]. On the initial MRI examination 28 (68%) children had abnormalities, either germinal matrix haemorrhage, IVH, ventricular dilatation, or diffuse and excessive high signal intensity in the white matter. At the term MRI examination at a median GA of 43 weeks, 22 (76%) children had diffuse and excessive high signal intensity in the white matter and 22 had dilatation of the lateral ventricles. The authors concluded that MRI abnormalities were commonly seen in the brain of preterm infants close to birth and that further abnormalities developed between birth and term.

MRI and outcomes

A high proportion of VLBW children without CP will have MRI abnormalities, but in associative studies these have not been related to performance in neurological tests [120,192]. Neurological examination is a better predictor of later developmental problems than MRI, and PVL is not uniformly associated with abnormal neurological findings [120]. In a Norwegian study of VLBW children assessed at 6 years of age, Skranes et al suggested a graded spectrum of PVL lesions, where discrete lesions may cause motor impairments [189]. Children with normal MRI scored significantly better in motor performance compared with children with abnormal MRI findings [130]. In a recent study of VLBW adolescents fine motor impairments were related to low fractional anisotropy measurements in the internal and external capsule and superior fasciculus, assessed by the newly developed MRI technique, diffusion tensor imaging (DTI) [132]. However, this VLBW population was also assessed with conventional cerebral MRI, where no significant differences were found in motor scores for those with and without abnormal MRI findings [192].

Subjects with abnormal MRI findings had more visual, refractive and persistent visual problems compared to VLBW adolescents with normal MRI [142].

Associations between pathological MRI findings and adverse cognitive function were not described [130,189,192,195]. However, VLBW children with severe abnormal MRI had

significantly higher risk of an IQ below 85 [130]. Associations between academic achievements, such as school reports, and MRI findings seem to be none-existent. No associations between PVL on MRI examinations and behavioural problems were found [190,195], while other studies have shown relations between behavioural problems and MRI abnormality [191].

A newly developed MRI technique, DTI, has been shown to give additional information about white matter microstructure with aberrations relating to motor, cognitive, perceptual, mental, and behavioural impairments [132,196]. The authors concluded that perinatal injury of white matter tracts persisted with clinical significance into adolescence.

Another recent method, MRI-based morphometric analysis, assessing the cortex, demonstrated regional thinning in the parietal, temporal and occipital lobes of cortical surface in VLBW children with the greatest changes in those with the lowest BW and shortest GA [197]. Cortical surface area and cortical volume were lower in the VLBW than in the control group and there was an association between cortical surface area and estimated IQ and between cortical volume and estimated IQ. Therefore, it is realistic to expect increasing knowledge of importance concerning relation between clinical examinations of VLBW subjects and brain imaging, where previously assessments using ultrasonography, computer tomography or conventional MRI have failed to show any abnormalities.

PERSONAL REMARKS

Being a neonatologist, is to a great extent a privilege, but also a challenge. I meet sick children at the beginning of their lives, and together with parents and other colleagues and nursing staff have to optimize the care for each child in order to give them a good start for their future lives. During a career with newborn children spanning almost three decades, I have experienced tremendous progress, not least in the improvement of survival rate in VLBW children. As a professional, I am now and then asked by parents and the community, as well as by health services staff, “How is the outcome for VLBW children”?

It is now more than twenty years since I became involved in this prospective study and neonatal intensive care has developed steadily from that time. It is therefore evident that research concerning the newborn child is an ongoing process with the purpose of improving medical care and nursing.

My ambition, which I share with the members of the research team, has been to contribute to knowledge of outcome with special reference to the VLBW children, with the purpose of giving correct information according to the prognosis based on scientific research.

AIMS OF THE THESIS

General aims

The general aims in the thesis were to evaluate long-term outcomes in a regional cohort of VLBW children born in the late 1980s regarding hospital readmissions, morbidity, neurological conditions, cognitive function, school achievements, behaviour, growth, general health, and social functioning in relation to gender, neonatal risk factors, and MRI findings.

The specific aims of each paper included in the thesis were:

Paper I

To retrospectively describe the general consumption of hospital care, the incidence of neurological and psychiatric disturbances and prospectively study visual function up to 15 years of age in relation to perinatal factors.

Paper II

To study neurological condition in VLBW children without overt neurological disability and relate the results to gender, neonatal risk factors, and MRI findings of the brain at 15 years of age.

Paper III

To study cognitive functioning, reading ability, school outcome, and behaviour in relation to gender, neonatal risk factors, growth, and MRI findings at 15 years of age.

Paper IV

To assess self-perceived health status, quality of life and social functioning at 20 years of age, and relate these health outcomes to neonatal risk factors and disability.

MATERIAL

Study group

The study group initially included all live-born VLBW children (n=107) born to 97 mothers resident in the south-east region of Sweden (the counties of Jönköping, Kalmar and Östergötland with a total population of 935,000) between 1 February 1987 and 30 April 1988, and thus born before the era of prenatal steroid and surfactant treatment. The total number of deliveries in the region during the same time-period was 14,787, equivalent to 0.72% with VLBW newborns.

Considerable efforts were made to obtain a complete registration of all infants. Antenatal steroids in at least 1 dose were given to 18 (18%) mothers and 86 (89%) were delivered by Caesarean section. A majority of the children (n=63; 59%) were born in the University Hospital, Linköping and another 9 were transferred there after birth. The other children were cared for in the Neonatal Units of the hospitals in Jönköping, Kalmar, Norrköping, and Västervik. Twenty-one (19.6%) of the live-borns died (mean BW 1001 g; range 545-1465 g; mean GA 28.4 weeks; range 24-34 weeks), none after the first 4 weeks. The BW- and GA-specific mortality and the number of SGA infants in each interval are shown in Table 1. The survival rates in the interval 24-26 weeks were: week 24: 0 out of 1; week 25: 2 out of 7; week 26: 3 out of 6.

Table 1. Birthweight- and gestational age-specific mortality and the number of SGA infants of the 107 live-born VLBW infants (percentages in parentheses)

BW (g)	Total n	Survived n (%)	Dead n (%)	SGA n (%)	GA (weeks)	Total n	Survived n (%)	Dead n (%)
≤ 750	11	4 (36)	7 (64)	4 (36)	24 - 26	14	5 (36)	9 (64)
751 - 1000	14	10 (71)	4 (29)	7 (50)	27 - 29	24	20 (83)	4 (17)
1001 - 1250	37	33 (89)	4 (11)	22 (59)	30 - 32	50	43 (86)	7 (14)
1251 - 1500	45	39 (87)	6 (13)	16 (36)	33 - 35	17	16 (94)	1 (6)
					≥ 36	2	2 (100)	0
In all	107	86 (80.4)	21 (19.6)	49 (46)		107	86 (80.4)	21 (19.6)

A total of 86 (80.4%) children (47 boys out of 60 and 39 girls out of 47 live-borns) survived the neonatal period and were recruited to the follow-up study. Data are shown in Table 2 for the total VLBW and control groups. Mean BW was 1191 g (SD 216 g), ranging from 685 to 1500 g, and mean GA was 30.6 weeks (SD 2.5 weeks) ranging from 25 to 37 weeks. Distribution of GA of the VLBW children is shown in Figure 2. There were neither

significant difference in anthropometric measurements at birth, nor significant differences in Apgar score, days in mechanical ventilation, or frequency of IVH between boys and girls.

The VLBW group included 4 pairs of twins and 10 of the children were one of a pair of twins. Surfactant treatment was not in use at that time. One child with Downs' syndrome was excluded in the follow-up assessments. One child had emigrated.

Table 2. Perinatal and neonatal data for surviving VLBW children and their controls

	VLBW n=86	Control n=86
Perinatal data		
Pre-eclampsia	16 (18.6%)	0
Antenatal steroids	18 (20.9%)	1 (1.2%)
Caesarean section	68 (79.1%)	5 (5.8%)
Twins	18 (20.9%)	2 (2.3%)
Neonatal data		
Birthweight (g), mean; SD	1191; 216	3581; 517
Birthweight (g), range	685-1500	2230-4860
Gestational age (weeks), mean; SD	30.6; 2.5	39.7; 1.3
Gestational age (weeks), range	25-37	37-42
Sex (male)	47 (54.6%)	45 (52.3%)
Small for Gestational Age (n)	44 (51.2%)	2 (2.3%)
Oxygen treatment (n)	65 (75.6%)	0
Oxygen treatment (days), mean; SD	14.1; 21.8	
Mechanical ventilation (n)	16 (18.6%)	0
Mechanical ventilation (days), mean; SD	8.4; 8.1	
Respiratory Distress Syndrome (n)	22 (25.6%)	0
Bronchopulmonary Dysplasia (n)	6 (7.0%)	0
Intraventricular Haemorrhage (grade 1-2) (n)	11 (12.7%)	0
Intraventricular Haemorrhage (grade 3-4) (n)	4 (4.6%)	0
Sepsis (n)	7 (8.1%)	0
Neonatal hospital stay (days), mean; SD	61.4; 42.5	5.2
Neonatal hospital stay (days), median, range	54 (14-366)	5 (3-9)

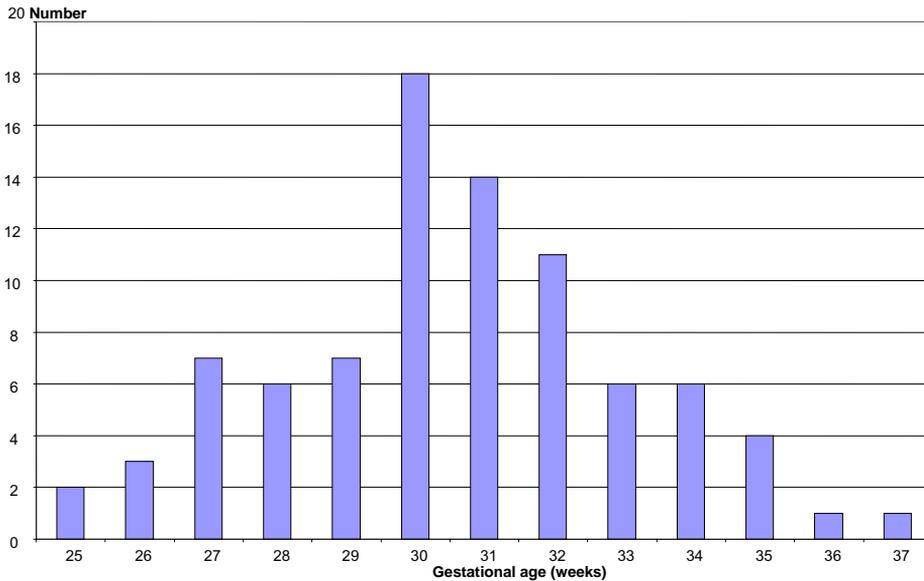


Figure 2. Distribution of surviving VLBW children according to gestational age (weeks).

Control group

A control group was selected in the neonatal period in the following way: for each VLBW-child who survived the first two days, an infant born term and next in order to the index child, with the same gender and parity and without malformation, was chosen at the hospital where the VLBW infant was born (or would have been born, if the mother had not been referred before birth). Some control children were retained in the study, although their VLBW child had died after two days, in order to compensate for a small number of VLBW children who were born in hospitals outside the region and thus included later.

A total of 86 children participated from the newborn period, 45 boys and 41 girls. This group included one pair of twins. One child had died and one had emigrated.

Participation at follow-up examinations

Follow-up examinations of the VLBW children and controls have also been performed at 6 and 18 months of age and at 4, 9, and 12 years of age and results have been published previously [82,83,109,175]. Data on participation and ages of VLBW boys and VLBW girls and their controls at follow-up examinations are shown in Table 3. A majority of VLBW males (91%), VLBW females (82%), control males (82%), and control females (76%) had participated in the follow-up examinations 5-6 times from 6 months to 15 years of age.

At 15 years of age, 58/80 (73%) VLBW children (30 boys; 28 girls) without overt disability and 53/86 (62%) controls (27 boys; 26 girls) participated in neurological assessment (Paper II), and 61/86 (71%) VLBW children (32 boys; 29 girls) and 57/86 (66%) controls (30 boys; 27 girls) participated in cognitive assessments (Paper III).

At the 20-year follow-up, 77 (90.6%) VLBW subjects (43 males, 91.5%; 34 females, 89.5%), and 69 (82.1%) controls (34 males, 79.1%; 35 females, 85.4%) completed questionnaires.

Table 3. Numbers and ages of VLBW and control participants at follow-up examinations.

		Males VLBW	Controls	p	Females VLBW	Controls	p
40 weeks (post-concep.)	n	45	43		31	38	
Weeks; mean (SD)		39.5 (1.4)	40.3 (1.3)	0.004	40.0 (1.2)	40.2 (1.1)	ns
6 months (corrected)	n	47	45		39	39	
Months; mean (SD)		6.2 (0.5)	6.4 (1.1)	ns	6.2 (0.5)	6.5 (0.6)	ns
18 months	n	44	43		37	38	
Months; mean (SD)		18.5 (1.0)	18.5 (1.1)	ns	18.3 (0.8)	18.5 (0.7)	ns
4 years	n	42	43		38	39	
Years; mean (SD)		4.1 (0.1)	4.1 (0.1)	ns	4.1 (0.2)	4.1 (0.1)	ns
9 years	n	41	36		29	37	
Years; mean (SD)		9.0 (0.1)	9.0 (0.1)	ns	9.1 (0.3)	9.0 (0.1)	ns
12 years	n	43	34		31	31	
Years; mean (SD)		12.6 (0.2)	12.7 (0.3)	ns	12.6 (0.2)	12.6 (0.2)	ns
15 years	n	33	29		29	27	
Years; mean (SD)		15.3 (0.4)	15.6 (0.5)	0.032	15.3 (0.5)	15.5 (0.4)	ns

METHODS

Neonatal data

Potential neonatal risk factors

Potential neonatal risk factors were identified: GA below 30 weeks, ELBW, SGA, mechanical ventilation (more than 24 hours), RDS, BPD, IVH, sepsis, and length of neonatal stay (LOS). GA was calculated by foetal ultrasonography or determined from the dates of last menstrual period. SGA was defined as $BW \leq 2$ SD from the mean according to the Swedish standard chart in use at that time (Karlberg P, Engström L and Selstam U; 1979). Mechanical ventilation was recorded as total days in respirator. RDS was defined on the basis of clinical and radiographic findings. BPD was defined on the basis of clinical (oxygen dependent at 36 weeks of GA) and radiographic findings. Cranial ultrasonography was performed at least three times in the VLBW group (day 1-3, day 6-10 and before discharge or at 40 weeks) and once during the first week of life in the control group. IVH was graded according to Papile et al [198]. Sepsis was defined as a positive blood culture in a child with clinical symptoms of infection. Number of days in neonatal care unit or days until discharge was defined as LOS.

Socio-economic data

Maternal age, parity, smoking habits, and parental educational levels (three categories: primary school, upper secondary school, university) were registered in connection with the neonatal care. Information about number of siblings and divorces was noted at the 4-year and the 9-year follow-ups. Data on parental educational level (three categories) at the 9-year follow-up and on parental profession at the 15-year examination were registered (five categories and according to Statistics Sweden; SEI 1982:4, new edition 1995).

Register data

Hospital readmissions

Information about diagnoses and dates of readmission and discharge was obtained from the Swedish Hospital Discharge Register, Epidemiological Centre, The National Board of Health and Welfare, Stockholm [199]. This register covers all inpatient care in Sweden since 1987 with less than 1% losses. It was possible to collect data for every hospital readmission from birth up until 2002, i.e. 15 years of age. The number of readmissions and total hospital days (HD) for every child were registered. Age at time of readmission was separated into four age groups: 0-0.99 years (uncorrected age); 1.00-3.99 years; 4.00-8.99 years and 9.00-15 years in order to match the follow-up ages.

Hospital diagnoses

Diagnoses according to International Classification of Diseases (ICD) 9 were used up to year 1996, and thereafter ICD 10. The main diagnoses were grouped into eight domains: infections, allergy and asthma, BPD, neurological (mainly CP, hydrocephalus, and epilepsy), surgical, traumatic and toxicological, specific paediatric diagnoses (e.g. celiac disease, spherocytosis, and hypoglycaemia), and unspecified symptoms and observations.

Child habilitation diagnoses

Data were collected up to 15 years of age from the region's nine child habilitation centres regarding date of first contact, kind of treatment, and diagnoses: cerebral palsy (CP), ADHD, MR. The functional status of CP, ADHD and MR was divided into mild, moderate, and severe. Mild CP was defined as walking without help, moderate CP as walking with help, and severe CP as inability to walk. The criteria for mild ADHD were having the diagnosis, but without known social implications; moderate ADHD with slight social implications, and severe ADHD with severe social implications. Mild MR was defined as IQ 70 to 50, moderate MR as IQ 49 to 35 and severe MR as IQ below 35.

Child psychiatric diagnoses

Data were collected up to 15 years of age from the region's eight child psychiatric outpatient clinics regarding date of first and last contact, diagnoses and kind of treatment. Children with ADHD diagnoses were registered as child habilitation diagnoses.

School performance

Final school reports from the 9-year compulsory school were requested from the municipal administrations. Four grades had been given for each school subject according to the official standard (failed, passed, passed with distinction, and passed with special distinction, designated 1-4, respectively). A summary score for 9 subjects (art education, English, home economics, physical education, mathematics, music education, handicraft, Swedish, and technology) was calculated. Information about school situation was registered. Children attending special classes or school for disabled children were excluded in the school report analysis (5 VLBW boys, 1 VLBW girl and 1 control girl).

Examinations

Neurological examination

Neonatal neurological examination

A detailed neonatal neurological examination adapted from Prechtel [200] was performed by a trained neonatologist at a corrected age of 40 weeks for the VLBW children and at day 5 in the maternity ward for the control children (Appendix 1). Muscle tonus (8 variables) and excitability (13 variables) were scored separately, and the optimal responses (9 variables) gave the optimality score. A high value for muscle tonus score indicates hypotonus, and a high value for excitability score indicates low excitability. Total scores were calculated for each infant [82,201].

Follow-up neurological examinations

Neurological assessments were performed in the outpatient paediatric clinics at the five hospitals at 4, 9 and 15 years of age by paediatricians who were trained in the methods but had no knowledge of the results from previous examinations. A trained physiotherapist performed the majority of the 15-year examinations. The examinations at 4 years (10 developmental and 5 neurological items) were based on Griffiths (psychomotor development) [202], and Touwen and Prechtel (neurology) (Appendix 2) [203]. The 9-year examination (12 neurological items) was modified after Stott (Appendix 3) [204]. High developmental scores indicated good skills, and high neurological scores indicated poor motor function. At 15 years of age, the short version of the Bruininks-Oseretsky Test of Motor Proficiency was used, which included 14 items reflecting gross and fine motor skills, coordination, and visual-motor controls (Appendix 4) [205]. High total scores indicated better results.

Visual function

Ophthalmological examinations, including screening for ROP, were performed at 40 weeks GA in the VLBW children and during the first neonatal week in the controls, at 4 and 15 years of age. At 4 years of age normal visual acuity (VA) was defined as ≥ 0.8 , mildly reduced as 0.3-0.65, and impaired as < 0.3 [84]. At the 15-year follow-up, the children were examined by the ophthalmologists in the research team. Methods are described by Hellgren et al [142]. Normal VA was defined as ≥ 1.0 , mildly reduced as 0.3-0.9, and impaired as < 0.3 . At 15 years of age, binocular and monocular best corrected VA were tested using the line letter KM chart [206]. The VA from the better eye was used for comparison between groups. The incidence of strabismus was examined with cover test and was noted to be latent or manifest. The wearing of eye glasses or not was noted. At 20 years of age, visual problems and need for glasses were inquired about in a questionnaire.

Hearing function

Data were collected from the Child Health Centres, where hearing test were performed with an audiometer in a standardized way at 4 years of age [207]. Abnormal test results were characterized of ≥ 25 decibel (dB) in two or more of the frequencies 1000, 2000 or 3000 Hz or ≥ 30 dB in one of the frequencies 500, 1000, 2000 or 3000 Hz. At 9 years of age, a whispering test was performed at the follow-up visit. At 20 years of age, hearing problems and need for hearing aid were inquired about in a questionnaire.

Growth

Weight, height, and occipito-frontal circumference (OFC) were assessed in a standardized manner at the follow-up visit at 15 years of age. Weight was taken in only underclothes and specified in kg with one decimal. Height was measured using a Stadiometer attached to the wall and after removing shoes. Results were specified in cm with one decimal. OFC was measured by the paediatrician with a measuring-tape and specified in cm with one decimal. Body mass index (BMI) was calculated from weight (kg)/height² (m) with one decimal. Correlation between growth outcome and results on WISC III were analysed using univariate linear regression.

At 20 years of age, data about weight and height were self-reported and registered in kg and cm respectively without any decimals. BMI was calculated.

Cognitive function

Cognitive function was assessed using the Wechsler Intelligence Scale for Children (WISC III, Swedish version), Verbal, Performance, and Full Scale IQ [208] by psychologists who

were unaware of group status. Examinations were performed in the outpatient paediatric clinics at the five hospitals at 15 years of age. Data obtained from habilitation centres and child psychiatric clinics were requested in order to evaluate earlier unknown children with MR or fulfilling the psychometric criterion for MR (IQ < 70) [209].

Reading skills

Reading ability was assessed by means of tests measuring word decoding, word recognition, and reading comprehension and described in detail by Samuelsson et al [176]. Word decoding was measured by means of a non-word reading test and a test of phonological choice [210,211]. Word recognition was assessed using a test of word reading, orthographic choice, and orthographic reading [210,212]. Reading comprehension was tested using subtests developed by the International Association for the Evaluation of Educational Achievement [213]. These tests were administered by the same examiners who performed the cognitive testing at 15 years of age.

Magnetic Resonance Imaging of the brain

VLBW children were investigated with MRI at 15 years of age. The examinations were conducted at six local hospitals, with imaging protocols that followed a predetermined general guideline (Appendix 5). We chose MRI sequences suitable for routine clinical examination and did not include the advanced imaging techniques employed by some other authors [132,196]. Assessment and classification of MRI findings were done by two paediatric neuroradiologists in consensus and without knowledge of the clinical outcome. WMD was recorded as absent or present, and its location recorded as anterior, central or posterior. According to the amount of involved cerebral white matter, findings were classified as mild (<25% loss of total white matter), moderate (25-50% loss), or severe (>50% loss), with emphasis on WMD of immaturity [122].

Questionnaires

Behaviour

Both children and parents separately answered Achenbach's questionnaires about emotional and behavioural problems at 15 years of age, the Youth Self-Report (YSR) [214] and the Child Behaviour Check List (CBCL) [215], respectively. YSR is a 112-item survey for ages

11 to 18 years which is scored to obtain nine narrow-band scales, a total problem score, and a social desirable scale. Two broad-band dimensions are also formed: internalizing and externalizing scale. CBCL contains 113 items which are scored by parents for children between the ages of 6 and 18 years. These items also generate eight narrow-band scale scores, a total score, an internalizing score, and an externalizing score. In both, a high problem score indicates more emotional and behavioural problems.

General health and transition to early adulthood

Three postal questionnaires were used at 20 years of age (December 2007) and sent to all surviving VLBW and control participants in the study. If the questionnaires were not returned in four weeks, a reminder was sent by post. Further failure to respond was followed by a phone call.

A study-specific questionnaire about health and social conditions

The questionnaire consisted of 11 questions about general health, frequency of hospital admission and medical attention over the previous 5 years, regular contact with a physician, use of medication, medical aids and assistance, use of tobacco and alcohol, and information about weight and height, and 5 questions about socio-economic conditions such as educational level (3 years at upper secondary school, with 17 different national programmes, and graduation at about 19 years of age is the most common form of education in Sweden), present occupation, living conditions and recreational activities (Appendix 6). It was possible to give up to 3 activities and each was assigned one of the following categories: artistic or aesthetic activity; being together with friends; individual sport activity; team sport activity; involved in a society; computer work, watching TV or films; outdoor activity; studying; and handcraft. BMI was calculated (kg/m^2).

SF-36

Medical Outcomes Study, Short Form, Swedish version with 36 questions (SF-36) was used. SF-36 is adequate for adolescents and older subjects and takes 10 minutes to complete [216-218]. High scores indicate better results. The questionnaire contained 21 questions about functioning (5 scales: physical functioning, role-physical, role-emotional, social functioning and bodily pain), 14 questions about well-being (3 scales: mental health, vitality and general health), and 1 question about health transition [218,219]. In addition to the 8 health scales, 2 dimensions were also calculated, viz. physical and mental health score (PCS and MCS), each as a summary of 4 scales: for PCS physical functioning, role-physical, bodily pain and general health, and for MCS vitality, social functioning, role-emotional and mental health. Low PCS and MCS scores were defined as scores below 2 SD from the mean against a reference group from Sweden aged between 15 and 29 [219].

Sense of Coherence

Sense of Coherence is a questionnaire with 29 questions and appropriate for adolescents and older. Three core dimensions are defined: comprehensibility as the cognitive component summarised from 10 items, manageability as the behavioural component summarised from 10 items, and meaningfulness is the component of motivation summarised from 8 items [184]. The total SOC score includes the core dimensions plus 1 item. High total scores indicate better results.

Statistical methods

Statistical Package for the Social Sciences (SPSS), versions 11.5 and 13.0 respectively, was used for registering and evaluating data. Parametric and non-parametric tests were used. The non-parametric method was applied as some groups contained small samples and normal distribution was not guaranteed. Student's t-test, the Mann-Whitney U test, the chi-square test, and logistic regression models were employed to analyse the differences between groups regarding normal and non-normal distributed values. Analyses were carried out separately for male and female participants, when appropriate. A p value below 0.05 was considered significant in all tests.

Specific tests in each paper:

Paper I: The associations between neonatal risk factors (GA below 30 weeks, ELBW, SGA, IVH grade II-IV, RDS, BPD, sepsis, mechanical ventilation, neonatal stay > 60 days, and male sex) and readmissions and HD were studied by means of univariate logistic regression. Fewer than 3 readmissions and fewer than 6 HD were chosen as cut-off in logistic regression analyses. Significant risk factors were then included in a multivariate model.

Paper II: Correlations between developmental/neurological scores and gender and seven neonatal risk factors (GA below 30 weeks, ELBW, SGA, mechanical ventilation, RDS, IVH grade I-IV, and sepsis) were studied by means of univariate linear regression analyses. Correlations between developmental and/or neurological outcome and gender, ELBW, mechanical ventilation, and IVH were studied by means of multivariate linear regression analyses. Associations between pathological findings from MRI and the seven neonatal risk factors were studied using univariate logistic regression analysis. Associations between pathological findings from MRI and developmental and neurological scores were studied in univariate logistic regression analysis. Reference population was VLBW children without pathological findings.

Paper III: Mean values and a summary score of nine school subjects (art education, English, home economics, physical education, mathematics, music education, handicraft, Swedish, and technology) were compared between the groups. Correlations between seven neonatal risk factors (GA below 30 weeks, ELBW, SGA, mechanical ventilation, BPD, IVH grade I-IV, and sepsis) and results on WISC III, reading skills (data from Samuelsson et al; [176]), a summary score of school subjects, YSR, and CBCL were analysed using univariate and multivariate linear regression. Correlation between growth outcome and results on WISC III were analysed using univariate linear regression. Associations between MRI findings and results on WISC III, readings skills, summary score of school subjects, YSR, and CBCL were analysed using a univariate linear regression model in comparison with children without WMD.

Paper IV: Handicap was defined as moderate or severe CP, moderate or severe ADHD, or MR (IQ<70). Correlations between six neonatal risk factors (GA below 30 weeks, ELBW, SGA, mechanical ventilation, BPD, and IVH grade I-IV), handicap and results of 8 health scales and 2 dimensions on SF-36 and 3 core dimensions and total score on SOC were analysed using univariate and multivariate linear regression. The reference population consisted of VLBW subjects with no identified neonatal risk factor or handicap, respectively.

Thesis: Associations between increasing number of neonatal risk factors and summary of 9 school reports, total motor score, Full Scale IQ, total score on YSR and CBCL at 15 years of age were analysed using univariate linear regression.

Ethical approval

All follow-up studies, and the questionnaire study were approved by The Ethical Committee of the Faculty of Health Sciences at Linköping University (Registration numbers: 02-157 and M190-07). Parents, and children at the 15-year follow-up examination, gave their informed consent to participate in the studies.

RESULTS

Neonatal data

For all included VLBW children (n=86) following neonatal data were obtained (Table 2): Twenty-four (28%) children had a GA below 30 weeks, 14 (16%) were ELBW, and 44 (52%) were SGA, according to the Swedish chart used at that time, with a GA of 32.4 vs. 29.4 weeks for appropriate for gestational age (AGA) children ($p<0.001$). Sixteen (19%) were treated with mechanical ventilation and 22 (26%) of the children had RDS. Surfactant treatment was not in use at that time. BPD was diagnosed in six (7%) of these children. In 15 (18%) IVH was found with cranial ultrasonography, and 4 of them had grade III-IV. Two children had suspected PVL and one of them had IVH grade I; two had PVL and IVH grade III-IV and were later given ventricular-peritoneal shunts due to hydrocephalus. In addition, one had post haemorrhagic hydrocephalus and was operated with a shunt. In 7 (8%) children sepsis was diagnosed and 30 (35%) had a neonatal stay of more than 60 days.

Socio-economic data

Data from the neonatal period showed no significant differences between VLBW and control groups as regards maternal age, parity, and smoking habits, and educational level, but fathers in the control group had a higher level of education ($p=0.006$ at the 15-year follow-up and $p=0.026$ at the 20-year follow-up) (Table 4). There were no differences regarding number of siblings and divorces between the groups at the 4-year and the 9-year follow-ups. There was no difference in maternal professional level at the 15-year follow-up, but control fathers had a higher level of profession ($p=0.045$).

Table 4. Socio-economic data concerning parents of VLBW and control subjects at birth and participating at 20 years of age.

	VLBW Birth	Controls Birth	VLBW 20 years	Controls 20 years
	n=86	n=86	n=77	n=69
<i>Mother smoking at child birth</i>	n=81	n=81	n= 73	n=64
Yes	28	23	25	17
<i>Mother's educational level</i>	n=80	n=79	n=72	n=62
Primary school	31	26	29	21
Upper secondary school	36	31	31	24
University	13	22	12	17
<i>Father's educational level*</i>	n=74	n=77	n=67	n=60
Primary school	31	19	28	16
Upper secondary school	30	31	28	22
University	13	27	11	22

* p=0.021 (Chi-square test) at birth

* p=0.026 (Chi-square test) at the 20-year follow-up

Register data

Hospital readmissions

Fifty-nine out of 85 (69.4%) VLBW children, 36 (76.6%) boys and 23 (60.5%) girls, and 51 of 85 (60%) controls, 28 (63.6%) boys and 23 (56.1%) girls, had been readmitted after the neonatal period. One child in the VLBW group was not discharged from hospital until one year of age.

Eighteen VLBW children had more than five readmissions and four of these had been readmitted to hospital more than 10 times. VLBW boys had a significantly higher risk of readmission than control boys up to 15 years of age (OR 4.1; 95% CI: 1.4-12.5; p=0.012). The risk of readmission for VLBW girls was not significantly higher than for control girls (OR 2.5; 95% CI: 0.68-8.9; p=0.171).

The mean numbers of readmissions and HD were significantly higher in VLBW boys than in control boys up to 1 year of age, between the ages of 4 and 9, and from neonatal discharge to 15 years of age (Table 5). VLBW boys accounted for the majority of the hospital readmissions (70%) and of the HD (72%) among VLBW infants.

Table 5. Readmissions and hospital days (mean and SD) between 0 and 15 years for 59/85 VLBW children and 51/86 controls.

	Boys		p	Girls		p
	VLBW n=36	Control n=28		VLBW n=23	Control n=23	
Readmissions						
Age at readmission						
0–0.99 years	1.4; 1.7	0.4; 0.6	0.016	0.5; 0.8	0.3; 0.6	0.578
1–3.99 years	1.1; 1.7	0.6; 0.7	0.454	1.3; 2.2	0.7; 1.0	0.180
4–8.99 years	1.0; 1.6	0.3; 0.7	0.021	0.5; 0.8	0.3; 0.5	0.284
9–15 years	0.6; 1.1	0.3; 0.5	0.660	0.5; 1.1	0.4; 0.5	0.441
Total	4.1; 4.7	1.6; 0.8	0.016	2.8; 2.9	1.7; 1.0	0.368
Hospital days						
Age at readmission						
0–0.99 years	5.6; 9.4	0.8; 1.4	0.007	2.3; 5.0	0.9; 2.2	0.507
1–3.99 years	3.7; 8.1	1.1; 1.7	0.496	3.6; 7.2	1.5; 3.0	0.224
4–8.99 years	2.9; 5.9	0.9; 2.0	0.032	1.4; 3.2	0.8; 2.2	0.383
9–15 years	1.6; 4.3	0.7; 2.3	0.680	1.2; 4.0	1.0; 2.1	0.363
Total	13.7; 21.8	3.4; 3.3	0.014	8.5; 11.6	4.2; 4.0	0.752

Hospital diagnoses

Infections were responsible for 39 readmissions for VLBW boys and 21 for control boys, and 23 readmissions for VLBW girls and 14 for control girls. Upper respiratory tract infections were the predominant causes. Surgical, mainly hernias, and neurological diseases were the second common causes for VLBW boys and symptoms with no specific diagnosis and neurological diseases for girls. The total and mean numbers of readmissions were significantly higher in VLBW boys in comparison with control boys ($p=0.010$), but also for asthma/allergy ($p=0.014$) and neurological diseases ($p=0.029$) (Table 6). VLBW girls and control girls did not differ significantly in any diagnostic field or in total number of readmissions.

Table 6. Total number and means of readmissions in all VLBW boys and girls and their controls in relation to diagnoses up to 15 years of age.

	Boys					Girls				
	VLBW		Controls		p	VLBW		Controls		p
	n=47	Mean	n=45	Mean		n=38	Mean	n=41	Mean	
Infectious diseases	39	0.83	21	0.47	0.468	23	0.61	14	0.34	0.207
Asthma/Allergy	17	0.36	0	0.00	0.014	4	0.11	0	0.00	0.068
BPD	2	0.04	0	0.00	0.328	5	0.13	0	0.00	0.299
Neurological diseases	28	0.60	1	0.02	0.029	14	0.37	1	0.02	0.134
Surgical diseases	28	0.60	7	0.16	0.063	2	0.05	4	0.10	0.693
Trauma/Toxicological diseases	9	0.19	9	0.20	0.919	5	0.13	8	0.20	0.450
Specific paediatric diseases	6	0.13	0	0.00	0.087	1	0.03	4	0.10	0.594
Symptoms without diagnoses/Observations	16	0.34	6	0.13	0.270	14	0.37	7	0.17	0.412
Total:	145	3.11	44	0.98	0.010	68	1.68	38	0.93	0.459

Child habilitation diagnoses

Fifteen (17.6%) VLBW children and one (1.2%) control child were registered at the child habilitation centres, three of them for a shorter period: two VLBW children and one control child for investigation of ADHD.

The distribution of the main diagnoses for the VLBW children (12 boys and 3 girls) was: CP (n=9), ADHD (n=5), and MR (n=1).

Most of the children with CP (7 boys and 2 girls) were diagnosed during the first two years of life at follow-up examinations. Four children had mild CP (3 with diplegia; 1 with hemiplegia); four moderate CP (3 with diplegia; 1 with hemiplegia), and one severe CP (tetraplegia). Two children with CP were SGA (1 with mild diplegia, and 1 with moderate hemiplegia). Of those with moderate/severe CP, three had mild MR and two, of whom one was autistic, moderate MR. BW and GA differed significantly between the five children with moderate/severe CP and the other VLBW children (BW: 843 vs. 1212 g, $p=0.002$; GA 27.3 vs. 31.1 weeks, $p=0.004$). The children with moderate and severe CP are presented in Table 7. Three children with moderate/severe CP had post-haemorrhagic hydrocephalus.

Five VLBW children, all boys, (5.8%) had ADHD; three of them had moderate/severe ADHD and two mild MR. Two children received treatment with central stimulant drugs. There were no significant differences between the children with ADHD and the other VLBW children according to BW, GA, or days of treatment in mechanical ventilator. One (1.2%) control child had a mild ADHD ($p=0.103$).

One VLBW child had MR without any other psychomotor dysfunctions. A total of 8 (9.4%) VLBW children had MR.

Table 7. Birthweight, gestational age, sex, mechanical ventilation, bronchopulmonary dysplasia, intraventricular haemorrhage, findings from magnetic resonance imaging, cerebral palsy, mental retardation, and other diagnoses for very low birthweight children with moderate/severe CP and therefore not included in the follow-up evaluation at 4, 9, and 15 years of age.

Case No	Sex	BW g	GA Weeks + d	Mechanical ventilation Yes/No	BPD Yes/No	IVH Grade	MRI Classification	CP Diagnose	MR Classification	Other diagnoses
1	F	740	25+5	Yes	Yes	I	Moderate	Diplegia, moderate	Moderate	Blindness (ROP)
2	M	750	25+4	Yes	Yes	IV	Severe	Diplegia, moderate	Mild	Hydrocephalus
3	M	795	26+6	Yes	Yes	I	Moderate	Diplegia, moderate	Mild	Twin
4	F	800	27+3	Yes	Yes	III	No examination	Tetraplegia, severe	Moderate	Hydrocephalus
5	M	1130	31+0	Yes	No	IV	Severe	Hemiplegia, moderate	Mild	Hydrocephalus

Child psychiatric diagnoses

In the VLBW group, eight children (9.3%; 7 boys and 1 girl) had had contact with a child psychiatric clinic compared with thirteen (15.1%; 6 boys and 7 girls) in the control group (ns). One VLBW and one control child had been treated in hospital. Three VLBW and three controls had behavioural problems (of which two VLBW and one control had ADHD; they are included in child habilitation diagnoses); one VLBW and five controls suffered from depressions; one VLBW had bipolar psychosis; three VLBW and five controls had different kinds of child psychiatric problems (psychosomatic symptoms, anxiety, crisis in family) of which one control had mild MR. No child in either group had social maladjustment as a main diagnosis. There were no significant differences between the groups as regards age at first contact.

School performance

At the 15-year examination, 27/32 (84.4%) of VLBW boys and 28/29 (96.6%) of VLBW girls and all control children except one girl were in mainstream schools. School reports could not be obtained for 3 VLBW boys, 2 VLBW girls, 4 control boys, and 2 control girls. VLBW boys had significantly lower mean results in mathematics ($p=0.006$) and technology ($p=0.050$) compared to control boys, but VLBW girls did not differ from control girls. There were no significant differences between groups in the summaries of nine school subjects.

VLBW children with IQ <70, but in mainstream school ($n=7$), had significantly lower means in all school subjects and in the summary of nine school subjects ($p=0.001$) compared to those with IQ 70 or more.

Examinations

Neurological examinations

Neurological examination in the neonatal period and at follow-ups did not include five children with diagnoses of moderate or severe CP, and they are presented in Table 7. Thus, 80 VLBW children (44 boys and 36 girls) without overt neurological disability and 86 controls (45 boys and 41 girls) were included in the assessments.

VLBW children performed less well at all neurological examinations compared with the controls. The differences were statistically significant in total score ($p<0.001$) at the neonatal examination, in developmental and neurological score ($p<0.001$ and <0.001 , respectively) at 4 years, and in total motor score ($p=0.005$) at 15 years, but not in neurological scores ($p=0.060$) at 9 years.

VLBW boys performed less well at all examinations compared with control boys. The differences were statistically significant in total score ($p=0.001$) at the neonatal examination, in developmental and neurological score ($p=0.014$ and 0.002 , respectively) at 4 years, and in total motor score ($p=0.005$) at 15 years. The difference in neurological scores ($p=0.138$) at 9 years was not statistically significant. VLBW girls did not differ significantly from their controls at the neonatal ($p=0.060$), 9-year ($p=0.302$) and 15-year ($p=0.245$) examinations, but did so at 4 years ($p<0.001$ in developmental score and $p=0.017$ in neurological score). VLBW girls had better developmental and neurological scores compared with VLBW boys at all examinations, but only results at 9 years were significant ($p=0.044$). Total motor score at 15 years was positively correlated to developmental score for VLBW children ($p=0.001$), but no correlation was found to neurological scores at 40 weeks, 4 years and 9 years.

Visual function

74 out of 86 VLBW children (86%) were screened for ROP during the neonatal period, at a GA of 40 weeks. One child was blind due to ROP and one had stage II ROP and was visually impaired at 15 years of age. At four years of age, there was no significant difference ($p=0.087$) in VA in the better eye between the groups, although there was a significantly higher ($p=0.044$) incidence of normal VA in the control group (74%) compared to the VLBW group (53%).

At 15 years of age, there were no differences in the incidence of normal VA ($p=0.366$; 98% and 93%, respectively), but the median VA in the best eye was better ($p=0.009$) in the control group (1.6; mean 1.47) than in the VLBW group (1.3; mean 1.32). A significantly larger proportion ($p=0.007$) of some kind of strabismus (latent or manifest) was observed in the VLBW children (32.2%) compared to the controls (10.9%). There was no significant difference in manifest strabismus (6.8% in the VLBW group and 1.8% in the control group). At age 15, 31% of the children in the VLBW group and 16% of the controls wore glasses frequently or occasionally, i.e. reading glasses ($p=0.083$).

At 20 years of age, 6 (8%) VLBW subjects, of which 2 had a handicap, and 1 (1%) control ($p=0.074$) reported visual problems last year. More VLBW subjects ($n=28$; 36%) were in need of glasses compared with controls ($n=15$; 22%) ($p=0.054$). VLBW males used glasses significantly more often than control males ($p=0.004$).

Hearing function

Data from Child Health Centres were available in 45 (53%) of the VLBW children and 48 (56%) of the controls at 4 years of age. Six VLBW and five control children had adverse hearing on one or both sides. Four VLBW children and one control child had contact with a speech therapist.

At the whispering test at 9 years of age, 3 out of 69 (4.3%) in the VLBW group and 3 out of 73 (4.1%) in the control group had some impairment. None in the two groups seemed to have permanently impaired hearing function.

At 20 years of age, 7 (9%) VLBW subjects, but no VLBW subjects with handicap, and 3 (4%) controls ($p=0.396$) reported hearing problems during the previous year. None in either group reported need of hearing aid.

Growth

At 15 years of age, VLBW boys differed significantly from control boys in weight ($p=0.029$), but not in height, in BMI, or OFC. VLBW girls differed significantly from control girls in all measurements: weight, height, BMI, and OFC (Table 8).

For both VLBW boys and VLBW girls, but not for control children, significant correlations were found between small OFC and low Verbal and Full Scale IQ (data not shown).

At 20 years of age, VLBW males and VLBW females differed significantly from their controls in weight and height (Table 8). VLBW females tended to have lower BMI than their controls ($p=0.052$). One VLBW male, 3 control males and 2 control females had a BMI above 30.

Table 8. Anthropometric data at 15 and 20 years of age for VLBW males, VLBW females and their controls. Data concerning weight and height at 20 years of age are self-reported. BMI is calculated.

	Males			Females		
	VLBW	Controls	p	VLBW	Controls	p
	n=33	n=28		n=28	n=27	
At 15 years of age						
Weight (kg), mean; SD	59.1; 9.8	66.4; 15.4	0.029	50.9; 5.6	58.2; 8.0	<0.001
Height (cm), mean; SD	169.9; 8.8	174.4; 9.4	0.056	160.0; 5.7	164.3; 3.9	0.002
BMI, mean; SD	20.4; 2.6	21.7; 3.8	0.135	19.9; 2.2	21.5; 2.9	0.021
Occipito-frontal circumference	55.8; 1.5	56.6; 1.8	0.083	53.8; 1.3	55.3; 1.2	<0.001
At 20 years of age						
	n=40	n=33		n=32	n=35	
Weight (kg), mean; SD	70.2; 11.4	79.4; 16.8	0.007	55.5; 6.2	62.7; 11.6	0.003
Height (cm), mean; SD	174.7; 8.6	181.1; 7.7	0.001	161.8; 6.4	165.9; 6.0	0.008
BMI, mean; SD	23.0; 3.3	24.1; 4.3	0.214	21.2; 2.5	22.8; 3.9	0.052

Cognitive function

The VLBW group had significantly lower values in WISC III on all scales compared with the control group (Table 9), with a mean difference of 12 in Full Scale IQ. Fifty-one percent of VLBW children vs. 79% of controls were above IQ 85, 29% vs. 19% between IQ 70-85.

Table 9. Cognitive functions tested with WISC III at 15 years of age in VLBW boys and VLBW girls and their controls.

			p	Boys	Girls	p
	VLBW	Controls		VLBW	VLBW	
	n=59	n=57		n=31	n=28	
Verbal IQ, mean; SD	86.0; 16.5	96.5; 13.6	<0.001	85.5; 17.1	86.5; 16.0	0.808
Performance IQ, mean; SD	87.0; 19.6	98.6; 15.8	0.001	86.0; 24.4	88.1; 12.7	0.684
Full Scale IQ, mean; SD	84.9; 17.5	97.1; 13.3	<0.001	84.1; 19.9	85.7; 14.7	0.737

Table 10. Description of cognitive function tested with WISC III at 15 years of age in VLBW and control children.

	IQ level	VLBW n=59 (%)	Controls n=57 (%)	Swedish reference*
Description of intelligence function				
Exceptionally high	≥130	0	0	2%
High	120-129	1 (1.7)	2 (3.5)	7%
Upper normal zone	110-119	3 (5.1)	7 (12.3)	16%
Normal zone	90-109	20 (33.9)	31 (54.4)	50%
Lower normal zone	80-89	15 (25.4)	13 (22.8)	16%
Low	70-79	8 (13.6)	3 (5.3)	7%
Exceptionally low	<70	12 (20.3)	1 (1.7)	2%

*Swedish reference according to Gabrielson et al [85]

IQ levels for VLBW children compared to their controls and a Swedish reference material are shown in Table 10. Twelve (20%) VLBW children (7 boys and 5 girls) and 1 control (2%) had a Full Scale IQ of less than 70, fulfilling the psychometric criterion for MR. Only two of these VLBW children had been identified earlier. Eight VLBW children with MR had no obvious neurological symptoms. VLBW boys did not differ significantly from VLBW girls in mean Full Scale IQ. In the VLBW group, SGA children had a mean Full Scale IQ of 82 compared with 88 for AGA children (ns).

Cognitive test results for children attending mainstream school showed significant differences between the VLBW and control groups in Verbal, Performance, and Full Scale IQ ($p=0.001$, 0.002 , and <0.001 , respectively).

Reading skills

VLBW children performed less well than control children in most aspects of reading skills, but only orthographic choice reached significance ($p=0.002$). VLBW boys did not differ in any reading skill compared to control boys, whereas VLBW girls differed significantly from their controls in all three parameters of word recognition (Table 11). There were no significant differences between boys and girls, although VLBW and control girls in general had higher means than boys.

Magnetic Resonance Imaging findings

Fifty-nine children (31 boys and 28 girls) participated. There were no significant differences in BW or GA between those who had been investigated with MRI and those who had not.

Sixteen of fifty-nine (27.1%) children had WMD: mild in 13, moderate in 1, and severe in 2 cases (Table 7). One child had one-sided abnormal neuronal migration. Both children with suspected PVL on ultrasound had mild WMD.

Paper II (VLBW children with disabilities were excluded): VLBW children with pathological MRI findings did not differ significantly in comparison with those with normal MRI in developmental and neurological scores at any follow-up examination.

Paper III (all participating VLBW children included): There were differences in Verbal, Performance and Full Scale IQ between those with pathological MRI findings and those without, but these differences were not significant (Table 12). VLBW boys with MRI deviations had significantly lower Performance IQ and Full Scale IQ compared with boys without WMD. VLBW girls with MRI abnormalities performed higher Verbal, Performance, and Full Scale IQ compared with girls without MRI findings, though these differences were not significant.

There were no significant correlations between abnormal MRI findings and reading skills, summary of school subjects, or total problem scores on YSR and CBCL.

Table 11. Means and SD on reading skills for VLBW boys and girls and their controls at 15 years of age.

	Boys			Girls					
	VLBW All (n=61)	Controls All (n=57)	p	VLBW n=32	Controls n=30	p	VLBW n=29	Controls n=27	p
Word decoding									
Non-word reading	29.1; 7.4	30.8; 6.5	0.190	27.7; 8.5	29.4; 6.6	0.375	30.7; 5.6	32.4; 6.2	0.298
Phonological choice	19.8; 7.0	22.0; 7.3	0.098	18.6; 7.9	20.4; 6.8	0.328	21.1; 5.7	23.7; 7.6	0.154
Word recognition									
Word reading	43.7; 9.5	46.5; 8.3	0.099	43.4; 11.6	44.9; 8.6	0.562	44.2; 6.7	48.3; 7.8	0.039
Orthographic choice	43.4; 20.1	54.0; 15.8	0.002	41.6; 22.3	48.7; 15.8	0.155	45.4; 17.5	59.9; 13.9	0.001
Orthographic reading	44.8; 7.3	47.0; 4.2	0.054	43.3; 9.6	46.1; 5.6	0.167	46.5; 2.0	47.9; 0.3	0.001
Reading comprehension									
	22.0; 4.7	23.6; 5.0	0.073	21.6; 5.3	23.1; 6.1	0.313	22.4; 4.0	24.2; 3.3	0.076

Table 12. Results on WISC III in VLBW children assessed with MRI at 15 years of age.

	Boys			Girls					
	MRI normal	MRI pathological	p	MRI normal	MRI pathological	p	MRI normal	MRI pathological	p
Verbal IQ, mean; SD	86.7; 17.3	83.4; 15.5	0.503	89.0; 17.0	76.3; 15.5	0.067	84.5; 17.7	92.4; 10.5	0.275
Performance IQ, mean; SD	91.1; 15.3	80.7; 26.1	0.069	95.6; 16.9	70.3; 29.4	0.006	86.5; 12.3	94.0; 13.4	0.185
Full scale IQ, mean; SD	87.4; 16.0	80.2; 21.4	0.174	91.2; 15.9	70.9; 22.9	0.010	83.6; 15.5	92.1; 12.2	0.201

Questionnaires

Behaviour

The VLBW group did not differ significantly from the control group on YSR scores. VLBW girls had significantly lower scores on thought ($p=0.047$) and delinquent problems ($p=0.002$), aggressive behaviour ($p=0.023$), externalizing ($p=0.007$), and total problems ($p=0.019$) than the control girls. Parental assessment according to CBCL showed no significant difference in behaviour between the VLBW and control group or between sexes in both groups. Four VLBW children (2 boys; 2 girls) scored high on CBCL subscales related to ADHD diagnoses (all had a Full Scale IQ below 70).

Health and social conditions at 20 years of age

VLBW subjects did not differ significantly from their controls in self-perceived health over the previous 5 years, frequency of hospital admission, emergency treatment and regular contact with a physician (Table 13).

Table 13. Self-perceived health, tobacco and alcohol use for non-handicapped and handicapped VLBW subjects and their controls at 20 years of age. Percentages in brackets.

	VLBW All n=77	VLBW Handicap n=16	Controls n=69	All VLBW vs. all controls p	VLBW with handicap vs. all controls p
Self-perceived health last 5 years					
Completely healthy	29 (38)	5 (31)	23 (33)	0.618	0.997
Mostly healthy	44 (57)	9 (56)	41 (60)		
Not healthy	3 (4)	1 (6)	5 (7)		
No information	1 (1)	1 (6)			
Hospital admissions last 5 years	20 (26)	6 (37)	20 (29)	0.842	0.158
Total hospital admissions last 5 years	38	16	32		
Emergency treatment last 5 years	24 (31)	7 (48)	28 (36)	0.192	0.014
Regular contact with physician	8 (10)	5 (31)	3 (4)	0.131	0.001
Regular medical treatment	14 (18)	5 (31)	8 (12)	0.282	<0.001
Self-perceived problems last year with:					
Vision	6 (8)	2 (13)	1 (1)	0.074	0.057
Hearing	7 (9)	0	3 (4)	0.257	0.396
Motor function	6 (8)	5 (31)	2 (3)	0.494	0.001
Reading and/or writing	6 (8)	3 (19)	4 (6)	0.634	0.089
Ability to concentrate	13 (17)	4 (25)	6 (9)	0.142	0.068
Depression	9 (12)	3 (19)	11 (16)	0.455	0.785
Glasses wearing	28 (36)	5 (31)	15 (22)	0.054	1.000

Injuries, fractures and surgical interventions were the most common reasons for admission, whereas neurological diseases and infections were few. VLBW and control subjects did not differ significantly in taking medication regularly, but more VLBW subjects used several pharmaceutical drugs. Among users, six out of eight VLBW females took asthma medication.

Problems with motor function, reading and writing, ability to concentrate and mental depression did not differ significantly between the VLBW and control groups. VLBW subjects with a handicap differed significantly from controls in frequency of emergency treatment over the previous 5 years, regular contact with physician, regular medical treatment and motor function problems. Four used a wheelchair or walker and 3 of these had a personal assistant. One control subject had a personal assistant.

Tobacco habits, i.e. use of cigarettes and moist snuff, were similar between VLBW and control subjects. More VLBW subjects were non-users of alcohol compared to controls ($p=0.043$).

Seventy-eight percent of VLBW subjects and 86% of controls had graduated from upper secondary school (ns). Twenty-three percent of VLBW subjects and 30% of controls had graduated from theoretical programmes (ns) (Table 14). There was no significant difference between males and females. Three VLBW males and 4 VLBW females attended schools for mentally retarded or disabled children and were thus incapable of attaining expected educational levels. Nine VLBW subjects with a handicap had graduated from upper secondary school, but none of them from theoretical programmes.

There were no significant differences in employment or living conditions between VLBW subjects and controls (Table 14), but significantly more subjects with a handicap lived at home.

Sports and outdoor activities were reported by more than 50% of both VLBW subjects and controls (Figure 3). There was no significant difference in frequency of or mean time spent weekly on recreational activities between the groups.

Table 14. Social data for non handicapped and handicapped VLBW subjects and their controls at 20 years of age. Percentages in brackets.

	VLBW All n=77	VLBW Handicap n=16	Controls n=69	All VLBW vs. all controls p	VLBW with handicap vs. all controls p
Graduation from upper secondary school					
Yes	60 (78)	9 (56)	59 (86)	0.239	0.008
No	17 (22)	7 (44)	10 (14)		
Programmes in natural or social sciences	18 (23)	0	21 (30)	0.408	<0.001
				0.684	0.187
Occupation					
Students:					
University	9 (12)	0	12 (18)		
Folk high school/municipal adult education	12 (15)	0	11 (16)		
Schools for mentally retarded/disabled	7 (9)	7 (43)	0		
Employed:					
Full-time	25 (32)	3 (18)	23 (33)		
Part-time	14 (18)	2 (13)	10 (15)		
Unemployed	6 (8)	2 (13)	9 (13)		
Parental leave/military service	2 (3)	0	3 (4)		
No information	2 (3)	2 (13)	1 (1)		
				0.600	0.046
Way of living					
Alone	16 (21)	2 (13)	21 (31)		
Cohabiting	15 (19)	1 (6)	13 (19)		
At home	43 (56)	10 (62)	34 (49)		
Other	2 (3)	2 (13)	1 (1)		
No information	1 (1)	1 (6)	0		

Handicap was defined as moderate or severe cerebral palsy, moderate or severe attention deficit hyperactivity disorder, or mental retardation (IQ<70). p-value concerns differences between all VLBW subjects and all controls, and between VLBW subjects with handicap and all controls.

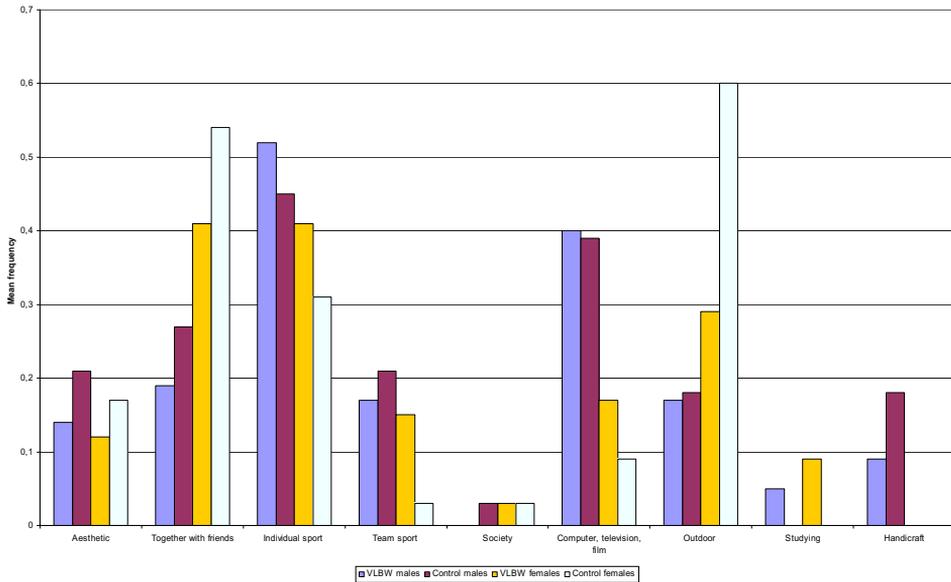


Figure 3. Frequency of recreational activities for VLBW males and VLBW females and their controls at 20 years of age.

SF-36

One VLBW female with CP and one control male did not answer all the questions and were excluded. VLBW subjects did not differ significantly from controls in self-perceived health. There was no difference in the number of VLBW males and females compared to their controls with low physical health score (PCS) and mental health score (MCS). VLBW males scored significantly higher than VLBW females in vitality and mental health ($p=0.037$ and 0.031 , respectively). VLBW subjects with a handicap differed significantly from controls only on physical functioning and PCS ($p<0.001$ and $p=0.035$, respectively).

Sense of Coherence

One VLBW female with CP and one control female did not answer all the questions and were excluded. There were no significant differences in mean scores for comprehensibility, manageability, meaningfulness and total SOC between VLBW subjects and controls or between VLBW subjects with a handicap and controls. Two VLBW females and two control males had low total scores.

Analyses of neonatal risk factors

Hospital readmissions and hospital days

GA less than 30 weeks, BW less than 1000 g, IVH grade II-IV, RDS, BPD, mechanical ventilation and long stay in the neonatal ward were significantly related to increased number of readmissions and/or number of HD up to 15 years of age. In a multivariate analysis, the readmission rate was significantly higher for children who had been treated with mechanical ventilation (OR 6.5; 95% CI: 1.8-23.5; $p=0.004$).

Neurological outcome

Univariate linear regression analyses showed that mechanical ventilation was significantly correlated to poorer scores at 4 and 9 years of age ($p=0.028$ in developmental score; $p=0.018$ in neurological score at 4 years; $p=0.036$ in neurological score at 9 years). RDS was associated with lower developmental scores ($p=0.006$) and with poorer neurological scores ($p=0.018$) at 4 years of age. IVH was correlated with poorer neurological outcome at 9 and 15 years ($p=0.047$ and 0.034 , respectively). None of the neonatal risk factors were related to neonatal neurological scores. Multivariate linear regression analyses showed that mechanical ventilation was significantly correlated to poorer developmental scores at 4 years and poorer neurological scores at 9 years, and IVH was significantly correlated to poorer total motor scores at 15 years of age.

Cognitive function, reading skills, school reports, and behavioural outcome

Data on correlation between neonatal risk factors and results on WISC III, reading skills (results from Samuelsson et al. [176]) and behavioural outcome (linear regression analyses) are shown in Table 15. There were significant correlations between mechanical ventilation and low Full Scale IQ, as well as between IVH and low Full Scale IQ. Significant correlations were also obtained between mechanical ventilation, BPD, and IVH and poorer results on reading skills, but not between neonatal risk factors and the summary of nine school subjects. GA below 30 weeks was significantly correlated with less externalizing behaviour and lower total problem scores. ELBW, SGA, and IVH were each correlated with more behavioural problems assessed in CBCL.

Table 15. Multivariate linear regression analyses of correlations (Coefficients and 95% CI) between neonatal risk factors and Full Scale IQ on the WISC III, reading skills (Non-word reading, Phonological choice, Word reading, Orthographic choice, Orthographic reading, and Reading comprehension), YSR and CBCL scores at 15 years of age in VLBW children. Only significant results are presented.

Neonatal risk factor	Test methods	Coefficient	95% CI Lower	95% CI Upper	p
GA <30 weeks	YSR, Externalizing	-3.3	-6.5	-0.2	0.038
	YSR, Total	-9.4	-18.2	-0.5	0.038
ELBW	CBCL, Externalizing	4.7	0.7	8.8	0.023
SGA	CBCL, Internalizing	3.5	1.8	5.2	<0.001
	CBCL, Externalizing	3.3	0.5	6.0	0.023
	CBCL, Total	13.5	5.7	21.3	0.001
Mechanical ventilation	Full Scale IQ	-19.9	-33.2	-6.7	0.004
	Phonological choice	-7.3	-12.3	-2.3	0.005
	Word reading	-7.3	-12.3	-2.3	0.005
	Orthographic choice	-22.2	-36.5	-8.0	0.003
	Orthographic reading	-6.9	-11.5	-2.4	0.003
BPD	Non-word reading	-11.9	-20.2	-3.7	0.005
	Orthographic reading	-11.1	-18.1	-4.1	0.002
IVH	Full Scale IQ	-15.9	-28.8	-3.9	0.011
	Orthographic reading	-5.2	-9.2	-1.1	0.014
	Reading comprehension	-4.8	-8.0	-1.7	0.003
	CBCL, Internalizing	3.1	0.8	5.4	0.009
	CBCL, Total	12.9	2.5	23.3	0.016

Health outcomes (SF-36 and SOC)

GA below 30 weeks, ELBW, mechanical ventilation, BPD, and IVH correlated significantly with lower scores on physical functioning, with remaining significant correlations for ELBW, BPD and IVH in multivariate analyses (Table 16). There were significant correlations between ELBW, BPD, and IVH, which remained for BPD and IVH in multivariate analyses, with lower scores on PCS. ELBW correlated significantly with higher scores in MCS. Handicap as CP, ADHD, or MR correlated significantly with lower scores on physical functioning and PCS.

There was significant correlation between ELBW and higher scores on comprehensibility, but not between any neonatal risk factor and manageability, meaningfulness, or total SOC. VLBW subjects with a handicap showed no significant correlation with lower scores on SOC.

Table 16. Univariate and multivariate linear regression analyses of correlation between neonatal risk factors and those with a handicap and scores on health scales and dimensions on SF-36 and core dimensions and total score on SOC at 20 years of age in VLBW subjects. Only significant results are presented.

	Univariate				Multivariate			
	Coeff.	95% CI Lower	95% CI Upper	p	Coeff.	95% CI Lower	95% CI Upper	p
Physical Functioning, SF-36								
GA < 30 weeks; Yes=19	-15.2	-25.0	-5.4	0.003				
ELBW; Yes=12	-24.3	-35.3	-13.3	<0.001	-10.5	-20.4	-0.6	0.037
Mechanical ventilation; Yes=12	-16.9	-28.6	-5.2	0.005				
BPD; Yes=5	-45.1	-60.0	-30.2	<0.001	-32.2	-46.3	-18.1	<0.001
IVH; Yes=13	-27.5	-37.7	-17.4	<0.001	-17.3	-26.8	-7.8	0.001
Handicap; Yes=16	-23.7	-33.7	-13.7	<0.001				
Role-Physical, SF-36								
IVH	-17.4	-32.9	-1.8	0.029				
PCS, SF-36								
ELBW	-7.0	-12.1	-1.9	0.008				
BPD	-11.8	-19.2	-4.4	0.002	-7.9	-15.1	-0.7	0.033
IVH	-10.0	-14.7	-5.4	<0.001	-8.4	-13.2	-3.6	0.001
Handicap	-7.4	-12.0	-2.8	0.002				
MCS, SF-36								
ELBW	7.5	0.1	15.0	0.045				
Comprehensibility, SOC								
ELBW	6.7	1.8	11.7	0.008				

Summary of neonatal risk factors and outcomes

Several of the potential listed neonatal risk factors were significantly correlated with adverse outcome at 15 and 20 years of age.

GA below 30 weeks correlated with more readmissions, higher total problem score on YSR and poorer score on Physical functioning.

ELBW correlated with more readmissions and HD, higher externalizing score on CBCL, poorer scores on Physical functioning and PCS.

SGA correlated with higher internalizing, externalizing and total scores on CBCL.

Mechanical ventilation correlated with more readmissions and HD, poorer developmental score at 4 years and poorer neurological score at 9 years of age, lower Full Scale IQ, poorer reading skills, and poorer score on Physical functioning.

RDS correlated with more readmissions, poorer developmental and neurological score at 4 years of age.

BPD correlated with more readmissions and HD, poorer reading skills, poorer scores on Physical functioning and PCS.

IVH correlated with more readmissions, poorer neurological score at 9 years and poorer motor score at 15 years of age, lower Full Scale IQ, poorer reading skills, higher internalizing and total score on CBCL, poorer scores on Physical functioning, Role physical and PCS.

According to our findings, the presence of IVH and mechanical ventilation during the neonatal period seem to have been the main neonatal risk factors.

There were significant correlations between increasing number of neonatal risk factors and lower summary of 9 school reports, total motor score, and Full Scale IQ (Table 17). For males the results were in accordance with the VLBW group, but females showed no significant correlations in any outcome variables (data not shown).

Table 17. Associations between increasing number of neonatal risk factors and main outcome scores.

	Summary of 9 school reports				Total motor score				Full Scale IQ			
	Coeff.	95% CI Lower	95% CI Upper	p	Coeff.	95% CI Lower	95% CI Upper	p	Coeff.	95% CI Lower	95% CI Upper	p
Increasing number of neonatal risk factors	-1.6	-2.7	-0.5	0.005	-7.1	-9.4	-4.7	<0.001	-7.3	-11.6	-3.1	0.001
	Total YSR score				Total CBCL score							
	Coeff.	95%CI Lower	95% CI Upper	p	Coeff.	95% CI Lower	95% CI Upper	p				
Increasing number of neonatal risk factors	-2.3	-5.9	1.3	0.198	3.4	-0.6	7.3	0.091				

DISCUSSION

The main purpose of the thesis has been to answer the question of outcome for VLBW children. In an attempt to find this answer different assessments have been performed in order to embrace varying and important aspects of life in this high-risk group. Thus, this thesis concerns very-long-term outcomes regarding morbidity, neurological conditions, academic achievements, behavioural problems, health, and social functioning in VLBW children born in the late 1980s in a geographically defined region. Outcome results have also been related to potential neonatal risk factors to understand possible relations with impaired neurological and intellectual functions, and MRI findings.

Strengths and limitations of the study

The study was based on a geographically defined cohort of all surviving VLBW children born over a 15-month period in the late 1980s and followed during a long period of 20 years. This cohort is therefore representative of the population, unlike hospital based cohorts, who are selected. Controls were recruited neonatally from the same geographic area and matched for date of birth, parity and sex in order to minimize socio-economic inequalities. In most other studies controls have been recruited later, which minimizes the comparability. There were no main differences in socio-economic conditions between the VLBW and control groups. Satisfactory socio-economic circumstances might partly explain the overall good prognosis for the VLBW subjects. However, fathers' level of education was significantly higher for controls, and they also had a higher professional level at the 15-year follow-up, which may contribute to an advantageous outcome [87]. Most previous studies have only reported the mothers' level of education. According to several international studies significant proportions of preterm children may come from a disadvantaged socio-economic background, which is an important determinant of outcome [35,46,58].

At 15 years of age, the participation rate was lower than at 12 and 20 years of age, a decline probably partly depending on deficient motivation in a sensitive phase of life. One of this study's strengths was that the children have been followed longitudinally on repeated occasions, with a fairly high degree of participation, not at least in the VLBW group, which also included disabled (except in Paper II) and mentally retarded persons. Participation was facilitated through regular contact during all years with information letters to the VLBW and control families. High drop-out rates are a dilemma in very long-term follow-up studies. Of

importance is the lack of differences in neonatal risk factors between participating and non-participating VLBW children, and ages between the groups at follow-up examinations. However, at the 15-year follow-up examination (Paper III), non-participant VLBW girls had significantly lower mean GA than participants and a more favourable outcome may therefore be possible in the follow-up group.

We used mainly validated and well accepted methods to assess several aspects of outcomes. However, a compromise was necessary to undertake between on the one hand detailed and extensive examinations and on the other hand not too time-consuming examinations. Otherwise, the risk of more drop-outs seems to be enlarged with increasing time in assessments spending.

The study on morbidity was made possible by using the Swedish Hospital Discharge Register, which covers all hospital admissions with only around 1% losses, and therefore gives reliable data of the consumption of hospital care [199]. Diagnoses at hospital readmissions were based on classification according to ICD 9 and ICD 10. All habilitation centres and child psychiatric clinics in the region reported without any losses. The Swedish system with personal identification numbers and uniform organization of health care minimizes the risk of underreporting.

Neurological examinations were based on standardized and reliable techniques and were appropriate for the ages in question [200,202-205]. The majority of the VLBW children were examined at 15 years using cerebral MRI. We chose MRI sequences suitable for routine clinical examination and did not include the advanced diffusion tensor imaging techniques employed by some other authors. MRI findings were assessed and classified by two experienced paediatric neuroradiologists blinded to neonatal background and outcomes from follow-up examinations.

Evaluation of cognitive functions and behavioural problems was based on standardized and reliable techniques [176,208,214,215]. School reports were obtained from public authorities. Three postal questionnaires were used. SF-36 and SOC are widely used [218,220]. SF-36 is adequate from 14 years of age upwards and has been validated in a Swedish version [216]. The SOC scale is a reliable, valid and cross-culturally applicable instrument [220]. Weight, height and head circumference were measured in a standardized way at 15 years of age.

We used BW 1500 g or below as specific inclusion criterion in our study, thus making it more favourable to compare outcome results with other studies. In addition, BW is characterized as a more exact measure than GA. However, by using BW, a higher frequency of children with growth deviation was included and the material was therefore composed of children with an extensive range of gestational ages. The VLBW population thus consisted

of both preterm AGA children and of more mature SGA children. The aetiology and neonatal outcome may differ between the two categories. The number of children in each category was too small, however, to allow the outcome findings to be analyzed separately. According to the Swedish standard chart in use in the 1980s, SGA children represented about 50% of the VLBW group. This is a higher proportion of SGA children than in several other studies of VLBW children [44,65,150], but almost the same as reported in a recent study [221]. Recent studies have shown that a large proportion of preterm children are growth retarded [148,222]. Selecting the material from gestational age only will thus still include both AGA and SGA children. As the number of ELBW children were rather few in our study, our results more reflect the outcome of infants born with BW between 1000 g and 1500 g.

Data about weight and height at 20 years of age were self-reported and therefore not precise, but this method has been used in other studies [66]. There is little or no doubt that self-reported figures agree well with measured data.

Outcome data in the study reflect perinatal managements of two decades ago, and practices have now changed considerably, an unavoidable problem in all long-term follow-up studies. Antenatal steroids were given to only a minority of the mothers and surfactant treatment was not in use, two later major improvements in perinatal care [6]. However, though survival rate has increased, neonatal and short-term morbidity among VLBW children seems to have remained unchanged over the last decade [6]. Thus, results from well-founded long-term follow-up studies, even concerning children born one or two decades ago, give valuable information regarding prognosis for high-risk newborns.

Hospital readmissions and diagnoses

As expected, and in agreement with other studies, most readmissions occurred during infancy [27,43,96,97], with VLBW boys dominating [27,28,96,98].

Infectious diseases were the main reason for readmission, both for VLBW boys and girls, as expected and reported elsewhere [43,96,97]. Surgical diseases were more common in VLBW boys than controls, as reported in other studies [43,96]. Not surprisingly, neurological disorders represented a fairly high proportion of readmissions for VLBW children, which is in agreement with Yüksel and Greenough [97]. The increase in the number of readmissions in asthma/allergy symptoms in VLBW boys may reflect airway infections with obstructive symptoms [97,104,109]. A previous study of this VLBW cohort showed a relationship between mechanical ventilation during the neonatal period and bronchial hyper-responsiveness at age 12 [109]. We also found that a history of asthma was twice as common among the VLBW as the control children. In addition, oxygen

supplementation for more than 9 days seemed to be associated with current asthma. Other authors have reported respiratory health in VLBW children comparable with term controls at 14 years of age [108].

Child habilitation and child psychiatric diagnoses

The incidence of moderate/severe CP (5.8%) was rather low and probably comparable with other Scandinavian studies [111,112]. There are divergent reports about the incidence of CP (moderate and severe) in VLBW cohorts (5.5–10.9%) [34,112,113], probably due to different criteria for CP diagnosis, but also real differences in the incidences between different birth years, hospitals and countries [46,110,114]. Escobar et al reported in a meta-analysis of 85 different VLBW cohorts a median incidence of CP among all the cohorts of 7.7% [32]. Follow-up examination at four years of age and data collection from all child habilitation centres in the region verify our results as correct. The children with CP had lower BW and GA than children without, which is in concordance with several reports [33,110,111].

The frequency of registered ADHD (5.8%) was low in comparison with some other reports (10-23%), which may be a reflection of different or very strict criteria for diagnosing ADHD in this material [173,180]. Our results were not based on specific screening for ADHD. In a Norwegian study, 4% of LBW children were diagnosed as having ADHD according to clinical diagnoses and 10% in the special screening [180]. In a recent study by Hack et al no differences between VLBW and control subjects were found in the young adult self-report of ADHD [40]. We found no significant differences in neonatal risk factors between children with ADHD and those without, although VLBW children have an increased risk for developing ADHD [161].

MR was found in eight VLBW children and in one control child according to data collected from the region's child habilitation centres and child psychiatric clinics. This may be underestimated in the VLBW cohort since these cases were only identified clinically. Mental retardation was for the most part associated with CP or ADHD.

The number of VLBW children in contact with a child psychiatric clinic was lower than the controls and lower than in another Swedish study of children between 0 and 17 years of age [223]. Behavioural problems as the main reason for contact were similar in the groups. Other studies have shown an increased incidence of emotional and behavioural problems in VLBW children [81,83,173], which may indicate that only some of these problems are dealt with in child psychiatry clinics.

School performance

Few individuals in our study were in special classes or at schools for disabled children. Considering cognitive test results the number should have been greater. The situation probably to some extent reflects school organization in Sweden, with the purpose of integrating children with minor/moderate impairments in mainstream school and rare use of screening with cognitive tests, or inability to detect children with cognitive impairments.

Of interest are also the final grades from compulsory school, and to our knowledge these results are novel. The scale of grades in Sweden involved only four levels, which makes differentiation more difficult. We found significantly lower means in mathematics and technology for VLBW boys, but in none of the school subjects for VLBW girls compared with their controls. Other authors have also reported differences in mathematics [35,165,166,174]. In a recent study from the UK, Pharoah et al reported significant differences in total points score between non-disabled VLBW subjects and controls attending mainstream schools on performance in the General Certificate of Secondary Education [224]. Not surprisingly, all children in our study with $IQ < 70$ had low grades in all theoretical subjects.

Neurological examination

The VLBW children without overt disability as a group were inferior in neurological function compared with controls at all follow-up examinations, which is in agreement with other studies [29-31,134,225]. In some of these studies, however, exclusion of children with overt disability was not accomplished. We could not find increased impairment with advancing ages, as was reported by O'Brien et al [135].

Poorer neurological performance was evident for VLBW boys at all examinations, except at 9 years, but VLBW girls did not differ from their controls at the 9-year and 15-year examinations. VLBW girls had better developmental and neurological scores than VLBW boys in all examinations, but only results at 9 years were significant. A recent multi-centre study of ELBW children showed favourable motor skills for girls [118], supporting the importance of gender-related analyses.

Visual and hearing function

Two VLBW children had any stage of ROP, which is a low prevalence compared to other studies, where a frequency of 21-40% has been reported [138,139]. In our study, an ophthalmological examination was not performed before 40 weeks GA, which may explain why transitory stages of ROP grade I and II were not detected [139].

At 15 years of age, a majority of VLBW children had a very good visual acuity, but there was a significant difference between the groups. The frequency of strabismus was also significantly higher among the VLBW children, although the majority had latent strabismus. Latent strabismus is known to cause asthenopic problems such as headache, reading problems and diplopia. A tendency towards a more frequent need for eye glasses was seen, which was also reported by Cooke et al [141].

At 20 years of age, self-perceived visual problems during the previous year were well in agreement with results at 15 years of age. More VLBW males than control males were in need of glasses.

The reported incidence of hearing impairment was low in VLBW children at 4 years of age. However, there were apparent difficulties in collecting data for all children from Child Health Centres, which may influence the conclusion. In addition, whispering test at 9 years and self-perceived data at 20 years of age strengthen the impression of low rate of hearing problems in the VLBW group. It had been necessary to perform specialized hearing tests in order to detect minor deficiencies. Hearing impairment was detected in 27% of VLBW children by brainstem auditory evoked responses at term [143], but follow-up studies have reported much lower rates of hearing loss [71,90].

Growth

VLBW boys and VLBW girls differed from their controls in weight, height, BMI, and OFC, though differences were significant only for VLBW boys in weight, but for girls in all growth measurements. Other studies have shown significant discrepancies in weight and height up to 14 years of age between VLBW children and controls, of which one study reported greater differences for girls than for boys [44,150]. For both VLBW boys and VLBW girls there were significant correlations between small OFC and low Verbal and Full Scale IQ, which is in agreement with earlier studies [44,45]. Intrauterine growth restriction and growth failure of the head during childhood have been shown to influence cognitive function early in life in VLBW children [149]. Weight and height differed significantly between male and female VLBW subjects and their respective controls at 20 years of age. These results are in agreement with the UK study and partly with an earlier Swedish study [66,77], whereas Hack et al found no significant differences in growth outcome between VLBW females and their controls [65]

Cognitive function and reading skills

Our study showed that VLBW children had poorer cognitive function compared with their controls, which is in agreement with most other studies [30,35,39,81,85]. Differences in

mean Full Scale IQ of 12 points between VLBW and control subjects are also in accordance with reports from a recent meta-analysis [161]. The distribution of IQ levels in VLBW children with one third in the normal zone (90 – 109) of IQ or above, and one third below 80 points is almost identical with the findings of a previous Swedish study that used these ranges and included immature preterm children [85]. Notable are our findings of 49% of VLBW children with IQ lower than 85. We could not observe any gender differences in the VLBW group as regards IQ, which is in agreement with the Swedish study [85]. A comparison of cognitive outcomes at 15 years of age with the results from the 9-year examination (Raven's matrices) indicates persistent group differences [83,176].

One important result of our study was the detection of children with exceptionally low IQ (i.e. below 70) who had not been identified before. A majority of these children attended mainstream school and had no obvious neurological symptoms, but significantly lower mean results in all school subjects. Stjernqvist and Svenningsen found that more than 50% of very preterm children with IQ below 70 had not been identified by parents or teachers at the age of ten [81]. It is serious that so many mentally retarded children were still unidentified when they left compulsory school. It seems logical that VLBW children should be IQ tested before beginning school.

Although IQ differences between the groups did not diminish between 9 and 15 years of age, differences in reading skills (word decoding, word recognition, and reading comprehension) did so, as we have shown earlier [176].

MRI findings

MRI findings were pathological in less than 30% of the VLBW children, an incidence somewhat lower than in previous studies [189,192,193], but in accordance with one earlier study of preterm children [195]. As anticipated in the VLBW children, MRI abnormalities were dominated by WMD of immaturity, which in many cases represents PVL. The incidence of PVL determined by neonatal ultrasound in our population was lower than by MRI at 15 years, partly due to technical inabilities in the late 1980s. Although cranial ultrasonography has been shown to be reliable in the detection of focal areas of cystic white matter injury, the value of this imaging technique in detecting the diffuse non-cystic cerebral white matter injuries is unclear [131,188].

Mild pathological MRI findings in adolescence in VLBW children without disability, although quite common, were not related to poor neurological outcome in our study, which is in agreement with several other studies [120,130,190,192].

Associations between pathological MRI findings, most of them mild, and adverse cognitive function were not found in our study for the whole VLBW group, which is also in

conformity with other studies [189,192,195,226], but to some extent for boys. However, in another study from our group, associations were found between visual dysfunction and abnormal MRI [142]. Neither reading skills nor summary of school reports were associated with abnormal MRI findings in our study. To our knowledge, no other comparable studies exist.

A newly developed technique of MRI, diffusion tensor imaging, gives additional information about WM microstructure with aberrations relating to motor, cognitive, perceptual, mental, and behavioural impairments [132,196].

Behaviour

The higher externalizing and total scores on YSR in control girls than VLBW girls are in agreement with two recent studies concerning adolescents and young adults [37,40]. Several studies have otherwise shown excessive behavioural problems in younger VLBW children [30,39,58,81]. These results suggest decreasing behavioural problems in VLBW children over time up to adolescence. Results from self-reports on behavioural problems in VLBW children, however, are to some extent contradictory. Dahl et al reported that VLBW adolescents stated fewer problems than parents [37], and Saigal et al found that differences were apparent only through parents' reports of ADHD and depression among ELBW teens [227]. Parents of VLBW children and controls in our study reported similar scores on total problems and all subscales. These findings are in agreement with our earlier published data that showed no significant differences in self-esteem at 12 years of age [83] or need for child psychiatric treatment up to age 15 [209].

Health and social conditions

We found similar self-perceived health between VLBW males and females and their controls at 20 years of age as assessed by the three instruments. These findings are in agreement with a few other reports. Hack et al assessed VLBW subjects with a self-reporting instrument at 20 years of age and found that VLBW and normal-weight subjects reported similar proportions of excellent, average and poor health profiles [70]. In a study by Cooke in the United Kingdom (UK), where only subjects previously in mainstream school were included, no differences were found in health status on SF-36, with the exception of poorer performance in physical functioning in VLBW subjects [66]. We found no significant differences in mean scores on the eight health scales and two dimensions (PCS and MCS) of SF-36 between VLBW and control subjects, VLBW males and control males or VLBW females and control females. VLBW subjects scored lower in physical functioning, which was in line with Cooke's findings, but the difference was not significant [66]. Females

scored lower than males, the difference being significant as regards vitality and mental health for VLBW subjects, as in the UK study [66]. Not surprisingly, handicapped subjects scored lower in physical functioning and PCS.

VLBW males and females did not differ from their controls in reported frequency of hospital admission and need of emergency treatment over the previous five years or regular contact with a physician. In a previous study, we found no significant differences in hospital readmission between 9 and 15 years of age for VLBW boys and VLBW girls in comparison with controls [209]. During infancy and early childhood, however, infections and neurological diseases had been common causes of readmission in VLBW children [209]. The frequency of these diseases decreased markedly thereafter and injuries, fractures and surgical interventions were the primary reasons for medical care during late adolescence and early adulthood. Hack et al reported significantly more long-term medical and surgical disorders, but fewer acute disorders in VLBW subjects compared to controls in early adulthood [70]. Regular use of drugs did not differ between the main groups, but a quarter of the VLBW females were in need of chronic medication, mainly for asthma, as Cooke also found [66]. Respiratory health in VLBW children has been reported as comparable with term controls at 14 years of age with rates of asthma in 21% of VLBW children and 21% in controls [108].

Use of tobacco, i.e. cigarettes and moist snuff, was similar between VLBW males and control males and between VLBW females and control females, varying between 21% and 30%. Cooke and Hack et al found no differences in smoking between VLBW and control groups [62,66]. In Sweden, the use of moist snuff is often more common than smoking, mainly among males, making it difficult to compare tobacco habits. Significantly more VLBW subjects were non-users of alcohol than control subjects, which is in line with other authors' findings [62,66]. Limited risk-taking behaviour, probably due to parental over-protective upbringing, has been postulated.

The number of subjects who had graduated from upper secondary school did not differ significantly between the groups, although seven VLBW subjects were still in schools for mentally retarded or disabled young people and thus unable to attain a normal educational level. According to official Swedish statistics, 72% of 20-year-olds complete upper secondary school compared with 78% of the VLBW individuals in our study [228]. However, the subgroup of VLBW subjects with a handicap differed significantly from controls as regards graduation and none had studied theoretical programmes. Fewer VLBW subjects had graduated from theoretical programmes, but this difference was not significant. Shorter schooling for VLBW subjects compared with controls has been reported, but also schooling without differences [66,68,77]. About 50% of our VLBW and control subjects

were employed and 27% of VLBW subjects and 33% of control subjects were studying. In a Dutch study, twice as many VLBW 19-year-olds were poorly educated and three times as many were neither employed nor in school, compared with age-peers in the general population [71]. We found no significant difference in occupation between the groups, contrary to Cooke and Hille et al [66,71]. Differences in outcomes may be explained to some extent by divergences in health care and school system, socio-economic conditions and year of birth. In both the UK and the Dutch study, participants were born in the early 1980s. Living conditions, e.g. alone, cohabiting or at home, were no different between VLBW subjects and their controls, which is in agreement with what Saigal et al have reported [68]. Other authors have found VLBW subjects to be more likely to live with their parents, especially VLBW females [66]. Unexpected to some degree were our findings that sports and outdoor activities were the predominant recreation for both VLBW males and females and their controls.

SOC scores did not differ significantly between VLBW subjects and controls regardless of gender. To our knowledge, no previous study has assessed VLBW subjects on SOC. In a recent Swedish study, a significant relation was found between psychosomatic complaints and lower scores on SOC among adolescents [229]. The absence of differences regarding SOC suggests that VLBW subjects experience their lives as being as good as that of normal-weight controls, which agrees with our previous results on self-esteem at 12 years of age and a smaller Swedish study of preterm children at 19 years of age [64,83].

Analyses of neonatal risk factors

Neonatal factors such as BW below 1000 g, mechanical ventilation, BPD, and long stay in the neonatal ward were related to more readmissions and days in hospital, which is in accordance with other studies [96-98,100,104]. SGA was not associated with increased risk of readmission and days in hospital.

Mechanical ventilation, RDS and IVH were associated with poorer neurological outcome and are some of the main risk factors for a non-optimal prognosis [31,36,86,130]. We could not confirm that GA, in children without overt disability, significantly correlated to adverse neurological outcome, as was found by Cooke [137].

Need for mechanical ventilation, BPD, and presence of IVH during the neonatal period correlated significantly with adverse cognitive function and reading skills as we previously found at 9 years of age [83]. There are other reports on associations between poor cognitive outcome and number of days on mechanical ventilation and parenchymal lesions in the brain [35,85]. Association between high postnatal morbidity and low Performance IQ has also been suggested [85]. There was a difference in IQ between SGA and AGA children, albeit

not significant, which is in agreement with an earlier Swedish follow-up study [230]. Several studies support the hypothesis of a global cognitive deficit in VLBW children [35], where intrauterine growth retardation, perinatal infections, or postnatal nutritional difficulties may be plausible causes rather than low GA or low BW per se [169,190]. Of interest, therefore, are the results from a Danish study where VLBW children born in the early 1980s were compared with ELBW children born in the mid-1990s on several cognitive functions [4]. The survival rate of the smallest babies improved without an increase in intellectual deficit in surviving children.

Significant correlations were not obtained between neonatal risk factors and the summary of nine school subjects, but as the scale of grades involved only four levels, differentiation may be more difficult. To our knowledge no other studies are published.

GA below 30 weeks was significantly correlated with less externalizing behaviour and lower total problem scores. We found that SGA was the most important neonatal risk factor to predict behavioural problems, as reported by parents, which was in accordance with a recent Norwegian study [37].

ELBW, BPD and IVH were neonatal risk factors associated with poorer scores on physical functioning and PCS on SF-36. Comparative studies concerning correlations between neonatal risk factors and results on SF-36 are sparse. We have shown relationships between ELBW, mechanical ventilation, BPD and increased risk of readmission and longer stay in hospital up to adolescence for VLBW children (Paper I). At the 15-year follow-up, we found that the need for mechanical ventilation, BPD and the presence of IVH during the neonatal period correlated significantly with adverse cognitive function (Paper III). These neonatal risk factors therefore seem to be of importance in evaluating long-term effects on health in VLBW subjects.

Our findings of significant correlations between ELBW and higher scores on MCS and comprehensibility are difficult to explain. Five of these ELBW subjects had a handicap and lower scores were therefore expected. Overestimations of self-perceived health or difficulties in understanding questions are conceivable explanations and further research seems necessary.

According to our findings, the presence of IVH and use of mechanical ventilation during the neonatal period were the main risk factors that influenced long-term health in VLBW subjects. Mechanical ventilation may be a risk factor per se, but may also reflect severity of illness, as the most critical ill children needed mechanical ventilation.

Increasing number of neonatal risk factors was significantly correlated with poorer summary of school reports, total motor score and Full Scale IQ, not surprisingly findings, but was not found with total scores on YSR and CBCL. The impact of neonatal risk factors

on behavioural in adolescence are suggested to be negligible. However, gender differences were evident with only males achieving lower scores on school reports, total motor scores and Full Scale IQ in relation to increasing number of neonatal risk factors.

CONCLUSIONS

In this prospective longitudinal case-controlled long-term regional follow-up study of children with BW 1500 g or less, we have found the following major results:

- The presence of IVH and/or use of mechanical ventilation during the neonatal period were neonatal risk factors that negatively influenced health, neurological function, cognition and reading skills.
- VLBW children (more often boys) had a higher risk of rehospitalization during infancy and childhood, with infections and neurological diseases as the most common causes.
- Non-disabled VLBW children, especially boys, performed less well in neurological examinations than controls.
- The visual acuity was similar to the controls, but the incidence of strabismus was higher in the VLBW group.
- VLBW children were lighter and shorter than controls at all follow-up ages. Those with small OFC performed suboptimally in cognitive function tests.
- VLBW children performed less well than controls in cognitive tests. Due to risk of not being identified in spite of very low IQ, all VLBW children should be recommended to be IQ tested before beginning school.
- VLBW children were at slightly higher risk of developing ADHD; otherwise behavioural problems did not differ from controls.
- MRI sequences suitable for routine clinical examination did not give substantial additional information regarding brain structure in non-disabled VLBW subjects in relation to clinical findings.
- VLBW subjects showed catch-up in reading skills; most of them achieved normal results in school reports, graduated from upper secondary school, continued studying or were employed.
- VLBW subjects perceived their health status to be as good as controls and a majority of younger adult VLBW subjects' lived independently, they had stimulating recreational activities and were satisfied with their life.

FUTURE PERSPECTIVES

Is it possible to improve outcomes and outcome studies in VLBW children?

Improvements in perinatal and neonatal management for all premature children are a great challenge, depend on successful care on several levels, and the complexity of immaturity must be taken into consideration. Major prenatal risk factors for the foetus are maternal infections, pre-eclampsia and premature birth per se. Recent studies have shown elevated risks for CP related to infections during pregnancy. The importance of early diagnosis and treatment of the mother and foetus can not be overestimated. Pre-eclampsia is associated with growth restriction of the foetus, which may influence health outcomes, not only neonatally but also later on. Prevention of premature birth is one of the greatest forthcoming challenges to improve outcomes in perinatal care. Hitherto, premature births have not been shown to decrease in rate.

According to our findings, the presence of IVH and use of mechanical ventilation during the neonatal period were the main risk factors that influenced long-term health in VLBW subjects. Neonatal and long-term morbidity among VLBW children are reported to be unchanged in recent decades, but two major outcomes, mortality rate and CP rate have decreased. Advances in perinatal and neonatal care have resulted in fewer VLBW infants with parenchymal cerebral haemorrhage and focal necrotic lesions of PVL. Antenatal corticosteroid and neonatal surfactant treatment, new technologies in ventilator settings and extended use of continuous positive airway pressure have shortened the need for mechanical ventilation. Although the prognosis has improved for VLBW and very preterm children, they are still subjected to considerably more problems than full term children. The outcomes in extremely immature children, i.e. born at the limit of viability, are even less favourable.

It is time to implement evident data from follow-up studies into clinical practice. Regular and specific follow-up examinations during childhood for all VLBW children are essential in order to find children who require physical and psychological support and guidance before beginning school. These assessments, specially designed for high-risks infants, should at least represent outcomes in growth, neurological, visual and hearing function, cognitive function and behaviour. Follow-up programmes should include neuro-developmental, visual and hearing examinations to 4-5 years of age. Cognitive assessments should be recommended before schooling to identify those who need adequate support in

school. Results from the follow-up programs should be included into regional and national registers to provide early feed-back for caregivers and be an essential part of quality care. In addition to such diagnoses as CP, ADHD and MR, complementary information about functional level are of great value.

In research, further controlled prospective population based studies of VLBW infants should have great priority, comprising also consideration of gender. It is also important that research continue from where our study ends, i.e. into adulthood and transition into professional life and parenthood. There are few such reports, and hitherto none regarding VLBW subjects from Scandinavia. Another important field of research is the association between premature birth, intrauterine growth retardation and cardiovascular disease and metabolic syndrome.

ACKNOWLEDGEMENTS

First, I wish to express my gratitude to all children (now young adults) and their families, who were my driving force to complete this thesis, for their participation in these studies.

This work would not have been possible without the help and support of many people and is a result of a true teamwork.

In particular I would like to thank:

Ingemar Leijon, my main supervisor and co-author, for your never-ending support, encouragement, patience, and friendship.

Orvar Finnström, my associate supervisor and co-author, for your advice, scientific support, and long, friendly collaboration in a unique project.

Kerstin Hellgren, Xiao-Mei Mai, Stefan Samuelsson, Gunilla Sydsjö, Marie Wadsby, and Chen Wang, my co-authors, for your valuable comments and for sharing interest in follow-up outcomes of these children.

Olof Flodmark, Lena Jacobsson, Lene Martin, Jan Ygge, Eva Aring, and Ann Hellström, additional members of the working group who planned and performed the 15-year examination, for collaboration and stimulating discussions.

Bengt Bylund, Torsten Cervin and Olle Wärngård, who were involved in this study from the first steps and devoted a lot of time in several follow-up examinations to keeping the study on the track.

Göran Oldaeus, head of Paediatric Clinic, Ryhov County Hospital, for support and giving me the opportunity to work with this thesis alongside my clinical commitments, and former heads **Boel Andersson-Gäre** and **Karl-Henrik Lundell**. Special thanks to my first boss **Astrid Thilén**, who allowed me to take part in this project at the very beginning and served as an excellent model of a paediatrician.

Per Brandström, Fredrik Ingemansson, Sven Johansson, Karin Malmgren, colleagues on the Neonatal Team, and former member **Nils-Olof Jonsson**, for understanding attitudes and friendly working conditions.

All colleagues at the Paediatric Clinic for the warm atmosphere. Special thanks to former colleagues, now retired **Helmut Hecht, Calle Johansson, Josef Kubista** and for good mentorship during the first steps in my paediatric career.

All staff at the Neonatal Unit, Ryhov County Hospital, for being enthusiastic, skilled, and receptive to improvements in the care of the sick newborn child.

Per-Ivar Hjort for being a genuine paediatric radiologist, never making a deviation from quality in radiological or ultrasonographical examinations, and for introducing ultrasonography of the newborns at the Neonatal Unit, Jönköping in the early 1980s.

Birgit Ljungqvist for kindly constructive statistical advice.

Christina Helander and **Ing-Marie Sandberg** for skilful work with the children and families.

Ann-Christine Gilmore-Ellis for help and support with administration.

Christina Alnervik and **Karin Fridolfsson** for help with collecting data.

Lena Wistedt for planning and carrying out the motor skill performance.

My three children and their relatives, and my **grandchildren** for giving me happiness.

Marianne, my wife, for being understanding and encouraging.

Wolfgang A Mozart for music like water in the desert.

Futurum – the Academy of Health Care, Jönköping County Council, **FORSS** - The Medical Research Council of Southeast Sweden, the **County Council of Östergötland**, and **Solstickan Foundation**, Stockholm, for financial support.

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APPENDICES

Appendix 1. Items in the neonatal neurological examination.

Muscular tonus:	Excitability:	Optimal items:
Spontaneous posture supine position	Optical blink reflex	Eyes following a red ball
Resistance to passive movements, body and neck	Acoustic blink reflex	Orientation to sound
Resistance against passive movements, arms	Glabellar reflex	Dolls' eye test
Resistance against passive movements, legs	Palmar grasp	Pupil's reaction to light
Recoil, arms	Withdrawal reflex	Patellar reflex
Traction response, arms	Rooting reflex	Moro reflex
Tractions response, head	Sucking reflex	Placing response
Head control, vertical position	Ability to suck	Automatic walking
	Asymmetric Moro	Self-quieting activity
	Moro tremor	
	Crawling	
	Spontaneous motility	
	Irritability	

Appendix 2. Items in developmental and neurological examination at follow-up at 4 years of age.

Developmental items:		Neurological items:
Gross motor function:	Intellectual function:	Active movements
Standing on one foot	Figure counting	Passive movements
Jumping on one foot	Apprehension of quantity	Strength
Balance: Walking heel to toe, steps	Names of colours	Extremity reflexes
Balance: Walking heel to toe, dm	Apprehension of colours	Extremity tonus
	Memory	
	Draw a man	

Appendix 3. Items in neurological examination at follow-up at 9 years of age.

Walking	Jumping on one foot	Tonus in arms and legs
Walking on toes	Balance on one foot	Reflexes in arms and legs
Walking on heels	Walking heel to toe	Foot clonus
Walking on lateral feet	Stretching arms straight up	Babinski's reflex

Appendix 4. Items reflecting gross and fine motor skills, coordination, and visual-motor controls at follow-up examination at 15 years of age, the short version of Bruininks-Oseretsky Test of Motor Proficiency.

Running speed	Standing long jump	Draw a circle
Balance on one foot	Catching a ball	Draw a figure
Walking heel to toe	Throwing a ball	Sorting cards
Bilateral coordination	Response speed	Making dots
Jumping up and clapping hands	Draw a line	

Appendix 5. Imaging sequences used at MRI examination on VLBW subjects at 15 years of age.

The imaging sequences included a T1-weighted sagittal (TR/TE 650/19-20 ms, 5 mm slice), T2-weighted transaxial and coronal (TR/TE 6450/85 ms, 5 mm slice), fluid-attenuated inversion recovery (TR/TE/inversion time 11000/140/2200 ms, 5 mm slice), and T1-weighted inversion recovery coronal acquisitions (TR/TE/inversion time 3000/20/250 ms, 4 mm slice).

Appendix 6. The study-specific questionnaire used at 20 years of age for VLBW and control subjects.

ENKÄT

Nedan följer frågor som rör Dina sociala förhållanden och hälsa. Du svarar genom att kryssa i rätt ruta eller i vissa frågor skriva svaret efter frågan.

Sociala förhållanden

- Hur bor Du?
 Ensamboende
 Sammanboende/gift
 Hos förälder/föräldrar
 Annat, nämligen: _____
- Vad är Din nuvarande sysselsättning?
 Studerande: Högskola/universitet Folkhögskola Annan _____
 Arbetsökande/arbetslös Hur länge? _____ månader
 Arbetar: Heltid Deltid Arbetar som: _____
 Föräldraledig/Militärtjänstgöring
 Annan: _____
- Har Du gått ut gymnasium?
 Ja Vilket år? _____ Vilket program: _____
 Nej Orsak: _____

4. Vilken utbildning/yrke har Du tänkt skaffa?

5. Vilken aktivitet/vilka aktiviteter sysslar Du mest med på Din fritid?

Hur många timmar lägger Du ner på denna/dessa varje vecka? _____

6. Hälsa

7. Har Du senaste fem åren varit frisk?

Ja, helt och hållet

Ja, oftast

Nej, inte alls

Av vilken anledning: _____

8. Har Du senaste fem åren vårdats på sjukhus?

Nej

Ja

Antal gånger: _____

Orsak: _____

9. Har Du senaste fem åren sökt läkare akut?

Nej

Ja

Antal gånger: _____

Orsak: _____

10. Har Du regelbunden kontakt med läkare?

Nej

Ja

Antal gånger/år: _____

Orsak: _____

11. Använder Du någon medicin regelbundet eller under längre tid?

Nej

Ja

Vilken/vilka: _____

12. Har Du senaste året haft besvär med

Synen Använder Du glasögon/linser?

Hörseln Använder Du hörapparat?

Rörelseförmågan Använder Du något hjälpmedel? Vilket? _____

Läs- och/eller skrivsvårigheter

Koncentrationssvårigheter

Depression

Annat, nämligen: _____

13. Har Du senaste året haft hjälp av personlig assistent?

Nej

Ja

Hur många timmar/vecka? _____

14. Hur mycket väger Du?

_____ kg

15. Hur lång är Du?

_____ cm

16. Använder Du tobak?

Nej

Ja

Vad? Snus Cigaretter

Hur ofta? Flera gånger dagligen Flera gånger i veckan Vid festliga tillfällen

17. Dricker Du alkohol?

Aldrig

Sällan eller en gång i månaden

Två till fyra gånger i månaden

Två till tre gånger i veckan

Minst fyra gånger i veckan

Hur mycket dricker du i genomsnitt per vecka?

_____ Stycken 45cl folköl

_____ Stycken 33cl starköl

_____ Stycken 15cl lättvin

_____ Stycken 8cl starkvin

_____ Stycken 4cl starksprit

END

What is clear is that the future of premature children has to be looked at from a lifespan perspective, as 'recovery' may not be evident until adulthood

Saroj Saigal