Kari Anne Indredavik Evensen

Born too soon or too small: Motor problems in adolescence

Thesis for the degree of Philosophiae Doctor

Trondheim, April 2010

Norwegian University of Science and Technology
Faculty of Medicine
Department of Laboratory Medicine, Children's
and Women's Health

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the degree of Philosophiae Doctor

Faculty of Medicine
Department of Laboratory Medicine, Children's and Women's Health

ISBN 978-82-471-2057-6 (printed ver.)
ISBN 978-82-471-2058-3 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2010:51

Printed by NTNU-trykk

Motoriske problemer hos tenåringer født for tidlig eller for små

Barn som er født for tidlig (premature) og/eller for små (med lav vekt for gestasjonsalder som indikasjon på intrauterin veksthemming) har høyere risiko for mortalitet og morbiditet enn barn født til termin med normal fødselsvekt. Blant motoriske problemer er cerebral parese den mest alvorlige følgetilstanden, men mindre motoriske problemer er også hyppig rapportert, spesielt blant barn født for tidlig. Hos de med lav vekt for gestasjonsalder er motoriske konsekvenser mindre dokumentert og studier har vist inkonsistente resultater.

Få studier har undersøkt motoriske ferdigheter hos disse barna i tenårene. Målet med denne studien var å undersøke prevalensen av motoriske problemer hos tenåringer født for tidlig med svært lav fødselsvekt (very low birth weight: VLBW) og hos tenåringer født til termin med lav vekt for gestasjonsalder (small for gestational age: SGA). Deretter ønsket vi å undersøke om synsvansker hadde betydning for motoriske problemer og om integrasjon av syn og propriosepsjon var redusert. Dessuten ville vi undersøke om tenåringer med motoriske problemer kunne identifiseres ved tidlige motoriske evalueringer i barnealder.

Vi fant at en høyere andel av VLBW- og SGA-tenåringer hadde motoriske problemer sammenlignet med kontroller, undersøkt med Movement Assessment Battery for Children. Mens både gutter og jenter i VLBW-gruppen hadde generelle motoriske vansker, i form av manuelle ferdigheter, ballferdigheter og balanse, hadde tenåringer i SGA-gruppen, og spesielt gutter, hovedsakelig problemer med manuelle ferdigheter. I VLBW-gruppen ble en betydelig del av de motoriske problemene påvirket av synsvansker, mens dette ikke var tilfelle i SGA-gruppen. VLBW-tenåringene hadde dårligere utførelse på oppgaver som undersøkte inter- og intra-sensorisk integrasjon sammenlignet med kontrollene. Imidlertid gjaldt dette hovedsakelig tenåringer med cerebral parese og lav estimert intelligenskvotient. SGA-tenåringene utførte disse oppgavene like bra som kontrollene, men de gjorde det relativt dårligere med sin ikke-dominante hånd sammenlignet med sin dominante hånd. De fleste av VLBW-tenåringene med motoriske problemer kunne identifiseres allerede ved ett år ved hjelp av den motoriske skalaen på Bayley Scales of Infant Development. Denne testen identifiserte imidlertid ikke SGA-barn som hadde motoriske problemer ved 14 år, mens Peabody Developmental Motor Scales kunne identifisere halvparten av dem ved fem års alder.

Resultatene i denne studien tyder på at motoriske problemer i VLBW-gruppen er resultat av en generell hjerneskade etter prematur fødsel, mens de motoriske problemene i SGA-gruppen kan skyldes mindre hjerneforandringer etter intrauterin veksthemming.

Kandidat: Kari Anne Indredavik Evensen
Institutt: Institutt for laboratoriemedisin, barne- og kvinnesykdommer
Veiledere: Torstein Vik, Ann-Mari Brubakk, Jon Skranes

Overnevnte avhandling er funnet verdig til å forsvares offentlig for graden philosophiae doctor i klinisk medisin.
Disputas finner sted i Auditoriet, Medisinsk teknisk forskningssenter
Fredag 9. april 2010 kl. 12.15.

Contents

Acknowledgements

This work was carried out at the Department of Laboratory Medicine, Children's and Women's Health at the Norwegian University of Science and Technology (NTNU), funded from a grant from Helse Midt-Norge. The data collection in the 14 year follow-up study was funded by the Regional Centre for Child and Adolescent Mental Health, Department of Neuroscience, NTNU, and Research Funds at St. Olav's Hospital. Part of the study population was recruited from a multicenter study sponsored by the US National Institute of Child Health and Human Development.

A lot of people have made this thesis possible. I would like to thank:

- The adolescents and their parents for participating in the study. Not only did they attend to motor evaluation, but have also taken part in hours of testing with pediatrician, child psychiatrist, psychologist and ophthalmologist, and even done MRI scans.
- Head of Department of Physical Medicine and Rehabilitation, St. Olav's Hospital, Gisle Meyer and Head of the Physiotherapy section, Anne-Lise Brein. I am grateful for the opportunity to take leave of absence from the clinic.
- My main supervisor and mentor, Professor Torstein Vik, Department of Laboratory Medicine, Children's and Women's Health, NTNU. Thank you for patiently working with me in manuscript writing, teaching me the principles of epidemiologic research, encouraging me and always being available for questions.
- Co-supervisor, Professor Ann-Mari Brubakk, Department of Laboratory Medicine, Children's and Women's Health, NTNU. Thank you for your great interest in research, for always being supportive and encouraging my work.
- Co-supervisor, Professor Jon Skranes, Department of Laboratory Medicine, Children's and Women's Health, NTNU, for giving me valuable input in completion of manuscripts as well as this thesis.

- Co-author, eye-doctor and “room-mate”, Susanne Lindqvist. Warm thanks for your great engagement in the research, patience in describing the visual systems to me and for always listening and offering good advice in research, as well as in other areas of life.
- My co-authors: Hermundur Sigmundsson, Jorunn Helbostad and Siri Kulseng, and all co-workers in the research group: Marit Martinussen, Gro Løhaugen, Line Knutsen Lund, Marius Widerøe and Tora Morken.
- Statistician Pål Romundstad for help and advice concerning statistical analyses in Paper III.
- Medical information specialist Ingrid Riphagen for thoroughly searching the literature upon my completion of this thesis.
- Colleagues at Department of Paediatrics, St. Olav’s Hospital and Head of the Paediatric Physiotherapy section, Anne Sørlie, for giving me the opportunity to work with children.
- My mother and co-author, Marit S. Indredavik, and my father, Bent Indredavik, for both scientific and “non-scientific” up-bringing and continuous support in my work.
- My dear husband, Jan-Tore, for hanging in there, and last, but not least, I am forever grateful for my children, Mathea and Erlend, who I love above all and who make me come home from work in time.

Trondheim, 17th of December, 2009

Kari Anne Indredavik Evensen

List of papers

Paper I

Motor skills in adolescents with low birth weight

Kari Anne I. Evensen, Torstein Vik, Jorunn Helbostad,
Marit S. Indredavik, Siri Kulseng, Ann-Mari Brubakk

Archives of Disease in Childhood. Fetal and Neonatal Edition 2004
volume 89, issue 5, page F451-F455

Paper II

Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents?

Kari Anne I. Evensen, Susanne Lindqvist, Marit S. Indredavik,
Jon Skranes, Ann-Mari Brubakk, Torstein Vik

European Journal of Paediatric Neurology 2009
volume 13, issue 1, page 47-56

Paper III

Inter- and intra-modal matching in very low birth weight and small for gestational age adolescents

Kari Anne I. Evensen, Hermundur Sigmundsson, Pål Romundstad,
Marit S. Indredavik, Ann-Mari Brubakk, Torstein Vik

Early Human Development 2007
volume 83, issue 1, page 19-27

Paper IV

Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children

Kari Anne I. Evensen, Jon Skranes, Ann-Mari Brubakk, Torstein Vik

Early Human Development 2009
volume 85, issue 8, page 511-518

Abbreviations

AGA = Appropriate for gestational age
BSID = Bayley Scales of Infant Development
CI = Confidence interval
CNS = Central nervous system
CP = Cerebral palsy
DCD = Developmental coordination disorder
GMFCS = Gross Motor Function Classification System
ICF = International Classification of Functioning, Disability and Health
IUGR = Intrauterine growth retardation
IQ_{est} = Estimated intelligence quotient
LBW = Low birth weight
NICU = Neonatal intensive care unit
Movement ABC = Movement Assessment Battery for Children
MRI = Magnetic resonance imaging
OR = Odds ratio
PDI = Psychomotor development index of Bayley Scales of Infant Development
PDMS = Peabody Developmental Motor Scales
PVL = Periventricular leukomalacia
SES = Socioeconomic status
SD = Standard deviation
SGA = Small for gestational age
VLBW = Very low birth weight
WHO = World Health Organization

Summary

Children born too soon (preterm) and/or too small (small for gestational age suggesting intrauterine growth restriction) have a higher risk of mortality and morbidity than children born at term with appropriate birth weight. Cerebral palsy is the most severe motor sequelae. However, minor motor problems are also frequently reported, particularly in children born preterm. Among children born small for gestational age, motor outcome is less documented and studies have shown inconsistent results.

Few studies have examined motor skills in these children in adolescence. The aim of this study was to assess the prevalence of motor problems in adolescents born preterm with very low birth weight (VLBW) and in adolescents born small for gestational age (SGA) at term. Furthermore, we wanted to study whether visual impairments influenced their motor problems, and whether integration of vision and proprioception was reduced. Finally, we wanted to examine if early motor evaluations could identify children with motor problems in adolescence.

We found that a higher proportion of VLBW and SGA adolescents had motor problems compared with controls, assessed by the Movement Assessment Battery for Children. While both VLBW boys and girls had general motor problems in terms of manual dexterity, ball skills and balance, the motor problems in the SGA group were mainly found among boys in manual dexterity. A substantial part of the motor problems in the VLBW group was influenced by visual impairments; however, this was not the case in the SGA group. The VLBW adolescents performed poorer in a task of inter- and intra-sensory integration compared with controls. However, the unfavourable results were mainly due to adolescents with cerebral palsy or low estimated intelligence quotient. The SGA adolescents performed as well as controls on this task, but had relatively poorer performance with their non-preferred hand compared with their preferred hand. Most of the VLBW adolescents with motor problems were identified already at one year, using the motor scale of the Bayley Scales of Infant Development. However, this test did not identify SGA children who had motor problems at age 14, whereas half of them were identified at five years of age using the Peabody Developmental Motor Scales.

The results of this study suggest that motor problems in the VLBW group are due to a general brain damage following preterm birth, whereas motor problems in the SGA group may be caused by subtle brain dysfunctions following intrauterine growth restriction.

1. Introduction

In 1976, Neligan and co-workers carried out a follow-up study of children "born too soon or too small".[1] The idea was to look for differences between infants of short gestation (i.e. born too soon) and those who had suffered suboptimal growth during pregnancy (i.e. born too small, but not too soon). This and other studies of that time[2;3] recognized that not all small babies are premature and not all premature babies are small, although the concepts of "premature" and "small" more or less had been treated as synonyms in previous research.[4]

It is well known that infants born too soon or too small both have an increased risk of perinatal mortality and morbidity. During the last decades, mortality among these infants has decreased as a result of improvements in obstetric and neonatal care. Accordingly, the main focus is now on the long-term outcome of these children.

Motor skills are an important part of daily functioning, particularly in childhood. Children need a certain motor competence in order to be independent and successful in playground activities. Poor motor skills can be problematic for the child per se, but can also be associated with other problems in school and in peer relationships.

Children born too soon are reported to have an excess of motor problems compared to the typical populations of term-born children, whereas motor outcome for children born too small at term has been less clear.

Physiotherapists are often engaged in the care of children with motor problems. They are responsible for assessment of degree and type of motor problem, routine follow-up and intervention when needed.

This thesis contains four separate papers. The first paper was written as part of my Master degree in Physiotherapy,[5] although it was greatly condensed later on prior to publication. However, since this paper constitutes an important basis for the other papers, I have chosen to include it in my thesis. The thesis will first draw attention to the prevalence of motor problems in a cohort of adolescents born too soon and too small, then seeking some underlying mechanisms for such problems and finally examine whether motor problems possibly can be identified at an early stage in life.

1.1 Born too soon or too small

This chapter deals with risk factors and general outcome for children born too soon or too small. Motor outcome and possible aetiology of motor problems in these groups of children will be discussed in section 1.3.

1.1.1 Historical background

The first long-term investigation of the effects of prematurity on later development appeared in 1919.[6] Together with other early studies from the same period, results seemed to indicate that prematurely born infants who survived were at risk of developing problems later in life. However, most of these studies were retrospective in nature, followed few children, and conclusions were based on clinical impressions rather than objective assessments.[7] The basis for studies conducted in the 1950s and 1960s was the need to determine if saving tiny infants in intensive care nurseries was a "triumph of neonatal paediatrics" or a "social and family disaster".[8] This is still the most prominent reason for doing longitudinal follow-up of these children.[8]

Traditionally, the concept of "low birth weight" (LBW) has been reserved for children with birth weight below 2500 g.[4] For most of the previous century, the presumed reason for infants to be born LBW was preterm delivery, and prematurity was defined as LBW by the World Health Organization (WHO) as late as in 1948.[9] As a consequence of this, the terms LBW and premature were used interchangeably in scientific literature from the 1920s to 1960s.[4] However, it became clear that not all infants weighing less than 2500 grams were premature, and at the same time some infants being born prematurely weighed more than the LBW cut-off. WHO recommended in 1961 that LBW no longer should be used as the official definition of prematurity.[10] The term intrauterine growth retardation (IUGR) was introduced when researchers in the 1970s were faced with a new problem; that infants born at term with a low birth weight also had a higher risk of mortality.[4]

In 1977, WHO defined a delivery before 37 completed weeks as a premature birth, and an infant whose birth weight was below the 10th centile for gestational age, as "small for gestational age" (SGA). Thus, from 1970 to 1980

there was a shift within LBW research from one label, i. e. “prematurity”, to two labels; “preterm” and “IUGR”.[4] Some studies in the 1970s included three groups of infants; preterm, full-term ”small for date” and full-term controls.[1-3] Later, studies tended to focus on only one (preterm versus controls) or the other (SGA versus controls). A proportion of the preterm literature also involves the subgroup of preterm SGA infants. However, as prematurity is so strongly associated with abnormal development, it is often hard to separate the effect of SGA from the effect of prematurity.[11]

During the 1970s and the 1980s neonatal intensive care improved dramatically resulting in increasing numbers of surviving preterm infants. In Norway, mortality decreased from 67% in 1967 to 11% in 2008 for live born infants with birth weight below 1500 g (Figure 1). However, negative effects of this development were increased prevalence of severely physically and/or mentally handicapped children[12], and also an increase in the number of children with more subtle difficulties. This began to cause concern.[13]

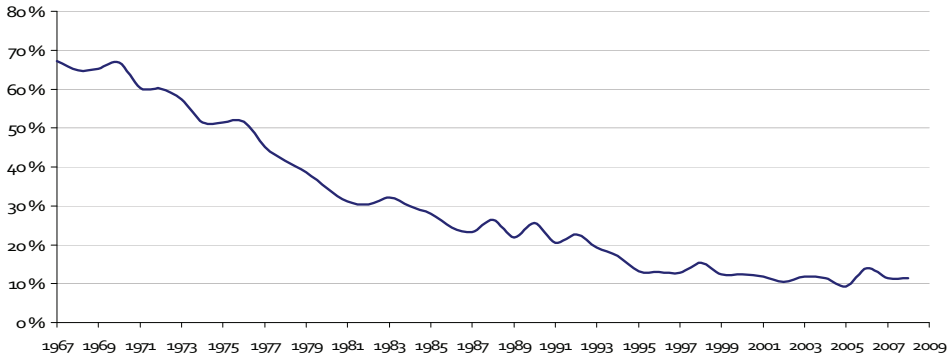


Figure 1. Neonatal mortality for live born infants with birth weight below 1500 g and gestational age above 22 weeks in Norway 1967-2008.[14]

After prematurity, fetal growth restriction is presently the second leading cause of perinatal morbidity and mortality.[15] Growth restricted infants are the result of 3-10% of all pregnancies.[16;17] Long term impairments in various domains have also been described in fetal growth restricted children born at term, although severe handicaps are less common.[15;18]

1.1.2 Concepts and definitions

Low birth weight

In the first paper, we used "low birth weight" as a common term for children born preterm, i.e. before week 37 of pregnancy, and children born small for gestational age at term. However, since this term might be associated with the older definition of 2500 g, we used the two different concepts of "very low birth weight" and "small for gestational age at term" in the subsequent papers.

Born too soon

In this thesis, "born too soon" is used to embrace the group with "Very Low Birth Weight" (VLBW), defined by a birth weight ≤1500 g. This cut-off does not include a specification of gestational age, but in practice all VLBW infants are born preterm. The advantage of using birth weight rather than gestational age is that it is more accurate. However, by using birth weight ≤1500 g as a single inclusion criterion, there will be a selection of those born small for gestational age (SGA) at the higher gestational ages and a higher proportion of those born appropriate for gestational age (AGA) at lower gestational ages, although SGA may occur at lower gestational ages as well. Also, by restricting our preterm group to 1500 g, we have not included all preterm infants, i.e. the moderately preterm. Despite these issues, 1500 g is a well-known cut-off widely used in research, which facilitates comparison. In Norway, the incidence of VLBW was 1.0% of all live births in 2008.[14]

Born too small

The term "born too small" is used to embrace the group born "Small for Gestational Age" (SGA) at term. The concept of SGA is used to identify those infants with reduced birth weight who may have been growth retarded *in utero*. SGA is defined as birth weight below the 10th centile, adjusted for gestational age, sex and parity.[19] However, using this definition, some infants who are genetically small and not growth restricted will fall into this category. On the other hand, some genetically large infants who have been growth restricted *in utero* may have birth weights above the 10th centile. Nonetheless, the 10th centile

is often used.[4;16;20] In Norway, the incidence of term SGA infants was 5600 in 2008 (10% of all term births).[14]

1.1.3 Risk factors for being born too soon or too small

Risk factors for preterm birth may include life style factors, such as heavy manual labour, alcohol and drugs, as well as biological components. Infection of intrauterine tissues and/or the fetus has been regarded as a substantial factor.[21] Abnormal programming of the hormonal regulation or the placenta during pregnancy has also been suggested. These risk factors may be strongly influenced by the psychological state, the neuroendocrine system and the immune system of the mother.[21] Twin or multiple pregnancies also carry an increased risk of preterm birth,[22] which has increased due to in-vitro fertilization and implantation of multiple eggs. A paradox of improved health care in pregnancy is that it may actually increase the numbers of preterm births, as more stillbirths are prevented by preterm delivery.[23]

Risk factors for being born SGA at term are slightly different, since some of these infants are simply genetically small. Others have suffered from a suboptimal intrauterine environment causing fetal growth restriction.[24] This may be a result of pathological conditions in the fetus, placenta, mother or the environment.[25] Among identified risk factors are fetal chromosomal anomalies, preeclampsia, infections, placental and umbilical anomalies. Maternal risk factors include low socioeconomic status, low pre-pregnancy weight or malnutrition, low weight gain during pregnancy, previous pregnancy with IUGR, heavy physical work load, cigarette smoking, alcohol and drug use, anaemia and systemic disease.[25] Some claim that growth restriction occurring early in pregnancy results in a symmetrical growth restricted infant with weight, length and head circumference equally affected, while growth restriction in the third trimester of pregnancy results in an asymmetrical growth restricted infant with poor weight gain, but relative sparing of length and head circumference.[26] Others have questioned this hypothesis, finding no evidence of brain sparing[27] or adverse neonatal outcome[28] in asymmetrical compared with symmetrical SGA infants.

1.1.4 Outcome for children born too soon or too small

A conceptual framework

The International Classification of Functioning, Disability and Health (ICF) of WHO describes health in the dimensions of *body functions and structures*, *activity* and *participation* (Figure 2).[29] The overall aim of the ICF is to provide a scientific basis for understanding and studying health and health-related states, outcomes and determinants.[30] In this framework motor skills and problems can be placed within the main dimension of *activity*, which refers to a person's execution of daily activities, from simple to more complex actions.[29] Activities also include learning, communicating, feeding, dressing and playing.[31] Motor problems may be caused or influenced by *body functions and structures*. Body functions include physiological functions of the systems in the body, as well as psychological functions,[29] such as attending, remembering and thinking. Body structures include the anatomical parts of the body, such as organs and limbs, and structures of the nervous, sensory and musculoskeletal systems.[31] Motor problems may in turn have consequences for academic and social functioning.[32] Thus, they may influence *participation*, which involves the person's functioning in the community and in life arenas like home, work/school and leisure activities.[29] For children this means participating in play groups, kindergarten and school, and other involvements in social groups.[31] In the long-term lack of motor competence may hinder successful integration in society.[33]

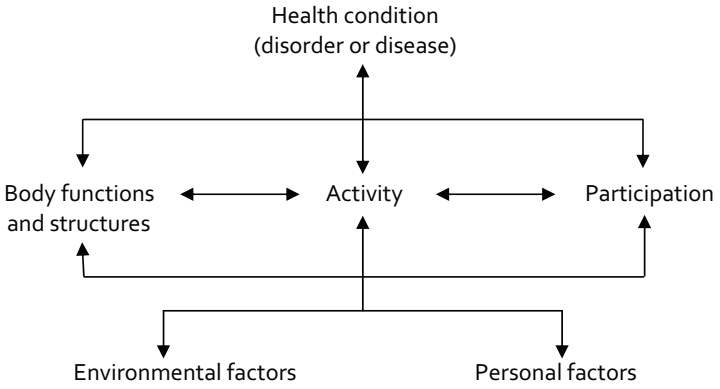


Figure 2. The International Classification of Functioning, Disability and Health.[29]

Born too soon

Using the framework of ICF, the general outcome of children born too soon is presented in Table 1. Within the domain of *body functions and structures*, VLBW infants are at risk of developing complications of prematurity, such as brain infarction,[34] peri- and intraventricular haemorrhage, retinopathy of prematurity and bronchopulmonal dysplasia,[35] as well as necrotizing entero-colitis, hyperbilirubinemia, nutritional deficiencies and neonatal infections.[36;37] VLBW children have a higher risk of cerebral palsy (CP)[12;13;38] and epilepsy,[38] as well as sensory deficits, such as blindness and deafness, which increases with lower gestation and birth weight.[35;38-40] Visual impairments, such as reduced visual acuity, strabismus, reduced contrast sensitivity, correction for myopia[41-44] and visuo-perceptual problems,[45-47] are more common in VLBW subjects than in controls. Reduced lung function[48-50] and asthma,[51] as well as other chronic medical conditions,[52] have been reported in childhood and young adulthood. Studies consistently report poor growth in VLBW children from childhood throughout adolescence and into young adulthood.[52;53] Furthermore, reduced muscular strength and reduced physical work capacity have been found in VLBW adolescents and young adults.[41;49] Lower intelligence quotient (IQ) scores compared with controls have been reported in childhood,[54;55] adolescence[55;56] and adulthood,[52] as well as poor executive functions.[57] Psychiatric symptoms and disorders are frequent,[58-61] especially attention-deficit hyperactivity disorder (ADHD)[55;58;62;63] and anxiety disorders.[58;60]

In the *activity* domain of ICF, motor problems are frequent (see section 1.3.1 for details), and VLBW subjects report less physical activity compared with controls.[50;64] They often experience general learning difficulties in school or poor performance compared with pupils in the same class.[65]

In the ICF domain of *participation* this causes the academic achievement of children born VLBW to be lower than their peers.[38;52;66] They often have need for special schooling, education below age level or special support in regular schools,[65] and fewer graduate from high school and complete university compared with controls.[38;52] This may in turn cause them to have lower job-related income.[38] In adolescence, reduced social skills,[67] poor peer relations[68]

and low self-esteem have been described in VLBW subjects,[69] as well as an increased risk of being bullied.[70] Despite a high prevalence of problems in many domains, VLBW subjects do not generally perceive their quality of life differently from controls.[64;71] However, parents of VLBW adolescents report lower quality of life for their offspring.[71]

Born too small

Studies of neurodevelopmental outcome in full-term SGA infants are less numerous,[72] as these children generally have less neurodevelopmental problems than children born at lower gestational ages. Nonetheless, in the ICF domain of *body functions and structures* (Table 1), SGA infants have increased risk of perinatal complications,[28] such as asphyxia, aspiration syndrome and pulmonary complications, as well as metabolic disturbances.[20;26] CP is generally not a frequent finding,[73] although the risk is slightly increased.[74;75] Visual and hearing impairments are less common,[74] but subtle changes have been reported, such as slightly more hypermetropia in SGA adolescents compared with controls,[43] and minor deficits in visual fields.[76] SGA children born at term also have lower height, weight and smaller head circumference than controls in childhood and adolescence,[77-81] although a large proportion catches up in height.[82] Lower IQ scores compared with controls have been reported in some studies of SGA children,[1;83;84] and adolescents,[78;85;86] but not in others.[80;87-89] SGA adolescents do not appear to have psychiatric diagnoses more often than controls.[60]

Nonetheless, within the *activity* domain of ICF, term SGA children often have increased learning difficulties in school.[79;84;87;90-95] At early school age, they are reported to show more behavioural problems than their peers; both hyperactivity and poor concentration have been described,[73] as well as more passive behaviour.[1;96] Parents and teachers have reported that SGA adolescents show inattention and more rule breaking behaviour than controls.[68;78;94] Studies of motor skills have shown inconsistent results (see section 1.3.2 for details).

Within the ICF domain of *participation*, some have found differences between SGA subjects and controls in late adolescence and young adulthood

when it comes to academic achievement and professional functioning,[79;95] whereas others have not.[68;97] Adolescents born SGA at term have been reported to have lower social competence and peer problems,[71;78] although this is not always reported in younger children.[73] Nonetheless, in young adulthood, they are likely to be employed, married and satisfied with life.[79]

Table 1. Overview of the most common sequelae after being born too soon or too small.

Born too soon: Preterm VLBW	Born too small: Term SGA
BODY FUNCTIONS AND STRUCTURES	
Physical:	Physical:
Perinatal complications	Perinatal complications
Chronic medical conditions	
Suboptimal growth	Suboptimal growth
Poor muscular strength	
Poor physical work capacity	
Neurological:	Neurological:
Brain lesions	Slight increased risk of cerebral palsy
Cerebral palsy	
Epilepsy	
Sensory:	Sensory:
Deafness	Subtle to no changes in visual functions
Blindness	
Visual impairments	
Perceptual impairments	
Cognitive:	Cognitive:
Low IQ	Mixed evidence of low IQ
Poor executive functions	
Psychiatric:	
ADHD, anxiety	
ACTIVITY	
Learning difficulties	Learning difficulties
Emotional/behavioural problems	Emotional/behavioural problems
Motor problems	Mixed evidence of motor problems
Low physical activity	
PARTICIPATION	
Low academic achievement	Mixed evidence of low academic achievement
Low professional attainment	Low professional attainment
Reduced social skills and peer problems	Reduced social skills and peer problems
Risk of being bullied	

1.2 Motor skills and motor problems

Motor skills, or tasks "that require voluntary body and/or limb movement to achieve a specific goal",[98] are an important part of daily life for children and adolescents. Children depend on having a certain motor competence to master practical tasks in everyday living.[99] This section deals with theories and classifications of motor skills, definitions and identification of motor problems, common motor tests and aetiology of motor problems.

1.2.1 Theories of motor development

Motor development can be seen as "the sequential, continuous, age-related process where an individual advances from simpler movements to complex motor skills".[100] It is closely tied to motor learning which can be defined as "a set of processes associated with practice or experience leading to relatively permanent changes in the ability to perform motor skills".[101]

There are different theories as to what guides motor development and motor learning. For many years, normal and abnormal motor development have been interpreted within the framework of the "neural-maturation theories".[102;103] These theories suggest that all movements are monitored by the central nervous system (CNS) and that development of motor skills is based on predestined sequences of maturation of the CNS.[103] These assumptions leave little room for environmental factors and experience in order to modify development.

In the late 1990s, the "dynamic systems theory" was introduced.[103] In this motor development is regarded as a complex, dynamic process which changes direction over time due to interaction of multiple components and subsystems, both within and outside the body.[104] This theory stresses the influence of environmental conditions on motor development, in which the CNS is just one of several factors.[105] Thus, the two theories differ, especially in their view on the role of the nervous system in the attainment of motor skills.

The two aforementioned views are combined in the "neuronal group selection theory", introduced by Edelman.[106;107] According to this theory, the brain is dynamically organized into variable networks, or neuronal groups. A

process of selection takes place within the neural system, as practice in a given task increases connections within specific areas of the brain.[108] Thus, the structure and function of these neuronal networks are modified by both development and behaviour.[102]

According to the neuronal group selection theory, normal motor development is characterized by phases of primary and secondary variability.[102;109] During the first phase, motor activity is variable and not tuned to environmental conditions. The infant develops various strategies for the execution of motor functions, for instance when it comes to reaching.[110] However, during the first half year of life movements become more efficient.[109] After this first phase, which results in selection and reduced variation of movements, the second phase begins, where a variable movement repertoire is created with efficient motor function for specific situations. Between two and three years of age, motor variation increases.[109] The emergence of coordinated movements is influenced both by the development of the brain and the growth of the musculoskeletal system.[106] By the time children reach school age, they have built up a repertoire of skills that enables them to function effectively in the classroom, playground and at home.[111] However, it is not until adolescence that the motor repertoire is fully mature and the individual can adapt movements exactly and efficiently to task-specific conditions.[102]

1.2.2 Classification of motor skills

Fundamental movement skills have been classified, assessed and evaluated in various ways since the 1920s.[112] Some use the dichotomy of gross and fine motor skills, where the former involves large muscles, or group of muscles, and less precise movements, and the latter involves smaller muscles, or groups of muscles, but more precision.[98] However, some skills may be in the continuum between gross and fine motor skills,[113] involving both small and large groups of muscles (i.e. catching a ball in the playground). Henderson and Sugden[113] arrange motor skills in the domains of manual dexterity, ball skills and static/dynamic balance. In this respect, manual dexterity involves manipulation of objects using one or both hands (i.e. writing, drawing and doing up buttons)

and ball skills involve catching and kicking a ball. Balance, or postural control, is hard to separate from other tasks, as it can be defined as the ability to maintain the body in equilibrium.[114] This can be at rest (static balance) or in motion (dynamic balance).

Gentile[115] also takes the environment into account when classifying tasks, in what has been called "Gentile's taxonomy" (Figure 3). In closed tasks the objects, other people and the environment are stable while the child performs the task; in open tasks, the objects, other people and the environment are changing. The complexity of the task increases from a closed to an open task, demanding more adaptation to the environment.[113;115]

		CHILD	
ENVIRONMENT		Stationary	*Moving*
	Stable	Section 1 (e.g. writing, drawing, cutting, static balance)	Section 2 (e.g. dynamic balance, walking, running)
	Changing	Section 3 (e.g. ball-catching/kicking)	Section 4 (e.g. ball game; running to catch a ball, playground activity; chasing another child)

Figure 3. Gentile's taxonomy (adopted from Movement ABC manual).[113]

1.2.3 Terminology

The term "clumsy children" was first introduced in 1937 by Orton,[116] who described these children as: "…somewhat delayed in learning even the simpler movements such as walking and running, have great difficulty in learning to use their hands and to copy motions shown to them." Since then, the concept of "clumsiness" has been discussed in the literature for more than 70 years.[117;118] There has been considerable debate over the nature and definition of the syndrome which would adequately embrace the everyday problems of these children.[119] In addition to "clumsiness",[116;120] authors have used terms like "motor infantilism",[121] "developmental dyspraxia or apraxia and agnosia",[120;122] "physical awkwardness"[117], "perceptuo-motor dysfunction",[7;123] "sensory integrative dysfunction"[124] and "minor neurological dysfunction".[125]

One reason for this diversity in terms may be that different professionals have been concerned with these children; paediatricians, neurologists, psychiatrists, psychologists, and physical and occupational therapists.[125;126] There has generally been agreement that the condition refers to individuals who are cognitively competent and who have no known neuromuscular involvement,[117] although some have suggested it to be a mild form of CP.[120;122;127] Others have considered the motor problems as part of a more complex picture, using terms like "minimal brain dysfunction" and "deficits in attention, motor control and perception".[128;129]

The diagnostic label of "developmental coordination disorder" (DCD) was introduced in the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R) by the American Psychiatric Association in 1987 and later revised in the fourth edition of the DSM (DSM-IV) in 1994.[130] DCD is defined as "a marked impairment in the development of motor coordination that is not explicable by mental retardation, and is not due to a known physical disorder". While the diagnosis of DCD was introduced to bring a uniform label to the problem, its use on populations of preterm or growth restricted children is questionable,[131;132] since they are shown to have an excess of cognitive and physical difficulties, as discussed in the previous section on general outcome (section 1.1.4). In this thesis, the term "motor problems" confines to low scores of the motor tests (see method section 3.3.1 for details).

1.2.4 Identification of motor problems

Determining the prevalence of motor problems is naturally linked to identification procedures and definitions.[117] Valid and reliable motor tests are essential tools used by clinicians to diagnose and evaluate motor performance in children.[133;134] Validity refers to whether the test actually measures what it is intended to measure.[135] Reliability is a prerequisite for validity, and refers to consistency in measurement,[135] or how stable a test is in measuring a child's level of the ability being assessed.[136] Standardized tests have the potential of objectifying our clinical evaluations, increasing the likelihood that the measurement is a true estimate of what we are assessing.[137] Although tests

cannot be regarded as complete, objective measures of a person's abilities or performance, but rather an expression of what a child can achieve on certain tasks in a certain situation,[113] they seem to be a beneficial contribution to the clinical judgement.

According to Kirshner and Guyatt[138] tests can be categorized with regard to the goals they serve. They can be discriminative, i.e. making a distinction between children who show features of a deviant motor function compared with the general, healthy population.[139] The second purpose is prediction, i.e. they are used as a tool to predict developmental outcome. Thirdly, tests can be evaluative, i.e. measure longitudinal change over time. Instruments are generally validated for only one of the three goals, and may or may not be a useful and valid instrument for other purposes.[134;140]

The major types of standardized tests are norm-referenced and criterion-referenced measures.[141] Norm-referenced tests measure the performance of a person in relation to a specific population, and are often used to discriminate whether a child's development is out of "normal" range, and if so, how impaired the development is.[134] Raw scores from these tests need to be compared with a population.[141] When norm-referenced tests are used, it is important that the test is standardized on a representative sample, as motor development may vary across different social and ethnic populations. Criterion-referenced tests have criteria or a minimum competence that must be reached in order to pass the test.[141] A criterion-referenced test contrasts the child's performance with the test content rather than a population,[141] and is often used to evaluate a child's change over time.[134] Some tests are referenced both by norm and by criterion.[136]

Discriminative tests must be sensitive in the area, or range, of discrimination. Thus, sensitivity and specificity are two measures of the test's validity.[142] Sensitivity refers to the ability of a test to detect a person with a condition (i.e. motor problem) when it is present. Specificity refers to the ability to correctly identify those without a condition (i.e. normal motor skills).[142] Although a test with both high sensitivity and high specificity is desirable, there is generally a trade-off between the two. For many clinical tests, some persons are clearly normal, some are clearly abnormal, and some fall into the grey zone.

When sensitivity increases, the probability of correctly classifying people with the condition is increased (true positives); however, a certain proportion of subjects without problems will be incorrectly classified (false positives). On the other hand, a very specific test is less likely to have false positives, but more likely to miss subjects with true problems (false negatives). Thus, altering the cut-off for abnormality will influence both sensitivity and specificity.[142]

There is no "gold standard" for identification of motor problems,[143] since no test covers the whole spectrum of motor skills.[144] Thus, a child may fail on one kind of motor ability, but perform relatively well on another.[143-145] Whether the child will perform below the cut-off depends on the type of tasks examined and the nature of the child's problems.[144] Different measures of movement ability may therefore identify different children as displaying motor problems.

1.2.5 Common motor tests

A number of different tests has been developed in order to identify children with motor problems or quantify motor development. Some of them are presented in Table 2. All these tests have discrimination as their main goal, although some are also able to predict future outcome and evaluate change over time. Most of the tests have shown good reliability and validity,[139;141] although intra-rater reliability, or consistency in measurements when performed by one tester on two or more occasions, has been documented only for a few.[146-149] In the ICF domain of *body functions and structures* we mainly find neurological tests, seeking underlying causes for the problems, and most of these tests are criterion-referenced. Some tests combine the two domains of *body functions and structures* and *activity,* involving both reflexes and functional tasks.[150-154] Within the domain of *activity* we mainly find developmental tests, which are most often norm-referenced and standardized on larger representative samples. Among these are the Bayley Scales of Infant Development (BSID),[155] the Peabody Developmental Motor scales (PDMS)[136] and the Movement Assessment Battery for Children (Movement ABC),[113] which have all been used in the present study. The Movement ABC is one of the most frequently used tests.[144;156] There are few tests assessing motor skills in adolescence.

Table 2. Different neurological and developmental tests used by different professionals to identify motor problems in children.

Test	Age range	Purpose and type of test		Items included in test
ICF BODY FUNCTIONS AND STRUCTURES				
Dubowitz Neurological Examination[157;158]	Birth	Discrimination	Criterion	34 items in 6 categories: tone, tone patterns, reflexes, movements, abnormal signs and behaviour
General Movements (GMs)[146]	Birth-4 mo	Discrimination Prediction	Criterion	Spontaneous motor behaviour in supine position; assessment of variability and complexity of movements
Motor Assessment of Infants (MAI)[148]	0-12 mo	Discrimination Evaluation	Criterion	65 test items in 4 sections: muscle tone, primitive reflexes, automatic reactions and volitional movement
Neuromotor Behavioural Inventory (NBI)[153;159]	0-12 mo + 3 yr	Discrimination	Criterion	5 categories; 0-12 mo: muscle tone, developmental motor abilities, quality of movements, neurological reflexes and reactions, and oral-motor behaviour; 3 yr: gross motor, fine motor, reaction to movement, neurological reflexes and reactions, and neuromotor outcome
Active and passive muscle power[160]	3-12 mo	Discrimination Prediction	Criterion	Emphasis on balance between active and passive muscle power
Touwen Infant Neurological Examination[150]	0 mo-walking	Discrimination	Criterion	Cranial nerves, posture, tone, reflexes and reactions, trunk coordination and gross and fine motor functions
Infant Neurological International Battery (Infanib)[161]	1-18 mo	Discrimination Evaluation	Norm	20 items in 5 categories: spasticity, vestibular function, head and trunk control, resting tone and description of motor behaviour of the legs
Primitive Reflex Profile[162]	0-2 yr	Discrimination	Criterion	9 primitive reflexes
Hammersmith Infant Neurological Examination (HINE)[154]	2-24 mo	Discrimination	Criterion	37 items in 3 sections: 1) Cranial nerve function, posture, movements, tone, reflexes and reactions (26 items), 2) developmental milestones (8 items) and 3) state of behaviour (3 items)
Amiel-Tison Neurological Examination[152]	0-6 yr	Discrimination	Criterion	Active and passive muscle tone, cranial nerves, motor milestones, spontaneous motor activity, reflexes and reactions, qualitative abnormalities
Neuro-Sensory Motor Develop-mental Assessment (NSMDA)[151]	1 mo-6 yr	Discrimination	Criterion	6 subscales: gross motor, fine motor, neurological, primitive reflexes, postural reactions, sensori-motor responses
ICF ACTIVITY				
Test of Infant Motor Performance (TIMP)[163]	Birth (32 wk)-4 mo	Discrimination Evaluation	Norm	42 items in 2 sections: observed (13 items) and elicited (29 scaled items - administered by the examiner in a standardized format)
Structured Observation of Motor Performance (SOMP-I)[149]	0-10 mo	Discrimination	Criterion	13 scales of motor development for each body part in supine and prone position and in the whole body when sitting, standing and during locomotion

Alberta Infant Motor Scale (AIMS)[147]	0-18 mo	Discrimination	Norm	58 items in 4 postural positions: prone, supine, sitting and standing
Posture and Fine Motor Assessment of Infants (PFMAI)[164]	2-12 mo	Discrimination	Criterion	PFMAI-I (2-6 mo): 18 posture and 21 fine motor items PFMAI-II (6-12 mo): 13 posture and 17 fine motor items
Infant Motor Profile (IMP)[165]	3-18 mo	Discrimination	Criterion	Observed or elicited behaviour grouped as 80 items in 5 subscales; variability - size of repertoire, variability - ability to select, symmetry, fluency and performance
Bayley Scales of Infant Development (BSID)[155]	0-30 mo	Discrimination Evaluation	Norm	Motor scale: 81 items; gross and fine motor behaviour (in addition a mental scale and a behaviour rating scale)
Toddler and Infant Motor Evaluation (TIME)[166]	4-42 mo	Discrimination Evaluation	Norm	5 primary subtests: mobility, motor organization, stability, social/emotional abilities and functional performance; 3 clinical subtests: quality rating, atypical positions and component analysis
Denver Developmental Screening test[167]	2 wk-6 yr	Discrimination	Norm	105 items in 4 domains: gross motor, language, fine motor-adaptive and personal-social
Peabody Developmental Motor Scales (PDMS)[136]	0-83 mo	Discrimination Evaluation	Criterion Norm	Gross Motor Scale: 10 items in 5 categories; reflexes, balance, non-locomotor, locomotor, receipt and propulsion of objects; Fine Motor Scale: 8 items in 4 categories; grasping, hand-use, eye-hand coordination, manual dexterity
Test of Gross Motor Development (TGMD)[168]	3-10 yr	Discrimination	Criterion Norm	12 items with 3-4 observable criteria specified for each movement skill; 2 subtests: locomotion and object control
McCarron Assessment of Neuro-muscular Development (MAND)[169]	3,5-18 yr	Discrimination	Norm	10 items divided in fine and gross motor skills (5 items in each category)
Movement Asesement Battery for Children (Movement ABC)[113]	4-12 yr	Discrimination	Norm	8 items in 3 subscores: manual dexterity (3 items), ball skills (2 items), static/dynamic balance (3 items)
Bruininks-Oseretsky Test of Motor Proficiency (BOTMP)[170]	4,5-14,5 yr	Discrimination Evaluation	Norm	46 items in 8 subtests; gross motor composite score (4 subtests), fine motor composite score (3 subtests) and battery composite (1 subtest)
Test of Motor Proficiency (TMP)[120]	8-12 yr	Discrimination	Criterion	8 items (shortened to 4 in 1978) in 3 categories: facial and lingual praxis, trunk and leg praxis, manual praxis
ICF PARTICIPATION				
Harris Infant Neuromotor Test (HINT)[171;172]	2.5-12.5 mo	Discrimination	Norm	4 general areas: 1) background information, 2) questions assessing the caregiver's level of concern about the infant's movement and play, 3) observational or testing section (21 items) and 4) overall clinical impression
Movement ABC Checklist[113]	5-11 yr	Discrimination Evaluation	Norm	4 motor sections based on Gentile's taxonomy of tasks: 48 items; 1) child stationary/environment stable, 2) child moving/environment stable, 3) child stationary/environment changing and 4) child and environment changing

1.2.6 Prevalence of motor problems

It is estimated that approximately 6% of all children have motor problems corresponding to DCD.[130;173] This is in accordance with studies in Norway, which have identified a prevalence of 5-6%.[174;175]

Boys have been reported to have motor problems more often than girls.[173] In Norway, one study identified a gender ratio of 3:1 in favour of girls at ten years of age.[175] Others claim that boys can be superior in some tasks, for instance carry out simple movements faster than girls, whereas girls can be faster in other and more complex tasks.[176]

Older children perform tasks more efficiently than younger children.[176] Some studies of children with motor problems[177] and minor neurological dysfunction[178] have reported improvements from childhood to adolescence, whereas others have reported that without intervention children with motor problems will continue to have such problems in adolescence.[32]

Motor problems are often associated with poor academic performance as well as emotional and social problems.[145;179;180] Thus, motor problems may influence the child's total function.

1.2.7 Aetiology of motor problems

Current theories of motor development suggest that development is a complex outcome of the maturation of multiple physiologic systems in combination with demands placed on the child by the environment and task-related experiences.[117] Thus, the aetiology of motor problems is likely to be multifactorial, involving both genetic and environmental factors.[179] Within the subject, motor, cognitive and sensory systems all play a role in the execution of motor skills.[103] Some claim that motor problems are caused by developmental delay, due to an immature CNS,[113;121] or to cerebral lesions[121;179] and cerebellar dysfunctions,[181] while others consider motor problems as part of the normal variation in motor skills.[182] Motor coordination is related to physical activity, as well as body weight.[183] A low level of physical activity may affect motor skills negatively; however, children experiencing motor problems are less likely to engage in physical activity.[99;183] Several researchers have regarded motor problems as a

result of sensory processing problems.[184;184;185] Of the six senses (vision, hearing, touch, smell, taste and proprioception), vision and proprioception are by far the most important in control of movement.[113] Some have suggested that motor problems are secondary to problems in visual-motor and visual-perceptual integration,[184;186;187] while others claim that motor problems are caused by deficits in proprioception.[188-190] Von Hofsten and Rösblad[191] have combined these two hypotheses in their investigation of the integration of sensory information in terms of inter- and intra-modal matching. Within the ICF framework, vision and proprioception are *body functions* that may influence motor skills and problems.

Vision

Vision is perhaps the most powerful sensory system functioning to regulate posture,[192] and the dominant sensory-perceptual mode in the initial phases of motor learning.[193] It is such a potent source of information that we will ignore or suppress input from other senses, even though information from them may be more relevant for efficient performance.[193]

Simplified, visual information passes via the optic nerves into the optic chiasm of the brain, where information from each eye is split vertically down the midline into two visual hemifields.[194] Information from each hemifield is guided to the contralateral occipital lobe in the posterior part of the brain, where the primary visual centre is situated.[194] From the primary visual centres arise two principal pathways serving higher visual function; the ventral stream and the dorsal stream.[195] The ventral stream connects the occipital and temporal lobe, and deals with visual recognition and memory. The dorsal stream connects the occipital area with the posterior parietal cortex, which serves the ability to process the whole visual scene and to pay attention to chosen components. The posterior parietal cortex is also thought to work in harmony with the motor cortex by subconsciously providing the action plan for visually guided movement of the limbs and body.[195] Thus, the ventral stream provides a conscious analysis and understanding of the visual world, while the dorsal

stream facilitates and brings about accurate movement of the body through visual space at a subconscious level. The two systems are closely integrated.[195]

The absence of vision has profound consequences.[113] For instance, blind children are known to be delayed in various domains, especially in postural control[196] and locomotion.[197] Minor visual impairments may also affect motor skills. Poor visual acuity, or sharpness of vision, may adversely affect motor performance in many sports, especially the ones requiring tracking and intercepting balls and hitting a distant target,[193] like tennis and basketball. Other aspects of visual functions can also have an impact on motor functions. Contrast sensitivity, stereoacuity and strabismus, as well as accommodative ability (the ability to focus at near), near point of convergence (the ability to converge gaze at close distance, and thus avoid diplopia at near) and visual perception, are all examples of such functions. For instance, it is often necessary to make precise judgements about moving objects in space, and about spatial relationships of the body to other individuals or objects, in order to perform many motor tasks effectively. These abilities depend upon visual perception.[193] However, a study by Mon-Williams et al.[198] reported no differences in visual functions in young school children with DCD compared with controls.

Proprioception

The other sense which plays an important role in the control of movement is proprioception or kinaesthetic sense, since we cannot always use vision to monitor our movements.[199] In comparison to vision, proprioception is a difficult sense to characterize. Whereas visual information is gathered through one set of sensory receptors, proprioceptive information is gathered through a number of quite different receptors located in the muscles, tendons and joints.[200] Proprioception informs us about the relative positions of the limbs and body without using vision.[200]

Proprioceptive information from one limb is transferred to the contra-lateral primary sensory cortex via the dorsal column-medial lemniscal system in the spinal cord.[200;201] In the sensory cortex each body part is somatotopically represented. From sensory cortex there are associations with posterior parietal

cortex, where sensory information is further processed, as well as forwarded to the motor cortex.[201]

The importance of proprioception is clearly demonstrated in a book by Oliver Sacks,[202] where a young woman who totally lost her proprioceptive sense after sensory neuropathy states: "I feel my body is blind and deaf to itself, it has no sense of itself". This woman was unable to stand if she did not always look at her feet. Furthermore, she was unable to manipulate objects in her hands, and her arms moved without her awareness. In accordance with this, Henderson and Sugden[113] have described children with movement difficulties as being "kinaesthetically blind".

Inter- and intra-modal matching

Von Hofsten and Rösblad[191] pointed out that coordinative actions usually demand close inter- and intra-sensory integration: "In most cases of manual behaviour, both vision and proprioception will affect the outcomes of manual movements. In fact, if such movements are to be smooth and well coordinated, it is of crucial importance that visual and proprioceptive means of controlling them are in correspondence. This implies that the parameters of space defined by each of these systems are in fine agreement. If both hands are involved in an act, it is also important that the proprioceptive space defined by one limb is in correspondence with the proprioceptive space defined by the other limb".

When matching vision to proprioception reference needs to be made from a retinotopic frame and a proprioceptive frame into a common perceptual code.[203] This has been termed inter-modal matching.[191] Such judgements must use some form of cross-mapping from a location specified in visual coordinates and a location specified by proprioceptive coordinates.[204] Matching proprioceptive signals from one limb to the other involves the adoption of mirror-limb locations; such that signals from the muscles and joints are equivalent across limbs (i.e. the left limb "feels like" the right limb). This has been termed intra-modal matching.[191]

Inter- and intra-modal matching may be crucial to the development and maintenance of motor competence.[205] Thus, studying these phenomena might

provide insight into the nature of motor problems.[206] A specific test, called the "manual matching task", has been developed in order to examine inter- and intra-modal matching.[191] Studies using this task in different groups of children have shown inconsistent results or data that are difficult to interpret. In healthy children, von Hofsten and Rösblad[191] found a distinct advantage of vision. In a series of studies of children with poor eye-hand coordination (i.e. poor manual dexterity subscore on the Movement ABC), Sigmundsson et al.[199;207-209] found that these children scored significantly worse than controls in both conditions, and with their non-preferred hand compared with their preferred hand.[199;207;208] When applied to DCD populations, studies have shown that these children made larger errors than controls in both conditions.[203;210] However, one study of DCD children,[203] as well as one study of adolescents with CP,[204] report relatively larger errors in the condition of matching vision to proprioception (inter-modal matching), suggesting that the primacy of visual information in such tasks cannot be assumed in cases of abnormal development.[203] Others have found relatively larger errors in the proprioceptive condition in DCD children (intra-modal matching),[210;211] supporting the advantage of vision, as in healthy children.[191] Yet, another study found no significant group differences between DCD children and control children in either condition.[212]

1.3 Motor outcome in children born too soon or too small

This section reviews the motor outcome in VLBW and term SGA children from infancy to adolescence (Appendix A and B). It also discusses possible patho-physiological mechanisms responsible for the motor problems described, and issues in early identification of motor problems.

1.3.1 Born too soon

VLBW children have a higher risk of CP, which can be defined as a non-progressive central nervous system disorder with abnormal muscle tone and control of movement and posture.[213] CP occurs in 5-10% of VLBW children compared with 1-3 per 1000 in normal populations.[12;38] But also VLBW children

without CP often show motor problems. Motor delay, assessed by the Alberta Infant Motor Scale (AIMS) and the BSID, has been consistently reported in VLBW populations during the first months[214-219] and years of life.[213;220-230] The motor delay seems to manifest itself as motor problems by the time these children enter school, as illustrated by poor fine and gross motor function, assessed by the PDMS[221;231] and the Movement ABC or its predecessor Test of Motor Impairment (TOMI).[232-237] Several studies using the Movement ABC[131;238-245] and the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP)[51;246-250] confirm the presence of motor problems in VLBW compared with controls in early school years. Although motor problems are found in all domains of the Movement ABC; i.e. manual dexterity, ball skills and balance, a recent meta-analysis indicates that VLBW children have more problems in keeping their balance than handling a ball, and although to a lesser extent, performing skilful actions with their hands and fingers.[251] Few studies have followed these children into adolescence, but those who have still report presence of motor problems, assessed by the Movement ABC[252] and the BOTMP.[253;254]

Among VLBW children, there seems to be a dose-response relationship between motor problems and lower birth weight/gestational age, with even worse motor outcome for subjects weighing less than 1000 g at birth.[242;253;255-257] In the recent meta-analysis by de Kieviet et al.,[251] lower birth weight and gestational age were strongly related to poorer motor outcome in the first years of development, but less robust relations were found with motor problems in school age and adolescence.[251]

Some studies have reported that preterm boys seem to have less favourable motor scores than preterm girls at preschool age[227] and at school age,[7;239;247;258] while others report equal performances for boys and girls.[221;242;248;249] Taylor et al.[253] studied VLBW children from seven to 14 years of age, and found that the initial superiority of girls disappeared with age. Wocadlo and Rieger[250] found that girls performed poorer than boys in running and strength, and Powls et al.[252] found that VLBW girls had poorer overall motor function than boys at 12-13 years of age. Studies presenting stratified

analyses by sex, have reported poorer motor skills in both preterm boys[259;259] and girls[254] compared with control boys and girls, respectively.

Few studies have examined the role of sensory systems on motor skills in VLBW children. In young children born prematurely, there seems to be a relationship between motor skills and stereoacuity,[235;260;261] visual acuity, strabismus and contrast sensitivity.[261] In VLBW adolescents, Powls et al.[42] reported a strong association between motor problems and strabismus, as well as poor contrast sensitivity. Inter- and intra-modal matching, assessed by the manual matching task, have been described in populations with known motor problems, such as DCD and CP, but not in general populations of preterm children. DeMaio-Feldman[262] used a tactile test in seven year old VLBW children and found that they seem to interpret somatosensory input differently than the normal population. The author claims that this shows a lack of integration at the most basic level of sensory development. Neligan et al.[1] studied the integration of auditory and visual systems, as well as the integration and discrimination of touch and vision in children both born preterm and SGA at term. They found significant differences between preterm and control children at six years of age, which were not longer present at seven years of age.[1]

1.3.2 Born too small

There are fewer studies on motor development and motor skills in term SGA children. CP is a rare finding[73], although the risk is increased by 2-3 times compared with the general population.[74] Although some studies report motor abnormalities and motor delay in the first days, months and years of life compared with controls,[263;264;264-273] outcome is not clear.[92;264;267;270;271;274;275] In a large American study, term SGA infants were twice as likely to show delay on the motor scale of the BSID.[72] At preschool age, Sommerfelt et al.[276] reported fine motor problems, seen on the grooved pegboard test, and borderline motor problems, assessed by the PDMS. Others have found motor problems in SGA children with early onset IUGR.[277;278] At early school-age, studies have reported neurological abnormalities, assessed by neurological examination,[73;87;279] and poor motor skills rated by teachers.[73] However, in the latter study SGA children

did not differ from controls in balance and gross motor function.[73] According to Neligan et al.[1] SGA children with birth weight <5th centile had poorer scores on TOMI than controls. Westwood et al.[80] reported no differences between non-asphyxiated SGA adolescents with birth weight <3rd centile and controls, assessed by neurological examination at 16 years of age. In a study on neuropsychological consequences, young adults born SGA had slower performance on the grooved pegboard test than controls, indicating poorer fine motor manipulative abilities.[280] Apart from this, there seems to be no studies of motor skills in SGA children in late childhood and adolescence.

There are no studies on the role of vision on motor skills in SGA adolescents. In the study by Neligan et al.[1] SGA children with birth weight <10th centile performed poorer on inter-sensory tests at six years of age. However, at seven years of age, differences only remained significant for the most growth restricted SGA children with birth weight <5th centile.[1]

In sum, there seems to be convincing evidence of motor problems in children born too soon, even though there are variations in sample size, tests used and birth weight cut-offs; however less convincing evidence in children born too small. There are also relatively few studies reporting on the role of vision with respect to motor outcome in VLBW children, and none in SGA children. Inter- and intra-modal matching with respect to vision and proprioception have not been described in these populations before.

1.3.3 Possible aetiology of motor problems in children born too soon or too small

The nervous system starts developing in early pregnancy and continues to do so after the time of term birth.[281] Neuronal proliferation, migration and physiological neuronal cell death characterize the first half of pregnancy.[125] Unfavourable events during this phase may result in brain dysfunction involving severe malformations or minor disorders.[125] Conditions occurring later in pregnancy may interfere with neuronal differentiation, axonal outgrowth and retraction, dendrite proliferation, synapse formation, myelination and glial cell

generation.[125] During the last trimester of pregnancy developmental processes are especially active in the periventricular areas and in the cerebellum.[125;282;283] Dobbing[284] claimed that brain structures with most rapid growth were most vulnerable to injury. Thus, harmful events occurring in the last phase of pregnancy, such as preterm birth and IUGR, may be expected to be particularly detrimental to periventricular structures and the cerebellum.[125] In addition, perinatal complications of preterm birth and IUGR, as well as pre- and perinatal stress, may further harm the structure and function of the nervous system.

Magnetic resonance imaging (MRI) has shown that brain abnormalities, such as changes in the white matter, ventricular dilatation and thinning of corpus callosum, often described as periventricular leukomalacia (PVL), are common in VLBW children and adolescents.[285-288] Additionally, abnormalities[283] and reduced volume of the cerebellum[289;290] have been reported in preterm populations. Motor problems in VLBW children may thus be caused by brain abnormalities visible on MRI scans. Injury to the periventricular regions and the cerebellum may cause dysfunctions of the corticospinal tract and pathways connecting the cerebellum to the cortex.[125] In the most severe form these present as CP. However, more subtle insults to the periventricular white matter, interfering with cell migration to the cortex, disrupting the cortical plate neurons and leading to abnormal development of cortical structures,[282] might cause minor motor problems, or "non-disabling degrees of PVL".[291] Martinussen et al.[292;293] have reported reduced total brain volume in SGA adolescents compared with controls, which indicates that also intrauterine growth restriction may impair cerebral development.[292]

Periventricular structures

PVL refers to focal or diffuse injury to cerebral white matter.[282] The focal component consists of localized necrosis in deep periventricular white matter with loss of all cells, which may be large in some cases (cystic PVL), but most often small, developing into glial scars (non-cystic PVL). The diffuse component, or "diffuse excessive high signal intensity" of white matter seen on MRI,[294] is characterized by disturbed maturation of premyelinating oligo-

dendrocytes, resulting in reduced myelination and enlarged ventricles.[282] The peak period of vulnerability for PVL coincides with the phase of rapid growth of axons in cerebral white matter (24-40 weeks of gestation).[282] Between 26 and 34 weeks of gestation the normal process of neuron loss and axon retraction is at its height, with increased metabolic activity (and vulnerability) around the area of the basal ganglia, the caudate nucleus, the cerebellum and the optic radiations.[256] These areas are all involved in critical aspects of motor control.

The corticospinal axons reach the lower cervical spinal cord by 24 weeks of gestation, and start myelinization by 40 weeks post-conceptual age.[295] The motor cortex also has strong interconnections with the premotor cortex and the supplementary motor area. The former is important for planning, preparation and sensory guidance of movement, and the latter for functions such as bimanual coordination and the generation and execution of motor sequences.[296] The vulnerability of these areas is further affected by a watershed zone-mechanism, increasing the detrimental effects of haemorrhage, ischemia and disturbances in cerebral blood flow.[256;282;297] CP caused by focal PVL is typically of the spastic diplegic type. Less severe neuromotor disorders may affect gross motor coordination, balance and motor planning, as well as fine motor skills that underlie manipulation, self-care skills and handwriting.[298] Studies have reported a relationship between MRI pathology of periventricular structures and motor problems.[299-302] In children with occipital PVL,[195;303] as well as in preterm children without PVL,[304] the dorsal and ventral stream systems are also found to be impaired, both affecting motor control and perception in varying degrees.

Cerebellum

The cerebellum also grows rapidly between 24 and 40 weeks of gestation, and relatively more rapid than the rest of the brain.[283;305] Hence, the cerebellum is particularly vulnerable to events occurring during this period of growth spurt. In fact, underdevelopment of the cerebellum, unrelated to haemorrhage or infarction, may represent the most common type of cerebellar abnormality of the premature infant.[283] The output projections of the cerebellum involve

mainly the premotor and motor systems of the cortex and the brain stem.[306] The cerebellum influences the motor systems by evaluating disparities between intention and action and by adjusting movements in progress, as well as during repetitions of the same task.[306] The cerebellum also plays a part in motor learning, in which cerebellar neurons are most active during the early stages of learning a task or when conditions change.[296] In the absence of cerebellar input performance has been shown to be slower and more variable.[296] Abnormality of the cerebellum may result in motor disturbances which range from poor coordination to overt ataxia, as well as deficits in motor planning and execution.[283] However, Allin et al.[289] failed to find a relationship between smaller cerebellum and poor motor outcome in VLBW adolescents. The authors speculate that this may be due to brain plasticity and compensation over the years. There are no studies relating cerebellar findings to motor function in SGA populations. Nonetheless, it is possible that subtle and diffuse brain dysfunctions in SGA subjects may be responsible for minor motor problems, especially affecting fine motor coordination and balance, if the cerebellum also has been growth restricted.

Although the periventricular structures and the cerebellum may be specific regions important for motor control, the preterm brain damage has been described as "encephalopathy of prematurity",[34] also involving the thalamus, basal ganglia and cerebral cortex,[292;293] which may play a role in motor function.

1.3.4 Early identification of motor problems

Ideally, the goal is to identify children with motor problems as early as possible to hopefully prevent further negative outcomes. However, motor performance is determined by multiple influences from the child, the environment and the demands of the task.[307] As a consequence, infant motor assessments have generally been disappointing in their ability to predict later motor outcome.[308;309] In a study of low and high risk infants tested longitudinally during the first year of life by the motor scale of BSID, Coryell et al.[310] found that results varied significantly from test to test in infants with normal

outcomes. Furthermore, Darrah et al.[311;312] performed serial assessments of motor function by the PDMS from nine months to four years of age in a group of normal children, showing that results were not stable over time, which could reflect a non-linear development. According to the neuronal group selection theory, the motor variations themselves constitute a fundamental developmental phenomenon during the first phase of primary variability.[102] After this first phase, selection and reduced variability occur, which can make prediction easier.[102] Thus, accuracy of assessments may improve with increasing age at testing.[313]

The instability of motor function over time may also be due to different psychometric properties of the tests used, i.e. the sensitivity in detecting motor problems.[310;311] For instance, the motor scale of the BSID focuses on motor milestone acquisition in a global manner.[147] The PDMS is also based on skill acquisition, and attempts to measure the emergence of new skills. However, in both tests some children may pass specific items, yet demonstrate abnormal movement patterns indicative of neuromotor dysfunction.[147]

Nonetheless, stability of motor function may be different in children born too soon or too small. The predictive validity of infant tests has shown to be better in clinical populations than in normal populations, particularly for children with neurological impairment, such as CP, and those with developmental delays.[313-315] In the abovementioned study, Coryell et al.[310] found that scores on the BSID for infants with "non-normal" outcomes did not vary significantly from test to test. Erikson et al.[237] reported stability of motor performance in VLBW children in half of the study group from five months to five years of age. Goyen and Lui[221] reported that gross motor problems, assessed by the PDMS, increased from 18 months to five years of age in "apparently normal" high risk infants with birth weight below 1000 g. Studies of VLBW children have also shown a close relationship between abnormal neurological findings at 12-18 months of age and neurological status at 2-3[218;316] and seven years of age.[317] In term SGA infants, a neonatal neurological examination has been reported to be a poor predictor of later neurological or cognitive outcome.[18]

Thus, early prediction of later problems may be reliable for infants functioning at the lower end of the developmental continuum.[313] Still, the plasticity of the brain can make it possible to compensate for small and early lesions,[102;295] and children may therefore "grow out" of motor problems. Thus, developmental changes in the brain during childhood may have important implications for the prediction of developmental problems at early age.[318] More subtle problems can be difficult to predict early in life because environmental and social factors may influence long-term outcome more than for infants with severe disabilities.[141]

It is important to optimize the accuracy of early assessment in order to identify subtle developmental delays and mild impairments that may result in more intrusive conditions at school age.[314] While many studies have looked only at the prediction of CP or abnormal motor development up to two years of age, few have studied long-term correlation of motor outcomes with standardized motor assessments.[141] Impaired motor development can be a risk factor for later poor cognitive performance, learning disabilities and behavioural problems.[251] A study group from Liverpool in UK found that good motor skills, assessed by the Movement ABC at school entry, were associated with satisfactory school performance, whereas poor motor skills were associated with learning disabilities at eight years,[243] and poor cognitive function at 12 years of age.[56] Thus, assessment of motor skills using valid instruments can be an important early indicator of other developmental problems as well.

2. Aims of thesis

The general aim was to assess the prevalence of motor problems at 14 years of age in two groups of low birth weight adolescents compared with a control group, to investigate the role of vision and proprioception in relation to motor problems, and to examine whether early motor evaluation could identify motor problems in adolescence.

More specifically, the aims of the separate papers were to examine:

I: whether VLBW and term SGA adolescents have an increased prevalence of motor problems compared with control adolescents

II: how visual impairments may be associated with the increased risk of motor problems in VLBW and term SGA adolescents

III: whether VLBW and term SGA adolescents have poorer performance in inter- and intra-modal matching than control adolescents

IV: if motor evaluations at one and five years of age can identify motor problems at 14 years of age in VLBW and term SGA children

3. Material and Methods

3.1 Study design

The adolescents included in this study were originally part of two separate studies, where one was a follow-up study of VLBW children,[319;320] and the other a large multicentre study on causes and consequences of intrauterine growth retardation (the SGA project).[19;321]

The first follow-up study included VLBW children born in 1986-1988 in the counties of Møre and Romsdal, Nord- and Sør-Trøndelag. These were all born prematurely (i.e. before week 37 of gestation) and had been hospitalized at the neonatal intensive care unit (NICU), St. Olav's University Hospital in the neonatal period. The children born in 1988 were assessed thoroughly at one and five years of age.[319;320]

In the second study, pregnant women living in the Trondheim region were enrolled before week 20 of pregnancy between January 1986 and March 1988 in a population based prospective multicentre study. A 10% random sample of women (with one or two previous pregnancies) was selected for follow-up during pregnancy. At birth, all SGA children and all children born to mothers in the random sample were examined by a paediatrician assigned to the project. Gestational age was based on the first day of the last menstrual period if it was accurately recalled ± three days. Ultrasound estimates were used if there was a discrepancy of more than 14 days, or if the last menstrual period could not be recalled accurately.[19;321] The reference standard (i.e. 10th centile) for classification of SGA was sex-specific for each gestational week based on data from the Norwegian Medical Birth Registry.[19;321]

3.2 Study population

Flow chart of participants is presented in Figure 4.

3.2.1 VLBW group

The VLBW group comprised all newborns with birth weight ≤1500 g from the counties of Nord- and Sør-Trøndelag admitted to the NICU at St. Olav's Hospital in 1986-88 (n=99). Of these, 23 children died in the neonatal period and one child with trisomy 21 was excluded. By the age of 14, six children had moved out of the region, leaving 69 children eligible for examination. Fifteen children did not consent to participation, thus 54 (78%) VLBW children (29 boys, 25 girls) had a motor assessment.

3.2.2 SGA group

Of 1200 eligible women in the SGA project, 104 (9%) gave birth to a term (i.e. born between 37 and 42 weeks of gestation) SGA child with birth weight below the 10th centile, adjusted for gestational age, sex and parity. By 14 years of age, 12 children had moved and 33 did not consent to participation. Thus, 59 (64%) SGA children (27 boys, 32 girls) were examined.

3.2.3 Control group

The control group comprised 120 children with birth weight ≥10th centile for gestational age, born at term to mothers in the 10% random sample of the 1200 participants. At the 14 year follow-up, 10 had moved and 27 were not willing to participate. Eighty-three (75%) controls (35 boys, 48 girls) were examined.

In Paper II and IV, numbers differed due to inclusion of a few VLBW participants outside the original cohort (children from Møre and Romsdal included), and the papers are confined to those who consented to motor, visual and cognitive evaluation (Paper II), and those with previous motor assessment at one and/or five years of age (Paper IV).

3.2.4 Exclusion criteria

Congenital anomalies (ICD9 diagnose number 740-759) present at neonatal examination were exclusion criteria in all three groups. Three adolescents (one SGA and two controls) with congenital anomalies diagnosed at birth were initially included in the study groups (Paper I and III), but excluded in the other papers. Results did not change significantly when reanalysed excluding these three subjects (see results section 4.1 and 4.2).

3.2.5 Non-participants

There were no differences in maternal age, duration of pregnancy, the infants' birth weight, body length and head circumference between those who participated and those who did not consent to participate in any of the groups. In Paper IV there were no significant differences in perinatal data or motor scores at one and five years either (details presented in paper).

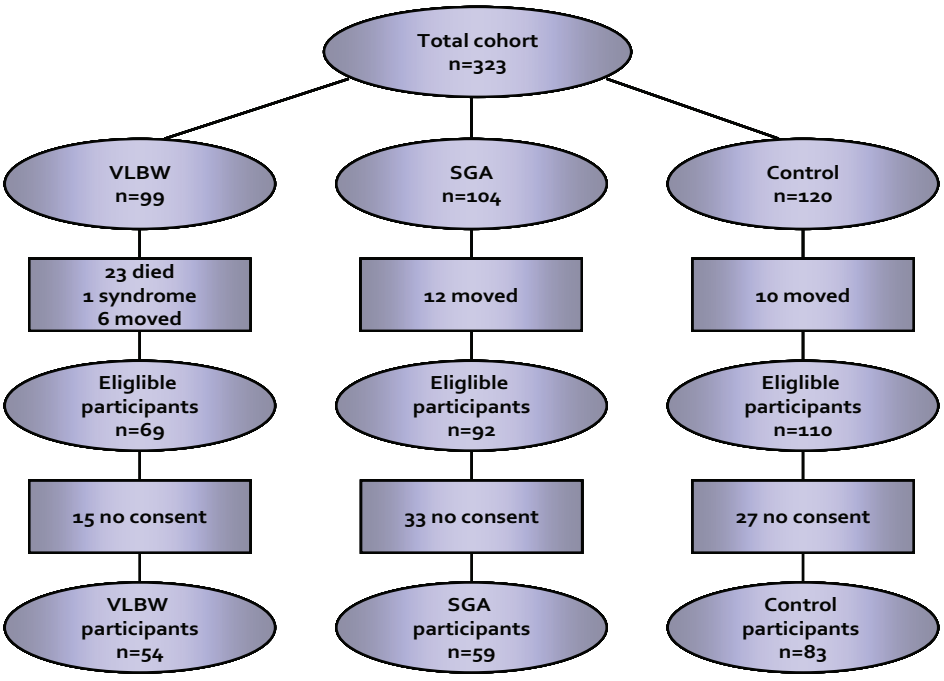


Figure 4. Flowchart of study population.

3.3 Methods

3.3.1 Assessment of motor skills

The Movement Assessment Battery for Children (Movement ABC) was carried out at 14 years of age by one physiotherapist, blinded to group assignment. The motor scale of Bayley Scales of Infant Development (BSID) and the Peabody Developmental Motor Scales (PDMS) were used at one and five years of age by examiners blinded to neonatal history in the VLBW group, and to group adherence in the SGA and control group.

Movement Assessment Battery for Children

The Movement ABC[113] is a norm-referenced standardized test, which measures manual dexterity, ball skills and static/dynamic balance in children aged 4-12 years. In this study, we used the highest age band, designed for 11-12 year old children (Table 3). Each item is assigned a score on a six-point scale (0-5), where a higher score is indicative of poorer skills. The Movement ABC is especially designed to identify children with motor problems, as only the most impaired 25% of the children get a score greater than zero. A total score is given as the sum of all eight items, and can be subdivided into the subscores of manual dexterity, ball skills and static/dynamic balance (Table 3). A score below the 5th centile is considered as "definite motor problems", whereas scores between the 5th and the 15th centile indicate "borderline motor problems".[113] A child has to fail at least three items in order to fall below the 15th centile.[144]

Table 3. Subtests and items with range of scores for the Movement ABC, age band 4.

Subtests	Items	Range of scores
(1) Manual dexterity	Turning pegs at pegboard (both hands tested) Tracing flower with a pencil Cutting out elephant between two guidelines	0-15
(2) Ball skills	One-hand catch of tennis ball (both hands tested) Throwing tennis ball at target on wall	0-10
(3) Static/dynamic balance	Balance on balance board Jumping over knee-high cord and clapping while in the air Walking backwards toe-to-heel on line	0-15
Total ABC score		0-40

The Movement ABC has been standardized on more than 1200 children aged 4-12 years from the UK, Canada and USA, and age-related norms are given for each subscore, as well as the total score.[113] As our study groups were older than the age group this test was designed for, we used the 5th centile derived from our control group. This corresponded to at total score of 14, a manual dexterity score of 4.5, a ball skills score of 5.9 and a balance score of 8.8.

Test-retest reliability of the Movement ABC has been documented in the manual, ranging from 73-97% agreement when the test is used on two different occasions, and inter-rater reliability, or consistency between examiners, has shown 75-98% agreement.[113] In the present study, intra-rater reliability was assessed by video-taping 34 children on items 1 (timing) and 4 (counting). Intraclass correlation coefficient was found to be 0.9996 for timing and 0.9935 for counting.[5]

Bayley Scales of Infant Development

The Bayley Scales of Infant Development (BSID)[155] measures both mental and motor development in children from birth to 30 months of age. In this study we used the results obtained from the motor scale, which consists of maximum 81 items. The motor scale assesses both fine and gross motor function, including fine manipulatory skills of the hands and fingers, control of the body and coordination of large muscle groups.[155] Items are arranged in order of difficulty and the children are tested from their basal level (the item preceding the earliest failure) up to their ceiling level (the item representing the most difficult success).

The BSID was standardized on 1262 American children ranging from two to 30 months of age. Raw scores (i.e. the total number of items the child has passed including all items below the basal level) on the motor scale are converted to age-adjusted standard scores called the psychomotor development index (PDI), which ranges from 50 to 150, corresponding to ± three standard deviations (SD) for the standardization sample. The development index provides a basis for establishing a child's current status and extent of deviation from normal expectancy.[155] According to the manual, we defined a "low score"

as scores below two SD and a "borderline low score" as scores below one SD in the control group.

Test-retest reliability and inter-rater reliability for the motor scale of the BSID are documented in the manual, with a mean agreement of 75.3±14.5% and 93.4± 3.2%, respectively.[155]

Peabody Developmental Motor Scales

The Peabody Developmental Motor Scales (PDMS)[136] is a standardized test that measures gross and fine motor skills of children from birth through 83 months. The gross and fine motor scale are divided into five and four skill categories, or subscales, respectively. Due to time constraints, three subscales of the test were selected in this study at age five; eye-hand coordination, balance and locomotor. Each item is scored on a three-point scale (0-2). According to the manual motor problems were defined as scores below the 5th centile.[136] With the modification by Sommerfelt et al.[276] applied to three subscales, "motor problems" in our study were defined as at least one of the three subscales below the 5th centile in our control group. "Borderline motor problems" were defined as at least one of the three subscales below the 15th centile.

The PDMS was standardized on 617 children, representative of the population in the USA. Correlation coefficients for test-retest reliability were 0.80 and 0.95 for the fine and gross motor scale, and inter-rater reliability was 0.94 and 0.97 for the fine and gross motor scale, respectively. Content and construct validity have been established, and the test has shown agreement with performance on other instruments and with clinical judgement.[136]

3.3.2 Assessment of visual functions

The visual examination at age 14 included assessment of visual acuity, contrast sensitivity, stereoacuity, strabismus, nystagmus, accommodation and convergence, performed by an ophthalmologist. More details on the assessments are included in Paper II. In addition, visual perception was assessed by a psychologist using the Visual Perception supplementary task of the Developmental Test of Visual-Motor Integration (VMI-IV).[322]

An *abnormality score* was calculated as the sum of visual impairments, including distance visual acuity, contrast sensitivity, stereoacuity, strabismus, nystagmus, accommodation, convergence and visual perception. An abnormality score of zero was given if an adolescent did not have impairments in any of the visual functions, and the highest possible abnormality score of eight would indicate impairments in all functions.

3.3.3 Assessment of inter- and intra-modal matching

The manual matching task was originally developed by von Hofsten and Rösblad.[191] The test procedure requires sensory matching of targets located visually (Inter-modal matching; Figure 5A) or with the hand (Intra-modal matching; Figure 5B). A mean of errors over four attempts with each hand in each condition was calculated, in terms of absolute, systematic and random errors (details are described in Paper III).

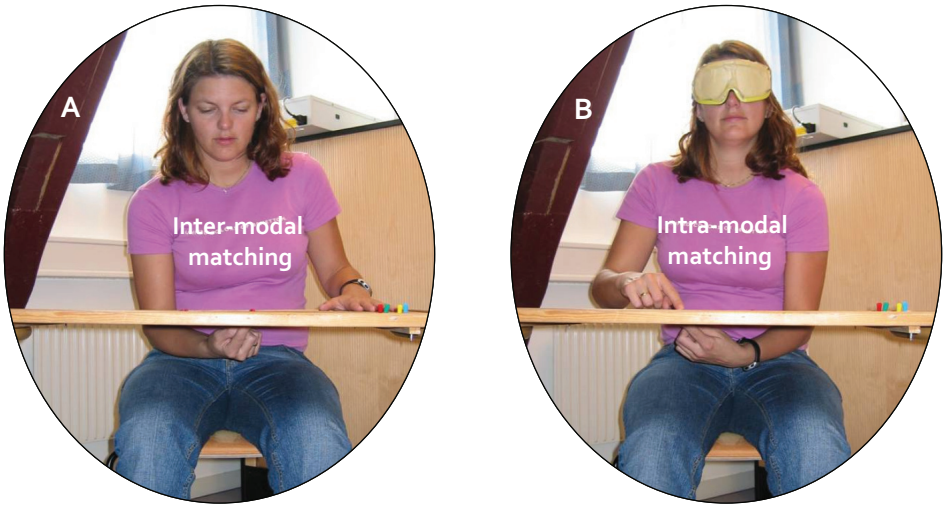


Figure 5. Illustration of the manual matching task.
A: Inter-modal matching (seen target). The subject looks at the target, and the objective is to place a pin with one hand from underneath the test board as close to the target as possible.
B: Intra-modal matching (felt target).The eyes of the subject are covered and the index finger is placed on the target of the upper side of the test board. The objective is to place a pin with the other hand from underneath the test board as close to the target as possible.

The idea was that the task could be used to pin-point areas of dysfunction in the brain that may underlie motor problems.[191] The transfer of sensory information when the target is seen is thought to differ from when the target is felt (Figure 6). In the inter-modal condition, visual information from each visual hemifield is first transferred to the visual cortex.[206] Thereafter, signals go via the posterior parietal cortex to the motor cortex on the contralateral side to where movement is observed (e.g. left hand). Feedback from the left hand is in turn projected to the sensory cortex to the posterior parietal cortex and then to motor cortex in order to adjust performance.[206]

In the intra-modal condition proprioceptive information from the right hand is projected to the contralateral sensory cortex and transmitted to the posterior parietal cortex, via the corpus callosum, to the posterior parietal cortex on the opposite side.[206] From there, signals go to motor cortex which controls the left hand. Proprioceptive feedback from the left hand may then be used to adjust performance.[206] Using the right hand in matching would require mirror-imaged projections.

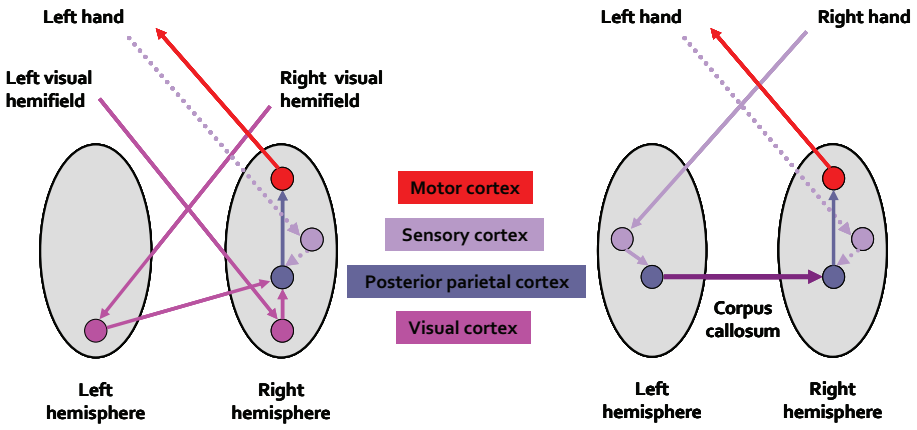


Figure 6. Hypothetic route of information-processing in the inter- and intra-modal condition, as described by Sigmundsson.[206]

The task has not yet been formally validated, but has been used in different age groups and populations.[191;199;203;204;207;209-212]

3.3.4 Other assessments

Anthropometric measurements

At birth, the SGA and control infants were weighed to the nearest 10 g on a standard scale, whereas the VLBW infants were weighed to the nearest g on an electronic scale. Body length and head circumference were recorded to the nearest 0.1 cm.

Neuropaediatric examination

Height was measured to the nearest 0.1 cm, and weight to the nearest 100 g on an electronic scale. A clinical neurological examination was performed by project paediatricians at age five and 14. Cerebral palsy (CP) was classified as diplegia, hemiplegia or quadriplegia. Functional level was assessed according to the Gross Motor Function Classification System (GMFCS) (Table 4).[323]

Table 4. The Gross Motor Function Classification System (GMFCS).[323]

Mobility	Going Outdoors or Into the Community	Level
walks without restriction	limited by more advanced gross motor skills	I
walks without assistive devices	limitations when walking outdoors or in the community	II
walks with assistive device	limitations when walking outdoors or in the community	III
limited self-mobility	going outdoors or about the community requires transportation or powered device	IV
self-mobility severely limited even with assistive device(s)	totally dependent; mobility severely limited	V

Cognitive abilities

An estimate of intelligence quotient (IQ_{est}) was calculated using four of ten subscales of Wechsler Intelligence Scales for Children (WISC-III):[324] Vocabulary, arithmetic, block design and picture arrangement. "Low IQ_{est}" was defined as a score more than two SD below the mean in the control group.

Socioeconomic status

Socioeconomic status was calculated according to Hollingshead's Two Factor Index of Social Position,[325] based on a combination of parents' education and occupation.

3.4 Ethics

The Regional Committee for Medical Research Ethics (Health Region IV) approved the study protocol May 5th 2000 (REK ref. nr. 78-00; May 29, 2000). Written informed consent was obtained from both children and their parents prior to examination. The Data Inspectorate assigned a license for establishing and maintaining the register containing personal data.

Methods were non-invasive and did not inflict pain. All methods are widely used in the clinic and in research. At the end of the consultation, the adolescents and parents received feedback on the motor examination. Multidisciplinary meetings were held on a regular basis where the adolescents' need for referral to health services was discussed. After publication of the first results, we held a seminar for the participants presenting the main group results from the study. Adolescents and parents who wanted an individual consultation with one or more of the professionals from the research team were given an appointment.

3.5 Statistical analyses

The Statistical Package for the Social Sciences version 11.5.1-15.0 (SPSS Inc., Chicago, IL) was used for data analyses and two-sided p-values less than 0.05 were considered statistically significant. Three-group comparisons were made using one way analysis of variance (ANOVA) for variables with a normal distribution and Kruskal-Wallis for variables with a non-normal distribution. Two-group comparisons were made by Scheffe's post hoc test or by Student's t-test for continuous variables with a normal distribution, and Mann-Whitney U test for ordinal variables or variables with a non-normal distribution. Differences in proportions between groups were analysed by the Pearson's chi-square test or Fischer's exact test.

In Paper I and II, odds ratio (OR) with 95% confidence intervals (CI) was calculated as an estimate of the relative risk that a child with low birth weight had motor problems, compared with the control group. In order to control for

possible confounding factors in Paper I, we used logistic regression to calculate adjusted odds ratios. This method was also applied in Paper II in order to assess the influence of visual functions on motor problems.

In Paper III, absolute, systematic and random errors were log normal, thus geometric means with 95% CI were presented for these variables. If the log-transformed data are normally distributed, the geometric mean of the original data is a good estimator of the median.

In Paper IV, receiver-operating characteristics (ROC) curves were used to calculate area under the curve (AUC) as an estimate of diagnostic accuracy. For sensitivity and specificity, 95% CI were calculated using Wilson's method.[326]

4. Main results

4.1 Group characteristics

Table 5 shows gestational age and anthropometric measurements at birth and at follow-up at 14 years of age for the population studied in Paper I when congenital anomalies are excluded. Although there were slight differences in the material for the other papers, the characteristics of the groups remained essentially the same.

Table 5. Gestational age and anthropometric measurements at birth and at follow-up in two groups of low birth weight children compared with a control group.

	VLBW	SGA	Control
	(n=54)	(n=58)[a)]	(n=81)[a)]
At birth:			
Gestational age (weeks)	28.9 (2.7)***	39.5 (1.1)	39.6 (1.2)
Birth weight (g)	1179 (234)***	2916 (212)***	3695 (459)
Body length (cm)[b)]	38.5 (2.8)***	48.4 (2.0)***	51.1 (1.8)
Head circumference (cm)[c)]	26.9 (2.5)***	33.8 (1.2)***	35.4 (1.1)
At follow up:			
Age at examination (years)	14.1 (0.3)	14.2 (0.3)	14.2 (0.3)
Weight (kg)	49.9 (12.1)***	52.1 (8.5)**	57.1 (10.6)
Height (cm)	161.2 (9.3)***	163.4 (7.1)**	167.5 (7.6)
Head circumference (cm)	54.3 (1.9)***	54.7 (2.0)***	56.0 (1.5)
Socioeconomic status	3.2 (1.3)*	3.4 (1.3)	3.8 (1.1)

Values are mean (SD)

* p<0.05, ** p<0.01, *** p<0.001 vs. controls

VLBW = Very Low Birth Weight

SGA = Small for Gestational Age

[a)] 1 SGA and 2 controls with congenital anomalies excluded

[b)] Body length was only measured for 35 children in the VLBW group

[c)] Head circumference was only measured for 41 children in the VLBW group

There were no significant differences between the groups in proportion of boys and girls. Ten (19%) VLBW adolescents (p<0.01 vs. controls) and four (7%) SGA adolescents (non-significant vs. controls) had low IQ_{est} compared with three (4%) controls. Seven VLBW adolescents (13%) and one SGA adolescent (2%) had CP. One of the VLBW adolescents with CP (diplegia, GMFCS level II) was misclassified as not having CP in Paper I, but correctly classified in subsequent papers. Two of the VLBW adolescents who had CP (one diplegia, one

quadriplegia) could not be tested with the Movement ABC, and for one VLBW adolescent with CP diplegia results were obtained for the manual dexterity subscore only. The VLBW adolescent with CP quadriplegia could not be tested with the manual matching task (Paper III). Table 6 shows the subtype and classification of the CP subjects according to the GMFCS, the reason why some of them did not have complete assessments, and which subjects were included in the material in the different papers.

Table 6. Characteristics of the adolescents with cerebral palsy.

Group	CP subtype	GMFCS	Wheelchair	Not cooperative	Paper I	Paper III	Paper IV
VLBW	Quadriplegia	V	X		-	-	-
VLBW	Diplegia	IV	X		Only manual dexterity	X	-
VLBW	Diplegia	I		X	-	X	-
VLBW	Hemiplegia	I			X	X	-
VLBW	Diplegia	II			X	X	-
VLBW	Diplegia	II			X	X	X
VLBW	Diplegia	II			X	X	X
SGA	Diplegia	II			X	X	X

GMFCS = Gross Motor Function Classification System
VLBW = Very Low Birth Weight
SGA = Small for Gestational Age

Total Movement ABC scores were additionally missing for one VLBW adolescent who could not be tested on static/dynamic balance due to an ankle sprain, and one control who could not be tested on manual dexterity due to a recent hand cast.

4.2 Results of papers included in thesis

Paper I: *Motor skills in adolescents with low birth weight*

In this paper we used the Movement ABC to identify motor problems in a population-based cohort of VLBW and term SGA adolescents. We found an increased prevalence of motor problems in the VLBW and the SGA group compared with the control group; one in four VLBW children (OR: 9.3; 95% CI: 2.5-34.5) and one in six SGA children (OR: 4.7; 95% CI: 1.2-18.4) had motor

problems compared with controls. There were no sex differences in the VLBW group, and this group had poorer results for all the subscores of the Movement ABC. In the SGA group, the increased risk of motor problems was particularly high for boys with respect to manual dexterity.

Analyses excluding children with CP[†] and/or low IQ_{est} suggested that poor motor skills are prevalent among low birth weight children without physical and/or mental deficiencies. Weight and height were identified as possible confounding factors; however, the increased risk of motor problems in the VLBW and the SGA group could not be explained by poor postnatal growth.

Excluding the three adolescents (one SGA, two controls) with congenital anomalies that were initially included in the study, strengthened our results; the odds of having motor problems were even higher in the VLBW and the SGA group.

Paper II: ***Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents?***

Among adolescents who attended both the motor and the visual examination, the odds of having motor problems were 10.4 (95% CI: 2.2-49.4) in the VLBW group and 5.1 (95% CI: 1.0-25.8) in the SGA group compared with the control group. In the VLBW group, the odds of having motor problems were influenced by all visual variables, and most by visual acuity, when these variables were adjusted for separately. The greatest reduction in OR was found when we adjusted for the abnormality score (adjusted OR: 6.8; 95% CI: 1.3-34.5). In particular, problems in manual dexterity were mainly affected by impairments in vision. In the SGA group the odds of having motor problems were relatively unaffected by the visual variables and the abnormality score.

Thus, we concluded that motor problems in the VLBW group, but not in the SGA group, were influenced by visual impairments, although the risk of motor problems remained high after adjusting for the visual variables.

[†] Excluding all seven adolescents with CP in the VLBW group, OR for motor problems was 6.4 (95% CI: 1.6-25.1) and not 7.1 (95% CI: 1.8-27.4) as reported in paper

Paper III: ***Inter- and intra-modal matching in very low birth weight and small for gestational age adolescents***

In this paper we used a manual matching task to examine inter- and intra-modal matching in the population-based cohort of VLBW and term SGA adolescents. We found that VLBW adolescents performed poorer in inter- and intra-modal matching compared with the control group. However, differences were non-significant when we excluded adolescents with CP and low IQ_{est}.

SGA adolescents displayed poorer performance with their non-preferred hand compared with their preferred hand in both inter- and intra-modal matching, whereas controls, and VLBW adolescents with normal IQ_{est} and without CP, performed equally well with both hands. There was a sex difference in the SGA group, where boys displayed hand asymmetry in the intra-modal condition, whereas in girls the asymmetry was found in inter-modal matching.

We concluded that the there were no large differences in inter- and intra-modal matching between VLBW and SGA adolescents compared with controls, and that the poorer results in the VLBW group on the manual matching task were mainly explained by a higher number of adolescents with CP and low IQ_{est} in the VLBW group.

The results on the manual matching task were unchanged after exclusion of the three subjects with congenital anomalies.

Paper IV: ***Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children***

This paper comprises the children who attended the one and 14 year follow-up and/or the five and 14 year follow-up. We found that motor problems in 14 year old VLBW children could be identified in a high proportion of cases, using either the Bayley Scales of Infant Development at one year (sensitivity: 0.80; 95%CI: 0.38-0.96, specificity: 1.0; 95%CI: 0.82-1.0) or the Peabody Developmental Motor Scales at five years (sensitivity: 0.83: 95% CI: 0.44-0.97, specificity: 0.83; 95% CI: 0.61-0.94). In contrast, motor problems in 14 year old children born SGA at term or with normal birth weight (controls) were not

identified by the Bayley Scales of Infant Development at one year. Moreover, in these two groups motor problems at age five identified only fifty percent of the children with motor problems at age 14. However, in the SGA group, sensitivity increased by including those with borderline low scores at one and five years (sensitivity: 0.75; 95% CI: 0.41-0.93). In particular, the five year examination identified seven of eight SGA children with later manual dexterity problems. For all groups, specificity and negative predictive values were high.

Thus, we concluded that both the Bayley Scales of Infant Development and the Peabody Developmental Motor Scales may be valuable early predictors of later motor function in VLBW children, and that children with normal motor function at an early time point were most likely to have normal motor skills at 14 years of age.

4.3 Unpublished results

4.3.1 Perinatal factors

There were no significant correlations between the continuous total Movement ABC score and birth weight, gestational age, head circumference or ponderal index at birth in any of the groups. Apgar score at one minute correlated with total ABC score in the VLBW group (Spearman's rho = -0.45, p=0.001). When the 5th centile cut-off was used, motor problems in the VLBW group were associated with birth weight, head circumference, Apgar score at one minute and days of stay in the NICU (Table 7). There were no differences in motor scores between the SGA and AGA subjects in the VLBW group (data not shown).

In the SGA group, motor problems were associated with lower Apgar score at one minute (Table 7). There were no differences in motor scores between subjects with symmetrical and asymmetrical growth restriction (defined by a ponderal index <2.40 for boys/2.51 for girls) (data not shown).

Table 7. Association between perinatal factors and a total ABC score <5th centile in VLBW, term SGA and control adolescents.

	VLBW		SGA		Control	
	<5th centile n=13	≥5th centile n=37	<5th centile n=8	≥5th centile n=50	<5th centile n=2	≥5th centile n=78
Gestational age	27.9 (3.2)	29.2 (2.5)	39.6 (1.1)	39.4 (1.2)	39.0 (0.0)	39.7 (1.2)
Birth weight	1059 (273)*	1242 (187)	2964 (190)	2909 (216)	3400 (99)	3699 (464)
Head circumference	25.5 (3.0)*	27.5 (2.2)	33.8 (1.0)	33.8 (1.2)	34.6 (0.6)	35.4 (1.1)
Ponderal index	2.14 (0.16)	2.11 (0.23)	2.51 (0.24)	2.58 (0.26)	2.72 (0.08)	2.79 (0.25)
Apgar score 1 min	4.4 (2.3)**	7.1 (1.9)	7.9 (2.8)*	9.0 (0.2)	9.0 (0.0)	8.9 (0.3)
Apgar score 5 min	7.3 (2.6)§	8.7 (1.2)	8.9 (3.2)	9.9 (0.3)	10.0 (0.0)	9.8 (1.1)
Days on ventilator	1 (0-63)	1 (0-13)	-	-	-	-
Days in NICU	71 (1-386)*	58 (25-115)	-	-	-	-

Values are mean (SD) and median (range)
** p <0.001, * p≤0.05 , § p=0.07 vs. subjects ≥5th centile (Mann-Whitney U test)
VLBW = Very Low Birth Weight
SGA = Small for Gestational Age

Figure 7 shows a statistically significant trend towards higher proportions of total motor and balance problems, as well as a borderline significant trend towards higher proportion of manual dexterity problems, across birth weight categories for VLBW adolescents.

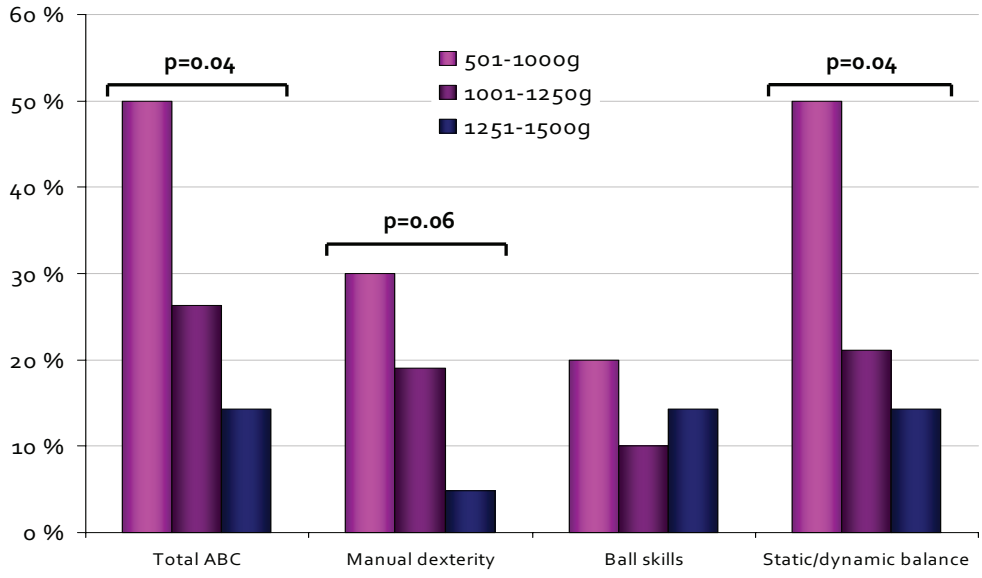


Figure 7. Proportion of children with scores below the 5th centile on the Movement ABC in the VLBW group by birth weight category (p-values for trend: linear-by-linear association).

4.3.2 Handedness

In the control group, eight of 81 children (10%) (three boys, five girls) used their left hand in writing, compared with 11 of 54 VLBW children (20%) (nine boys, two girls) (p=0.08 vs. controls) and ten of 58 SGA children (17%) (four boys, six girls) (p=0.20 vs. controls). None of the eight left-handers in the control group had motor problems compared with five of ten left-handers tested with the Movement ABC in the VLBW (p=0.04 vs. controls) and three of ten in the SGA group (non-significant vs. controls). In the VLBW group, three of nine left-handed boys had manual dexterity problems, whereas in the SGA group all four left-handed boys had poor manual dexterity. Left-handed VLBW adolescents had poorer scores on the Movement ABC, both total ABC score and all subscores, whereas left-handed SGA adolescents had poorer manual dexterity, compared with right-handed subjects in each group, respectively (Table 8). There were no differences in scores between left- and right-handed controls.

Table 8. Movement ABC scores in left- and right-handed subjects in the VLBW, the SGA and the control group.

	VLBW		SGA		Control	
Preferred hand in writing	Left n=10	Right n=42	Left n=10	Right n=48	Left n=8	Right n=73
Manual dexterity	5.4 (4.3)**	1.8 (2.1)	4.3 (4.5)*	1.7 (2.5)	0.4 (0.5)	1.3 (1.7)
Ball skills	3.9 (2.3)*	2.4 (2.5)	2.0 (1.9)	1.1 (1.4)	2.6 (2.9)	1.4 (1.7)
Balance	8.8 (4.4)**	5.0 (3.6)	3.9 (3.3)	3.6 (2.9)	2.3 (2.2)	3.5 (2.9)
Total ABC score	18.1 (10.2)**	9.2 (6.0)	10.2 (7.2)	6.4 (4.9)	5.4 (3.0)	6.2 (4.2)

Values are mean (SD)
* p≤0.05, ** p≤0.01 vs. right hand (Mann-Whitney U test)
VLBW = Very Low Birth Weight
SGA = Small for Gestational Age

On the manual matching task there were no significant differences between left- and right-handed subjects in any of the three groups (data not shown).

4.3.3 Association between manual dexterity on Movement ABC and the manual matching task

There were no significant correlations between absolute errors on the manual matching task and the total ABC score in any of the groups. However, in the VLBW group, adolescents who scored below the 5th centile in manual dexterity on the Movement ABC had significantly larger absolute (Table 9), systematic and random (data not shown) errors in the visual condition using either hand on the manual matching task. These results remained statistically significant when adolescents with CP were excluded (data not shown). There were no significant associations between results on the manual matching task and scores below the 5th centile on the manual dexterity subscore in the SGA or the control group (Table 9). Performance with non-preferred compared with preferred hand did not differ according to poor manual dexterity in any of the groups (data not shown).

Table 9. Association between results on the manual matching task and manual dexterity scores <5th centile in VLBW, term SGA and control adolescents.

Manual dexterity / Absolute errors	VLBW		SGA		Control	
	<5th centile n=8	≥5th centile n=44	<5th centile n=10	≥5th centile n=48	<5th centile n=2	≥5th centile n=78
Visual preferred hand	23.4* (15.6-35.0)	15.7 (13.9-17.8)	13.0 (10.2-16.6)	14.3 (12.3-16.6)	14.6 (6.5-32.8)	15.0 (13.6-16.5)
Visual non-preferred hand	26.1** (21.0-32.5)	15.3 (13.6-17.3)	15.0 (10.8-20.9)	17.2 (15.0-19.7)	13.7 (7.7-24.4)	15.1 (13.7-16.6)
Proprioceptive preferred hand	25.2 (19.1-33.3)	21.1 (18.6-23.9)	24.7 (18.8-32.4)	19.8 (17.6-22.2)	19.6 (8.0-48.4)	21.5 (19.4-23.9)
Proprioceptive non-preferred hand	29.8 (21.5-41.2)	24.0 (20.8-27.6)	23.2 (17.6-30.6)	24.4 (21.3-27.9)	20.0 (6.0-66.3)	21.2 (19.2-23.4)

Values are geometric mean (95% confidence intervals)
* p≤0.05, ** p≤0.01 vs. ≥ 5th centile
VLBW = Very Low Birth Weight
SGA = Small for Gestational Age

4.3.4 Concomitant problems

Figure 8 and 9 show the prevalence of different problems in VLBW and SGA adolescents in our study, as reported in papers from our study group.[60;327;328]

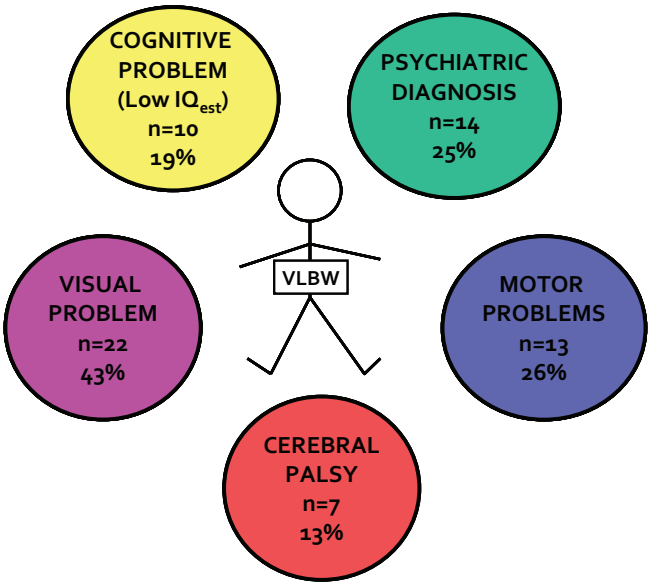


Figure 8. Prevalence of problems in different domains in VLBW adolescents.

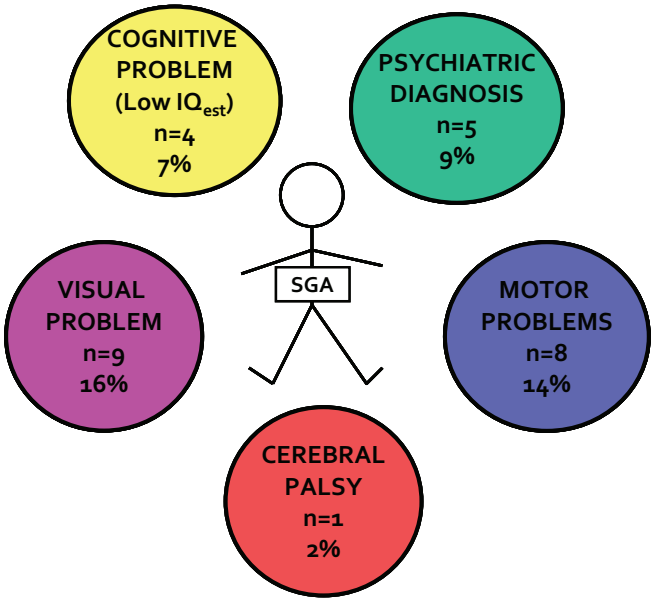


Figure 9. Prevalence of problems in different domains in SGA adolescents.

The two controls with motor problems did not have problems in other domains (Table 10). In comparison, 12 of the 13 (92%) VLBW adolescents (six boys and six girls) (p=0.002 vs. controls) and two of eight (25%) SGA adolescents (boys) (non-significant vs. controls) with motor problems also had problems in one or more of the other domains. In addition, three VLBW adolescents with CP who did not obtain complete assessments of motor skills had concomitant problems (data not shown).

Table 10. Concomitant problems in boys and girls in the VLBW, the SGA and the control group.

	VLBW													SGA								Control	
Sex	♂	♂	♂	♂	♂	♂	♂	♀	♀	♀	♀	♀	♀	♂	♂	♂	♂	♂	♂	♀	♀	♂	♀
Motor problems	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cerebral palsy	X	X						X	X					X									
Low IQ_{est}								X	X	X	X	X		X	X								
Visual impairments	X	X	X	X	X			X	X	X		X		X	X								
Psychiatric diagnosis	X	X	X	X		X		X			X		X	X	X								

♂ = boys ♀= girls

X indicates problem in an area

Blue and pink colours indicate multiple problems in boys and girls, respectively

VLBW = Very Low Birth Weight
SGA = Small for Gestational Age

5. Discussion

5.1 Main findings of thesis

In this study we found that VLBW adolescents had more general and pronounced problems, whereas SGA adolescents had more specific and less pronounced problems. The VLBW group had poorer results for all subscores of the Movement ABC; i.e. manual dexterity, ball skills and static/dynamic balance, as well as the total ABC score. The increased risk of motor problems was similar in boys and girls. Lower birth weight and left-handedness were associated with poorer motor skills.§ Almost every VLBW adolescent with motor problems had CP, low IQ_{est}, visual impairments or a psychiatric diagnosis.§ A substantial part of the motor problems in the VLBW group was influenced by visual impairments, as the odds of having motor problems decreased significantly after adjusting for visual acuity and the abnormality score. Furthermore, we found that VLBW adolescents performed poorer than controls in inter- and intra-modal matching, but not after excluding subjects with CP and low IQ_{est}. However, the VLBW adolescents with poor manual dexterity had larger errors on the manual matching task when vision was matched with proprioception than VLBW adolescents with normal manual dexterity.§ Finally, in this study we were able to identify most VLBW children with later motor problems as early as one year of age by the Bayley Scales of Infant Development (BSID).

In the SGA group the increased risk of motor problems was especially found for left-handed§ boys in manual dexterity. There was no association between motor problems and birth weight, and motor problems were not associated with problems in other domains.§ The motor problems in SGA adolescents were relatively unaffected by visual impairments and not specifically due to problems in inter- and intra-modal matching. Still, in the SGA group there were differences in performance on the manual matching task between hands, which varied according to sex. Boys had larger errors with their non-preferred hand when matching vision and proprioception, whereas girls

§ results not reported in papers

had larger errors matching the proprioceptive space of one hand to the proprioceptive space of the other. There were no significant associations between errors on the manual matching task and manual dexterity problems.§ The motor scale of the BSID did not identify SGA children with motor problems at age 14, whereas half of them were identified at five years of age by the Peabody Developmental Motor Scales (PDMS).

5.2 Validity of the study

The study was based on a geographically defined cohort of all surviving VLBW children, all term-born SGA children and a random sample of control children from the same geographic area, born over a period of two years in the mid-eighties and followed up to 14 years of age. In the following, I will address issues concerning the validity of the study; i.e. methodological considerations, chance, bias and confounding.

5.2.1 Methodological considerations

Inclusion criteria

We used birth weight of 1500 g or below as inclusion criterion for VLBW in our study, in accordance with most other studies.[215;216;225;231;234-237;245;247;253;254;329-332] This cut-off secured inclusion of only preterm children in this group (Figure 10).

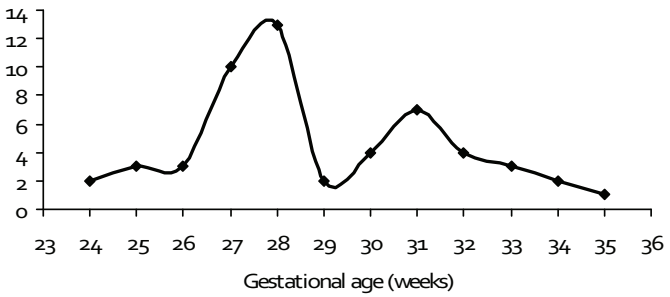


Figure 10. Distribution of gestational ages in the VLBW group.

§ results not reported in papers

However, by using birth weight as inclusion criterion in the VLBW group, a proportion of children who had been growth restricted *in utero* was included, and the study group therefore comprised children with an extensive range of gestational ages. Thus, the VLBW group consisted of both preterm AGA children and more mature preterm SGA children (as indicated by the right slope of the curve in Figure 10). The aetiology and outcome may differ between children in the two categories; however we chose to treat them as one group, since they were all born preterm, as a contrast to the SGA children born at term. Furthermore, subsequent analyses[§] showed no differences in motor scores between the two subgroups (results section 4.3.1). Thus, for this study it seems appropriate to treat them as one group.

We are aware of that SGA is a statistical description of the birth weight of infants born at a particular gestational age.[75] Thus, SGA is a heterogeneous group, including those born small due to pathological reasons and those born small due to genetic and non-pathological causes.[11] The 10th centile definition may therefore include a proportion of normal small infants, whereas some large and growth restricted infants may have been classified as controls. Thus, non-significant differences between SGA and control adolescents may be under-estimates of the real differences.

Outcome measures

Prevalence of motor problems will always depend on what definition is used, and various motor tests offer different possibilities and limitations in diagnosing motor problems. We have used the 5th centile on the Movement ABC to identify adolescents with motor problems. The manual recommends using scores below the 5th centile to identify children with definite motor problems and scores between the 5th and 15th centile as indicative of borderline motor problems.[113] According to Geuze et al.[144] the 5th centile is recommended as cut-off in research, while the 15th centile is suggested used in the clinic. By using the 5th centile in this study we are quite confident that the adolescents identified

[§] results not reported in papers

really had motor problems. Thus, it is unlikely that the prevalence reported is overestimated.

The Movement ABC is a reliable and valid test, especially designed to identify children with motor problems (i. e. being sensitive in the lower range of centiles). However, some claim that it is unable to identify children with specific motor coordination difficulties, such as handwriting problems[144] and poor proprioceptive abilities.[333] Test-retest and inter-rater reliability have been documented in the manual.[113] In the present study, one physiotherapist did all motor evaluations at 14 years of age, avoiding issues of inter-rater reliability. Intra-rater reliability has not been documented in the manual of the Movement ABC. However, in this study, intra-rater reliability was found to be high. Thus, the examiner was not a source to variation in Movement ABC scores for the adolescents in our study.

Validity has proved to be satisfactory when comparing the Movement ABC to other test instruments.[113] The test seems useful to different groups of professionals and has been applied to different groups of children.[113] One might question the use of the test on subjects with CP, as the main goal of the Movement ABC is to diagnose DCD. However, the test is increasingly used for children "at risk", i.e. low birth weight children, and Henderson et al.[334] do not preclude use of the test in conditions where the "cause" of the child's movement difficulties is already known, and an assessor wants to measure the extent and severity of the difficulties.[334] Nonetheless, in Paper I we also presented results excluding subjects with CP, and in Paper II adolescents with CP were excluded initially.

In this study, we used the Movement ABC at 14 years of age, although the test is designed for children up to the age of 12 years. A ceiling effect might mask differences at the higher end of motor functioning. However, in this study, we were more concerned about lower motor functioning. As the norms developed for children aged 11-12 years would perhaps cause us to underestimate the prevalence of motor problems, we used the 5th centile derived from our own control group as cut-off. This turned out to be well in accordance with the 5th centile in the manual.

The Movement ABC assesses tasks that are relevant for children in daily life. However, as mentioned in the introduction (section 1.2.4), motor performance in a test situation may not be an accurate estimate of problems in the real world. A limitation may be that the child is only examined in a stable environment and not in more complex tasks where the environment is changing, as in a playground and in many sports. According to Gentile's taxonomy of tasks,[115] one might imagine increased problems when the environment is constantly changing.

The BSID is one of the most commonly used tests in smaller children. Test-retest and inter-rater reliability have been found satisfactory. Validity has not been documented in the manual, but later studies have found good agreement with other measures, especially with gross motor functions,[309] and for children with various handicaps.[335] Although the BSID is widely used, Palisano[309] claims that the motor scale contains a small number of items for each level of development and omits stages in the motor developmental sequence. Thus, it does not provide an in-depth motor assessment or discriminate gross and fine motor abilities.[309]

In contrast, the PDMS consists of separate gross and fine motor scales, allowing a more detailed assessment of motor development.[309] Examination of reliability and validity has proved the PDMS to be a highly stable assessment instrument, showing agreement with other instruments and with clinical judgement.[136] As for the Movement ABC, authors of the PDMS acknowledge that some examiners may assume that a test standardized on non-handicapped children cannot be used on handicapped children. However, the PDMS was developed to give information about the motor skill development of children, and may also be applied to children having various handicaps.[136]

The manual matching task was developed in order to assess the integrity of sensory systems.[191] As a consequence, the motor component is minimal and the task is relatively simple. A main limitation of the manual matching task is that reliability and validity have not been established. However, several researchers have found differences in test results according to motor abilities of the subject.[199;203;207;210]

5.2.2 Chance

The motor outcome reported in this study was significantly worse for the VLBW and the SGA group. The highly significant results in both groups, even after exclusion of subjects with CP and low IQ_{est}, indicate an association which is unlikely to be due to chance, although confidence intervals were broad due to limited sample size. The association between motor problems and visual impairments was also strong in the VLBW group, but not in the SGA group. Differences on the manual matching task were less striking, with p-values below 0.05 for some comparisons only. Nonetheless, our main findings are unlikely to be due to chance.

5.2.3 Bias

Information bias

The examiners were blinded to the adolescents' group assignment and to results of the other assessments at 14 years of age. At one and five years of age, the follow-up of VLBW and SGA children were done in two separate studies (see methods section 3.1), which means that the examiner was blinded for group adherence concerning SGA and control children, but knew which child was born VLBW. However, the examiner was blinded to neonatal history. Thus, information bias is unlikely, in particular regarding the final outcome at 14 years of age.

Selection bias

It is a strength of our study that it is population based and prospective, as this minimizes selection bias. Although the aim of every study is maximum participation, loss to follow-up is inevitable in a long-term follow-up study, and rates of 50-80% participation have been suggested to be acceptable in cohort studies.[336] Of the adolescents eligible for the study, 78% participated in Paper I and III. In the two papers relating motor problems to visual impairments (Paper II) and to results of earlier motor evaluations (Paper IV), attendance was lower (67-80%). However, loss to follow-up may be less detrimental in a correlational than in a prevalence study. Nonetheless, our attendance is comparable to other

studies with a similar length of follow-up.[336;337] The influence of attrition depends on characteristics and outcome of lost children. In our study, non-participants did not differ from participants on known background data. However, subjects performing worse may have a stronger tendency to drop out.[338] Thus, loss to follow-up may have caused us to underestimate the prevalence of problems in Paper I and III. In addition, loss to follow-up has an impact on study power in that it reduces sample size.[336] Thus, this may have affected our power to detect differences in Paper III.

5.2.4 Confounding

In order to control for possible confounding factors (i.e. factors associated with both independent and dependent variables, which could explain the result), we used three different strategies; (1) stratified analysis, (2) multivariable analysis and (3) exclusion.

Sex

Sex was somewhat unevenly distributed in our material (54 % male in the VLBW group, 46 % in the SGA and 42 % in the control group), and although not statistically significant, this could influence results. Stratified analyses (strategy 1) for sex were carried out in Paper I and III, and sex was controlled for in logistic regression analysis (strategy 2) in Paper II. We found that motor problems were as frequent in girls as in boys in the VLBW group; however, boys were a lot worse off in the SGA group (Paper I). In the control group there were no differences in motor scores by sex. The association between motor problems and visual impairments was not affected by sex (Paper II). In Paper III, SGA boys seemed to have poorer inter-modal matching with their non-preferred hand compared with their preferred hand, while for SGA girls this was the case in intra-modal matching.

Postnatal growth

Weight and height at 14 years of age were identified as possible confounders of the association between low birth weight and motor problems (Paper I). When

we adjusted for these factors in regression analyses (strategy 2), the odds of having motor problems in the VLBW and the SGA group increased.

Socioeconomic status

Socioeconomic status (SES) has been shown to correlate strongly to the developmental outcome of high-risk infants,[339] and motor behaviour in children may partly depend on social factors and the educational levels of their parents.[340] SES was lower in the VLBW group in Paper I and III, but not in Paper II due to a slightly different sample. Nevertheless, the increased risk of motor problems reported in Paper I persisted after adjusting for SES.

Cerebral palsy and low estimated IQ

It can be argued that CP and low IQ_{est} should not be considered as confounders when studying low birth weight children, since they could be factors in the causal chain between low birth weight and outcome. Nonetheless, in Paper I and III, results were analysed both including and excluding (strategy 3) subjects with CP and low IQ_{est}. Excluding subjects with CP and low IQ_{est} reduced the risk of motor problems in the VLBW and SGA group (Paper I), although the increased risk of having motor problems persisted. In Paper II, however, we excluded subjects with CP initially, since we did not want our results to be determined by extreme abnormal values. Controlling for low IQ_{est} in regression analysis (strategy 2) did not change the association between motor problems and visual impairments. In Paper III, the unfavourable results in the VLBW group were mainly due to the adolescents with CP and low IQ_{est}.

5.2.5 Generalizability

In sum, there was a strong statistical association between VLBW and motor problems, which is unlikely to be due to chance, bias or confounding. Thus, the internal validity of the study may be acceptable.

However, although results are internally valid, the may not be externally valid. External validity refers to what extent the results may be applicable to other similar populations.[142] The population studied seems representative for

similar populations born in the same period.[254] One problem common to all long-term follow-up studies is that the outcomes are determined well after the newborn period. Additionally, mortality has decreased significantly since the 1980s, when our study population was born, resulting in increased survival of premature infants. Thus, results may be less relevant to the children born too soon or too small today. However, until more contemporary data is available, the motor outcome reported in this thesis provides the best estimate of what infants born too soon or too small will be at 14 years of age. Despite increased survival, neonatal and short-term morbidity among VLBW children has remained relatively unchanged over the last decades.[341] As more immature and sick infants survive, one might also imagine even more morbidity in the future than was found in our study. Thus, results from long-term follow-up studies give valuable information regarding prognosis for infants at high risk, and there is reason to believe that the results of this thesis have relevance to current survivors of preterm birth and intrauterine growth restriction as well.

5.3 Motor outcome after being born too soon or too small

In order to assess causality, i.e. whether the results in the study groups reflect a cause-effect relationship, strength of the association, biological credibility and consistency with the research literature will be discussed in the following.

5.3.1 Strength of the association

The main finding was an association between both low birth weight groups and motor problems, assessed by the Movement ABC. The strength of the association, reflected by the high odds ratios for motor problems (9.3; 95% CI: 2.5-34.5 for VLBW and 4.7; 95% CI: 1.2-18.4 for SGA compared with control adolescents, respectively), indicates a genuine effect of VLBW and SGA, and points to a possible biological cause-effect relationship. Likewise, there was a strong association between motor problems and visual impairments in the VLBW group. However, the association between low birth weight and inter- and

intra-modal matching was weaker and may not confirm that poor sensory integration is a consequence of low birth weight.

5.3.2 Biological credibility

Born too soon

Poorer performance in all subscores of the Movement ABC in the VLBW adolescents suggests a comprehensive and general deficit, and may be an expression of complex minor neurological dysfunction, which is associated with birth before 33 weeks of gestation, and suggested to be a result of early brain lesions.[342] In our VLBW group, this may have affected the development of motor skills with regard to both primary, as well as secondary variability, during childhood.[125] It is likely that the high prevalence of motor problems found in VLBW adolescents is related to the high prevalence of brain abnormalities seen on MRI in preterm populations.[285;286;288] In our study group, there was an association between white matter reduction and total Movement ABC, as well as balance score, although this association was no longer significant after excluding subjects with CP.[343] This may suggest a widespread brain dysfunction that is difficult to pinpoint with conventional MRI techniques. Brain plasticity and compensation over the years may also play a role, as suggested by Allin et al.[289] However, on diffusion tensor imaging we have reported a correlation between motor problems, in particular poor manual dexterity, and reduced white matter integrity, indicated by low fractional anisotropy (FA) values in the external and internal capsule, as well as the corpus callosum and the inferior, middle and superior fascicles.[302] Specifically, low FA values in the posterior limb of the internal capsule may reflect disturbed myelination and connectivity of somatosensory and motor fibres, contributing to motor problems in the VLBW adolescents.[302]

Left-handedness is suggested to be an indicator of aberrant brain development in preterm children.[291] The prevalence of left-handedness was twice as high in the VLBW group, and although only borderline significant compared with controls, the poorer performance on the Movement ABC in left-

handed VLBW subjects§ may support that brain development has not been optimal.

Vision was also reduced in VLBW adolescents compared with controls in our study,[43;44] and since vision is important in initial phases of motor learning,[193] one can imagine that a VLBW child with impaired vision will not have optimal motor learning. In this way, poor visual functions may be the cause of motor problems. However, both the optic radiations and the corticospinal tracts pass through periventricular white matter, and both visual impairments and motor problems may therefore be result of a comprehensive brain injury (i.e. "encephalopathy of prematurity") in preterm children.[34]

Inter- and intra-modal matching depend on transfer of information across hemispheres, either via the visual pathways or via the corpus callosum. As both periventricular white matter and the corpus callosum are known to be impaired in VLBW, this may have contributed to poorer results on the manual matching task. However, differences in errors were small and no longer statistically significant when subjects with CP and low IQ_{est} were excluded. This may be related to the difficulty of assessing the integrity of the proprioceptive system as a whole in a simple way.[113] As the purpose of the manual matching task was to minimize the influence of movement in order to assess the integrity of sensory systems, the task is relatively simple. Nonetheless, precision in inter-modal matching may require stability in both the ocular-motor system and in manual control.[203] Analyses within the VLBW group showed that subjects with poor manual dexterity had significantly larger absolute, systematic and random errors in the visual condition, using either hand, compared with subjects scoring above the 5th centile on manual dexterity.§ Thus, there might be problems in sensory integration of vision and proprioception in the subgroup of VLBW adolescents with manual dexterity problems. Although not statistically significant, errors in the proprioceptive condition were also higher for VLBW subjects with poor manual dexterity,§ and power may have been too low to detect differences when splitting the group in this manner.

§ results not reported in papers

The high sensitivity of the early motor evaluations in the VLBW group may reflect the perinatal aetiology of motor problems in this group, since we were able to identify most children with later motor problems, including the two children with CP, as early as one year of age.

The co-morbidity found with cognitive, visual and psychiatric problems in this study,§ support the notion of "preterm brain injury", which was not restricted to adolescents with CP. Hadders-Algra[125] speculates that the presence of neural dysfunction may induce vulnerability to the development of other problems, such as specific learning disorders or attention problems. Thus, motor problems seem to be part of a spectrum of impairments in the domains of cognitive function, language, attention and social functioning.[291]

Born too small

The increased risk of motor problems in the SGA group was particularly seen in boys. These findings may be related to minor neurological damage,[344] or be an expression of simple minor neurological dysfunction.[125;342] In contrast to the complex type, as suggested in the VLBW group, this may reflect normal, but non-optimal brain function. However, it can also be caused by pre- or perinatal stress associated with severe intrauterine growth retardation.[342] Children with this type satisfactorily pass the developmental stages of primary variability and selection, but have problems in fine-tuning motor output to task specific conditions.[345] This may fit well with the findings of poor manual dexterity in the SGA group.

It is also possible that the motor problems of the SGA adolescents are related to smaller brain volumes shown on magnetic resonance imaging in this group.[292;293] Furthermore, poor manual dexterity may be caused by perinatal circulation disturbances and hypoxia in the watershed areas of the parasagittal region of the brain, as lesions in this area affect upper, more than lower, limbs.[346] In addition, infants suffering growth restriction may suffer from non-optimal development of the cerebellum, which grows fast in late pregnancy. The cerebellum is particularly involved in fine motor coordination and fine tuning of

§ results not reported in papers

movements. Some speculate that cerebellar dysfunction may be a cause of motor coordination problems in normal populations as well.[181]

The sex difference seen, with SGA boys having more problems, is in accordance with the increased prevalence of male DCD in normal populations.[173;175;347] The male fetus seems to be more vulnerable to impairment than the female.[7;348] Some speculate on a greater risk of disrupted development because each phase of the brain development seems to take longer in males.[347] On the other hand, there are indications of higher growth velocities in male than in female fetuses in the third trimester,[349-351] which may bring an increased vulnerability for growth restriction during this period in SGA boys. Cigarette smoking was not investigated in this thesis. However, smoking in pregnancy has a well-known association with intrauterine growth restriction and affects males more than females.[352]

The findings of poorer manual dexterity scores in left-handed SGA adolescents, and boys in particular,[§] may support a relationship between brain pathology and male vulnerability in the SGA group.

The odds of having motor problems in the SGA group were relatively unaffected by visual impairments. This is consistent with lack of major differences in visual functions between SGA and control adolescents in our study.[43;44] It may also fit well with the lack of statistically significant differences in the visual condition (inter-modal matching) between SGA and control adolescents, although SGA boys had poorer performance with their non-preferred hand compared with their preferred hand. If motor problems in SGA boys have a cerebellar aetiology, it may be reasonable that vision and visual perception are less affected, as these are predominantly cerebral functions.[194] The reason for hand asymmetry in the proprioceptive condition (intra-modal matching) in SGA girls is difficult to understand, as they had no evidence of poor manual dexterity, and we can not rule out a chance finding.

The problem of early identification of SGA children with later motor problems may be related to the subtle aetiology of motor problems. Especially during the first years of life, prediction can be difficult, as variation in

[§] results not reported in papers

development is inherent in motor development.[110] At five years of age, we were able to identify half of the SGA children who had motor problems at 14 years of age. This may be in accordance with the view of Larroque et al.,[95] who claim that subtle developmental disabilities might not be obvious in early childhood and can only be reliably tested for later in life.

It is important to acknowledge that motor skills are not solely determined by insults to the central nervous system, although our results in the VLBW group suggest that this plays a major role. When performing motor skills, the complexity of the task and the environment in which the task is performed, are contributing factors to success, in addition to features in the subject.[307] Additionally, motor development and learning may very well be influenced by a whole range of factors, such as inheritance, parental attitudes, socioeconomic status, exercise and experience, which might be more important as the child grows older. For instance, one can imagine that proprioceptive abilities, whether vision is additionally used or not, may have been practised during computerized tasks and games, which were less common decades ago. This may also explain why VLBW adolescents without CP or low estimated IQ did not have major difficulties on the manual matching task.

5.3.3 Consistency with other investigations

Prevalence of motor problems

The high prevalence of motor problems found in this study (26%) is in accordance with other studies reporting motor outcome in preterm populations. Studies using the 5th centile on the Movement ABC as cut-off have reported prevalences varying from 9.5-34%.[7;131;234;237;241;245;252;332] Differences may rely on variations in inclusion criteria and age at assessment (Figure 11). Some studies have excluded subjects with major neurodevelopmental handicaps, like CP.[131;241;244;245;252] The prevalence of motor problems in our VLBW group fell to 20% when we excluded subjects with CP, still well in accordance with other studies.

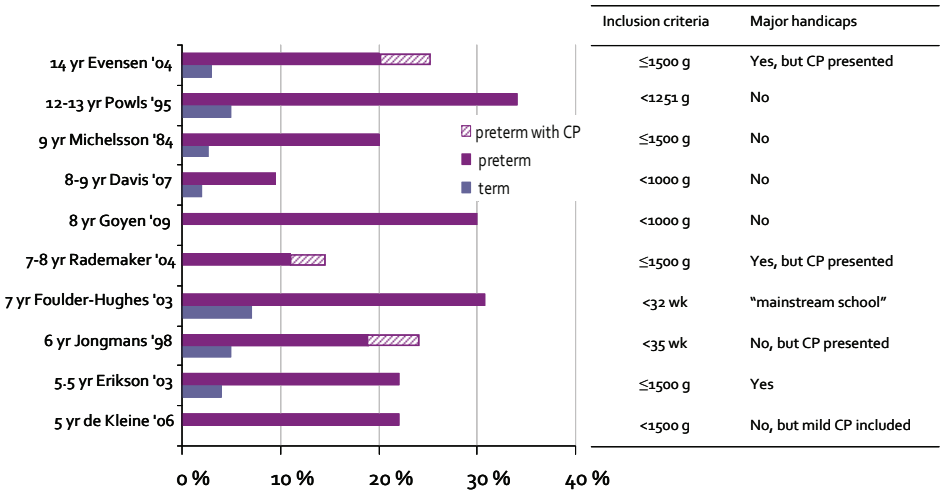


Figure 11. Motor problems <5th centile on the Movement ABC in preterm populations.

The finding of poorer performance across all subscores of the Movement ABC, in which the increased risk was most pronounced for poor balance, followed by poor manual dexterity and only borderline significant for poor ball skills, is in accordance with the recent meta-analysis by de Kieviet et al.[251]

Some studies have reported a disadvantage for preterm boys,[239;247;254;353] while other studies report poorer motor outcome in girls.[250;252] In line with a study of children with birth weight below 2000 g,[259] we found increased risk of motor problems in both VLBW boys and girls compared with control boys and girls. Our results may also be in accordance with the study by Taylor et al.[253] who found that sex differences at early school age disappeared with increasing age.

While some have reported a beneficial effect of puberty on neurological function,[178] the findings of this study indicate that motor problems in VLBW subjects do persist in adolescence. This is in accordance with the meta-analysis by de Kieviet et al.,[251] who report a non-significantly greater motor deficit with increasing age during elementary school and early adolescence, assessed by the Movement ABC.

In term SGA adolescents we found a relatively high prevalence of motor problems, in particular poor manual dexterity, compared with controls. In childhood, there seems to be mixed evidence of motor problems. The only study that we have been able to identify evaluating motor function in adolescence, reported no differences between SGA and control subjects on a neurological examination at 16 years of age.[80] However, a neurological examination only partly overlaps with a motor evaluation. Our results may be consistent with studies reporting poor eye-hand coordination and poor fine motor function in children[73;276;278] and young adults.[280]

A specific finding of our study was the higher prevalence of motor problems in SGA boys. This may be in accordance with the results of Walther et al.,[73] which indicated a more adverse effect of intrauterine growth retardation in boys compared with girls.

In the SGA group we found no relationship between motor problems and ponderal index,§ a finding supported by others at eight months[72] and two years of age.[268]

Influence of vision

Studies investigating visual factors in VLBW children have found poorer results on the Movement ABC in children with reduced visual function, such as poor visual acuity, stereoacuity, contrast sensitivity and strabismus.[42;235;260;261] We found that visual acuity, and the combined visual impairment score, influenced motor problems most in VLBW adolescents.

We did not find that reduced visual function influenced motor problems in SGA adolescents. No other studies have investigated the association between motor problems and visual impairments in term SGA children. However, the lack of differences in visual functions between SGA adolescents and controls in our study is in accordance with a study reporting no differences in screening tests of vision between SGA and control children at five years of age.[274] Furthermore, visual function was not related to motor problems in children aged five to seven years with DCD.[198]

§ results not reported in papers

Inter- and intra-modal matching

Some studies using the manual matching task have reported differences between control children and children with DCD[203;210;211] and eye-hand coordination problems (determined by the manual dexterity subscore of the Movement ABC).[199] This may be in contrast to our findings, as we would expect that both VLBW and SGA adolescents had larger errors than controls, given their high prevalence of manual dexterity problems. The lack of differences on the manual matching task between controls and SGA adolescents, as well as VLBW adolescents without CP and low IQ_{est}, may be in accordance with another study using the modality task on DCD children.[212] The mean size of errors reported in Paper III, ranging from 15-26 mm in all groups, seems consistent with the literature,[199;210] although some report even larger errors in the proprioceptive condition,[199] and in subjects with CP.[204] Asymmetrical performances, as we found in the SGA group, have been reported before,[199;207;208] although the reason for these findings might be less clear.

However, stratified analyses by manual dexterity within groups,[§] where VLBW adolescents with poor manual dexterity had larger errors on the manual matching task, may be in agreement with the findings of Sigmundsson et al.,[209] although there were no differences within the SGA group. A study by Schoemaker et al.[212] also failed to demonstrate a relationship between the manual matching task and the Movement ABC.

Early identification

Few studies have examined the predictive value of the BSID and the PDMS in low birth weight populations. In a group of children with "suspicious neurological function" at one and seven years of age, the motor scale of the BSID provided modest discriminating power.[354] In normal populations, MacCobb et al.[355] found that the motor scale of the BSID at 18 months of age correlated with the subtests of bilateral coordination and balance on the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) at nine years of age.

[§] results not reported in papers

This may be in accordance with our findings in the VLBW group, who had general motor problems, although we used the Movement ABC as outcome. However, MacCobb et al.[355] found no correlation between the motor scale of the BSID and upper limb coordination on the BOTMP. This, on the other hand, may fit well with the poor prediction by the BSID in the SGA group, who were more likely to have manual dexterity problems. The BSID is mainly a measure of motor milestones, and does not discriminate between fine and gross motor skills. Accordingly, it has been shown to correlate with the gross motor scale of the PMDS, and not the fine motor scale.[309]

In contrast to the BSID, the PDMS allows for separate assessment of fine and gross motor skills. This could be the reason why PDMS proved the most sensitive measure in the SGA group, identifying half of the SGA children with later motor problems. Consistent with our study, Goyen and Lui[241] found that motor problems at eight years of age in the majority of children with birth weight below 1000 g could be identified by the PDMS at three years of age.

5.3.4 Additional criteria for causality

One additional criterion for assessing causality is temporality, i.e. the cause must precede its effect. Since our outcome variables were measured long after birth, the time-sequence is considered to be appropriate. Another additional criterion is dose-response relationship, i.e. a gradient of risk associated with degree of exposure.[142] We found a dose-response relationship of increased motor problems across birth weight in the VLBW group,[§] supporting a causal relationship between VLBW and motor problems. This is in accordance with other studies,[242;255;256;356] although a recent meta-analysis indicates a decrease in the effect of perinatal factors, such as birth weight, on motor development as age increases.[251] In SGA adolescents we did not find increased motor problems across birth weight or ponderal index at birth,[§] suggesting that having a birth weight below 10th centile, rather than how small or thin the infant is, constitutes a risk factor per se.

[§] results not reported in papers

In sum, the association between motor problems and low birth weight is strong, a hypothesis of biological vulnerability is credible, main results are consistent with the literature, there is an appropriate time-sequence and a dose-response relationship is possible, in particular for those being born too soon.

6. Clinical implications

Many parents report that adolescence is especially difficult for children with motor problems.[179] The importance of gross motor functioning is sometimes underestimated, but it is a significant contributor to playground success and peer acceptance.[255;357] Motor skills play an important role in establishing a child's reputation among peers and in the development of self-esteem, at least in western societies,[358] and competitive sports play a particular important role in peer interactions during adolescence.[179] There is evidence that poor motor performance and poor social skills lead to exclusion from social activities, creating a cycle of decreasing participation, decreasing competence and low self-esteem.[69;359] Wall et al.[117] also describes how lack of confidence and negative affect toward physical activity are likely to result in less participation which prevents an increase in skill, thus reinforcing the tendency to dislike situations requiring motor competence. In our VLBW group, poor ball skills, which may affect successful participation in popular sport activities like football, were associated with increased risk of being bullied at 14 years of age.[70]

Furthermore, academic demands increase in middle school and high school.[179] Children spend as much as 31-60% of their school day performing handwriting or fine motor tasks.[246] Paper-pencil fine motor skills, as well as typing on computer keyboards, are essential in the academic setting, because children are often classified and graded on academic subjects, based on their written work performance.[255] Thus, poor writing communication skills can seriously interfere with academic achievement,[179] and be increasingly important in adolescence when decisions have to be made regarding future education, work and independent living, which are likely to have a life-long impact. Thus, motor problems seem to have consequences reaching beyond the *activity* domain of ICF, as they also are most likely to affect *participation*.

Our results should draw attention to the fact that motor problems are common in VLBW and SGA populations, even in adolescence. Ideally, children with motor difficulties should be diagnosed early in life so that interventions can be implemented to prevent or minimize further problems.[359] The high sensitivity of the motor scale of the BSID in the VLBW group warrants the need

for a thorough motor examination at one year of age. The influence of vision on motor problems should draw attention to optimal visual treatment in order to improve development and learning of motor skills. For VLBW children, the widespread motor problems may be problematic per se, and may additionally directly affect other areas of life. However, being born VLBW also carries a high risk of concomitant problems, all of which are likely due to the perinatal injury. These problems may not be discovered until school age; in particular cognitive functions have been difficult to assess at an early age.[360] Thus, motor problems at one year of age may be an early marker for other problems, which can imply that children detected early by physiotherapists may need referrals for assessments by other professionals as well (i.e. cognitive, visual and psychiatric evaluations).

For SGA children one might question the clinical importance of their poor motor skills. The simple form of minor neurological dysfunction has only shown weak relations to learning and behavioural problems.[125;342] In this study, few of the SGA adolescents with motor problems had problems in other domains. However, poor manual dexterity may be a disadvantage in writing performance at school. A motor evaluation of SGA children at preschool age may therefore be particularly relevant in order to identify these problems.

Thus, recognizing children born too soon or too small as having significant risk factors for later motor (and other) difficulties may have important implications for prevention and early intervention strategies. One might speculate that these children should be treated differently in the clinic. Early intervention for infants born too soon may focus on enhancing primary variability. At preschool age, both groups may benefit from specific intervention focusing on active practice, enhancing the process of selection and better adapted motor behaviour.[102] This kind of intervention might help children born too small with specific manual dexterity problems, whereas environmental adaptations may additionally benefit children born too soon.

7. Conclusions

Being born too soon with a birth weight below 1500 g brings on an increased risk of motor problems in adolescence, involving manual dexterity, ball skills and balance. A substantial part of the motor problems in VLBW adolescents was influenced by visual impairments, suggesting that motor and visual dysfunction frequently appear in the same subjects. We also found a slight deficit in transfer of sensory information in VLBW adolescents with cerebral palsy and low estimated IQ. It is likely that the high prevalence of motor problems in the VLBW group is due to early brain injury, supported by the fact that we were able to identify most children with later motor problems as early as one year of age, and that they were likely to have problems in multiple domains.

Being born too small with a birth weight below the 10th centile at term also carries an increased risk of motor problems, especially among boys in manual dexterity. However, this was not explained by visual impairments or poor sensory integration, and we were not able to identify the motor problems early in life. The biological basis for the motor problems in this group may be more subtle and diffuse.

8. Implications for future research

A great interest in the more subtle brain correlates to minor motor problems emerged during this work, and is a topic that needs further exploration. In the present study, we have performed conventional and volumetric MRI. Some results are published,[288;292;293;302;343;361] while others, linking for instance hand function and laterality to regional motor cortical thickness,[362] are in progress.

We have just finished the follow-up at 19 years of age with broad-based clinical assessments and even more extensive quantitative MRI techniques, such as tractography and 3D morphometry. This will hopefully increase our knowledge about structural-functional relationships in the developing brain of subjects with low birth weight.

Whether the present results are applicable for the children being born prematurely today, is a never-ending issue. However, with the increasing number of surviving children with extremely low birth weight during the last two decades, we speculate that our findings are more of an underestimate than an overestimate of existing long-term impairments and disabilities following preterm birth. This hypothesis will be explored in new cohorts of very low birth weight children.

The concomitant problems can be further explored to see if there are strengths that can be employed in intervention strategies. Future studies can also address the relationship between these impairments of manual dexterity, ball skills and balance with activity limitations and participation restrictions.[132]

As far as intervention is concerned, every skill seems to improve with practice and for some children intervention and compensatory technical aids (like computers for writing) may give them opportunities to participate in activities they otherwise would not. However, research needs to be done in order to look for adaptive neural changes as a consequence of intervention.

9. References

(1) Neligan GA, Kolvin I, Scott DM, Garside RF. Born too soon or born too small: A follow-up study to seven years of age. London: William Heinemann Medical Books Ltd.; 1976.

(2) Parmelee AH, Schulte FJ. Developmental testing of pre-term and small-for-date infants. Pediatrics 1970; 45:21-28.

(3) Schulte FJ, Michaelis R, Linke I, Nolte R. Motor nerve conduction velocity in term, preterm, and small-for-dates newborn infants. Pediatrics 1968; 42:17-26.

(4) Wilcox AJ. On the importance - and the unimportance - of birthweight. Int J Epidemiol 2001; 30:1233-1241.

(5) Indredavik KA. Kartlegging av motoriske ferdigheter hos tenåringer med lav fødselsvekt ved hjelp av Movement Assessment Battery for Children - en populasjonsbasert oppfølgingsstudie. Bergen: University of Bergen; 2003.

(6) Dunn PM. Arvo Ylppö (1887-1992): pioneer of Finnish paediatrics. Arch Dis Child Fetal Neonatal Ed 2007; 92:F230-F232.

(7) Jongmans MJ, Mercuri E, Dubowitz LM, Henderson SE. Perceptual-motor difficulties and their concommitants in six-year-old children born prematurely. Hum Mov Sci 1998; 17:629-653.

(8) Schraeder BD, Evoy-Shields K. Development and longitudinal follow-up of low-birth-weight infants. NAACOGS Clin Issu Perinat Womens Health Nurs 1992; 3:147-173.

(9) World Health Organization. Regional consultation towards the development of a strategy for optimizing fetal growth and development. Cairo: 2005.

(10) World Health Organization. Public health aspects of low birth weight. Third report of the expert committe on maternal and child health. Geneva: 1961.

(11) Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. Best Pract Res Clin Endocrinol Metab 2008; 22:477-488.

(12) McCormick MC. The outcomes of very low birth weight infants: are we asking the right questions? Pediatrics 1997; 99:869-876.

(13) Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. Arch Dis Child 1991; 66:204-211.

(14) Medical Birth Registry of Norway. 2009.

(15) Walker DM, Marlow N. Neurocognitive outcome following fetal growth restriction. Arch Dis Child Fetal Neonatal Ed 2008; 93:F322-F325.

(16) Mandruzzato G, Antsaklis A, Botet F, Chervenak FA, Figueras F, Grunebaum A et al. Intrauterine restriction (IUGR) . J Perinat Med 2008; 36:277-281.

(17) Lin CC, Santolaya-Forgas J. Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology . Obstet Gynecol 1998; 92:1044-1055.

(18) Allen MC. Developmental outcome and followup of the small for gestational age infant. Semin Perinatol 1984; 8:123-156.

(19) Vik T, Markestad T, Ahlsten G, Gebre-Medhin M, Hoffman HJ, Jacobsen G et al. Body proportions and early neonatal morbidity in small-for-gestational-age infants of successive births. Acta Obstet Gynecol Scand Suppl 1997; 165:76-81.

(20) Neerhof MG. Causes of intrauterine growth restriction. Clin Perinatol 1995; 22:375-385.

(21) Ruiz JR, Fullerton J, Dudley DJ. The interrelationship of maternal stress, endocrine factors and inflammation on gestational length. Obstet Gynecol Surv 2003; 58:415-428.

(22) MacGillivray I. Multiple pregnancy. In: Turnbull A, Chamberlain G, editors. Obstetrics. London: Churchill Livingstone; 1989. 493-502.

(23) Joseph KS, Kramer MS, Marcoux S, Ohlsson A, Wen SW, Allen A et al. Determinants of preterm birth rates in Canada from 1981 through 1983 and from 1992 through 1994. N Engl J Med 1998; 339:1434-1439.

(24) Blair E, Stanley F. Intrauterine growth and spastic cerebral palsy. I. Association with birth weight for gestational age. Am J Obstet Gynecol 1990; 162:229-237.

(25) Haram K, Gjelland K. Vekstretardasjon hos fosteret. Tidsskr Nor Laegeforen 2007; 127:2665-2669.

(26) Rosenberg A. The IUGR newborn. Semin Perinatol 2008; 32:219-224.

(27) Vik T, Vatten L, Jacobsen G, Bakketeig L. Prenatal growth in symmetric and asymmetric small-for-gestational-age infants. Early Hum Dev 1997; 48:167-176.

(28) Kramer MS, Olivier M, McLean FH, Willis DM, Usher RH. Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. Pediatrics 1990; 86:707-713.

(29) World Health Organization. ICF Introduction. In: World Health Organization, editor. International Classification of Functioning, Disability and Health. Geneva: 2001. 1-25.

(30) Campbell SK. Evidence-based decision making in pediatric physical therapy. In: Campbell SK, Vander Linden DW, Palisano RJ, editors. Physical therapy in children. 3 ed. St. Louis: Saunders Elsevier; 2006. 3-32.

(31) Msall ME. Measuring functional skills in preschool children at risk for neurodevelopmental disabilities. Ment Retard Dev Disabil Res Rev 2005; 11:263-273.

(32) Losse A, Henderson SE, Elliman D, Hall D, Knight E, Jongmans M. Clumsiness in children - do they grow out of it? A 10-year follow-up study. Dev Med Child Neurol 1991; 33:55-68.

(33) Henderson SE. Problems of motor development: Some theoretical issues. Adv Spec Educ 1986; 5:147-186.

(34) Volpe JJ. The encephalopathy of prematurity - brain injury and impaired brain development inextricably intertwined. Semin Pediatr Neurol 2009; 16:167-178.

(35) Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003; 289:1124-1129.

(36) Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001; 107:E1.

(37) Perlman JM. Neurobehavioral deficits in premature graduates of intensive care - potential medical and neonatal environmental risk factors. Pediatrics 2001; 108:1339-1348.

(38) Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008; 359:262-273.

(39) Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999; 53:193-218.

(40) Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000; 343:378-384.

(41) Ericson A, Källén B. Very low birthweight boys at the age of 19. Arch Dis Child Fetal Neonatal Ed 1998; 78:F171-F174.

(42) Powls A, Botting N, Cooke RWI, Stephenson G, Marlow N. Visual impairment in very low birthweight children. Arch Dis Child 1997; 76:F82-F87.

(43) Lindqvist S, Vik T, Indredavik MS, Brubakk AM. Visual acuity, contrast sensitivity, peripheral vision and refraction in low birthweight teenagers. Acta Ophthalmol Scand 2007; 85:157-164.

(44) Lindqvist S, Vik T, Indredavik MS, Skranes J, Brubakk AM. Eye movements and binocular function in low birthweight teenagers. Acta Ophthalmol 2008; 86:265-274.

(45) Jongmans M, Mercuri E, de Vries L, Dubowitz L, Henderson SE. Minor neurological signs and perceptual-motor difficulties in prematurely born children. Arch Dis Child 1997; 76:F9-F14.

(46) Hård A-L, Niklasson A, Svensson E, Hellström A. Visual function in school-aged children born before 29 weeks of gestation: a population-based study. Dev Med Child Neurol 2000; 42:100-105.

(47) Luoma L, Herrgard E, Martikainen A. Neuropsychological analysis of the visuomotor problems in children born preterm at < or = 32 weeks of gestation: a 5-year prospective follow-up. Dev Med Child Neurol 1998; 40:21-30.

(48) Parat S, Moriette G, Delaperche M-F, Escourrou P, Denjean A, Gaultier C. Long-term pulmonary functional outcome of bronchopulmonary dysplasia and premature birth. Pediatr Pulmonol 1995; 20:289-296.

(49) Evensen KAI, Steinshamn S, Tjønna AE, Stølen T, Høydal MA, Wisløff U et al. Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. Early Hum Dev 2009; 85:239-245.

(50) Vrijlandt EJLE, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. Am J Respir Crit Care Med 2006; 173:890-896.

(51) Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Andreias L et al. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. JAMA 2005; 294:318-325.

(52) Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in Young Adulthood for Very-Low-Birth-Weight Infants. N Engl J Med 2002; 346:149-157.

(53) Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical Growth and Current Health Status of Infants Who Were of Extremely Low Birth Weight and Controls at Adolescence. Pediatrics 2001; 108:407-415.

(54) Horwood LJ, Mogridge N, Darlow BA. Cognitive, educational, and behavioural outcomes at 7 to 8 years in a national very low birthweight cohort. Arch Dis Child Fetal Neonatal Ed 1998; 79:F12-F20.

(55) Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002; 288:728-737.

(56) Botting N, Powls A, Cooke RWI, Marlow N. Cognitive and educational outcome of very-low-birthweight children in early adolescence. Dev Med Child Neurol 1998; 40:652-660.

(57) Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009; 124:717-728.

(58) Botting N, Powls A, Cooke RWI. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. J Child Psychol Psychiatry 1997; 38:931-941.

(59) Elgen I, Sommerfelt K. Low birthweight children: coping in school? Acta Paediatr 2002; 91:939-945.

(60) Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004; 89:F445-F450.

(61) Levy-Shiff R, Einat G, Mogilner MB, Lerman M, Krikler R. Biological and environmental correlates of developmental outcome of prematurely born infants in early adolescence. J Pediatr Psychol 1994; 19:63-78.

(62) Stevenson CJ, Blackburn P, Pharoah PO. Longitudinal study of behaviour disorders in low birthweight infants. Arch Dis Child Fetal Neonatal Ed 1999; 81:F5-F9.

(63) Elgen I, Sommerfelt K, Markestad T. Population based, controlled study of behavioural problems and psychiatric disorders in low birthweight children at 11 years of age. Arch Dis Child Fetal Neonatal Ed 2002; 87:F128-F132.

(64) Hack M. Young adult outcomes of very-low-birth-weight children. Semin Fetal Neonatal Med 2006; 11:127-137.

(65) Wolke D. Psychological development of prematurely born children. Arch Dis Child 1998; 78:567-570.

(66) Hagen EW, Palta M, Albanese A, Sadek-Badawi M. School achievement in a regional cohort of children born very low birthweight. J Dev Behav Pediatr 2006; 27:112-120.

(67) Hille ET, den Ouden AL, Saigal S, Wolke D, Lambert M, Whitaker A et al. Behavioural problems in children who weigh 1000 g or less at birth in four countries. Lancet 2001; 357:1641-1643.

(68) Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Brubakk AM. Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires. Eur Child Adolesc Psychiatry 2005; 14:226-236.

(69) Rickards AL, Kelly EA, Doyle LW, Callanan C. Cognition, academic progress, behavior and self-concept at 14 years of very low birth weight children. J Dev Behav Pediatr 2001; 22:11-18.

(70) Grindvik AS, Hodøl JS, Vik T, Evensen KA, Skranes J, Brubakk AM et al. Bullying among adolescents with very low birth weight. Acta Paediatr 2009; 98:1049-1051.

(71) Indredavik MS, Vik T, Heyerdahl S, Romundstad P, Brubakk AM. Low-birthweight adolescents: quality of life and parent-child relations. Acta Paediatr 2005; 94:1295-1302.

(72) Jelliffe-Pawlowski LL, Hansen RL. Neurodevelopmental outcome at 8 months and 4 years among infants born full-term small-for-gestational-age. J Perinatol 2004; 24:505-514.

(73) Walther FJ. Growth and development of term disproportionate small-for-gestational age infants at the age of 7 years. Early Hum Dev 1988; 18:1-11.

(74) Goldenberg RL, Hoffman HJ, Cliver SP. Neurodevelopmental outcome of small-for-gestational-age infants. Eur J Clin Nutr 1998; 52:S54-S58.

(75) Yanney M, Marlow N. Paediatric consequences of fetal growth restriction. Semin Fetal Neonatal Med 2004; 9:411-418.

(76) Martin L, Ley D, Marsal K, Hellström A. Visual function in young adults following intrauterine growth retardation. J Pediatr Ophthalmol Strabismus 2004; 41:212-218.

(77) Hadders-Algra M, Touwen BC. Body measurements, neurological and behavioural development in six-year-old children born preterm and/or small-for-gestational-age. Early Hum Dev 1990; 22:1-13.

(78) Pryor J, Silva PA, Brooke M. Growth, development and behaviour in adolescents born small-for-gestational-age. J Paediatr Child Health 1995; 31:403-407.

(79) Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. JAMA 2000; 283:625-632.

(80) Westwood M, Kramer MS, Munz D, Lovett JM, Watters GV. Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: follow-up through adolescence. Pediatrics 1983; 71:376-382.

(81) Teberg AJ, Walther FJ, Pena IC. Mortality, morbidity, and outcome of the small-for-gestational age infant. Semin Perinatol 1988; 12:84-94.

(82) Lundgren EM, Cnattingius SHM, Jonsson GB, Tuvemo TH. Linear catch-up growth does not increase the risk of elevated blood pressure and reduces the risk of overweight in males. J Hypertens 2001; 19:1533-1538.

(83) Sommerfelt K, Andersson HW, Sonnander K, Ahlsten G, Ellertsen B, Markestad T et al. Cognitive development of term small for gestational age children at five years of age. Arch Dis Child 2000; 83:25-30.

(84) Hill RM, Verniaud WM, Deter RL, Tennyson LM, Rettig GM, Zion TE et al. The effect of intrauterine malnutrition on the term infant. A 14-year progressive study. Acta Paediatr Scand 1984; 73:482-487.

(85) Paz I, Gale R, Laor A, Danon YL, Stevenson DK, Seidman DS. The cognitive outcome of full-term small for gestational age infants at late adolescence. Obstet Gynecol 1995; 85:452-456.

(86) Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T. Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. Pediatr Res 2001; 50:91-96.

(87) Fitzhardinge PM, Steven EM. The small-for-date infant. II. Neurological and intellectual sequelae. Pediatrics 1972; 50:50-57.

(88) Fattal-Valevski A, Leitner Y, Kutai M, Tal-Posener E, Tomer A, Lieberman D et al. Neurodevelopmental outcome in children with intrauterine growth retardation: a 3-year follow-up. J Child Neurol 1999; 14:724-727.

(89) Hawdon JM, Hey E, Kolvin I, Fundudis T. Born too small - is outcome still affected? Dev Med Child Neurol 1990; 32:943-953.

(90) Low JA, Handley-Derry MH, Burke SO, Peters RD, Pater EA, Killen HL et al. Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years. Am J Obstet Gynecol 1992; 167:1499-1505.

(91) Hertzig ME. Neurological 'soft' signs in low-birthweight children. Dev Med Child Neurol 1981; 23:778-791.

(92) Rubin RA, Rosenblatt C, Balow B. Psychological and educational sequelae of prematurity. Pediatrics 1973; 52:352-363.

(93) O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics 2003; 112:301-307.

(94) Hollo O, Rautava P, Korhonen T, Helenius H, Kero P, Sillanpaa M. Academic achievement of small-for-gestational-age children at age 10 years. Arch Pediatr Adolesc Med 2002; 156:179-187.

(95) Larroque B, Bertrais S, Czernichow P, Leger J. School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. Pediatrics 2001; 108:111-115.

(96) Parkinson CE, Scrivener R, Graves L, Bunton J, Harvey D. Behavioural differences of school-age children who were small-for-dates babies. Dev Med Child Neurol 1986; 28:498-505.

(97) Paz I, Laor A, Gale R, Harlap S, Stevenson DK, Seidman DS. Term infants with fetal growth restriction are not at increased risk for low intelligence scores at age 17 years. J Pediatr 2001; 138:87-91.

(98) Magill RA. Motor learning. Concepts and applications. 6 ed. New York: McGraw-Hill Companies; 2001.

(99) Sigmundsson H, Haga M. Barn og motorisk kompetanse. Tidsskr Nor Laegeforen 2000; 120:3048-3050.

(100) Haywood K. Life span motor development. 3 ed. Campaign: Human Kinetics; 2001.

(101) Schmidt R. Motor learning principles for physical therapy. Contemporary management of motor problems. Proceedings of the II STEP conference 1990. USA: Foundation for Phys Ther; 1991. 49-63.

(102) Hadders-Algra M. The neuronal group selection theory: promising principles for understanding and treating developmental motor disorders. Dev Med Child Neurol 2000; 42:707-715.

(103) Campbell SK. The child's development of functional movement. In: Campbell SK, Vander Linden DW, Palisano RJ, editors. Physical therapy for children. 3 ed. St. Louis: Saunders Elsevier; 2006. 33-76.

(104) Thelen E. Motor development. A new synthesis. Am Psychol 1995; 50:79-95.

(105) Hadders-Algra M. Early brain damage and the development of motor behavior in children: clues for therapeutic intervention? Neural Plast 2001; 8:31-49.

(106) Sporns O, Edelman GM. Solving Bernstein's problem: a proposal for the development of coordinated movement by selection. Child Dev 1993; 64:960-981.

(107) Edelman GM. Bright air, brilliant fire. New York: Basic Books; 1992.

(108) Haga M, Pedersen AV, Sigmundsson H. Interrelationship among selected measures of motor skills. Child Care Health Dev 2008; 34:245-248.

(109) Hadders-Algra M. The neuronal group selection theory: a framework to explain variation in normal motor development. Dev Med Child Neurol 2000; 42:566-572.

(110) Touwen BC. How normal is variable, or how variable is normal? Early Hum Dev 1993; 34:1-12.

(111) Astill S. Can children with developmental coordination disorder adapt to task constraints when catching two-handed? Disabil Rehabil 2007; 29:57-67.

(112) Branta C, Haubenstricker J, Seefeldt V. Age changes in motor skills during childhood and adolescence. Exerc Sport Sci Rev 1984; 12:467-520.

(113) Henderson S, Sugden D. Movement Assessment Battery for Children. Manual. London: The Psychological Corporation; 1992.

(114) Shumway-Cook S, Woollacott MH. Motor control. Theory and practical applications. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

(115) Gentile A. Skill aquistion: Action, movement and neuromotor processes. In: Carr J, Shepherd R, editors. Movement science. Foundations for physical therapy in rehabilitation. 2 ed. Gaithersburg: Aspen Publisher; 2000. 111-187.

(116) Orton ST. Reading, writing and speech problems in children. New York: Norton; 1937.

(117) Wall AE, Reid G, Paton J. The syndrome of physical awkwardness. In: Reid G, editor. Problems in movement control. Amsterdam: North-Holland; 1990. 283-316.

(118) Sigmundsson H. Perceptual deficits in clumsy children: Inter- and intra-modal matching approach - A window into clumsy behavior. Neural Plas 2003; 10:27-38.

(119) Sigmundsson H, Pedersen AV, Whiting HTA, Ingvaldsen RP. We can cure your child's clumsiness! A review of intervention methods. Scand J Rehabil Med 1998; 30:101-106.

(120) Gubbay SS. Clumsy children in normal schools. Med J Aust 1975; 1:233-236.

(121) Annell AL. School problems in children of average or superior intelligence; a preliminary report. J Ment Sci 1949; 95:901-909.

(122) Denckla M. Developmental dyspraxia. In: Levine M, Satz P, editors. Middle childhood: Development and dysfunction. Boston: University Park Press; 1984.

(123) Laszlo JI, Sainsbury KM. Perceptual-motor development and prevention of clumsiness. Psychol Res 1993; 55:167-174.

(124) Ayres AJ. Characteristics of types of sensory integrative dysfunction. Am J Occup Ther 1971; 25:329-334.

(125) Hadders-Algra M. Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. Dev Med Child Neurol 2002; 44:561-571.

(126) Magalhaes LC, Missiuna C, Wong S. Terminology used in research reports of developmental coordination disorder. Dev Med Child Neurol 2006; 48:937-941.

(127) Dare MT, Gordon N. Clumsy children: a disorder of perception and motor organisation. Dev Med Child Neurol 1970; 12:178-185.

(128) Landgren M, Kjellman B, Gillberg C. Attention deficit disorder with developmental coordination disorders. Arch Dis Child 1998; 79:207-212.

(129) Gillberg C. Deficits in attention, motor control, and perception: a brief review. Arch Dis Child 2003; 88:904-910.

(130) American Psychiatric Association. Developmental coordination disorder. Diagnostic and statistical manual of mental disorders: DSM-IV. 4 ed. Washington DC: American Psychiatric Association; 1994. 53-55.

(131) Foulder-Hughes LA, Cooke RWI. Motor, cognitive, and behavioural disorders in children born very preterm. Dev Med Child Neurol 2003; 45:97-103.

(132) Majnemer A. Motor incoordination in children born preterm: coordinated efforts needed. Dev Med Child Neurol 2007; 49:324.

(133) Smits-Engelsman BCM, Fiers MJ, Henderson SE, Henderson L. Interrater reliability of the Movement Assessment Battery for Children. Phys Ther 2008; 88:286-294.

(134) Rosenbaum P. Screening tests and standardized assessments used to identify and characterize developmental delays. Semin Pediatr Neurol 1998; 5:27-32.

(135) Polit D, Hungler BP. Nursing research. Principles and methods. 6 ed. Philadelphia: Lippincott; 1999.

(136) Folio MR, Fewell RR. Peabody developmental motor scales and activity cards. Manual. Austin: DLM Teaching Resources; 1983.

(137) Wilson BN, Polatajko HJ, Kaplan BJ, Faris P. Use of the Bruininks-Oseretsky test of motor proficiency in occupational therapy. Am J Occup Ther 1995; 49:8-17.

(138) Kirshner B, Guyatt G. A methodological framework for assessing health indices. J Chronic Dis 1985; 38:27-36.

(139) Heinemann KR, Hadders-Algra M. Evaluation of neuromotor function in infancy - a systematic review of available methods. J Dev Behav Pediatr 2008; 29:315-323.

(140) Ketelaar M, Vermeer A, Helders PJ. Functional motor abilities of children with cerebral palsy: a systematic literature review of assessment measures. Clin Rehabil 1998; 12:369-380.

(141) Spittle AJ, Doyle LW, Boyd RN. A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life. Dev Med Child Neurol 2008; 50:254-266.

(142) Hennekens CH, Buring JE. Epidemiology in medicine. Philadelphia: Lippincott Williams & Wilkins; 1987.

(143) Crawford SG, Wilson BN, Dewey D. Identifying developmental coordination disorder: consistency between tests. Phys Occup Ther Pediatr 2001; 20:29-50.

(144) Geuze RH, Jongmans MJ, Schoemaker MM, Smits-Engelsman BCM. Clinical and research diagnostic criteria for developmental coordination disorder: a review and discussion. Hum Mov Sci 2001; 20:7-47.

(145) Dewey D, Wilson BN. Developmental coordination disorder: what is it? Phys Occup Ther Pediatr 2001; 20:5-27.

(146) Einspeiler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants. London: Mac Keith Press; 2004.

(147) Piper MC, Darrah J. Motor Assessment of the Developing Infant. Philadelphia: Saunders; 1994.

(148) Chandler LS, Andrews MS, Swanson MW. Movement Assessment of Infants (MAI). Rolling Bay: Infant Movement Research; 1980.

(149) Persson K, Strömberg B. A protocol for structured observation of motor performance in preterm and term infants. Ups J Med Sci 1993; 98:65-76.

(150) Touwen BCL. Neurological development in infancy. Philadelphia: Lippincott; 1976.

(151) Burns YR, O'Callaghan M, Tudehope DI. Early identification of cerebral palsy in high risk infants. Aust Paediatr J 1989; 25:215-219.

(152) Amiel-Tison C, Gosselin J. Neurological development from birth to six years. Guide for examination and evaluation. Baltimore and London: The Johns Hopkins University Press; 2000.

(153) Gorga D, Stern FM, Ross G. Trends in neuromotor behavior of preterm and fullterm infants in the first year of life: a preliminary report. Dev Med Child Neurol 1985; 27:756-766.

(154) Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999; 135:153-161.

(155) Bayley N. Manual for the Bayley scales of infant development. New York: The Psychological Corporation; 1969.

(156) Geuze RH. Static balance and developmental coordination disorder. Hum Mov Sci 2003; 22:527-548.

(157) Dubowitz L, Dubowitz V. The Neurological Assessment of the preterm and Full-Term Newborn Infant. London: William Heinemann Medical Books Ltd.; 1981.

(158) Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. J Pediatr 1998; 133:406-416.

(159) Gorga D, Stern FM, Ross G, Nagler W. The neuromotor behavior of preterm and full-term children by three years of age: quality of movement and variability. J Dev Behav Pediatr 1991; 12:102-107.

(160) de Groot L, Hopkins B, Touwen BC. A method to assess the development of muscle power in preterms after term age. Neuropediatrics 1992; 23:172-179.

(161) Ellison PH, Horn JL, Browning CA. Construction of an Infant Neurological International Battery (Infanib) for the assessment of neurological integrity in infancy. Phys Ther 1985; 65:1326-1331.

(162) Capute AJ, Palmer FB, Shapiro BK, Wachtel RC, Ross A, Accardo PJ. Primitive reflex profile: a quantitation of primitive reflexes in infancy. Dev Med Child Neurol 1984; 26:375-383.

(163) Campbell SK, Kolobe TH, Osten ET, Lenke M, Girolami GL. Construct validity of the Test of Infant Motor Performance. Phys Ther 1995; 75:585-596.

(164) Case-Smith J, Bigsby R, Clutter J. Perceptual-motor coupling in the development of grasp. Am J Occup Ther 1998; 52:102-110.

(165) Heineman KR, Bos AF, Hadders-Algra M. The Infant Motor Profile: a standardized and qualitative method to assess motor behaviour in infancy. Dev Med Child Neurol 2008; 50:275-282.

(166) Miller LJ, Roid GH. The TIME Toddler and Infant Motor Evaluation, a Standardized Assessment. San Antonio: Therapy Skill Builders; 1994.

(167) Frankenburg WK, Dodds JB. The Denver developmental screening test. J Pediatr 1967; 71:181-191.

(168) Ulrich D. Test of gross motor development. 2 ed. Austin: Pro-Ed; 2000.

(169) McCarron LT. MAND McCarron Assessment of Neuromuscular Development: Fine and gross motor abilities. Dallas: Common Market Press; 1982.

(170) Bruininks RH. Manual of the Bruininks-Oseretsky test of motor proficiency. Circle Pines: American Guidance Service; 1978.

(171) Harris SR, Daniels LE. Content validity of the Harris Infant Neuromotor Test. Phys Ther 1996; 76:727-737.

(172) Westcott MS, Bowman A, Smith-Blockley J, Sanders K, Megens AM, Harris SR. Harris Infant Neuromotor Test: comparison of US and Canadian normative data and examination of concurrent validity with the Ages and Stages Questionnaire. Phys Ther 2009; 89:173-180.

(173) Smyth TR. Impaired motor skill (clumsiness) in otherwise normal children: a review. Child Care Health Dev 1992; 18:283-300.

(174) Søvik N, Mæland A. Children with motor problems (clumsy children). Scand J Ed Res 1986; 30:53.

(175) Mæland A. Identification of children with motor coordination problems. Adapt Phys Activ Q 1992; 9:330-342.

(176) Largo RH, Fischer JE, Rousson V. Neuromotor development from kindergarten age to adolescence: developmental course and variability. Swiss Med Wkly 2003; 133:193-199.

(177) Gillberg CI, Gillberg C, Groth J. Children with preschool minor neurodevelopmental disorders. V: Neurodevelopmental profiles at age 13. Dev Med Child Neurol 1989; 31:14-24.

(178) Soorani-Lunsing RJ, Hadders-Algra M, Huisjes HJ, Touwen BC. Minor neurological dysfunction after the onset of puberty: association with perinatal events. Early Hum Dev 1993; 33:71-80.

(179) Campbell SK, Vander Linden DW, Palisano RJ. Developmental coordination disorder. In: Campbell SK, Vander Linden DW, Palisano RJ, editors. Physical therapy for children. 3 ed. St. Louis: Saunders Elsevier; 2006. 559-589.

(180) Zubrick SR, Macartney H, Stanley FJ. Hidden handicap in school-age children who received neonatal intensive care. Dev Med Child Neurol 1988; 30:145-152.

(181) Ivry RB. Cerebellar involvement in clumsiness and other developmental disorders. Neural Plas 2003; 10:141-153.

(182) Hall DM. Clumsy children. Br Med J (Clin Res Ed) 1988; 296:375-376.

(183) Wrotniak BH, Epstein LH, Dorn JM, Jones KE, Kondilis VA. The relationship between motor proficiency and physical activity in children. Pediatrics 2006; 118:e1758-e1765.

(184) Hulme C, Biggerstaff A, Moran G, McKinlay I. Visual, kinaesthetic and cross-modal judgements of length by normal and clumsy children. Dev Med Child Neurol 1982; 24:461-471.

(185) Ayres AJ. Types of sensory integrative dysfunction among disabled learners. Am J Occup Ther 1972; 26:13-18.

(186) Lord R, Hulme C. Perceptual judgments of normal and clumsy children. Dev Med Child Neurol 1987; 29:250-257.

(187) Parush S, Yochman A, Cohen D, Gershon E. Relation of visual perception and visual-motor integration for clumsy children. Percept Mot Skills 1998; 86:291-295.

(188) Wilson PH, McKenzie BE. Information processing deficits associated with developmental coordination disorder: A meta-analysis of research findings. J Child Psychol Psychiatry 1998; 39:829-840.

(189) Laszlo JI, Bairstow PJ. Perceptual motor behaviour: Developmental assessment and therapy. London: Holt, Rinehart and Winston; 1985.

(190) Piek JP, Coleman-Carman R. Kinaesthetic sensitivity and motor performance of children with developmental co-ordination disorder. Dev Med Child Neurol 1995; 37:976-984.

(191) von Hofsten C, Rösblad B. The integration of sensory information in the development of precise manual pointing. Neuropsychologia 1988; 26:805-821.

(192) Bradley NS. Motor control: Developmental aspects of motor control in skill acquisition. In: Campbell SK, Vander Linden DW, Palisano RJ, editors. Physical therapy for children. 2 ed. Philadelphia: W.B. Saunders Company; 2000. 45-87.

(193) Sage GH. Visual perception and motor behaviour. In: Sage GH, editor. Motor learning and control. A neuropsychological approach. Dubuque: Brown; 1984. 129-153.

(194) Wurtz RH, Kandel ER. Central visual pathways. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of Neural Science. 4 ed. New York: McGraw-Hill; 2000. 523-547.

(195) Dutton G, Saaed A, Fahad B, Fraser R, McDaid G, McDade J et al. Association of binocular lower visual field impairment, impaired simultaneous perception, disordered visually guided motion and inaccurate saccades in children with cerebral visual dysfunction-a retrospective observational study. Eye 2004; 18:27-34.

(196) Prechtl HFR, Cioni G, Einspieler C, Bos AF, Ferrari F. Role of vision on early motor development: lessons from the blind. Dev Med Child Neurol 2001; 43:198-201.

(197) Tröster H, Hecker W, Brambring M. Longitudinal study of gross-motor development in blind infants and preschoolers. Early Child Dev Care 1994; 104:61-78.

(198) Mon-Williams MA, Pascal E, Wann JP. Ophthalmic factors in developmental coordination disorder. Adapt Phys Activ Q 1994; 11:170-178.

(199) Sigmundsson H, Ingvaldsen RP, Whiting HTA. Inter- and intra-sensory modality matching in children with hand-eye co-ordination problems. Exp Brain Res 1997; 114:492-499.

(200) Gardner EP, Martin JH, Jessell TM. The bodily senses. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4 ed. New York: McGraw-Hill; 2000. 430-450.

(201) Brodal P. Det somatosensoriske system. In: Brodal P, editor. Sentralnervesystemet. Bygning og funksjon. 2 ed. Oslo: Tano; 1995. 197-253.

(202) Sacks O. The man who mistook his wife for a hat. Picador; 2007.

(203) Mon-Williams MA, Wann JP, Pascal E. Visual-proprioceptive mapping in children with developmental coordination disorder. Dev Med Child Neurol 1999; 41:247-254.

(204) Wann JP. The integrity of visual-proprioceptive mapping in cerebral palsy. Neuropsychologia 1991; 29:1095-1106.

(205) Lee DN, Daniel BM, Turnbull J, Cook ML. Basic perceptuo-motor dysfunctions in cerebral palsy. In: Jeannerod M, editor. Attention and performance XIII: Motor representation and control. Hillsdale: Erlbaum; 1990. 593-603.

(206) Sigmundsson H. Inter- and intra-sensory modality matching in motor-impaired children. Trondheim: Norwegian University of Science and Technology; 1998.

(207) Sigmundsson H, Ingvaldsen RP, Whiting HTA. Inter- and intrasensory modality matching in children with hand-eye coordination problems: exploring the developmental lag hypothesis. Dev Med Child Neurol 1997; 39:790-796.

(208) Sigmundsson H, Whiting HTA. Hand preference in children with developmental coordination disorders: Cause and effect? Brain Cogn 2002; 49:45-53.

(209) Sigmundsson H. Inter-modal matching and bimanual co-ordination in children with hand-eye co-ordination problems. Nord Fysioter 1999; 3:55-64.

(210) Smyth MM, Mason UC. Planning and execution of action in children with and without developmental coordination disorder. J Child Psychol Psychiatry 1997; 38:1023-1037.

(211) Rösblad B, von Hofsten C. Perceptual control of manual pointing in children with motor impairments. Physiother Theory and Pract 1992; 8:223-333.

(212) Schoemaker MM, van der Wees M, Flapper B, Verheij-Jansen N, Scholten-Jaegers S., Geuze RH. Perceptual skills of children with developmental coordination disorder. Hum Mov Sci 2001; 20:111-133.

(213) Vohr BR, Msall ME, Wilson D, Wright LL, McDonald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. Pediatrics 2005; 116:123-129.

(214) van Haastert IC, de Vries LS, Helders PJ, Jongmans MJ. Early gross motor development of preterm infants according to the Alberta Infant Motor Scale. J Pediatr 2006; 149:617-622.

(215) Wolf M-J, Koldewijn K, Beelen A, Smit B, Hedlund R, de Groot IJM. Neurobehavioral and developmental profile of very low birthweight preterm infants in early infancy. Acta Paediatr 2002; 91:930-938.

(216) Boo NY, Ong LC, Lye MS, Chandran V, Teoh SL, Zamratol S et al. Comparison of morbidities in very low birthweight and normal birthweight infants during the first year of life in a developing country. J Paediatr Child Health 1996; 32:439-444.

(217) Sun J, Mohay H, O'Callaghan M. A comparison of executive function in very preterm and term infants at 8 months corrected age. Early Hum Dev 2009; 85:225-30.

(218) Ross G, Lipper EG, Auld PA. Consistency and change in the development of premature infants weighing less than 1,501 grams at birth. Pediatrics 1985; 76:885-891.

(219) Pin TW, Darrer T, Eldridge B, Galea MP. Motor development from 4 to 8 months corrected age in infants born at or less than 29 weeks' gestation. Dev Med Child Neurol 2009; 51:739-745.

(220) Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD, The National Institute of Child Health and Human Development Neonatal Research Network. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993-1999. Pediatrics 2005; 115:1645-1651.

(221) Goyen T-A, Lui K. Longitudinal motor development of "apparently normal" high-risk infants at 18 months, 3 and 5 years. Early Hum Dev 2002; 70:103-115.

(222) Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992-1995. Arch Pediatr Adolesc Med 2000; 154:725-731.

(223) Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. Pediatrics 2007; 119:37-45.

(224) O'Callaghan MJ, Burns Y, Gray P, Harvey JM, Mohay HI, Rogers Y et al. Extremely low birth weight and control infants at 2 years corrected age: a comparison of intellectual abilities, motor performance, growth and health. Early Hum Dev 1995; 40:115-125.

(225) Ong LC, Boo NY, Chandran V. Predictors of neurodevelopmental outcome of Malaysian very low birthweight children at 4 years of age. J Paediatr Child Health 2001; 37:363-368.

(226) Stoelhorst GMSJ, Rijken M, Martens SE, van Zwieten PHT, Feenstra J, Zwinderman AH et al. Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997. Early Hum Dev 2003; 72:83-95.

(227) Janssen AJWM, Nijhuis-van der Sanden MWG, Akkermans RP, Oostendorp RAB, Kollée LAA. Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. Dev Med Child Neurol 2008; 50:926-931.

(228) Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr 2003; 143:163-170.

(229) Agustines LA, Lin YG, Rumney PJ, Lu MC, Bonebrake R, Asrat T et al. Outcomes of extremely low-birth-weight infants between 500 and 750 g. Am J Obstet Gynecol 2000; 182:1113-1116.

(230) Vohr BR, Wright LL, Poole WK, McDonald SA, The NICHD Neonatal Research Network Follow-up Study. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics 2005; 116:635-643.

(231) Goyen TA, Lui K, Woods R. Visual-motor, visual-perceptual, and fine motor outcomes in very-low-birthweight children at 5 years. Dev Med Child Neurol 1998; 40:76-81.

(232) Johnson S, Ring W, Anderson P, Marlow N. Randomised trial of parental support for families with very preterm children: outcome at 5 years. Arch Dis Child 2005; 90:909-915.

(233) Hoff Esbjørn B, Hansen BM, Greisen G, Mortensen EL. Intellectual development in a Danish cohort of prematurely born preschool children: specific or general difficulties? J Dev Behav Pediatr 2006; 27:477-484.

(234) de Kleine MJK, Nijhuis-van der Sanden MWG, den Ouden AL. Is paediatric assessment of motor development of very preterm and low-birthweight children appropriate? Acta Paediatr 2006; 95:1202-1208.

(235) Torrioli MG, Frisone MF, Bonvini L, Luciano R, Pasca MG, Lepori R et al. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. Brain Dev 2000; 22:163-168.

(236) Levene M, Dowling S, Graham M, Fogelman K, Galton M, Phillips M. Impaired motor function (clumsiness) in 5 year old children: correlation with neonatal ultrasound scans. Arch Dis Child 1992; 67:687-690.

(237) Erikson C, Allert C, Carlberg EB, Katz-Salamon M. Stability of longitudinal motor development in very low birthweight infants from 5 months to 5.5 years. Acta Paediatr 2003; 92:197-203.

(238) Jakobson LS, Frisk V, Downie ALS. Motion-defined form processing in extremely premature children. Neuropsychologia 2006; 44:1777-1786.

(239) Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics 2007; 120:793-804.

(240) Marlow N, Roberts BL, Cooke RWI. Motor skills in extremely low birthweight children at the age of 6 years. Arch Dis Child 1989; 64:839-847.

(241) Goyen T-A, Lui K. Developmental coordination disorder in 'apparently normal' school children born extremely preterm. Arch Dis Child 2009; 94:298-302.

(242) Hall A, McLeod A, Counsell C, Thomson L, Mutch L. School attainment, cognitive ability and motor function in a total Scottish very-low-birthweight population at eight years: a controlled study. Dev Med Child Neurol 1995; 37:1037-1050.

(243) Marlow N, Roberts L, Cooke R. Outcome at 8 years for children with birth weights of 1250 g or less. Arch Dis Child 1993; 68:286-290.

(244) Davis NM, Ford GW, Anderson PJ, Doyle LW. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. Dev Med Child Neurol 2007; 49:325-330.

(245) Michelsson K, Lindahl E, Parre M, Helenius M. Nine-year follow-up of infants weighing 1 500 g or less at birth. Acta Paediatr Scand 1984; 73:835-841.

(246) Feder KP, Majnemer A, Bourbonnais D, Platt R, Blayney M, Synnes A. Handwriting performance in preterm children compared with term peers at age 6 to 7 years. Dev Med Child Neurol 2005; 47:163-170.

(247) Dewey D, Crawford SG, Creighton DE, Sauve RS. Long-term neuropsychological outcomes in very low birth weight children free of sensorineural impairments. J Clin Exp Neuropsychol 1999; 21:851-865.

(248) Whitfield MF, Grunau RVE, Holsti L. Extremely premature (< or = 800 g) school-children: multiple areas of hidden disability. Arch Dis Child Fetal Neonatal Ed 1997; 77:F85-F90.

(249) Holsti L, Grunau RVE, Whitfield MF. Developmental coordination disorder in extremely low birth weight children at nine years. J Dev Behav Pediatr 2002; 23:9-15.

(250) Wocadlo C, Rieger I. Motor impairment and low achievement in very preterm children at eight years of age. Early Hum Dev 2008; 84:769-776.

(251) de Kieviet JF, Piek JP, arnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. JAMA 2009; 302:2235-2242.

(252) Powls A, Botting N, Cooke RW, Marlow N. Motor impairment in children 12 to 13 years old with a birthweight of less than 1250 g. Arch Dis Child Fetal Neonatal Ed 1995; 73:F62-F66.

(253) Taylor GH, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: neuropsychological findings. J Int Neuropsychol Soc 2004; 10:149-163.

(254) Gäddlin P-O, 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.

(255) Crowe TK, Deitz JC, Bennett FC, TeKolste K. Preschool motor skills of children born prematurely and not diagnosed as having cerebral palsy. J Dev Behav Pediatr 1988; 9:189-193.

(256) Mutch L, Leyland A, McGee A. Patterns of neuropsychological function in a low-birthweight population. Dev Med Child Neurol 1993; 35:943-956.

(257) The Scottish Low Birthweight Study Group. The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment. Arch Dis Child 1992; 67:675-681.

(258) Elliman AM, Bryan EM, Elliman AD, Walker J, Harvey DR. Coordination of low birthweight seven-year-olds. Acta Paediatr Scand 1991; 80:316-322.

(259) Chaudhari S, Otiv M, Chitale A, Pandit A, Hoge M. Pune low birth weight study - cognitive abilities and educational performance at twelve years. Indian Pediatr 2004; 41:121-128.

(260) Jongmans M, Mercuri E, Henderson S, de Vries L, Sonksen P, Dubowitz L. Visual function of prematurely born children with and without perceptual-motor difficulties. Early Hum Dev 1996; 45:73-82.

(261) Cooke RWI, Foulder-Hughes L, Newsham D, Clarke D. Ophthalmic impairment at 7 years of age in children born very preterm. Arch Dis Child Fetal Neonatal Ed 2004; 89:F249-F253.

(262) DeMaio-Feldman D. Somatosensory processing abilities of very low-birth weight infants at school age. Am J Occup Ther 1994; 48:639-645.

(263) Leijon I, Billström G, Lind I. An 18-month follow-up study of growth-retarded neonates. Relation to biochemical tests of placental function in late pregnancy and neurobehavioural condition in the newborn period. Early Hum Dev 1980; 4:271-285.

(264) Low JA, Galbraith RS, Muir D, Killen H, Karchmar J, Campbell D. Intrauterine growth retardation: a preliminary report of long-term morbidity. Am J Obstet Gynecol 1978; 130:534-545.

(265) Als H, Tronick E, Adamson L, Brazelton TB. The behavior of the full-term but underweight newborn infant. Dev Med Child Neurol 1976; 18:590-602.

(266) Grantham-McGregor SM, Lira PIC, Ashworth A, Morris SS, Assuncao AMS. The development of low birth weight term infants and the effects of the environment in northeast Brazil. J Pediatr 1998; 132:661-666.

(267) Campos D, Santos DCC, Goncalves VMG, Goto MMF, Campos-Zanelli TM. Motor performance of infants born small or appropriate for gestational age: a comparative study. Pediatr Phys Ther 2008; 20:340-346.

(268) Tenovuo A, Kero P, Korvenranta H. Developmental outcome of 519 small-for-gestational age children at the age of two years. Neuropediatrics 1988; 19:41-45.

(269) Michaelis R, Schulte FJ, Nolte R. Motor behavior of small for gestational age newborn infants. J Pediatr 1970; 76:208-213.

(270) Juneja M, Shankar A, Ramji S. Neurodevelopmental, functional and growth status of term low birth weight infants at eighteen months. Indian Pediatr 2005; 42:1134-1140.

(271) Gagliardo HG, Goncalves VM, Lima MC, Francozo Mde F, Aranha Netto A. Visual function and fine-motor control in small-for-gestational age infants. Arq Neuropsiquiatr 2004; 62:955-962.

(272) Leijon I, Finnström O, Nilsson B, Ryden G. Neurology and behaviour of growth-retarded neonates. Relation to biochemical placental function tests in late pregnancy. Early Hum Dev 1980; 4:257-270.

(273) Walther FJ, Ramaekers LH. Developmental aspects of subacute fetal distress: behaviour problems and neurological dysfunction. Early Hum Dev 1982; 6:1-10.

(274) Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J. Intrauterine growth retardation: a study of long-term morbidity. Am J Obstet Gynecol 1982; 142:670-677.

(275) Markestad T, Vik T, Ahlsten G, Gebre-Medhin M, Skjaerven R, Jacobsen G et al. Small-for-gestational-age (SGA) infants born at term: growth and development during the first year of life. Acta Obstet Gynecol Scand Suppl 1997; 165:93-101.

(276) Sommerfelt K, Sonnander K, Skranes J, Andersson HW, Ahlsten G, Ellertsen B et al. Neuropsychologic and motor function in small-for-gestation preschoolers. Pediatr Neurol 2002; 26:186-191.

(277) Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational-age babies. Pediatrics 1982; 69:296-300.

(278) Fancourt R, Campbell S, Harvey D, Norman AP. Follow-up study of small-for-dates babies. Br Med J 1976; 6023:1435-1437.

(279) Hadders-Algra M, Huisjes HJ, Touwen BC. Preterm or small-for-gestational-age infants. Neurological and behavioural development at the age of 6 years. Eur J Pediatr 1988; 147:460-467.

(280) Viggedal G, Lundalv E, Carlsson G, Kjellmer I. Neuropsychological follow-up into young adulthood of term infants born small for gestational age. Med Sci Monit 2004; 10:CR8-16.

(281) Brodal P. Nervesystemets utvikling, aldring og plastisitet. In: Brodal P, editor. Sentralnervesystemet. Bygning og funksjon. 2 ed. Oslo: Tano; 1995. 131-172.

(282) Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009; 8:110-124.

(283) Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol 2009; 24:1085-1104.

(284) Dobbing J. The later growth of the brain and its vulnerability. Pediatrics 1974; 53:2-6.

(285) Mercuri E, Jongmans M, Henderson S, Pennock J, Chung YL, de Vries L et al. Evaluation of the corpus callosum in clumsy children born prematurely: A functional and morphological study. Neuropediatrics 1996; 27:317-322.

(286) Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999; 353:1653-1657.

(287) Skranes JS, Nilsen G, Smevik O, Vik T, Brubakk AM. Cerebral MRI of very low birth weight children at 6 years of age compared with the findings at 1 year. Pediatr Radiol 1998; 28:471-475.

(288) Skranes JS, Martinussen M, Smevik O, Myhr G, Indredavik M, Vik T et al. Cerebral MRI findings in very-low-birth-weight and small-for-gestational-age children at 15 years of age. Pediatr Radiol 2005; 35:758-765.

(289) Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MHS, Stewart AL et al. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 2001; 124:60-66.

(290) Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA 2000; 284:1939-1947.

(291) Bracewell M, Marlow N. Patterns of motor disability in very preterm children. Ment Retard Dev Disabil Res Rev 2002; 8:241-248.

(292) Martinussen M, Fischl B, Larsson HB, Skranes J, Kulseng S, Vangberg TR et al. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. Brain 2005; 128:2588-2596.

(293) Martinussen M, Flanders DW, Fischl B, Busa E, Løhaugen GC, Skranes J et al. Segmental brain volumes and cognitive and perceptual correlates in 15-year-old adolescents with low birth weight. J Pediatr 2009; 155:848-53.

(294) Counsell SJ, Shen Y, Boardman JP, Larkman DJ, Kapellou O, Ward P et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. Pediatrics 2006; 117:376-386.

(295) Eyre JA. Corticospinal tract development and its plasticity after perinatal injury. Neurosci Biobehav Rev 2007; 31:1136-1149.

(296) Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. Child Dev 2000; 71:44-56.

(297) Rushe TM, Rifkin L, Stewart AL, Townsend JP, Roth S.C., Wyatt JS et al. Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. Dev Med Child Neurol 2001; 43:226-233.

(298) Msall ME. Optimizing neuromotor outcomes among very preterm, very low-birth-weight infants. JAMA 2009; 302:2257-2258.

(299) Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E et al. Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 2003; 111:939-948.

(300) Olsén P, Pääkkö E, Vainionpää L, Pyhtinen J, Järvelin M-R. Magnetic resonance imaging of periventricular leukomalacia and its clinical correlation in children. Ann Neurol 1997; 41:754-761.

(301) Rademaker KJ, Uiterwaal CSPM, Beek FJA, van Haastert IC, Lieftink AF, Groenendaal F et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arch Dis Child Fetal Neonatal Ed 2005; 90:F489-F493.

(302) Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KAI, Martinussen M et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007; 130:654-666.

(303) Dutton GN, Jacobson LK. Cerebral visual impairment in children. Semin Neonatol 2001; 6:477-485.

(304) Santos A, Duret M, Mancini J, Gire C, Deruelle C. Preterm birth affects dorsal-stream functioning even after age 6. Brain Cogn 2009; 69:490-494.

(305) Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 2005; 115:688-695.

(306) Chez C, Thack TW. The cerebellum. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4 ed. New York: McGrawHill; 2000. 832-852.

(307) Newell KM. Contraints on the development of coordination. In: Wade MG, Whiting HTA, editors. Motor development in children: Aspects of coordination and control. Boston: Martinus Nijhoff; 1986. 341-360.

(308) Deitz JC, Crowe TK, Harris SR. Relationship between infant neuromotor assessment and preschool motor measures. Phys Ther 1987; 67:14-17.

(309) Palisano RJ. Concurrent and predictive validities of the Bayley Motor Scale and the Peabody Developmental Motor Scales. Phys Ther 1986; 66:1714-1719.

(310) Coryell J, Provost B, Wilhelm IJ, Campbell SK. Stability of Bayley Motor Scale scores in the first year of life. Phys Ther 1989; 69:834-841.

(311) Darrah J, Hodge M, Magill-Evans J, Kembhavi G. Stability of serial assessments of motor and communication abilities in typically developing infants - implications for screening. Early Hum Dev 2003; 72:97-110.

(312) Darrah J, Magill-Evans J, Volden J, Hodge M, Kembhavi G. Scores of typically developing children on the Peabody Developmental Motor Scales - Infancy to preschool. Phys Occup Ther Pediatr 2007; 27:5-19.

(313) Salt A, Redshaw M. Neurodevelopmental follow-up after preterm birth: follow up after two years. Early Hum Dev 2006; 82:185-197.

(314) Johnson S, Marlow N. Developmental screen or developmental testing? Early Hum Dev 2006; 82:173-183.

(315) Johnson S, Fawke J, Hennessy E, Rowell V, Thomas S, Wolke D et al. Neurodevelopmental disability through 11 years of age in children born before 26 weeks of gestation. Pediatrics 2009; 124:e249-e257.

(316) Peralta-Carcelen M, Moses M, Adams-Chapman I, Gantz M, Vohr BR. Stability of neuromotor outcomes at 18 and 30 months of age after extremely low birth weight status. Pediatrics 2009; 123:e887-e895.

(317) Vohr BR, Garcia Coll CT. Neurodevelopmental and school performance of very low-birth-weight infants: a seven-year longitudinal study. Pediatrics 1985; 76:345-350.

(318) de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: What is happening when? Early Hum Dev 2006; 82:257-266.

(319) Skranes JS, Vik T, Nilsen G, Smevik O, Andersson HW, Rinck P et al. Cerebral magnetic resonance imaging (MRI) and mental and motor function of very low birth weight infants at one year of corrected age. Neuropediatrics 1993; 24:256-262.

(320) Skranes JS, Vik T, Nilsen G, Smevik O, Andersson HW, Brubakk AM. Cerebral magnetic resonance imaging and mental and motor function of very low birth weight children at six years of age. Neuropediatrics 1997; 28:149-154.

(321) Bakketeig LS, Jacobsen G, Hoffman HJ, Lindmark G, Bergsjø P, Molne K et al. Pre-pregnancy risk factors of small-for-gestational age births among parous women in Scandinavia. Acta Obstet Gynecol Scand 1993; 72:273-279.

(322) Beery KE. Administration, scoring, and teaching manual for the Beery-Buktenica Developmental Test of Visual-Motor Integration with supplemental tests of visual perception and motor coordination. New Jersey: Modern Curriculum Press; 1997.

(323) Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000; 80:974-985.

(324) Wechsler D. Wechsler Intelligence Scale for Children, Manual. 3 ed. Stockholm: Psykologiförlaget AB; 1999.

(325) Hollingshead AS. Two factor index of social status. New Haven: Yale University; 1958.

(326) Altman DG. Diagnostic tests. In: Altman DG, Machin D, Bryant TN, Gardner MJ, editors. Statistics with confidence. 2 ed. London: BMJ Books; 2000. 105-119.

(327) Evensen KAI, Vik T, Helbostad JL, Indredavik MS, Kulseng S, Brubakk AM. Motor skills in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004; 89:F451-F455.

(328) Evensen KAI, Lindqvist S, Indredavik MS, Skranes J, Brubakk AM, Vik T. Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents? Eur J Paediatr Neurol 2009; 13:47-56.

(329) Chen PS, Jeng SF, Tsou KI. Developmental function of very-low-birth-weight infants and full-term infants in early childhood. J Formos Med Assoc 2004; 103:23-31.

(330) Jeng SF, Yau KI, Liao HF, Chen LC, Chen PS. Prognostic factors for walking attainment in very low-birthweight preterm infants. Early Hum Dev 2000; 59:159-173.

(331) Ross G, Lipper E, Auld PA. Early predictors of neurodevelopmental outcome of very low-birthweight infants at three years. Dev Med Child Neurol 1986; 28:171-179.

(332) Rademaker KJ, Lam JNGP, van Haastert I, Uiterwaal CSPM, Lieftink AF, Groenendaal F et al. Larger corpus callosum size with better motor performance in prematurely born children. Semin Perinatol 2004; 28:279-287.

(333) Smyth MM, Mason UC. Use of proprioception in normal and clumsy children. Dev Med Child Neurol 1998; 40:672-681.

(334) Henderson SE, Sugden DA, Barnett AL. Movement Assessment Battery for Children-2. Examiner's manual. 2 ed. London: Pearson Assessment; 2007.

(335) Harris SR, Thompson M, McGrew L. Motor assessment tools: their concurrent validity in evaluating children with multiple handicaps. Arch Phys Med Rehabil 1983; 64:468-470.

(336) Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008; 93:458-461.

(337) 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.

(338) Pennefather PM, Tin W, Clarke MP, Dutton J, Fritz S, Hey EN. Bias due to incomplete follow up in a cohort study. Br J Ophthalmol 1999; 83:643-645.

(339) Escalona SK. Babies at double hazard: early development of infants at biologic and social risk. Pediatrics 1982; 70:670-676.

(340) Sommerfelt K. Long-term outcome for non-handicapped low birth weight infants - is the fog clearing? Eur J Pediatr 1998; 157:1-3.

(341) Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007; 196:147-148.

(342) Hadders-Algra M. Developmental coordination disorder: is clumsy motor behavior caused by a lesion of the brain at early age? Neural Plas 2003; 10:39-50.

(343) Skranes J, Evensen KI, Løhaugen GC, Martinussen M, Kulseng S, Myhr G et al. Abnormal cerebral MRI findings and neuroimpairments in very low birth weight (VLBW) adolescents. Eur J Paediatr Neurol 2008; 12:273-283.

(344) Roth S, Chang TC, Robson S, Spencer JAD, Wyatt JS, Stewart AL. The neurodevelopmental outcome of term infants with different intrauterine growth characteristics. Early Hum Dev 1999; 55:39-50.

(345) Hadders-Algra M, Brogren E, Katz-Salamon M, Forssberg H. Periventricular leucomalacia and preterm birth have different detrimental effects on postural adjustments. Brain 1999; 122:727-740.

(346) Volpe JJ. Neurology of the newborn. 4 ed. Philadelphia: WB Saunders Company; 2001.

(347) Goodman R. Developmental disorders and structural brain development. In: Rutter M, Casear P, editors. Biological risk factors for psychosocial disorders. New York: Cambridge University Press; 1991. 20-49.

(348) Singer JE, Westphal M, Niswander KR. Sex differences in the incidence of neonatal abnormalities and abnormal performance in early childhood. Child Dev 1968; 39:103-112.

(349) Morales-Rosello J, Martinez-Gonzalez L, Santonja-Lucas JJ. Predicted and actual fetal weight throughout the last trimester. J Ultrasound Med 1997; 16:711-717.

(350) Spinillo A, Capuzzo E, Nicola S, Colonna L, Iasci A, Zara C. Interaction between fetal gender and risk factors for fetal growth retardation. Am J Obstet Gynecol 1994; 171:1273-1277.

(351) Thomas P, Peabody J, Turnier V, Clark RH. A new look at intrauterine growth and the impact of race, altitude, and gender. Pediatrics 2000; 106:E21.

(352) Zaren B, Lindmark G, Bakketeig L. Maternal smoking affects fetal growth more in the male fetus. Paediatr Perinat Epidemiol 2000; 14:118-126.

(353) Sommerfelt K, Ellertsen B, Markestad T. Low birthweight and neuromotor development: a population based, controlled study. Acta Paediatr 1996; 85:604-610.

(354) Berk RA. The discriminative efficiency of the Bayley Scales of Infant Development. J Abnorm Child Psychol 1979; 7:113-119.

(355) MacCobb S, Greene S, Nugent JK, O'Mahony P. Measurement and prediction of motor proficiency in children using Bayley infant scales and the Bruininks-Oseretsky test. Phys Occup Ther Pediatr 2005; 25:59-79.

(356) Taylor GH, Klein N, Hack M. School-age consequences of birth weight less than 750 g: a review and update. Dev Neuropsychol 2000; 17:289-321.

(357) Sigmundsson H. Disorders of motor development (clumsy child syndrome). J Neural Transm Suppl 2005;51-68.

(358) Krombholz H. Physical performance in relation to age, sex, birth order, social class, and sports activities of preschool children. Percept Mot Skills 2006; 102:477-484.

(359) Yoon DY, Scott K, Hill MN, Levitt NS, Lambert EV. Review of three tests of motor proficiency in children. Percept Mot Skills 2006; 102:543-551.

(360) Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005; 116:333-341.

(361) Skranes J, Løhaugen GC, Martinussen M, Indredavik MS, Dale AM, Haraldseth O et al. White matter abnormalities and executive function in children with very low birth weight. Neuroreport 2009; 20:263-266.

(362) Evensen KAI, Brubakk AM, Håberg A, Martinussen M, Eidheim OC, Vik T et al. Cortical thinning is related to left-handedness and reduced fine motor function in very low birth weight adolescents. Pediatric Academic Societies Annual Meeting 2009; May 2-5, Baltimore, USA.

Appendix A. Studies of motor outcome in VLBW subjects from infancy through adolescence.

Study	n	Included	Handi-caps	Country	Born	Age	Test	Results
MOTOR STUDIES IN INFANCY								
van Haastert et al.[214]	n=800	≤32 wk	+	Netherlands	1993-2005	1-18 mo	AIMS	Very preterm < normative test sample for all time points (0.025 > p > 0.0001)
Wolf et al.[215]	n=20	<1500 g, <32 wk	- severe IVH	Netherlands	1999	3-6 mo	BSID-II	**20%** <2SD / **60%** <1SD at 6 mo; VLBW < controls in mean PDI at 3 mo (p<0.0001) and 6 mo (p=0.004)
Pin et al.[219]	n=58	<29 wk	+	Australia	2006-07	4-8 mo	AIMS	Preterm < controls in total score (p<0.001) and all subscores at 4 mo; in total score (p<0.001) and two of four subscores at 8 mo
Jeng et al.[330]	n=92	≤1500 g	+	Taiwan	1995-97	6-12 mo	AIMS	VLBW < controls in mean scores at 6, 9 and 12 mo (p<0.001)
Sun et al.[217]	n=37	<1250 g, ≤32 wk	-	Australia	1998-99	8 mo	BSID-II	VLBW < controls in mean PDI (p<0.001)
Boo et al.[216]	n=127	<1500 g	+	Malaysia	1989-92	12 mo	BSID	VLBW < controls in mean PDI (95% CI for difference in mean; -17.6 to -6.0)
Ross et al.[218]	n=94	≤1500 g	+	USA	1978-79	12 mo-3 yr	BSID + neurological examination	**13%** <2SD / **36%** <1SD on PDI; consistency in neurological classification over time (p<0.001) (no control group)
MOTOR STUDIES IN PRESCHOOL AGE								
Vohr et al. [230]	n=3785	<32 wk, <1000 g	+	USA	1993-98	18 mo	BSID-II	**21.5%** <2SD on PDI for ELBW born in 1997-98 (improved over time, p=0.04); increasing with decreasing ga (p<0.0001) (no control group)
Hintz et al.[220]	n=763	<1000 g, < 25 wk	+	USA	1993-99	18-22 mo	BSID-II	**31%** <2SD / **57%** <1SD on PDI for those born in 1996-99 (unchanged between epochs) (no control group)
Stoelhorst et al.[226]	n=163 / 144	<32 wk	+	Netherlands	1996-97	18 and 24 mo	BSID	**8%** <2SD / **30%** <1SD; Very preterm < controls in mean PDI at 18 mo (p=0.03) and 24 mo (p=0.02)

Goyen & Lui[221]	n=58	<1000 g / <29 wk	-	Australia	1992-93	18 mo, 3-5 yr	PDMS	**40%** <2SD / **81%** <1SD gross motor; **24%** <2SD / **64%** <1SD fine motor; consistency over time; boys = girls (no control group)
Hack et al.[222]	n=221	<1000 g	+	USA	1992-95	20 mo	BSID-II	**40%** <2SD / **71%** <1SD (worse outcome for neurosensory abnormal) (no control group)
Wilson-Costello et al.[223]	n=1478	<1000 g	+	USA	1982-02	20 mo	BSID	**15%** <2SD / **37%** <1SD for those born 2000-02 (no control group)
O'Callaghan et al.[224]	n=58	<1000 g	+/-	Australia	1988-90	2 yr	NSMDA	ELBW < controls on fine and gross motor ($p<0.05$)
Latal-Hajnal et al.[228]	n=219	<1250 g	+	Switzerland	1983-95	2 yr	BSID	**10%** <2SD / **22%** <1SD on PDI; worst outcome for growth restricted VLBW (no control group)
Agustines et al.[229]	n=36	<750 g	+	USA	1990-95	2,5 yr	BSID	**42%** <2SD / **58%** <1SD on PDI (no control group)
Janssen et al.[227]	n=437	≤32 wk	-	Netherlands	1996-2001	2-3 yr	BSID-II	**27%** <2SD / **46.5%** <1SD on PDI; Very preterm < controls in mean scores ($p<0.01$); boys < girls ($p<0.01$)
Chen et al.[329]	n=225	<1500 g	+	Taiwan	1995-96	3 yr	BSID-II	**16%** <2SD on PDI ($p<0.003$ vs. controls)
Ong et al.[225]	n=104	<1500 g	-	Malaysia	1989-92	4 yr	M-ABC	**27.5%** <15th centile (no control group)
Torrioli et al.[235]	n=34	<1500 g	-	Italy	1991-93	5 (4-6) yr	M-ABC	**71%** <15th centile; VLBW < controls in total score ($p<0.001$)
de Kleine et al.[234]	n=404	<1500 g, <32 wk	- severe CP	Netherlands	1992-94	5 yr	M-ABC	**22%** <5th centile / **43.5%** <15th centile (no control group)
Goyen et al.[231]	n=83	<1500 g	-	Australia	1986-89	5 yr	PDMS ; Fine motor	**10 %** <2SD /**23%** 1.5-2SD / **65%** < 1SD on fine motor subscale (no control group)
Johnson et al.[232]	n=198	<33 wk	-	UK	1990-93	5 yr	M-ABC	Preterm < reference group in total score ($p<0.01$)
Hoff Esbjørn et al.[233]	n=207	<1000 g / < 28 wk	+/-	Denmark	1994-95	5 yr	M-ABC	ELBW < controls in total score ($p<0.001$)
Levene et al.[236]	n=152	<1501 g	+	UK	1984-85	5 yr	TOMI	VLBW < controls for total score and all subscores ($p<0.001$)

Erikson et al.[237]	n=165	≤1500 g	+	Sweden	1988-93	5.5 yr	M-ABC	**22%** <5th centile / **36%** <15th centile (p<0.01 vs controls)
MOTOR STUDIES IN SCHOOL AGE								
Jakobson et al.[238]	n=43	≤30 wk	- severe	Canada	1993-95	6 yr	M-ABC	Preterm < controls in total score (p<0.05)
Marlow et al.[240]	n=53	<1251 g	-	UK	1980-81	6 yr	TOMI	VLBW < controls in total score and all subscores (p<0.01)
Marlow et al.[239]	n=180	<26 wk	-	UK, Ireland	1995	6 yr	M-ABC; 3 items	Extremely preterm < controls for the three items tested (posting coins, heel-toe walking, one-leg balance) (p<0.03); boys < girls (p<0.03)
Feder et al.[246]	n=42	<1250 g, <34 wk	-	Canada	1992-94	6-7 yr	BOTMP; Fine motor	Preterm < controls in mean fine motor composite scores (p=0.01)
Foulder-Hughes & Cooke[331]	n=280	<32 wk	- (main-stream school)	UK	1991-92	7 yr	M-ABC	**31%** <5th centile / **41%** <10th centile / **48%** <15th centile; Very preterm < controls in total score and all item scores (p<0.001)
Rademaker et al.[332]	n=204	≤1500 g, ≤32 wk	+/-	Netherlands	1991-93	7-8 yr	M-ABC	**15%** <5th centile (11% - CP), **26%** <15th centile (22% - CP) (no control group)
Hack et al.[51]	n=219	<750 g	+/-	USA	1992-95	8 yr	BOTMP	**27%** <2SD /**47%** <1SD (p<0.001 vs. controls); still significant after exclusion of neurosensory impairments (15% <2SD / 37% <1SD)
Marlow et al.[243]	n=53	≤1250 g	-	UK	1980-81	8 yr	TOMI	VLBW < controls in total score and all subscores (p≤0.05)
Hall et al.[242]	n=324	<1500 g	+/- special school	Scotland	1984	8 yr	M-ABC	**42.0%** <10th centile ; VLBW < controls in total score and all item scores (p<0.01); ELBW << controls (p<0.001); boys = girls
Goyen & Lui[241]	n=50	<1000 g / <29 wk	-	Australia	1992-95	8 yr	M-ABC	**30%** <5th centile / **42%** <15th centile; ELBW < controls in total score, manual dexterity and balance (p<0.001), borderline in ball skills (p=0.08)
Wocadlo & Rieger[250]	n=323	<30 wk	-	Australia	1987-97	8 yr	BOTMP	**31%** <15th centile (no control group); girls < boys in running and strength (p<0.01)

Davis et al.[244]	n=255	<1000 g, <28 wk	+/-	Australia	1991-92	8-9 yr	M-ABC	**9.5%** <5th centile; ELBW < controls in total score and all subscores (p<0.0001)
Michelsson et al.[245]	n=41	≤1500 g		Finland	1971-74	9 yr	TOMI	**20%** <5th centile; VLBW < controls in mean scores (p<0.01)
Dewey et al.[247]	n=38	<1500 g	+	Canada	1979-87	9 yr	BOTMP	VLBW < controls (p<0.05); VLBW "cognitive suspect" << controls; boys < girls
Whitfield et al.[248]	n=90	≤800 g	+/-	Canada	1974-85	9 yr	BOTMP	ELBW < controls in fine (p=0.0001) and gross motor function (p=0.01); boys = girls
Holsti et al.[249]	n=91	<800 g	-	Canada	1982-87	9 yr	BOTMP	**51%** <1SD; ELBW < controls in mean scores (OR:17.5; CI: 2.2–138.3); boys = girls
MOTOR STUDIES IN ADOLESCENCE								
Taylor et al.[253]	n=130	<1500 g, <750 g	+/-	USA	1982-86	7-14 yr	BOTMP	VLBW < controls; ELBW << controls (p<0.01) at all time points; initial superiority of girls which dissipated with age
Powls et al.[252]	n=47	<1251 g	-	UK	1980-81	12-13 yr	M-ABC	**34%** <5th centile / **51%** <15th centile; VLBW < controls in total score and 6 of 8 items (p≤0.01); girls < boys (p=0.008)
Gäddlin et al.[254]	n=58	≤1500 g	-	Sweden	1987-88	15 yr	BOTMP	VLBW < controls (p=0.005); VLBW boys < control boys (p=0.005); VLBW girls < control girls (p=0.245)

"-" = major handicaps (i.e. cerebral palsy, mental retardation, blindness, deafness) excluded;
"+" = all children included;
"+/-" = results presented both with and without handicaps

AIMS = Alberta Infant Motor Scale
BOTMP = Bruininks-Oseretzy's Test of Motor Proficiency
BSID = Bayley Scales of Infant Development
ELBW = Extremely low birth weight
IVH = Intraventricular haemorrhage
M-ABC = Movement Assessment Battery for Children
NSMDA = Neuro-Sensory Motor Developmental Assessment
PDI = Psychomotor Development Index of the BSID
PDMS = Peabody Developmental Motor Scales
TOMI = Test of Motor Impairment (predecessor of M-ABC)

Appendix B. Studies of motor outcome in SGA subjects born at term (≥ 37 weeks of gestation) from infancy through adolescence.

Study	n	Included	Country	Born	Age	Test	Results
MOTOR STUDIES IN INFANCY							
Rubin et al.[92]	n=38-46	≤2500 g	USA	1960-64	30-60 hr, 4 mo, 8 mo, 12 mo, 7 yr	Neurological examination + BSID (8 mo)	Neurological : SGA < controls at 30-60 hr ($p<0.01$); SGA = controls at 4 mo; SGA girls < control girls at 12 mo ($p<0.01$); SGA < controls at 7 yr ($p<0.01$) BSID: SGA = controls in mean PDI at 8 mo
Als et al.[265]	n=10	PI <10th centile	USA	1973-74	1-10 days	Neurological examination	SGA < controls in motor behaviour and muscle tone ($p<0.05$)
Michaelis et al.[269]	n=22	<5 centile	Germany	Not reported	3-7 days	Neurological examination	SGA < controls ($p<0.02$)
Leijon et al.[272]	n=29	<-1SD / <-2SD	Sweden	1975-77	5 days	Neurological examination	Both SGA groups < controls in muscle tone ($p<0.05$) at five days
Gagliardo et al.[271]	n=11-14	<10th centile	Brazil	2000-01	1-3 mo	BSID-II	SGA < controls in mean PDI at 2 mo ($p=0.03$); SGA = controls at 1 and 3 mo
Campos et al.[267]	n=18-25	<10th centile	Brazil	2000-03	1-6 mo	BSID-II	SGA < controls in mean PDI at 2 mo ($p<0.01$) and 6 mo ($p<0.04$); SGA = controls at 1 and 3 mo
Leijon et al. 1980[263]	n=29	<-1SD / <-2SD	Sweden	1975-77	5 -18 mo	Neurological examination + Griffiths scales	Both SGA groups < controls in eye-hand coordination at 5 and 10 mo ($p<0.05$); SGA (<-2SD) < controls on neurological exam at 10 mo ($p<0.01$); SGA = controls in locomotor
Low et al.[264]	n=86	<10th centile	Canada	Not reported	6 / 12 mo	BSID	SGA = controls in mean PDI at 6 mo; SGA < controls at 12 mo ($p<0.01$)
Grantham-McGregor et al.[266]	n=102	1500-2499 g	Brazil	1993-94	6 / 12 mo	BSID	SGA < controls in mean PDI at 6 and 12 mo ($p<0.001$)
Jelliffe-Pawlowski & Hansen[72]	n=3120	≤10th centile	USA	1959-66	8 mo	BSID	SGA < controls in mean PDI regardless of SES ($p\leq0.001$)

Markestad et al.[275]	n=265	<10th centile	Norway, Sweden	1986-88	13 mo	BSID	SGA = controls in mean PDI
MOTOR STUDIES IN PRESCHOOL AGE							
Juneja et al.[270]	n=50	<2000 g	India	2001-02	18 mo	BSID-II	**24%** <1SD on PDI (p=0.03 vs. controls), non-significant difference in mean values (p=0.09)
Low et al.[274]	n=76	<10th centile	Canada	Not reported	24-60 mo	BSID, McCarthy motor subscales + neurological examination	SGA = controls in mean PDI at 24 mo and on the other tests at 36-60 mo
Tenovuo et al.[268]	n=442	<10th centile	Finland	1981-82	2 yr	Denver developmental screening test	SGA < controls in total score (p<0.005), especially in walking and manual performance (p<0.005)
Walther & Raemaekers[273]	n=25	<10th centile	Netherlands	1976-77	3 yr	Touwen's neurological examination	SGA < controls in total score (p<0.0001), and in subsystems of posture (p<0.02), quality of movements (p<0.004) and (dys)kinesia (p<0.01)
Fancourt et al.[278]	n=57	<10th centile	UK	Not reported	4 yr	Griffiths scales	SGA with early onset IUGR < controls in eye-hand coordination and motor development (p<0.01)
Sommerfelt et al.[276]	n=321	<10th centile	Norway, Sweden	1986-88	5 yr	PDMS	**14%** <5th centile; SGA < controls in overall score (p=0.047), but not in subscores
Harvey et al.[277]	n=51	<10th centile	UK	Not reported	5 yr	McCarthy motor subscales	SGA with early onset IUGR < controls (p<0.01)
MOTOR STUDIES IN SCHOOL AGE							
Hadders-Algra et al.[279]	n=166	<10th centile	Netherlands	1977-78	6 yr	Touwen's neurological examination	SGA < controls (p<0.05)
Fitzhardinge & Steven[87]	n=96	< -2SD / 3th centile	Canada	1960-66	6 yr	Neurological / clinical examination	SGA higher prevalence of minor neurological abnormalities (indicating minor neurological dysfunction) vs. controls (p<0.05)

Neligan et al.[1]	n=141	<10th / <5th centile	UK	1960-62	7 yr	TOMI	SGA (<5th centile) < controls (p<0.001)
Walther et al.[73]	n=25	<10th centile	Netherlands	1976-77	7 yr	Touwen's neurological examination	SGA < controls in total score (p<0.0005), subtests of coordination, fine manipulative ability and (dys)kinesia (p<0.05), but not gross motor functions and balance; boys < girls (not analysed in depth due to limited sample)
MOTOR STUDIES IN ADOLESCENCE							
Westwood et al.[80]	n=33	< -2SD / 3th centile non-asphyxia	Canada	1960-66	16 yr	Neurological examination	SGA = controls

BSID = Bayley Scales of Infant Development
PDI = Psychomotor Develoment Index of the BSID
PDMS = Peabody Developmental Motor Scales
PI = Ponderal index
TOMI = Test of Motor Impairment

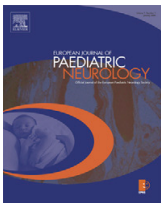
Paper I

Is not included due to copyright

Paper II

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 13 (2009) 47–56

Official Journal of the European Paediatric Neurology Society



Original article

Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents?

Kari Anne I. Evensen[a,d,*], *Susanne Lindqvist*[a,e], *Marit S. Indredavik*[b,f], *Jon Skranes*[a,g], *Ann-Mari Brubakk*[a,g], *Torstein Vik*[c]

[a]*Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*
[b]*Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*
[c]*Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*
[d]*Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Norway*
[e]*Department of Ophthalmology, St. Olavs Hospital, Trondheim University Hospital, Norway*
[f]*Department of Child and Adolescent Psychiatry, St. Olavs Hospital, Trondheim University Hospital, Norway*
[g]*Department of Pediatrics, St. Olavs Hospital, Trondheim University Hospital, Norway*

ARTICLE INFO

Article history:
Received 26 March 2007
Received in revised form
1 October 2007
Accepted 11 February 2008

Keywords:
Very low birth weight
Small for gestational age
Motor problems
Visual impairments
Adolescents

ABSTRACT

Background: Increased prevalence of motor and visual problems has been reported in low birth weight populations, but the association between them is less studied.
Aim: To examine how visual impairments may be associated with the increased risk of motor problems in low birth weight adolescents.
Methods: Fifty-one very low birth weight adolescents (VLBW), 56 term small for gestational age (SGA) and 75 term control adolescents, without cerebral palsy, were examined at the age of 14. Motor skills were examined by the Movement Assessment Battery for Children. Visual functions included visual acuity, contrast sensitivity, nystagmus, strabismus, stereoacuity, accommodation, convergence and visual perception (Visual-Motor Integration test). An abnormality score was calculated as the sum of visual impairments. We used odds ratio as an estimate of the relative risk of having motor problems.
Results: The odds of having motor problems were 10.4 (95% CI: 2.2–49.4) in the VLBW group and 5.1 (95% CI: 1.0–25.8) in the SGA group compared with the control group. The odds of having motor problems in the VLBW group were influenced by all visual variables, and most by visual acuity, when we adjusted for these separately. The greatest reduction in OR was found when adjusting for the abnormality score (adjusted OR: 6.8; 95% CI: 1.3–34.5). In the SGA group the odds of having motor problems were relatively unaffected by the visual variables and the abnormality score.
Conclusions: Visual impairments influence motor problems in VLBW adolescents, whereas motor problems in SGA adolescents seem to be unaffected by visual impairments.

*Corresponding author at: Department of Laboratory Medicine, Children's and Women's Health, St. Olavs Hospital, Olav Kyrres Gate 11, N-7006 Trondheim, Norway. Tel.: +47 7257 4659; fax: +47 7386 7708.
E-mail address: karianne.i.evensen@ntnu.no (K.A.I. Evensen).
1090-3798/$ - see front matter
doi:10.1016/j.ejpn.2008.02.009

1. Introduction

Premature birth and intrauterine growth restriction both represent risk factors for motor problems and visual impairments. Motor problems are frequently seen in children with birth weight below 1500 g (very low birth weight: VLBW) at preschool[1–3] and school age.[4–7] Some studies also report motor problems in VLBW adolescents.[8,9]

VLBW children and adolescents also have poorer visual functions, including poorer visual acuity,[10–14] stereoacuity,[2,10,11,15] contrast sensitivity[10,13] and more strabismus[10–13] than controls. Visual perception is also more frequently reduced in preterm children.[16–18]

Children who have been growth retarded in utero are usually diagnosed by having a low birth weight for their gestational age (small for gestational age: SGA). Studies on motor skills in term SGA children are few and have shown inconsistent results.[19–23] We have previously reported that term SGA adolescents, in particular boys, more often had motor problems, especially poor manual dexterity, compared with non-SGA adolescents.[9] Also, visual functions have been less studied in SGA populations, primarily in infants[22,24] and young children.[20] A couple of studies have found some support for impaired visual function among adolescents who were born SGA.[25,26]

Vision is one of the most important sources of information for motor control[27,28] and plays an essential role in both motor and cognitive development.[29] Vision is necessary to identify objects and movements important for interacting with the environment and for controlling body movements.[27] Poor visual perception has been shown to contribute to movement problems of clumsy children.[30]

Associations between visual functions and motor skills have been less studied in low birth weight populations, but there seems to be a relationship between motor skills and stereoacuity[2,11,15] as well as visual acuity, strabismus and contrast sensitivity[11] in younger VLBW children. In VLBW adolescents, a strong association between impaired vision and motor problems has been reported, especially in children with strabismus and poor contrast sensitivity.[10]

None of these previous studies of VLBW children have looked at the risk of motor problems and how this risk may be affected by visual functions. Secondly, no studies have looked at the association between vision and motor skills in SGA children or adolescents.

In this study, we wanted to examine how visual impairments may be associated with the increased risk of motor problems in VLBW and SGA adolescents.

2. Material and methods

2.1. Study design

This is a follow-up study of two groups of adolescents with low birth weight (VLBW and term SGA) compared with a control group of normal birth weight. The VLBW adolescents had been admitted to the Neonatal Intensive Care Unit (NICU) at the University Hospital in Trondheim in 1986-88. The SGA and control children were born in the same time period to mothers enrolled before week 20 of pregnancy in a multicenter study,[31,32] where a 10% random sample of women (with one or two previous pregnancies) was selected for follow-up during pregnancy. At birth, all SGA children and all children born to mothers in the random sample were included for follow-up. Children with cerebral palsy (CP) and congenital malformations were excluded.

At 14 years of age, motor, visual and neuropsychological examinations were performed as part of a comprehensive follow-up assessment. We have previously reported the prevalence of motor, visual and neuropsychological problems in VLBW and SGA adolescents.[9,26,33,34,61]

2.2. Study population

2.2.1. VLBW adolescents

One hundred and twenty-one children with a birth weight $\leqslant$1500 g were admitted to the NICU at the University Hospital in Trondheim (the referral hospital) in 1986–88. Of these, 33 died, one child with trisomy 21 was excluded, eight had CP and six children had moved. Of the remaining 73 children, 22 did not consent to at least one of the examinations (motor, visual and/or neuropsychological examination). Thus, a total of 51 (70%) VLBW adolescents (28 boys, 23 girls) underwent all three examinations.

2.2.2. SGA adolescents

Of 1200 eligible women, 104 (9%) gave birth to a SGA child, defined by a birth weight <10th centile, adjusted for gestational age, gender and parity. One child had CP and one child had a congenital malformation. At follow-up, 12 children had moved. Of the remaining 90 children, 34 did not consent to motor, visual and/or neuropsychological examination, leaving 56 (62%) SGA children (25 boys and 31 girls) in this study group.

2.2.3. Control adolescents

The control group comprised 120 children with birth weight $\geqslant$10th centile for gestational age, born at term to mothers in the 10% random sample. Two children had congenital malformations. At follow-up, 10 children had moved, while 33 did not consent to at least one of the examinations. In total, 75 (69%) children in the control group (32 boys and 43 girls) were examined.

2.2.4. Non-participants

There were no significant differences in maternal age, duration of pregnancy, the infants' birth weight, body length and head circumference between those who participated and those who did not consent to participation in any of the groups.

3. Methods

All examiners were blinded to group assignment.

Table 1 – Gestational age, birth weight and anthropometric measurements at follow-up in two groups of adolescents with low birth weight compared with a control group

	VLBW ($n = 51$) Mean (SD)	SGA ($n = 56$) Mean (SD)	Control ($n = 75$) Mean (SD)
Birth weight (g)	1206 (228)[a]	2919 (214)[a]	3679 (431)
Gestational age (weeks)	29.4 (2.7)[a]	39.5 (1.1)	39.6 (1.1)
Age at follow-up (years)	14.2 (0.3)	14.2 (0.3)	14.2 (0.3)
Weight (kg)	52.1 (13.7)[c]	52.3 (8.6)[b]	57.5 (10.7)
Height (cm)	162.4 (9.0)[b]	163.4 (7.2)[b]	167.6 (7.6)
Head circumference (cm)	54.6 (1.8)[a]	54.8 (2.0)[a]	56.0 (1.5)

[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$ vs. controls (gestational age and birth weight were the selection criteria, and differed by definition vs. the control group).

3.1. *Background data*

At birth, the VLBW infants were weighed to the nearest gram on an electronic scale, whereas the SGA and control infants were weighed to the nearest 10 g on a standard scale.

At follow-up, weight was measured on an electronic scale to the nearest 100 g. Height and head circumference was measured to the nearest 0.1 cm.

Gestational age, birth weight and anthropometric measurements at follow-up are shown in Table 1.

Socioeconomic status (SES) was calculated according to Hollingshead's Two Factor Index of Social Position.[35]

An estimate of intelligence quotient (IQ_{est}) was calculated using four subscales (vocabulary, arithmetic, block design and picture arrangement) of Wechsler Intelligence Scales (WISC-III).[36,37] We defined "low IQ_{est}" as below two standard deviations (SDs) of the control group mean value.

3.2. *Motor skills*

Each adolescent was tested with the Movement Assessment Battery for Children (Movement ABC)[38] by a physiotherapist (KAIE). The Movement ABC consists of eight items, scored between zero (optimal score) and five, and grouped as three subscores: manual dexterity, ball skills and static/dynamic balance. Scores below the 5th centile indicate definite motor problems and scores below the 15th centile indicate borderline motor problems.[38] We used the highest age band, designed for 11–12-year-old children. Since the study population was examined at 14 years of age, we used the 5th and 15th centile derived from all adolescents in the control group who met for motor assessment ($n = 81$). This corresponded to a total score of 14 and 10.5, well in accordance with the 5th and 15th centile in the manual.

3.3. *Visual functions*

All visual examinations were performed by a paediatric ophthalmologist (SL). In addition to the following examinations, subjects were also examined in a split lamp and with indirect binocular ophthalmoscopy.

3.3.1. *Visual acuity*

Binocular distance visual acuity was examined by a Snellen letter chart at 4 m distance. Two VLBW adolescents were tested with Lea Hyvärinen symbols test[39] for distance due to problems with naming letters.

Visual acuity was assessed both with own (if any) correction, and also with best correction after subjective refraction. Poor visual acuity was defined as visual acuity below 1.0 Snellen decimals.

3.3.2. *Contrast sensitivity*

Contrast sensitivity was assessed by the Vistech contrast sensitivity chart for near at 40 cm distance.[40] Both eyes were tested monocularly. The Vistech chart tests at five frequencies: 1.5, 3, 6, 12, and 18 cycles per degree. At each frequency the lowest contrast at which the direction of lines could be detected was noted. A frequency was regarded as normal if the result was equal to, or better than, the minimum level designated as normal by the manufacturer of the test.[40] We defined poor contrast sensitivity as having one or more values below normal in at least one eye. Since visual acuity has been shown to correlate with contrast sensitivity in the higher frequencies,[41] analysis was also done excluding the 18 cycles per degree frequency in order to minimise the influence of visual acuity on the results.

3.3.3. *Stereoacuity*

Stereoacuity was measured with the TNO test (Lameris Ootech BV, Nieuwegein). If a subject did not manage the easiest stereograms on the TNO test (480 s of arc), the Titmus test (Stereo Optical, Chicago, IL, USA), which examines stereoacuity up to 3600 s of arc, was used. Those who still did not manage to prove stereoacuity were tested with the Bagolini striated glasses at distance and near, and a positive Bagolini was given a numerical value larger than 3600 s of arc. We defined poor stereoacuity as above 240 s of arc.

3.3.4. *Strabismus*

Strabismus was measured with the alternating prism cover test at distance and near. Presence of strabismus was defined as a heterophoria or heterotropia (i.e. manifest or latent strabismus) with any prism deviation below the 5th and

above the 95th centile in the control group; i.e. any esodeviation, exodeviations larger than −8 prism diopters (PD) at near, or −2 PD at distance and any vertical deviations.

3.3.5. *Nystagmus*

Investigation for nystagmus was done in all directions of gaze, mono- and binocularly, as well as with magnification during examination in a split lamp. Only pathological nystagmus was included, cases of physiological end point nystagmus were not recorded as nystagmus.

3.3.6. *Accommodation*

Accommodative amplitude was measured with a Royal Air Force (RAF) ruler. The adolescents were instructed to report when an image, which was slowly moved towards them, got sustainedly blurred. The mean value for the right and the left eye was used in the analysis in this study. Poor accommodation was defined as any value below the 5th centile in the control group, i.e. below 6.5 diopters.

3.3.7. *Convergence*

The near point of break of convergence was measured with an RAF ruler. Poor convergence was defined as a near point of convergence larger than 10 cm.[42,43]

3.3.8. *Visual perception*

Visual perception was assessed by the Visual Perception supplementary task of the Developmental Test of Visual-Motor Integration (VMI-IV)[44] by a psychologist. The VMI consists of 27 geometric designs in increasing order of difficulty that have to be copied. The Visual Perception task requires the adolescent to identify the exact match for as many as possible of the designs that he/she has copied earlier. The time limit to complete this task is three minutes. The number of correct performances was judged and scored according to the manual.[44] Poor performance was defined as a score below 22, corresponding to 1 SD below the mean in the control group.

3.3.9. *Abnormality score*

An *abnormality score* was calculated as the sum of visual impairments, including distance visual acuity (best correction), contrast sensitivity, stereoacuity, strabismus, nystagmus, accommodation, convergence and visual perception. An abnormality score of zero was given if an adolescent did not have impairments in any of the visual functions, and the highest possible abnormality score of eight would indicate impairments in all functions.

3.4. *Ethics*

The Regional Committee for Medical Research Ethics approved the study protocol. Written informed consent was obtained from both adolescents and parents.

3.5. *Statistical analysis*

SPSS 13.0 was used for data analysis, and a significance level of 0.05 was chosen. Two-group comparisons were made using the Student's t-test for variables with a normal distribution and the Mann-Whitney U test for variables with a non-normal distribution. The chi-square test was used to analyse differences in proportions between groups.

We used odds ratio (OR) as an estimate of the relative risk of having motor problems in the low birth weight groups compared with the control group. The visual variables were used as dichotomous variables and entered separately in the model to calculate adjusted odds ratios. The abnormality score for visual problems was used as a continuous variable in the logistic regression model.

4. Results

4.1. *Background data (Table 1)*

The VLBW and SGA adolescents were shorter, lighter and had a smaller head circumference than control adolescents at follow-up (Table 1), whereas socioeconomic status did not differ between the groups (data not shown). There were seven (14%) VLBW (non-significant vs. controls), three (5%) SGA and three (4%) control adolescents with low IQ_{est}. Of these, four VLBW (non-significant vs. controls), one SGA and no control adolescents had motor problems (Total ABC score below the 5th centile).

4.2. *Motor skills (Tables 2 and 3)*

4.2.1. *Definite motor problems*

The VLBW group had poorer median scores on the Movement ABC, both total score and all subscores (Table 2), and a higher proportion of adolescents in this group (22%) had definite motor problems (total ABC score below the 5th centile) compared with 3% in the control group (OR: 10.4; 95% CI: 2.2–49.4) (Table 3).

In the SGA group, the median scores on the Movement ABC did not differ significantly from the scores in the control group (Table 2). However, a higher proportion of SGA adolescents (13%) had definite motor problems (OR: 5.1; 95% CI: 1.0–25.8) (Table 3).

Both in the VLBW and the SGA group a higher proportion of adolescents had poor manual dexterity compared with the control group, whereas there were no significant group differences regarding ball skills. In the VLBW group a higher proportion of adolescents had poor balance compared with the control group (Table 3).

4.2.2. *Borderline motor problems*

Forty-five percent of the VLBW group had borderline motor problems (total ABC score below the 15th centile) compared with 14% of the control group (OR: 5.2; 95% CI: 2.2–12.5) (Table 3). The VLBW group also had a higher proportion of adolescents with manual dexterity and balance scores below the 15th centile compared with the control group (Table 3). There was no difference in borderline motor problems, ball or balance problems between the SGA and the control group (Table 3). However, although not statistically significant, 27% of the SGA group had borderline manual dexterity compared with 15% in the control group (OR: 2.1, 95% CI: 0.9–5.0).

Table 2 – Median scores and interquartile range of the Movement ABC in two groups of adolescents with low birth weight and a control group

	VLBW ($n = 51$)		SGA ($n = 56$)		Control ($n = 75$)	
Total ABC	10.0	(5.0–14.0)[a]	5.3	(4.0–9.5)	6.5	(3.0–9.0)
Manual dexterity	1.5	(0.5–3.5)[b]	1.0	(0.0–3.0)	0.5	(0.0–2.5)
Ball skills	2.0	(0.5–4.0)[b]	1.0	(0.0–2.0)	1.0	(0.0–2.5)
Static/dynamic balance	5.0	(3.0–7.5)[b]	3.0	(2.0–5.0)	3.0	(1.0–5.0)

[a] $p < 0.001$.
[b] $p < 0.01$ vs. controls.

Table 3 – Odds ratio (OR) with 95% confidence intervals (CI) as an estimate of the relative risk for definite and borderline motor problems in two groups of adolescents with low birth weight compared with a control group

	<5th centile		<15th centile	
	n (%)	Crude OR (95% CI	*n* (%)	Crude OR (95% CI)
Total ABC				
VLBW ($n = 49$)	11 (22)	10.4 (2.2–49.4)	22 (45)	5.2 (2.2–12.5)
SGA ($n = 56$)	7 (13)	5.1 (1.0–25.8)	8 (14)	1.1 (0.4–2.9)
Control ($n = 74$)	2 (3)	1.0	10 (14)	1.0
Manual dexterity				
VLBW ($n = 51$)	8 (16)	4.4 (1.1–17.5)	15 (29)	2.4 (1.0–5.7)
SGA ($n = 56$)	9 (16)	4.5 (1.2–17.6)	15 (27)	2.1 (0.9–5.0)
Control ($n = 74$)	3 (4)	1.0	11 (15)	1.0
Ball skills				
VLBW ($n = 51$)	6 (12)	3.2 (0.8–13.4)	9 (18)	1.8 (0.6–5.0)
SGA ($n = 56$)	0 (0)	[a]	3 (5)	0.5 (0.1–1.9)
Control ($n = 75$)	3 (4)	1.0	8 (11)	1.0
Static/dynamic balance				
VLBW ($n = 49$)	11 (22)	6.9 (1.8–26.4)	12 (25)	5.8 (1.7–19.1)
SGA ($n = 56$)	6 (11)	2.9 (0.7–12.1)	6 (11)	2.1 (0.6–7.9)
Control ($n = 75$)	3 (4)	1.0	4 (5)	1.0

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

4.3. *Visual functions (Table 4 and Fig. 1)*

Table 4 shows the results of the ophthalmologic examination and the visual perception task in the three groups.

Poor *visual acuity* was significantly more frequent in the VLBW, than in the control group. Visual acuity ranged from 0.5 to 2.0 in the VLBW group, from 0.8 to 2.0 in the SGA group and from 1.0 to 2.0 in the control group. Mean visual acuity was 1.2 in the VLBW group and 1.3 in both the SGA and control group. The difference in means between VLBW and control group did not reach statistical significance.

A higher proportion of VLBW adolescents also had *strabismus* compared with the control group ($p < 0.05$).

The higher proportions of poor *contrast sensitivity* ($p = 0.07$), *nystagmus* ($p = 0.06$) and poor *visual perception* ($p = 0.06$) in the VLBW group did not reach statistical significance. The results for contrast sensitivity were unchanged when we excluded the 18 cycles per degree frequency, which may correlate with visual acuity.

Stereoacuity, *accommodation* and *convergence* did not differ between VLBW and control adolescents.

The SGA group did not differ from the control group in any of the visual functions.

Fig. 1 shows the abnormality score for visual impairments in each of the three groups. Whereas approximately 50% of SGA and control adolescents were free of visual impairments, this was the case for only 30% of the VLBW adolescents ($p = 0.05$ vs. controls). In the VLBW group, 22 (43%) adolescents had two or more visual impairments (i.e. abnormality score equal to or above two) compared with 10 (13%) in the control group ($p < 0.001$) and 8 (14%) in the SGA group (non-significant vs. controls) (Table 4).

The ophthalmologic examination did not reveal any major ocular pathology such as retinal detachments or cataracts. ROP screening had not yet started when these VLBW children were born, thus no information about their ROP status is available, although we know that no children in this study were treated with cryotherapy, and no

Table 4 – Visual functions in two groups of adolescents with low birth weight compared with a control group

	VLBW ($n = 51$) n (%)	SGA ($n = 56$) n (%)	Control ($n = 75$) n (%)
Visual impairment			
Visual acuity < 1.0 Snellen decimals	4 (8)[b]	1 (2)	0 (0)
Poor contrast sensitivity	23 (45)	12 (21)	22 (29)
Nystagmus	3 (6)	1 (2)	0 (0)
Strabismus	14 (28)[b]	11 (20)	8 (11)
Stereoacuity > 240 s of arc	4 (8)	3 (5)	1 (1)
Accomodation < 6.5 D	3 (6)	2 (4)	2 (3)
Convergence > 10 cm	12 (24)	4 (7)	9 (12)
Visual perception < 1 SD	14 (28)	7 (13)	10 (14)
Abnormality score			
⩾1 Visual impairment(s)	36 (71)[b]	26 (46)	40 (53)
⩾2 Visual impairments	22 (43)[a]	8 (14)	10 (13)

[a] $p < 0.001$.
[b] $p \leqslant 0.05$ vs. controls.

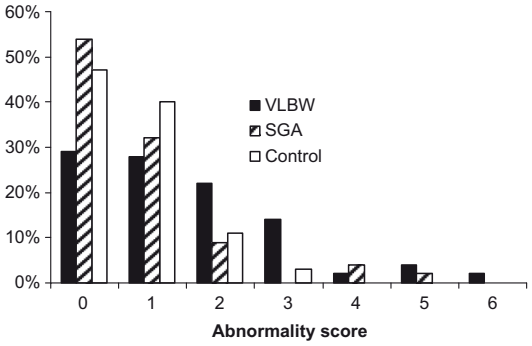


Fig. 1 – Proportion of adolescents with no, one or more visual impairments. The x-axis shows the number of visual impairments (abnormality score) and the y-axis shows the proportion of adolescents in each group.

sequelae of severe ROP were found at the examination at 14 years of age.

4.4. *Association between visual functions and motor skills (Tables 5 and 6)*

4.4.1. *Total ABC score*

In the VLBW group, the OR for definite motor problems was reduced when we adjusted for each of the visual variables separately (Table 5). Of these, the greatest reduction in the crude OR of 10.4 was seen when we adjusted for visual acuity (adjusted OR: 7.8; 95% CI: 1.6–38.5). When we separately adjusted for the abnormality score the OR was reduced even more (adjusted OR: 6.8; 95% CI: 1.3–34.5) (Table 6). Still, the increased odds of having motor problems were significant.

In the SGA group, the greatest reduction in odds of having definite motor problems was observed when we adjusted for strabismus and nystagmus (Table 5). However, adjusting for the abnormality score did not change the odds of having definite motor problems (Table 6).

4.4.2. *Manual dexterity*

Adolescents in the VLBW and the SGA group had about 4.5 times increased odds of having poor manual dexterity compared with the control group. In the VLBW group, OR was however no longer significantly higher when adjusting separately for visual acuity, strabismus, stereoacuity (Table 5) and the abnormality score (Table 6).

In the SGA group nystagmus and strabismus each reduced the odds of having manual dexterity problems from 4.5 to 4.0 (95% CI: 1.0–16.0), whereas the other visual variables only had small effects (Table 5) and the abnormality score did not have any effect on the OR (Table 6).

4.4.3. *Ball skills*

In the VLBW group the crude OR of 3.2 (95% CI: 0.8–13.4) for having poor ball skills was reduced when we adjusted separately for each of the visual variables (Table 5) and for the abnormality score (Table 6).

None of the SGA adolescents had poor ball skills.

4.4.4. *Static and dynamic balance*

The increased odds of having definite balance problems in the VLBW group were most reduced when we adjusted separately for visual acuity, nystagmus and stereoacuity (Table 5). Adjusting for the abnormality score reduced the OR to 4.9 (95% CI: 1.2–20.1) (Table 6). However, the odds of having poor balance were still significantly increased after adjustment (Tables 5 and 6).

The SGA group did not have significantly increased odds of having poor balance.

4.4.5. *Borderline motor problems*

The odds of having a total ABC score below the 15th centile were also influenced by visual functions, although the percentage reduction in OR was somewhat smaller (data not shown). Again, the greatest reduction in OR was found when adjusting for visual acuity in the VLBW group (adjusted OR: 4.7; 95% CI: 1.9–11.4). The effect of the other visual variables on borderline manual dexterity, ball skills and balance were essentially the same as for definite problems (data not shown). Table 6 shows that the abnormality score reduced the odds considerably in the VLBW group, both for the total ABC score and for all subscores.

In the SGA group, the odds of borderline motor problems, both total ABC and all subscores, were non-significant compared with the control group, and relatively unaffected by visual impairments (data not shown) and the abnormality score (Table 6).

Table 5 – Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) as an estimate of the relative risk of definite motor problems in two groups of adolescents with low birth weight compared with a control group

	<5th centile	Adjusted OR (95% CI) for each of the visual variables separately					
	Crude OR (95% CI)	Visual acuity	Contrast sensitivity	Nystagmus	Strabismus	Stereoacuity	Visual perception
Total ABC							
VLBW	10.4 (2.2–49.4)	7.8 (1.6–38.5)	9.4 (1.9–45.8)	8.8 (1.8–42.6)	9.1 (1.9–44.0)	9.4 (1.8–50.3)	9.7 (2.0–46.7)
SGA	5.1 (1.0–25.8)	5.3 (1.0–26.4)	4.7 (0.9–24.1)	4.4 (0.9–22.7)	4.2 (0.8–21.9)	4.8 (0.9–24.4)	5.4 (1.0–28.0)
Control	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Manual dexterity							
VLBW	4.4 (1.1–17.5)	2.8 (0.6–12.4)	4.3 (1.1–17.2)	4.0 (1.0–16.5)	3.8 (0.9–15.6)	3.5 (0.8–14.9)	5.4 (1.1–27.6)
SGA	4.5 (1.2–17.6)	4.6 (1.2–18.0)	4.2 (1.1–16.6)	4.0 (1.0–16.0)	4.0 (1.0–16.0)	4.3 (1.1–17.0)	7.8 (1.5–39.6)
Control	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ball skills							
VLBW	3.2 (0.8–13.4)	2.2 (0.5–10.5)	2.9 (0.7–12.3)	2.2 (0.5–10.2)	2.8 (0.6–12.3)	2.3 (0.5–10.7)	2.6 (0.6–11.3)
SGA	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Control	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Static/dynamic balance							
VLBW	6.9 (1.8–26.4)	6.0 (1.5–23.5)	6.3 (1.6–24.4)	5.8 (1.5–22.9)	6.6 (1.7–25.8)	6.0 (1.4–24.8)	6.5 (1.7–25.3)
SGA	2.9 (0.7–12.1)	2.9 (0.7–12.3)	2.6 (0.6–11.2)	2.9 (0.7–12.3)	2.5 (0.6–10.9)	3.0 (0.7–12.7)	2.8 (0.7–12.0)
Control	1.0	1.0	1.0	1.0	1.0	1.0	1.0

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

4.4.6. *Visual variables that did not affect the odds of motor problems*

Accommodation and convergence did not reduce the odds of having motor problems in any of the low birth weight groups.

4.4.7. *Possible confounders*

The results were essentially the same when including sex or low IQ_{est} as possible confounders of the association between visual functions and motor skills (data not shown).

5. Discussion

In this study, we found that visual impairments significantly influenced motor problems among VLBW adolescents. In particular, problems in manual dexterity were mainly affected by impairments in vision. However, the risk of total motor and balance problems in this group were still increased after adjustment for visual impairments.

Among term SGA adolescents, motor problems were essentially unaffected by visual impairments.

One physiotherapist did all motor evaluations, one paediatric ophthalmologist performed all visual examinations and one psychologist did all neuropsychological tests, avoiding any problems of inter-tester reliability. The three examiners were blinded to group assignment and to the results of the other assessments, reducing the risk of information bias.

In all, 33% of eligible adolescents did not meet for follow-up. However, it is unlikely that the association between vision and motor skills in these adolescents were systematically different from those who met.

Since we wanted to examine associations between visual functions and motor skills that were not determined by extreme abnormal values, we excluded children with CP. Moreover, the results were essentially the same when controlling for sex and low IQ_{est} as possible confounders.

Movement ABC is standardised up to 12 years of age, whereas we have studied 14-year-old children. A ceiling effect could mask subtle differences in motor skills. However, a ceiling effect would theoretically affect mean and top centile values, whereas we have studied adolescents with scores below the 5th and 15th centile derived from our own control group. Thus, in our opinion, a possible ceiling effect is unlikely to influence our results.

The 5th centile cut-off for defining motor problems is common[2,5,8,11] and in accordance with the Movement ABC manual.[38] We also included analysis with a less strict cut-off, i.e. scores below the 15th centile, which indicates borderline motor problems. These analyses gave essentially the same results as using the 5th centile, which gives further support to our conclusions.

Other studies of VLBW populations have also reported associations between motor problems and visual functions, in particular stereoacuity,[2,10,11,15] visual acuity, contrast sensitivity and strabismus.[10,11] Which of these that are most important for motor skills varies between the studies. In our study, total motor problems were most strongly associated with impaired visual acuity, but apart form this observation the material is not large enough to safely allow speculation on the internal relative importance of the other visual variables.

The number of participants in this study was too small to include more than two variables in regression analysis. However, when we adjusted for the abnormality score

Table 6 – Crude odds ratios (OR) with 95% confidence intervals (CI) as an estimate of the relative risk of definite and borderline motor problems and adjusted for abnormality score for visual impairments in two groups of adolescents with low birth weight compared with a control group

	<5th centile		<15th centile	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Total ABC				
VLBW	10.4 (2.2–49.4)	6.8 (1.3–34.5)	5.2 (2.2–12.5)	4.0 (1.6–10.1)
SGA	5.1 (1.0–25.8)	5.1 (1.0–25.6)	1.1 (0.4–2.9)	1.1 (0.4–2.9)
Control	1.0	1.0	1.0	1.0
Manual dexterity				
VLBW	4.4 (1.1–17.5)	3.0 (0.7–13.4)	2.4 (1.0–5.7)	1.4 (0.5–3.8)
SGA	4.5 (1.2–17.6)	4.5 (1.2–17.5)	2.1 (0.9–5.0)	2.1 (0.9–5.0)
Control	1.0	1.0	1.0	1.0
Ball skills				
VLBW	3.2 (0.8–13.4)	1.7 (0.3–8.4)	1.8 (0.6–5.0)	1.2 (0.4–3.8)
SGA	[a]	[a]	0.5 (0.1–1.9)	0.4 (0.1–1.8)
Control	1.0	1.0	1.0	1.0
Static/dynamic balance				
VLBW	6.9 (1.8–26.4)	4.9 (1.2–20.1)	5.8 (1.7–19.1)	4.4 (1.2–15.7)
SGA	2.9 (0.7–12.1)	2.9 (0.7–12.1)	2.1 (0.6–7.9)	2.1 (0.6–8.0)
Control	1.0	1.0	1.0	1.0

[a] OR cannot be computed due to the value 0 in one cell (no SGA adolescents had poor ball skills).

(i.e. the sum score of all visual variables), the odds of having motor problems in the VLBW group were reduced more than by each visual variable separately. Our results therefore indicate that several visual functions are important for motor problems, and that additive effects may play an important role. None the less, we found that even after adjustment for visual impairments, adolescents born VLBW had a substantially increased risk of motor problems in general (total ABC) and in static and dynamic balance in particular.

There are several ways in which visual abilities may affect motor skills in VLBW adolescents. Vision plays an essential role in early motor learning and development,[27,45,46] and tends to dominate as a source of sensory information in the control of coordinated, voluntary movement.[28] Even in persons with otherwise normal neurodevelopment, visual deficits may directly affect their motor skills, as seen in elderly populations.[27,47]

Motor skills seem to be affected by the whole range of visual acuity, from the most severe effects seen in congenital blindness[45,46] to an association between superior motor ability and visual acuity seen in athletes.[48] Subtle visual disturbances, such as deficits in stereoacuity and contrast sensitivity, are also important.[10] Good stereoacuity is known to be an advantage especially at near distance and in tasks requiring complex hand–eye coordination.[48–50] Contrast sensitivity is important in control of movement, since it allows the detection of shape and edges of objects.[27] Improvement in contrast sensitivity has been shown to improve visually guided behaviour,[51] and reduction in contrast sensitivity on the other hand has been shown to affect tasks requiring distance judgements and mobility.[52]

There is a well known increased prevalence of brain lesions, especially periventricular leucomalacia (PVL), in VLBW children, which is not found in term SGA and control children.[53] Both the optic radiations and the corticospinal motor tracts pass through the periventricular white matter and therefore PVL is strongly associated with cerebral visual impairment as well as cerebral palsy.[54] So, in addition to the above-mentioned cause-and-effect theory, with visual impairments leading to motor deficits, the association between visual and motor problems in the VLBW group may be of a shared common aetiology. This point of view has also been advocated by other authors.[10,11] Cooke et al.[11] claim that the association of poor visual acuity and low contrast sensitivity with minor motor impairment suggests a diffuse lesion such as defective myelination of the cerebrum, which has been shown to occur in preterm infants.[55]

Finally, our finding of increased total motor and balance problems even after adjusting for visual deficits, may suggest that specific motor areas, independent of vision, have also been insulted.

We are not aware of other studies describing the association between vision and motor skills in SGA children or adolescents. Our results suggest that the motor problems in SGA adolescents cannot be explained by poor visual functions.

We have previously argued that the motor problems in term SGA adolescents may have a different origin than those of VLBW adolescents[9,33] The different effects of visual impairments on motor problems in the current study support this. Martinussen et al.[56] found reduced brain volume in SGA adolescents; however there is no evidence of increased cortical thinness[56] or increased prevalence of white matter

reduction, ventricular dilatation or thinning of corpus callosum compared with controls.[53]

Animal studies have shown that growth restriction before and after birth may result in reduced myelination and weight of the cerebellum.[57,58] In the previous study we speculated whether this mechanism may be responsible for the manual dexterity problems seen in the SGA group.[9] If this is the case, it may be reasonable to assume that deficits in visual functions may not influence the motor problems in this group, since vision and visual perception is predominantly a cerebral function.[59]

It has also been shown in animal studies that intrauterine growth retardation (IUGR) does not affect all cerebral metabolic pathways equally[60] and perhaps visual functions are dependent on pathways more resilient to IUGR.

Interestingly, the proportions of SGA adolescents with definite and borderline motor problems were approximately the same. This suggests that there is a subgroup of the SGA adolescents with very poor performance, especially in manual dexterity, whereas the rest of the SGA group does not have motor problems.

The strong associations between visual impairments and motor problems found in VLBW children in this and previous studies[2,10,11,15] suggest that visual functions are of importance for motor skills in this population. The nature of this association may be both one of cause and effect (visual impairment causing motor problems) and one of a shared common aetiology.

Our results may contribute to an increased understanding among caregivers, teachers and health professionals that it is insufficient to address visual and motor problems independently. Instead, combinations of minor impairments in different functions need to be met by a multidisciplinary approach. Especially, the findings highlight the importance of a wide assessment of visual functions in VLBW children, since having several visual impairments is more frequent among VLBW adolescents.

Although our study was not set up to investigate this, it seems possible that some visual problems may be improved with adequate treatment, for instance optimal correction for refractive errors, thereby improving motor skills.

In conclusion, visual impairments influence the motor problems in VLBW adolescents, whereas the motor problems in SGA adolescents seem to be relatively unaffected by visual impairments.

Acknowledgments

We want to thank the adolescents themselves and their parents for their co-operation and interest in the study. We also thank psychologist Siri Kulseng for providing data on visual perception.

Part of the study population was recruited from a multicenter study sponsored by the US National Institute of Child Health and Human Development, NIH (NICHD Contract nos. 1-HD-4-2803 and 1-HD-1-3127), and was funded by the Trondheim University Hospital; St. Olavs Hospital's Research Fund, and Department of Child and Adolescent Psychiatry, Norwegian University of Science and Technology.

REFERENCES

1. The Scottish Low Birthweight Study Group (Mutch L). The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment. *Arch Dis Child* 1992;**67**:675–81.
2. Torrioli MG, Frisone MF, Bonvini L, Luciano R, Pasca MG, Lepori R, et al. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. *Brain Dev* 2000;**22**:163–8.
3. Herrgard E, Luoma L, Tuppurainen K, Karjalainen S, Martikainen A. Neurodevelopmental profile at five years of children born at ⩽32 weeks gestation. *Dev Med Child Neurol* 1993;**35**:1083–96.
4. Marlow N, Roberts BL, Cooke RWI. Motor skills in extremely low birthweight children at the age of 6 years. *Arch Dis Child* 1989;**64**:839–47.
5. Jongmans M, Mercuri E, de Vries L, Dubowitz L, Henderson SE. Minor neurological signs and perceptual-motor difficulties in prematurely born children. *Arch Dis Child* 1997;**76**:F9–F14.
6. Marlow N, Roberts L, Cooke R. Outcome at 8 years for children with birth weights of 1250 g or less. *Arch Dis Child* 1993;**68**:286–90.
7. Cooke RWI, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. *Arch Dis Child* 2003;**88**:482–7.
8. Powls A, Botting N, Cooke RW, Marlow N. Motor impairment in children 12 to 13 years old with a birthweight of less than 1250 g. *Arch Dis Child Fetal Neonatal Ed* 1995;**73**:F62–6.
9. Evensen KAI, Vik T, Helbostad JL, Indredavik MS, Kulseng S, Brubakk A-M. Motor skills in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F451–5.
10. Powls A, Botting N, Cooke RWI, Stephenson G, Marlow N. Visual impairment in very low birthweight children. *Arch Dis Child* 1997;**76**:F82–7.
11. Cooke RWI, Foulder-Hughes L, Newsham D, Clarke D. Ophthalmic impairment at 7 years of age in children born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F249–53.
12. Holmstrom G, el Azazi M, Kugelberg U. Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus. *Br J Ophthalmol* 1999;**83**:143–50.
13. O'Connor AR, Stephenson T, Johnson A, Tobin MJ, Moseley MJ, Ratib S, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. *Pediatrics* 2002;**109**:12–8.
14. Larsson EK, Rydberg AC, Holmström GE. A population-based study on the visual outcome in 10-year-old preterm and full-term children. *Arch Ophthalmol* 2005;**123**:825–32.
15. Jongmans M, Mercuri E, Henderson S, de Vries L, Sonksen P, Dubowitz L. Visual function of prematurely born children with and without perceptual-motor difficulties. *Early Hum Dev* 1996;**45**:73–82.
16. Fazzi E, Bova SM, Uggetti C, Signorini SG, Bianchi PE, Maraucci I, et al. Visual-perceptual impairment in children with periventricular leukomalacia. *Brain Dev* 2004;**26**:506–12.
17. Hård A-L, Niklasson A, Svensson E, Hellström A. Visual function in school-aged children born before 29 weeks of gestation: a population-based study. *Dev Med Child Neurol* 2000;**42**:100–5.
18. Luoma L, Herrgard E, Martikainen A. Neuropsychological analysis of the visuomotor problems in children born preterm at ⩽32 weeks of gestation: a 5-year prospective follow-up. *Dev Med Child Neurol* 1998;**40**:21–30.
19. Sommerfelt K, Sonnander K, Skranes J, Andersson HW, Ahlsten G, Ellertsen B, et al. Neuropsychologic and motor function in small-for-gestation preschoolers. *Pediatr Neurol* 2002;**26**:186–91.

20. Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J. Intrauterine growth retardation: a study of long-term morbidity. *Am J Obstet Gynecol* 1982;**142**:670–7.
21. Neligan GA, Kolvin I, Scott DM, Garside RF. *Born too soon or born too small: a follow-up study to seven years of age*. London: William Heinemann Medical Books Ltd; 1976.
22. Gagliardo HGRG, Goncalves VMG, Lima MCMP, Francozo MFC, Aranha Netto A. Visual function and fine-motor control in small-for-gestational age infants. *Arq Neuropsiquiatr* 2004;**62**:955–62.
23. Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational-age babies. *Pediatrics* 1982;**69**:296–300.
24. Thordstein CM, Sultan BL, Wennergren MM, Törnqvist E, Lindecrantz KG, Kjellmer I. Visual evoked potentials in disproportionately growth-retarded human neonates. *Pediatr Neurol* 2004;**30**:262–70.
25. Martin L, Ley D, Marsal K, Hellström A. Visual function in young adults following intrauterine growth retardation. *J Pediatr Ophthalmol Strabismus* 2004;**41**:212–8.
26. Lindqvist S, Vik T, Indredavik MS, Brubakk A-M. Visual acuity, contrast sensitivity, peripheral vision and refraction in low birthweight teenagers. *Acta Ophthalmol Scand* 2007; **85**:157–64.
27. Shumway-Cook S, Woollacott MH. *Motor control. theory and practical applications*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
28. Magill RA. *Motor learning. concepts and applications*, Sixth ed. New York: McGraw-Hill Companies, Inc.; 2001.
29. van Hof-van Duin J, Cioni G, Bertuccelli B, Fazzi B, Romano C, Boldrini A. Visual outcome at 5 years of newborn infants at risk of cerebral visual impairment. *Dev Med Child Neurol* 1998;**40**:302–9.
30. Lord R, Hulme C. Perceptual judgments of normal and clumsy children. *Dev Med Child Neurol* 1987;**29**:250–7.
31. Bakketeig LS, Jacobsen G, Hoffman HJ, Lindmark G, Bergsjø P, Molne K, et al. Pre-pregnancy risk factors of small-for-gestational age births among parous women in Scandinavia. *Acta Obstet Gynecol Scand* 1993;**72**:273–9.
32. Vik T, Markestad T, Ahlsten G, Gebre-Medhin M, Hoffman HJ, Jacobsen G, et al. Body proportions and early neonatal morbidity in small-for-gestational-age infants of successive births. *Acta Obstet Gynecol Scand Suppl* 1997;**165**:76–81.
33. Evensen KAI, Sigmundsson H, Romundstad P, Indredavik MS, Brubakk A-M, Vik T. Inter- and intra-modal matching in very low birth weight and small for gestational age adolescents. *Early Hum Dev* 2007;**83**:19–27.
34. Kulseng S, Jennekens-Schinkel A, Naess P, Romundstad P, Indredavik M, Vik T, et al. Very-low-birthweight and term small-for-gestational-age adolescents: attention revisited. *Acta Paediatr* 2006;**95**:224–30.
35. Hollingshead AS. *Two factor index of social status*. New Haven, CT: Yale University; 1958.
36. Wechsler D. *Wechsler intelligence scale for children-third edition, manual*. Stockholm: Psykologiförlaget AB; 1999.
37. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F445–50.
38. Henderson S, Sugden D. *Movement assessment battery for children. Manual*. The Psychological Corporation; 1992.
39. Hyvärinen L, Näsänen R, Laurinen P. New visual acuity test for pre-school children. *Acta Ophthalmol (Copenh)* 1980;**58**:507–11.
40. *Vistech contrast sensitivity test. Manual*. Dayton, OH: Vistech Consultants, Inc.; 1988.
41. Pesudovs K, Hazel CA, Doran RML, Elliot DB. The usefulness of Vistech and FACT contrast sensitivity charts for cataract and refractive surgery outcomes research. *Br J Ophthalmol* 2004;**88**:11–6.
42. Duane A. The norms of convergence. In: Jackson E, Crisp WH, Finnoff WC, editors. *Contributions to Ophthalmic Science*. Menasha, Wisconsin: George Banta Publishing Company; 1926. p. 34–46.
43. Hayes GJ, Cohen BE, Rouse MW, De Land PN. Normative values for the nearpoint of convergence of elementary school-children. *Optom Vis Sci* 1998;**75**:506–12.
44. Beery KE. *Administration, scoring, and teaching manual for the beery-buktenica developmental test of visual-motor integration with supplemental tests of visual perception and motor coordination*. New Jersey: Modern Curriculum Press; 1997.
45. Levtzion-Korach O, Tennenbaum A, Schnitzer R, Ornoy A. Early motor development of blind children. *J Paediatr Child Health* 2000;**36**:226–9.
46. Prechtl HFR, Cioni G, Einspieler C, Bos AF, Ferrari F. Role of vision on early motor development: lessons from the blind. *Dev Med Child Neurol* 2001;**43**:198–201.
47. West CG, Gildengorin G, Haegerstrom-Portnoy G, Schneck ME, Lott L, Brabyn JA. Is vision function related to physical functional ability in older adults? *J Am Geriatr Soc* 2002;**50**:136–45.
48. Laby DM, Rosenbaum AL, Kirschen DG, Davidson JL, Rosenbaum LJ, Strasser C, et al. The visual function of professional baseball players. *Am J Ophthalmol* 1996;**122**:476–85.
49. Fielder AR, Moseley MJ. Does stereopsis matter in humans? *Eye* 1996;**10**:233–8.
50. Hrisos S, Clarke MP, Kelly T, Henderson J, Wright CM. Unilateral visual impairment and neurodevelopmental performance in preschool children. *Br J Ophthalmol* 2006;**90**:836–8.
51. Haegerstrom-Portnoy G. New procedures for evaluating vision functions of special populations. *Optom Vis Sci* 1993;**70**: 306–14.
52. Rubin GS, Roche KB, Prasada-Rao P, Fried LP. Visual impairment and disability in older adults. *Optom Vis Sci* 1994;**71**:750–60.
53. Skranes JS, Martinussen M, Smevik O, Myhr G, Indredavik M, Vik T, et al. Cerebral MRI findings in very-low-birth-weight and small-for-gestational-age children at 15 years of age. *Pediatr Radiol* 2005;**35**:758–65.
54. Edmond JC, Foroozan R. Cortical visual impairment in children. *Curr Opin Ophthalmol* 2006;**17**:509–12.
55. Huppi PS, Schuknecht B, Boesch C, Bossi E, Felblinger J, Fusch C, et al. Structural and neurobehavioral delay in postnatal brain development of preterm infants. *Pediatr Res* 1996;**39**:895–901.
56. Martinussen M, Fischl B, Larsson HB, Skranes J, Kulseng S, Vangberg TR, et al. Cerebral cortex thickness in 15-year-old adolescents with low birth weight measured by an automated MRI-based method. *Brain* 2005;**128**:2588–96.
57. Bourre JM, Mor O, Chanez C, Dumont O, Flexor MA. Influence of intrauterine malnutrition on brain development: alteration of myelination. *Biol Neonate* 1981;**39**:96–9.
58. Dobbing J, Hopewell JW, Lynch A. Vulnerability of developing brain. VII. Permanent deficit of neurons in cerebral and cerebellar cortex following early mild undernutrition. *Exp Neurol* 1971;**32**:439–47.
59. Wurtz RH, Kandel ER. Central visual pathways. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Principles of Neural Science*. 4th ed. New York: McGraw-Hill; 2000. p. 523–47.
60. Kjellmer I, Thordstein M, Wennegren M. Cerebral function in the growth-retarded fetus and neonate. *Biol Neonate* 1992;**62**:265–70.
61. Susanne Lindqvist Vik, Marit S. Indredavik, jon Skranes, Ann-Mari Brubakk (2008) Eye movements and binocular function in low birthweight teenagers. Acta Ophthalmologica (OnlineEarly Articles) doi:10.1111/j.1600-0420.2007.01133.x.

Paper III

Early Human Development (2007) **83**, 19–27

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/earlhumdev

Inter- and intra-modal matching in very low birth weight and small for gestational age adolescents ☆

Kari Anne Indredavik Evensen [a,e,*], Hermundur Sigmundsson [b,e], Pål Romundstad [c,e], Marit S. Indredavik [d,e], Ann-Mari Brubakk [a,e], Torstein Vik [c,e]

[a] *Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norway*
[b] *Department of Sociology and Political Science, Faculty of Social Sciences and Technology Management, Norway*
[c] *Department of Public Health and General Practice, Faculty of Medicine, Norway*
[d] *Department of Neuroscience, Faculty of Medicine, Norway*
[e] *Norwegian University of Science and Technology, Trondheim, Norway*

Accepted 23 March 2006

Abstract

Background: Motor problems in low birth weight children may be related to problems in sensorimotor integration processes. Specific tests of inter- and intra-modal matching have not been used in low birth weight populations.
Aim: Examine whether low birth weight adolescents have poorer performance in inter- and intra-modal matching than normal birth weight adolescents.
Study design: A population based follow up study of very low birth weight and small for gestational age children at 14 years of age.
Subjects: Fifty-three very low birth weight adolescents (VLBW: birth weight ≤1500 g), 59 term small for gestational age (SGA: birth weight <10th centile) and 82 adolescents with birth weight ≥10th centile at term (reference group).
Outcome measures: Inter- and intra-modal matching was assessed by a manual matching task and results were presented for the preferred and the non-preferred hand in the visual (inter-modal) and proprioceptive (intra-modal) condition.
Results: VLBW adolescents performed poorer in inter- and intra-modal matching compared with the reference group. However, the results were mainly due to a higher number of adolescents with cerebral palsy (CP) and a low estimated intelligence quotient (IQ_{est}) in the VLBW group. SGA adolescents showed poorer performance with their non-preferred hand compared with their preferred hand in both inter- and intra-modal matching, whereas adolescents in the reference group and VLBW adolescents with normal IQ_{est} and without CP performed equally well with both hands.

☆ ETHICS APPROVAL: The Regional Committee for Medical Research Ethics (Health Region IV) approved the protocol May 5th 2000.

* Corresponding author. Department of Laboratory Medicine, Children's and Women's Health, St. Olavs Hospital HF, N-7006 Trondheim, Norway.
E-mail address: karianne.i.evensen@ntnu.no (K.A.I. Evensen).

0378-3782/$ - see front matter
doi:10.1016/j.earlhumdev.2006.03.015

Conclusion: VLBW adolescents with normal IQ_{est} and without CP do not have major problems in inter- and intra-modal matching. The poorer performance with the non-preferred hand in the SGA group may suggest a specific effect of intrauterine growth retardation.

1. Introduction

Prematurity and intrauterine growth restriction both represent risk factors for motor problems. Several studies have reported increased prevalence of motor problems in children with birth weight below 1500 g (very low birth weight: VLBW) at preschool [1—4] and school age [5—9]. We have previously reported that VLBW adolescents have increased risk of motor problems both in manual dexterity, ball skills and balance compared with a reference group [10].

Children who have been growth retarded in utero are usually diagnosed by having a low birth weight for their gestational age (small for gestational age: SGA). Studies on motor problems among younger SGA children born at term have shown inconsistent results [11—13]. We found that SGA adolescents, particularly boys, had increased risk of motor problems in manual dexterity [10].

Motor problems in children with low birth weight may be related to problems in sensorimotor integration processes. Such processes may involve different sensoric modalities and include transfer of information from one hemisphere to the other. It has been widely reported that low birth weight children also have problems related to visuo-motor functions [5,14—20] which could in part explain the motor problems in these children.

A specific test matching vision with proprioception (inter-modal matching) and the proprioceptive space of one hand with the proprioceptive space of the other (intra-modal matching) has been developed [21]. Associations between poor inter- and intra-modal matching and increased risk of motor problems in children in normal populations have been reported [22—26]. Although both VLBW and SGA children are at increased risk of having motor problems, inter- and intra-modal matching have not been examined in these risk groups.

Moreover, in low birth weight children tests of inter- and intra-modal matching may be particularly relevant since studies using magnetic resonance imaging (MRI) have reported a higher prevalence of ventricular dilatation [27—33], white matter reduction [29—31], thinning of corpus callosum [28,30—32] and periventricular gliosis/leukomalacia [27,29,30,32] in VLBW than in normal birth weight children and adolescents.

Thus, the aim of this study was to examine whether low birth weight adolescents have poorer performance in inter- and intra-modal matching than adolescents with appropriate birth weight, assessed by a manual matching task.

2. Method

2.1. Study design

The study is a population based follow up study of two groups of adolescents with low birth weight; one group of preterm very low birth weight (VLBW) adolescents and one group of term small for gestational age (SGA) adolescents. The groups are being compared with a reference group of normal birth weight.

The VLBW adolescents were born to mothers living in the two counties of North- and South-Trøndelag (total population approximately 375,000) and admitted to the Neonatal Intensive Care Unit (NICU) at the University Hospital in Trondheim (the referral hospital) between January 1986 and December 1988. Children born in 1988 were assessed thoroughly at one and six years of age [27,34].

The SGA and reference adolescents were born to mothers living in the Trondheim region (total population approximately 135,000). They were enrolled before week 20 of pregnancy in a multicenter study between January 1986 and March 1988 [35,36]. A 10% random sample of women (para 1 and 2) was selected for follow up during pregnancy. At birth, all children born to mothers in the random sample and all the SGA children were included for follow up. The children were examined by project paediatricians at one and five years of age [37].

The present follow up study was carried out from November 2000 to October 2002, when the children were 14 years old, as part of a larger study. The follow up examination included assessment of motor and intellectual abilities, in addition to neuropediatric and psychiatric evaluation.

2.2. Study population

2.2.1. VLBW adolescents

Ninety-nine children with a birth weight ≤1500 g were admitted to the NICU in 1986—1988. Of these children, 23 died, one child with trisomi 21 was excluded, and six had moved out of the region. Of the remaining 69 children, 15 (22%) did not consent to participate and one child with CP (quadriplegia) was not able to do the test. Thus, a total of 53 VLBW children (29 boys and 24 girls) were examined.

In the VLBW group, 19 adolescents were born SGA, whereas 34 were born non-SGA, according to Norwegian standards [38]. However, we have treated them as one group since there were no differences between SGA and non-SGA VLBW adolescents on any of the inter- or intra-modal matching tests.

2.2.2. SGA adolescents

Of 1200 eligible women, 104 (8.7%) gave birth to a SGA child, defined by a birth weight <10th centile, adjusted for gestational age, gender and parity. At follow-up, 12 children had moved. Of the remaining children, 33 (36%) did not consent to participate, leaving 59 SGA children (27 boys and 32 girls) for further examination.

2.2.3. Non-SGA adolescents

The reference group comprised 120 children with birth weight ≥10th centile for gestational age, born at term to mothers in the 10% random sample. Ten children had moved, while 28 (25%) did not consent. In total, 82 children in the reference group (35 boys and 47 girls) were examined.

2.2.4. Non-participants

There were no significant differences in maternal age, duration of pregnancy, the infants' birth weight, body length and head circumference between those who participated and those who did not consent to participation in any of the groups.

Gestational age and anthropometric measurements at birth are shown in Table 1.

2.3. Methods

Each adolescent was tested with a manual matching task according to von Hofsten and Rösblad [21]. This manual matching task has been used in different age groups and populations [21—24].

The manual matching task uses a test board measuring 60 × 80 cm. The task is to match pins from underneath the test board to targets at the top of the board. Two different conditions to locate the target were examined; one when the target is seen (Fig. 1A: Inter-modal matching; matching of vision and proprioception) and one when the target is felt (Fig. 1B: Intra-modal matching; matching of the proprioceptive space of one hand with the proprioceptive space of the other). The subjects had four attempts with each hand (preferred and non-preferred hand) in each condition.

X- and *y*-coordinates were used to measure the distance between the pin position and the target. *Absolute error* (*a*), the distance in mm between the pin (p) and the target (T), was calculated according to the equation $a = \sqrt{x_p^2 + y_p^2}$. Mean absolute error was calculated as the sum of the absolute errors over the four trials ($a_1 - a_4$) divided by four $\left(\bar{a} = \sum_{a=1}^{4} a/4\right)$.

The *systematic error* (*s*) reflects a systematic shift between the system (visual or proprioceptive) that indicates the position of the target and the proprioceptive system of the matching arm [21]. The systematic error is the distance between the centre of the four pin positions (P_c) and the target (T) (Fig. 2). The coordinates of P_c are calculated by the mean position in the *x*- and *y*-directions. The systematic error is calculated by the formula $\left(s = \sqrt{x_{P_c}^2 + y_{P_c}^2}\right)$.

The *random error* (*r*) reflects the level of precision in pointing [21], and is the distance between the pin position (p) to the centre of pin positions (P_c) (Fig. 2). The mean random error is calculated as the sum of the random errors over the four trials ($r_1 - r_4$) divided by four $\left(\bar{r} = \sum_{r=1}^{4} r/4\right)$.

Mean *directional error* was calculated for the horizontal and vertical direction as the mean of the distance between the four pin positions and the target in *x*- and *y*-directions separately.

All tests were performed by the first author, who was blinded to group assignment.

Cerebral palsy (CP) was diagnosed and classified as diplegia, hemiplegia and quadriplegia by project paediatricians [39].

An estimate of intelligence quotient (IQ_{est}) was calculated using the vocabulary, arithmetic, block design and picture arrangement subscales of Wechsler Intelligence Scales (WISC-III) [40,41]. We defined "low IQ_{est}" below 2 SD of the reference group mean value.

Socioeconomic status (SES) was calculated according to Hollingshead's Two Factor Index of Social Position [42].

2.4. Ethics

The Regional Committee for Medical Research Ethics approved the study protocol. Written informed consent was obtained from both adolescents and parents.

2.5. Statistical analysis

SPSS for windows version 12.0.1 (SPSS Inc, Chicago, IL) was used for data analysis, and a significance level of 0.05 was chosen. Two-group comparisons were made by Student's *t*-test for variables with a normal distribution and Mann—Whitney *U*-test for variables with a non-normal distribution. The χ^2 test was used to analyse differences in proportions between groups.

Absolute, systematic and random errors were log normal, thus geometric means with 95% confidence intervals are presented for these variables. We used parametric methods on the log transformed data.

With a power of 80% ($\beta = 0.20$) and $\alpha = 0.05$, this study may detect a 3.8 mm difference in mean absolute error in the

Table 1 Gestational age and anthropometric measurements at birth in two groups of low birth weight children and a non-SGA reference group in a follow-up study

	VLBW ($n = 53$)		SGA ($n = 59$)		Reference group ($n = 82$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Gestational age (weeks)	28.9	(2.7)***	39.5	(1.1)	39.6	(1.2)
Birth weight (g)	1180	(236)***	2916	(210)***	3699	(455)
Body length (cm)†	38.5	(2.8)***	48.4	(2.0)***	51.0	(1.8)
Head circumference (cm)‡	26.9	(2.5)***	33.8	(1.2)***	35.4	(1.1)

***$p < 0.001$ vs. the non-SGA reference group (gestational age and birth weight were the selection criteria, and differed by definition vs. the reference group).

†Body length was only measured for 34 children in the VLBW group.

‡Head circumference was only measured for 41 children in the VLBW group.

VLBW = Very Low Birth Weight.

SGA = Small for Gestational Age.

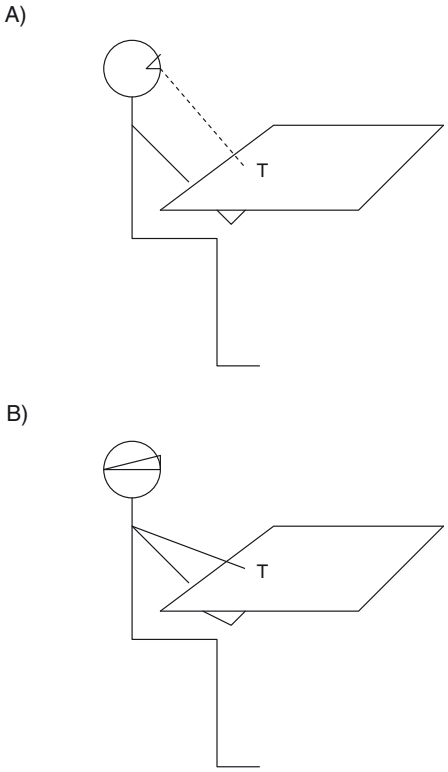


Figure 1 Illustration of the inter- and intra-modal matching test. Upper panel (A): Inter-modal matching (seen target). The subject looks at (stippled line) the target (T), and the objective is to place a pin with one hand (solid line) from underneath the test board as close to the target as possible. The subject undertakes four attempts with the preferred hand and four attempts with the non-preferred hand. All four attempts are used in the calculations (see Fig. 2 and text). Lower panel (B): Intra-modal matching (felt target). The eyes of the subject are covered and the index finger is placed on the target (T) of the upper side of the test board. The objective is to place a pin with the other hand from underneath the test board as close to the target as possible. The subject undertakes four attempts with each hand (preferred and non-preferred). All four attempts are used in the calculations (see Fig. 2 and text).

visual condition (preferred hand) and a 5.7 mm difference in the proprioceptive condition (preferred hand) between the VLBW and the reference group.

3. Results

VLBW and SGA adolescents were shorter, lighter and had smaller head circumference than the reference group, whereas body mass index did not differ between the groups (Table 2). IQ_{est} and SES were lower in the VLBW group than in the reference group. There were no differences between groups with respect to age or sex. In the reference group, eight of 82 (9.8%) adolescents were left-handed, compared with 10 of 53 (18.9%) VLBW and 10 of 59 (16.9%) SGA adolescents (n.s.).

Six (11.3%) adolescents in the VLBW group (four boys, two girls) had CP; five had diplegia, one hemiplegia. One (1.7%) adolescent in the SGA group (a boy) had diplegia. Nine (17%) adolescents in the VLBW group (one boy, eight girls) and four (6.8%) adolescents in the SGA group (all boys) had a low IQ_{est} compared with three (3.7%) adolescents in the reference group (two boys, one girl).

3.1. Absolute errors

Mean absolute error was higher in the VLBW group compared with the reference group in the proprioceptive condition with the non-preferred hand (Table 3). There were no significant differences in mean absolute errors between the SGA group and the reference group. However, both VLBW and SGA adolescents had higher mean absolute errors with their non-preferred hand compared with their preferred hand in the proprioceptive condition (mean difference in mm: 5.1; 95% CI: 1.2;8.9 and 4.0; 95% CI: 0.9;7.1 respectively) (Table 5). The SGA group also had higher mean absolute error for the non-preferred hand than the preferred hand in the visual condition (Table 5). These differences between hands were not found in the reference group.

When we excluded subjects with CP and low IQ_{est}, the difference between the VLBW group and the reference group in mean absolute error for the non-preferred hand using proprioception disappeared. Also, the difference between hands in the VLBW group in the proprioceptive condition was no longer statistically significant. In the SGA group the differences remained statistically significant (data not shown).

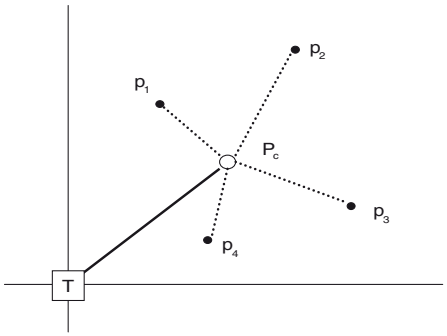


Figure 2 Illustration of the measurements used in the calculation of systematic and random error (adapted from von Hofsten and Rösblad [21]). The pin positions (the subject's four trials) are labelled p_1, p_2, p_3 and p_4. The errors of the four trials were transformed into one coordinate system, in which the correct position of a pin, the target (T), defines the origo. The centre of pin positions is labelled P_c. Systematic error is the distance between P_c and T. Random error is the distance between each of the pin positions (p_1—p_4) and P_c. The mean random error is calculated as the sum of the random errors over the four trials divided by four.

Table 2 Age, height, weight, body mass index, head circumference and socioeconomic status in two groups of low birth weight adolescents and a non-SGA reference group

	VLBW ($n=53$)		SGA ($n=59$)		Reference group ($n=82$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	14.1	(0.3)	14.2	(0.3)	14.2	(0.3)
Height (cm)	162	(8.7)***	164	(7.4)**	167	(7.7)
Weight (kg)	50.4	(11.5)**	52.2	(8.5)**	56.8	(10.8)
Body Mass Index (kg/m^2)	19.2	(3.8)	19.5	(2.9)	20.2	(3.0)
Head circumference (cm)	54.4	(1.9)***	54.7	(2.0)***	55.9	(1.5)
Estimated intelligence quotient (IQ_{est})	79.7	(19.1)***	90.2	(17.8)	94.5	(16.6)
Socioeconomic status	3.2	(1.3)*	3.4	(1.3)	3.8	(1.1)

*$p<0.05$ **$p<0.01$ ***$p<0.001$ vs. the non-SGA reference group.
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.

3.2. Systematic errors

Systematic errors did not differ significantly between the low birth weight groups and the reference group (Table 4). However, the VLBW group had higher systematic error with the non-preferred hand compared with the preferred hand in the proprioceptive condition (mean difference in mm: 4.4; 95% CI: 0.6;8.3) (Table 5). The SGA group had higher systematic errors with the non-preferred hand than the preferred hand in both the visual (mean difference in mm: 3.0; 95% CI: 0.4;5.5) and the proprioceptive condition (mean difference in mm: 4.6; 95% CI: 0.9;8.2) (Table 5).

When we excluded subjects with CP and low IQ_{est}, the difference between hands in the VLBW group in the proprioceptive condition was no longer statistically significant. In the SGA group the results were unchanged (data not shown).

3.3. Random errors

Mean random errors were higher in the VLBW group compared with the reference group using both the preferred and the non-preferred hand in the visual condition, and the non-preferred hand in the proprioceptive condition (Table 6). There were no differences in mean random errors between the SGA and the reference group.

When we excluded subjects with CP and low IQ_{est}, the mean random error for the preferred hand using vision remained higher in the VLBW group compared with the reference group, while the differences with the non-preferred hand using vision and proprioception disappeared.

There were no differences in mean random errors between the preferred and the non-preferred hand in either condition in any of the groups (data not shown).

3.4. Directional errors

The VLBW group pointed more to the left with their preferred hand in the visual condition compared with the reference group ($p=0.04$). This difference disappeared when we excluded subjects with CP and low IQ_{est} (data not shown).

There were no significant differences in the vertical direction (over/undershots) between any of the low birth weight groups and the reference group (data not shown).

Table 3 Results of the manual matching task: *Mean absolute error* (geometric mean with 95% confidence intervals) in two groups of low birth weight adolescents and a non-SGA reference group

Condition	VLBW		SGA	Reference group
	Including cases with CP/low IQ_{est}	Excluding cases with CP/low IQ_{est}		
	($n=53$) Mean† (95% CI)	($n=40$) Mean† (95% CI)	($n=59$) Mean† (95% CI)	($n=82$) Mean† (95% CI)
Visual preferred hand	16.9 (15.0;19.1)	16.4 (14.4;18.6)	14.3 (12.6;16.3)	15.0 (13.7;16.4)
Visual non-preferred hand	17.1 (15.0;19.5)§	15.8 (13.8;18.1)	16.9 (15.0;19.1)	14.8 (13.5;16.3)
Proprioceptive preferred hand	22.3 (19.7;25.2)	20.4 (17.9;23.3)	20.8 (18.7;23.1)	21.7 (19.6;24.0)
Proprioceptive non-preferred hand	25.7 (22.3;29.5)*	23.6 (20.6;27.1)	24.2 (21.5;27.2)	21.5 (19.5;23.7)

†Geometric mean (mm).
*$p<0.05$ vs. the non-SGA reference group (Student's t-test).
§$0.05\leq p\leq 0.07$ vs. the non-SGA reference group (Student's t-test).
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
CP = Cerebral Palsy.
IQ_{est} = Estimated Intelligence Quotient.

Table 4 Results of the manual matching task: *Systematic error* (geometric mean with 95% confidence intervals) in two groups of low birth weight adolescents and a non-SGA reference group

Condition	VLBW		SGA	Reference group
	Including cases with CP/low IQ_{est}	Excluding cases with CP/low IQ_{est}		
	($n=53$) Mean† (95% CI)	($n=40$) Mean† (95% CI)	($n=59$) Mean† (95% CI)	($n=82$) Mean† (95% CI)
Visual preferred hand	13.1 (10.8;15.9)	12.3 (9.8;15.3)	10.4 (8.5;12.8)	11.8 (10.2;13.5)
Visual non-preferred hand	13.7 (11.6;16.1)	12.7 (10.6;15.1)	13.7 (11.5;16.3)	11.6 (10.2;13.2)
Proprioceptive preferred hand	16.7 (13.6;20.5)	14.6 (11.4;18.7)	15.2 (12.7;18.1)	16.2 (13.8;19.1)
Proprioceptive non-preferred hand	18.9 (15.1;23.7)	16.8 (13.1;21.7)	18.7 (15.2;23.0)	16.8 (14.6;19.4)

†Geometric mean (mm).
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
CP = Cerebral Palsy.
IQ_{est} = Estimated Intelligence Quotient.

3.5. Gender differences

When stratified by gender, the differences in mean absolute and systematic error between hands were essentially the same in the VLBW group (Table 7). Also, the higher mean random errors with the preferred and the non-preferred hand using vision compared with the reference group were essentially the same for boys and girls, although only significant for VLBW boys with the preferred hand compared with reference boys ($p=0.03$). However, VLBW boys had higher mean random error with the preferred hand also in the proprioceptive condition ($p=0.02$). The results were unchanged when we excluded subjects with CP and low IQ_{est} (data not shown).

In the SGA group, the difference in mean absolute error and systematic error between the non-preferred and the preferred hand in the visual condition was mainly found in boys (Table 7). In the proprioceptive condition, the difference between hands was mainly due to a difference in mean absolute error and systematic error in girls. These results remained unchanged when we excluded subjects with CP and low IQ_{est} (data not shown).

4. Discussion

In this study, we found that VLBW adolescents performed poorer in inter- and intra-modal matching compared with a reference group. However, the results were mainly

Table 5 Results of the manual matching task: Difference between the non-preferred and the preferred hand in *mean absolute error* and *systematic error* with 95% confidence intervals in two groups of low birth weight adolescents and a non-SGA reference group

Condition	VLBW		SGA	Reference group
	Including cases with CP/low IQ_{est}	Excluding cases with CP/low IQ_{est}		
	($n=53$) Mean (95% CI)	($n=40$) Mean (95% CI)	($n=59$) Mean (95% CI)	($n=82$) Mean (95% CI)
Difference between visual non-preferred and preferred hand in mean absolute error (mm)	0.5 (−2.3;3.2)	−0.6 (−3.2;2.0)	2.6 (0.2;4.9)*	−0.2 (−1.8;1.4)
Difference between proprioceptive non-preferred and preferred hand in mean absolute error (mm)	5.1 (1.2;8.9)*	3.9 (−0.1;7.9)§	4.0 (0.9;7.1)*	−0.5 (−3.3;2.4)
Difference between visual non-preferred and preferred hand in systematic error (mm)	0.3 (−2.5;3.1)	−0.4 (−3.2;2.4)	3.0 (0.4;5.5)*	−0.4 (−2.3;1.4)
Difference between proprioceptive non-preferred and preferred hand in systematic error (mm)	4.4 (0.6;8.3)*	3.6 (−1.0;8.2)	4.6 (0.9;8.2)*	−0.2 (−3.5:3.1)

*$p<0.05$ (paired t-test).
§$0.05\leq p\leq 0.07$ (paired t-test).
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
CP = Cerebral Palsy.
IQ_{est} = Estimated Intelligence Quotient.

Table 6 Results of the manual matching task: *Mean random error* (geometric mean with 95% confidence intervals) in two groups of low birth weight adolescents and a non-SGA reference group

Condition	VLBW		SGA	Reference group
	Including cases with CP/low IQ_{est}	Excluding cases with CP/low IQ_{est}		
	($n=53$) Mean† (95% CI)	($n=40$) Mean† (95% CI)	($n=59$) Mean† (95% CI)	($n=82$) Mean† (95% CI)
Visual preferred hand	9.4 (8.6;10.3)*	9.3 (8.4;10.3)*	8.2 (7.4;9.1)	8.0 (7.4;8.7)
Visual non-preferred hand	9.6 (8.6;10.8)*	8.9 (7.8;10.1)	8.5 (7.6;9.5)	8.3 (7.5;9.1)
Proprioceptive preferred hand	12.8 (11.4;14.2)	11.9 (10.7;13.2)	12.0 (10.9;13.1)	11.9 (11.0;12.9)
Proprioceptive non-preferred hand	14.1 (12.7;15.7)*	13.3 (12.2;14.5)	12.7 (11.4;14.2)	12.1 (11.2;13.1)

†Geometric mean (mm).
*$p<0.05$ vs. the non-SGA reference group (Student's t-test).
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
CP = Cerebral Palsy.
IQ_{est} = Estimated Intelligence Quotient.

explained by a higher number of adolescents with CP and low IQ_{est} in the VLBW group. SGA adolescents showed poorer performance with their non-preferred hand compared with their preferred hand in both inter- and intra-modal matching, whereas adolescents in the reference group and VLBW adolescents with normal IQ_{est} and without CP performed equally well with both hands. We are not aware of other studies that have used the manual matching task in low birth weight populations.

The 10th centile definition of SGA is crude, and a certain proportion of normal small infants could have been classified as SGA, whereas some infants who may have been growth retarded in utero, could have been classified as belonging to the reference group. This may have contributed to an underestimation of potential differences between SGA and reference adolescents. The VLBW adolescents were classified according to a birth weight ≤1500 g. In the VLBW group, 36% were born SGA. However, there were no differences in inter- and intra-modal matching between SGA and non-SGA VLBW adolescents, and we have therefore chosen to treat them as one group, as a contrast to the adolescents born at term.

The reason why 76 adolescents (28%) did not want to participate in this study is not known. We found, however, no significant differences in key variables between mothers and children who participated and those who did not consent to participate. It is therefore unlikely that the results are due to selection bias.

The examiner was blinded to the adolescents' group assignment, thus, it is unlikely that there is information bias.

Table 7 Results of the manual matching task by gender: Difference between the non-preferred and the preferred hand in *mean absolute error* and *systematic error* with 95% confidence intervals in two groups of low birth weight adolescents and a non-SGA reference group

Group	Difference between hands in mean absolute error visual condition (mm)	Difference between hands in mean absolute error proprioceptive condition (mm)	Difference between hands in systematic error visual condition (mm)	Difference between hands in systematic error proprioceptive condition (mm)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
VLBW				
Boys ($n=29$)	0.8 (−3.6;5.3)	5.6 (−0.5;11.7)§	0.5 (−4.0;5.1)	3.8 (−2.1;9.7)
Girls ($n=24$)	0.03 (−3.1;3.2)	4.5 (−0.3;9.2)§	−0.01 (−3.4;3.4)	5.2 (−0.02;10.4)§
SGA				
Boys ($n=27$)	4.2 (0.4;8.0)*	0.8 (−4.4;6.1)	4.9 (1.0;8.8)*	2.0 (−4.2;8.2)
Girls ($n=32$)	1.2 (−2.0;4.3)	6.7 (2.9;10.4)**	1.4 (−2.1;4.8)	6.8 (2.3;11.2)**
Reference group				
Boys ($n=35$)	0.03 (−2.2; 2.3)	2.3 (−2.7; 7.3)	−0.4 (−3.1;2.3)	3.3 (−2.7;9.3)
Girls ($n=47$)	−0.3 (−2.7; 2.0)	−2.6 (−5.9; 0.8)	−0.4 (−3.1;2.2)	−2.8 (−6.4;0.9)

*$p<0.05$, **$p<0.01$ (paired t-test).
§$0.05\leq p\leq 0.07$ (paired t-test).
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.

The only finding in the inter-modal matching condition (i.e. matching of vision and proprioception) was higher random errors in the VLBW group, which may imply a slight deficit in the transfer between visual input and motor output, leading to less precise matching. This may be consistent with the finding of reduced visuo-motor integration in VLBW children [5,14—20].

In the intra-modal matching condition (i.e. matching of the proprioceptive space of one hand with the proprioceptive space of the other), the VLBW group demonstrated poorer performance with the non-preferred hand than the reference group in terms of higher mean absolute and random errors. However, these results were no longer statistically significant when we excluded subjects with CP and low IQ_{est}.

Power analyses suggested that we were able to detect differences of approximately 5 mm between groups in both conditions. Smaller differences may be biologically interesting, but are less likely to be of major clinical importance. Compared with other known impairments in VLBW populations, both in motor abilities [1—10] and in visuo-motor integration [5,14—20], it may be somewhat surprising that the VLBW adolescents did not differ more from adolescents born at term on these tasks. This could suggest that the regions of the brain concerned with manual matching tasks are preserved in VLBW adolescents. One may also speculate whether other parts of the brain have adjusted their capacity in order to process such information adequately [43].

However, we discovered a difference in performance between hands in both the VLBW and the SGA group, but not in the reference group. The VLBW group had poorer performances with their non-preferred hand compared with their preferred hand in the intra-modal matching condition, reflected by higher mean absolute error and systematic error. There were no gender differences in this group, and the differences between hands disappeared when we excluded subjects with CP and low IQ_{est}.

The SGA group had poorer performances with their non-preferred hand compared with their preferred hand in both inter- and intra-modal matching conditions (mean absolute error and systematic error), and these differences remained significant when we excluded subjects with CP and low IQ_{est}. The gender differences in the SGA group were striking; the boys seem to have poorer inter-modal matching with the non-preferred hand, which may imply a deficit in visual input and/or motor output in this hand. This may be in accordance with their poor manual dexterity on the Movement ABC [10]. For the SGA girls, the difference between hands seemed to manifest itself only in the intra-modal matching condition.

Asymmetrical performances have also been found in studies on other groups of children with motor problems [22—24,44]. Sigmundsson and Whiting [24] argue that these findings could be accounted for by insufficiency within the hemisphere controlling the non-preferred hand, with or without a dysfunctional corpus callosum. Our finding that this asymmetry was more evident in the SGA than in the VLBW group, may suggest a specific effect of intrauterine growth retardation. The reason why the asymmetry manifested itself differently in boys and girls cannot be answered in this study.

5. Conclusion

VLBW adolescents with normal IQ_{est} and without CP do not seem to have major problems in inter- and intra-modal matching as assessed by the manual matching task. However, SGA adolescents performed poorer with their non-preferred than their preferred hand both in inter- and intra-modal matching. This asymmetry may be a part of the complex aetiology of motor problems in this group, and may be a specific effect of intrauterine growth retardation.

Acknowledgements

We want to thank the teenagers themselves and their parents for their co-operation and interest in the study. We also thank psychologist Siri Kulseng for providing data on intellectual abilities.

Part of the study population was recruited from a multicenter study sponsored by the US National Institute of Child Health and Human Development, NIH (NICHD contract No. 1-HD-4-2803 and No. 1-HD-1-3127), and was funded by Trondheim University Hospital; St. Olavs Hospital's Research Fund, and Department of Child and Adolescent Psychiatry, Norwegian University of Science and Technology.

References

[1] The Scottish Low Birthweight Study Group. (Mutch L. The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment. Arch Dis Child 1992;67(6):675–81.
[2] Ong LC, Boo NY, Chandran V. Predictors of neurodevelopmental outcome of Malaysian very low birthweight children at 4 years of age. J Paediatr Child Health Aug 31 2001; 37(4):363–8.
[3] Torrioli MG, Frisone MF, Bonvini L, Luciano R, Pasca MG, Lepori R, et al. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. Brain Dev 2000;22(3):163–8.
[4] Herrgard E, Luoma L, Tuppurainen K, Karjalainen S, Martikainen A. Neurodevelopmental profile at five years of children born at < or = 32 weeks gestation. Dev Med Child Neurol 1993;35(12):1083–96.
[5] Jongmans M, Mercuri E, de Vries L, Dubowitz L, Henderson SE. Minor neurological signs and perceptual-motor difficulties in prematurely born children. Arch Dis Child 1997;76(1):F9–14.
[6] Marlow N, Roberts BL, Cooke RWI. Motor skills in extremely low birthweight children at the age of 6 years. Arch Dis Child 1989;64(6):839–47.
[7] Marlow N, Roberts L, Cooke R. Outcome at 8 years for children with birth weights of 1250 g or less. Arch Dis Child 1993;68(3 Spec No):286–90.
[8] Cooke RWI, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child Jun 1 2003;88(6):482–7.
[9] Powls A, Botting N, Cooke RW, Marlow N. Motor impairment in children 12 to 13 years old with a birthweight of less than 1250 g. Arch Dis Child Fetal Neonatal Ed 1995;73(2):F62–6.
[10] Evensen KAI, Vik T, Helbostad JL, Indredavik MS, Kulseng S, Brubakk A-M. Motor skills in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004;89(5):F451–5.
[11] Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J. Intrauterine growth retardation: a study of long-term morbidity. Am J Obstet Gynecol 1982;142(6 Pt 1):670–7.

[12] Sommerfelt K, Sonnander K, Skranes J, Andersson HW, Ahlsten G, Ellertsen B, et al. Neuropsychologic and motor function in small-for-gestation preschoolers. Pediatr Neurol Mar 2002; 26(3):186–91.
[13] Neligan GA, Kolvin I, Scott DM, Garside RF. Born too soon or born too small: a follow-up study to seven years of age. London: William Heinemann Medical Books Ltd.; 1976.
[14] Taylor GH, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: neuropsychological findings. J Int Neuropsychol Soc 2004;10(2):149–63.
[15] Luoma L, Herrgard E, Martikainen A. Neuropsychological analysis of the visuomotor problems in children born preterm at < or = 32 weeks of gestation: a 5-year prospective follow-up. Dev Med Child Neurol 1998;40(1):21–30.
[16] Foulder-Hughes LA, Cooke RWI. Motor, cognitive, and behavioural disorders in children born very preterm. Dev Med Child Neurol 2003;45(2):97–103.
[17] Olsen P, Vainionpaa L, Paakko E, Korkman M, Pyhtinen J, Jarvelin MR. Psychological Findings in Preterm Children Related to Neurologic Status and Magnetic Resonance Imaging. Pediatrics Aug 1 1998;102(2):329–36.
[18] Taylor HG, Klein N, Minich NM, Hack M. Middle-school-age outcomes in children with very low birthweight. Child Dev 2000;71(6):1495–511.
[19] Pietz J, Peter J, Graf R, Rauterberg-Ruland I, Rupp A, Sontheimer D, et al. Physical growth and neurodevelopmental outcome of nonhandicapped low-risk children born preterm. Early Hum Dev Sep 2004;79(2):131–43.
[20] Caravale B, Tozzi C, Albino G, Vicari S. Cognitive development in low risk preterms at three to four years of life. Arch Dis Child Fetal Neonatal Ed 2005;90(6):F474–9.
[21] von Hofsten C, Rösblad B. The integration of sensory information in the development of precise manual pointing. Neuropsychologia 1988;26(6):805–21.
[22] Sigmundsson H, Ingvaldsen RP, Whiting HTA. Inter- and intrasensory modality matching in children with hand—eye coordination problems. Exp Brain Res 1997;114(3):492–9.
[23] Sigmundsson H, Ingvaldsen RP, Whiting HTA. Inter- and intrasensory modality matching in children with hand—eye coordination problems: exploring the developmental lag hypothesis. Dev Med Child Neurol 1997;39(12):790–6.
[24] Sigmundsson H, Whiting HTA. Hand preference in children with developmental coordination disorders: cause and effect? Brain Cogn 2002;49(1):45–53.
[25] Sigmundsson H. Inter-modal matching and bimanual co-ordination in children with hand—eye co-ordination problems. Nordisk Fysioter 1999;3:55–64.
[26] Hulme C, Biggerstaff A, Moran G, McKinlay I. Visual, kinaesthetic and cross-modal judgements of length by normal and clumsy children. Dev Med Child Neurol 1982;24(4):461–71.
[27] Skranes JS, Nilsen G, Smevik O, Vik T, Brubakk AM. Cerebral MRI of very low birth weight children at 6 years of age compared with the findings at 1 year. Pediatr Radiol 1998;28(6):471–5.
[28] Mercuri E, Jongmans M, Henderson S, Pennock J, Chung YL, de Vries L, et al. Evaluation of the corpus callosum in clumsy children born prematurely: a functional and morphological study. Neuropediatrics 1996;27(6):317–22.
[29] Olsén P, Pääkkö E, Vainionpää L, Pyhtinen J, Järvelin M-R. Magnetic resonance imaging of periventricular leukomalacia and its clinical correlation in children. Ann Neurol 1997;41(6): 754–61.
[30] Skranes JS, Martinussen M, Smevik O, Myhr G, Indredavik M, Vik T, et al. Cerebral MRI findings in very-low-birth-weight and small-for-gestational-age children at 15 years of age. Pediatr Radiol Aug 2005;35(8):758–65.
[31] Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born preterm. Lancet 1999;353(9165):1653–7.
[32] Cooke RWI, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. Arch Dis Child Fetal Neonatal Ed 1999; 81(2):F116–21.
[33] Maalouf EF, Duggan PJ, Rutherford MA, Counsell SJ, Fletcher AM, Battin MR, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. J Pediatr 1999; 135(3):351–7.
[34] Skranes JS, Vik T, Nilsen G, Smevik O, Andersson HW, Brubakk AM. Can cerebral MRI at age 1 year predict motor and intellectual outcomes in very-low-birthweight children? Dev Med Child Neurol 1998;40(4):256–62.
[35] Bakketeig LS, Jacobsen G, Hoffman HJ, Lindmark G, Bergsjø P, Molne K, et al. Pre-pregnancy risk factors of small-for-gestational age births among parous women in Scandinavia. Acta Obstet Gynecol Scand 1993;72(4):273–9.
[36] Vik T, Markestad T, Ahlsten G, Gebre-Medin M, Hoffman HJ, Jacobsen G, et al. Body proportions and early neonatal morbidity in small-for-gestational-age infants of successive births. Acta Obstet Gynecol Scand Suppl 1997;76:80–5.
[37] Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. Early Hum Dev 1996;45(3):245–55.
[38] Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand Jun 1 2000;79(6):440–9.
[39] Russman BS. Disorders of motor execution I. Cerebral palsy. In: David RB, editor. Child and adolescent neurology. St. Louis: Mosby-Year Book, Inc.; 1998. p. 453–68.
[40] Wechsler D. Wechsler Intelligence Scale for Children — Third Edition, Manual. Stockholm: Psykologiförlaget AB; 1999.
[41] Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM. Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004;89(5): F445–50.
[42] Hollingshead AS. Two factor index of social status. New Haven, CT: Yale University; 1958.
[43] Saper CB, Iversen S, Frackowiak R. Integration of sensory and motor function: the association areas of the cerebral cortex and the cognitive capabilities of the brain. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science, 4th ed. USA: McGraw-Hill; 2000. p. 349–80.
[44] Estil LB, Whiting HTA. The validity of the inter- and/or intrahemispheric deficit hypothesis as an explanation of the co-occurrence of motor and language impairments. Exp Brain Res 2002;143(1):126–9.

Paper IV

Early Human Development 85 (2009) 511–518

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children

Kari Anne I. Evensen [a,b,*], Jon Skranes [a,c], Ann-Mari Brubakk [a,c], Torstein Vik [a]

[a] Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[b] Department of Physical Medicine and Rehabilitation, St. Olav's University Hospital, Trondheim, Norway
[c] Department of Pediatrics, St. Olav's University Hospital, Trondheim, Norway

ARTICLE INFO

Article history:
Received 30 January 2009
Received in revised form 15 April 2009
Accepted 23 April 2009

Keywords:
Bayley scales of infant development
Motor problems
Movement ABC
Peabody developmental motor scales
Small for gestational age
Very low birth weight

ABSTRACT

Background: Motor problems are common in children born preterm or small for gestational age.
Aim: To study the predictive value of early motor assessments for later motor skills.
Subjects: Twenty-eight children born preterm with very low birth weight (VLBW: birth weight ≤1500 g), 57 children born small for gestational age (SGA: birth weight <10th centile) at term and 77 term-born controls with normal birth weight.
Methods: The psychomotor development index (PDI) of the Bayley Scales of Infant Development was used as a measure of motor skills at age one, the Peabody Developmental Motor Scales (PDMS) at age five and the Movement Assessment Battery for Children (Movement ABC) at age 14. Low/borderline low scores were defined as <−2SD/−1SD (PDI) or <5th/15th centile (PDMS; Movement ABC).
Results: In the VLBW group, motor problems in adolescence were identified both by low PDI (sensitivity: 0.80; 95%CI:0.38–0.96) and PDMS scores (sensitivity: 0.83; 95%CI:0.44–0.97). In the SGA and the control group sensitivity was poor for low PDI and moderate for low PDMS scores. However, in the SGA group, sensitivity increased when borderline low PDMS scores were used as cut-off (sensitivity: 0.75; 95%CI:0.41–0.93). Specificity of PDI and PDMS was high in all three groups.
Conclusions: Both PDI and PDMS may be valuable tools for early identification of motor problems in VLBW children, whereas PDMS best predicted motor problems in the two other groups. In all three groups, a normal motor examination at 1 and 5 years was highly predictive of normal motor skills at age 14.

1. Introduction

Very low birth weight (VLBW) children have an increased risk for delayed motor development during the first year of life [1–4], often developing into more established motor problems at preschool [5–8] and school age [9–13]. Furthermore, these children do not seem to grow out of their motor problems as they enter adolescence [14–16].

In contrast, results of studies in children born small for gestational age (SGA) at term are less clear. Whereas some authors have reported motor delay at some stages in infancy [17,18] and a higher prevalence of motor problems in young children [19] and adolescents [15], other studies do not support these findings [20–23].

Early identification of children with motor impairments is important in order to provide support and intervention for the child (and parents) as early as possible. Optimal treatment for motor problems may reduce academic and psychosocial problems [24].

Accurate tools for measuring motor development are central in identification, classification and diagnosis of motor deficiencies [25,26], and a number of tests have been developed in order to evaluate motor behaviour and motor skills in infants and children [27–37]. Among these, the Motor Scale of the Bayley Scales of Infant Development (BSID), the Peabody Developmental Motor Scales (PDMS) and the Movement Assessment Battery for Children (Movement ABC) are all commonly used tests both in clinical work and in scientific studies [38–40]. The BSID and the PDMS are cumulative scales testing young children up to their ceiling level of motor performance [28,29]. The Movement ABC is one of the few tests that can be used for older children and is more specifically designed to identify children with motor problems, without focusing especially on their maximum performance [31].

Several studies have used BSID [1–4,41–43], PDMS [42,44–46] and Movement ABC [5,6,8,12,14,47] to evaluate motor skills in low birth weight populations. However, we have not been able to identify studies who have examined the predictive value of early motor evaluation with respect to long-term motor outcome in adolescence.

* Corresponding author. Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway. Tel.: +47 7257 4660; fax: +47 7386 7708.
E-mail address: karianne.i.evensen@ntnu.no (K.A.I. Evensen).

0378-3782/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2009.04.007

In a follow-up study of 14 year old adolescents we have previously reported a high prevalence of motor problems in VLBW children, whereas children born SGA at term in particular had increased risk for poor manual dexterity [15]. Most of the adolescents also had their motor skills assessed by BSID at 1 year of age and by PDMS at 5 years of age.

The aim of the present study was to examine the predictive value of motor assessments performed at an early age in these populations.

2. Methods

2.1. Study design

In this study we used data from a previously reported follow-up study of three groups of children born during 1986–88 [15,48,49]. One group comprised children born prematurely with very low birth weight (VLBW; birth weight ≤1500 g), the second consisted of children born at term with low weight/small for gestational age (SGA; birth weight <10th centile adjusted for gestational age, sex and parity), while the third group comprised control children born at term with a birth weight ≥10th centile.

The VLBW children were admitted after birth to the Neonatal Intensive Care Unit (NICU) of St. Olav's University Hospital in Trondheim, Norway, but only those born in 1988 were originally invited to participate in the one and five year follow-up [48]. The SGA and control children were born in 1986–88 to mothers who had been enrolled before week 20 of pregnancy in a multicenter study on causes and consequences of intrauterine growth retardation [49]. A 10% random sample of women was selected for follow-up during pregnancy, and at birth all children born to mothers in the random sample and all the SGA children were included for follow-up.

Motor examinations were performed at 1, 5 and 14 years of age. Between 70 and 80% of the children met for each examination, however, not every child was examined at all three examinations. Since our main objective was to study the predictive value of motor examination performed at 1 and 5 years of age, we chose to use all available data. The principal analyses were therefore done for participants who met at 1 and 14 years of age and for children who met at 5 and 14 years of age separately. Thus, the number of participants is not identical in the two comparisons. In addition, we also restricted the analyses to children who met for all three examinations in order to examine changes in classifications throughout the years.

2.2. Study groups

2.2.1. VLBW group

Fifty-one children with a birth weight ≤1500 g were admitted to the NICU of St. Olav's University Hospital in Trondheim (the referral hospital) in 1988. Eleven of these children died during the neonatal period and one child with trisomy 21 was excluded. At 1 year (corrected age), eight children had moved. Among the remaining 31 VLBW children, a successful motor examination was obtained in 28. At 14 years of age, five of these did not consent, leaving 23 VLBW children (12 boys, 11 girls) with motor assessments at 1 and 14 years of age.

At 5 years of age, five additional children born in 1987 were also invited to participate. From the original cohort, nine children had moved and six did not consent. Thus, 29 VLBW children were examined, with complete test results in 28. At 14 years of age, three children did not consent, leaving 25 children (16 boys, 9 girls) with assessments at 5 and 14 years of age.

Two of the children (boys) participating at 1, 5 and 14 years of age had cerebral palsy (CP) of spastic diplegic type of functional level II according to the Gross Motor Function Classification System (GMFCS) (walking independently, but with limitations on uneven surfaces or on inclines) [50].

2.2.2. SGA group

Of 1200 eligible women, 104 (9%) gave birth to a SGA child, defined by a birth weight <10th centile, adjusted for gestational age, sex and parity. One child had a congenital malformation (oesophagal atresia) and was excluded. At 1 year of age, three children had moved and 28 were not able or willing to participate. Thus, 72 children were examined. At follow-up at 14 years, further five children had moved and 22 children did not consent, leaving 45 SGA children (19 boys, 26 girls) with assessments at 1 and 14 years of age.

At 5 years of age, eight had moved and 17 were not able or willing to participate. Thus, 78 SGA children were examined, and complete test results were obtained in 77. At 14 years, three of these had moved and 25 did not consent, leaving 49 SGA children (22 boys, 27 girls) with assessments at 5 and 14 years of age.

One of the participating boys had spastic diplegic CP of GMFCS level II.

2.2.3. Control group

The control group comprised 120 children with birth weight ≥10th centile for gestational age, born at term (i.e. between 37 and 42 weeks gestation) to mothers in the 10% random sample of the 1200 participants. Two children with congenital malformations (Goldenhar syndrome and urinary tract malformation) were excluded.

At 1 year of age, three children had moved and 18 were not able or willing to participate. Thus, 97 control children were examined. Of these, further seven had moved and 19 did not consent at 14 years, leaving 71 children in the control group (32 boys, 39 girls) with assessments at 1 and 14 years of age.

At 5 years, eight children had moved and 14 did not consent. Thus, 96 controls were examined. At 14 years, further five children had moved and 18 did not consent, leaving 73 control children (34 boys, 39 girls) with assessments at 5 and 14 years of age.

2.2.4. Non-participants

Among the children examined at an early age (i.e. eligible for this study) there were no differences in maternal age, duration of pregnancy, birth weight, head circumference or Apgar scores after 1 and 5 min between those who participated, and those who did not consent at 14 years of age, in any of the groups. In the VLBW group, prevalence of intraventricular hemorrage (IVH) and length of stay in NICU did not differ significantly, but non-participants had more days on mechanical ventilator compared with participants ($p = 0.02$). There was a non-significantly higher proportion of non-participating children with low motor scores at age one in the VLBW group (40%) and at age five in the SGA (36%) and the control group (17%) compared with participants (Tables 3 and 5).

2.3. Methods

2.3.1. Bayley scales of infant development (BSID)

At age one, all children were examined by one test technician with the Bayley Scales of Infant Development (BSID) [28], which measures both mental and motor development in children from 0.1 to 30 months of age. In this study we used the results obtained from the motor scale, which consists of maximum 81 items. The motor scale of the BSID at this age involves activities common in children's daily life including standing up, standing, walking, throwing a ball etc. The children were tested from their basal level up to their ceiling level and raw scores (i.e. the total number of items the child has passed including all items below the basal level) on the motor scale were converted to age-adjusted standard scores; the psychomotor development index (PDI), ranging from 50 to 150 (which corresponds to ±3SD for the standardisation sample).

According to the manual, we defined low scores ('abnormal') as a PDI more than two standard deviations (SD) below the mean of all children in the control group ($n = 97$), corresponding to a PDI<86. We defined borderline low scores as a PDI<1 SD, corresponding to a PDI<98.

2.3.2. Peabody developmental motor scales (PDMS)

At age five, motor skills were assessed by one paediatrician (JS) with the eye-hand coordination (fine motor, scale C), balance (gross motor, scale B) and locomotor (gross motor, scale D) subscales of the Peabody Developmental Motor Scales (PDMS) [29]. The eye-hand coordination scale consists of items such as copying various designs using wooden blocks, cutting with scissors and drawing. The balance scale includes both static balance (such as standing on one foot) and dynamic balance (walking on a wooden beam on the floor). The locomotor scale consists of jumping, hopping, skipping, galloping and rolling forward. Each item was scored in agreement with the manual: 0 = cannot perform item, 1 = clear resemblance to correct performance and 2 = correct performance, giving a maximal cumulative raw score of 86 for eye-hand coordination, 66 for balance and 116 for locomotor.

We defined low scores ('abnormal') as at least one of the three subscales <5th centile [20] in our control group ($n=96$), corresponding to a cumulative raw score of 75 for eye-hand coordination, 51 for balance and 90 for locomotion. Borderline low scores were defined as at least one of the three subscales <15th centile (77 for eye-hand coordination, 54 for balance and 100 for locomotor).

2.3.3. Movement assessment battery for children (Movement ABC)

At age 14, the children were tested with the Movement Assessment Battery for Children (Movement ABC) [31] by one physiotherapist (KAIE) who was blinded to group adherence and to the previous test results. The Movement ABC consists of eight items grouped as three subscores: Manual dexterity (three items), ball skills (two items) and static/dynamic balance (three items). Each item is scored between zero (optimal score) and five, giving a total ABC score ranging from zero to 40. According to the manual, scores <5th centile indicate definite motor problems [31]. We used the highest age band, designed for 11 to 12 year old children. Since the study population was examined at 14 years of age, we used the 5th centile derived from all the children in the control group who met for motor assessment ($n=81$). This corresponded to a total ABC score of 14, well in accordance with the 5th centile in the manual.

Manual dexterity score was missing for one control due to a recent hand cast and static/dynamic balance score was missing for one VLBW subject due to an ankle sprain. Thus, total ABC scores were missing for these two children.

2.3.4. Ethics

The study was approved by the Ethical committee for medical research in Mid-Norway. Written informed consent was obtained from the children and their parents.

2.3.5. Statistical analysis

SPSS 15.0 was used for data analyses. Two-sided p-values less than 5% were considered statistically significant. The Mann Whitney *U*-test was used to analyse differences in ordinal or scalar variables. The Pearson's chi-square test or Fisher's exact test was used to analyse differences in proportions between groups. Receiver-operating characteristics curves (ROC curves) were used to calculate area under the curve (AUC) as an estimate of diagnostic accuracy of the PDI and the PDMS with respect to outcome on the Movement ABC. Where appropriate, 95% confidence intervals (CI) are given. For proportions, these were calculated using Wilson's method, as recommended by Altman [51].

Table 1
Birth weight, head circumference, gestational age and Apgar scores in preterm VLBW, term SGA and control children who were examined at 1 and 14 and/or 5 and 14 years of age.

	VLBW ($n=28$)		SGA ($n=57$)		Control ($n=77$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Birth weight (grams)	1187	(210)	2919	(212)	3720	(454)
Head circumference (cm)	26.8	(2.6)	33.8	(1.2)	35.4	(1.1)
Gestational age (weeks)	28.7	(2.5)	39.5	(1.1)	39.7	(1.2)
Apgar score 1 min	6.8	(2.3)	8.8	(1.1)	8.9	(0.3)
Apgar score 5 min	8.4	(1.4)	9.8	(1.3)	9.8	(1.0)

VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.

Table 2
Mean values and standard deviations (SD) of the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development at age one, the Peabody Developmental Motor Scales (PDMS) at age five and the Movement ABC at age 14 in preterm VLBW, term SGA and control children.

	VLBW		SGA		Control	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
PDI at age one						
Number of children[a]	23		45		71	
Corrected age in months	12.3	(0.3)	13.3	(0.6)	13.3	(0.6)
PDI	100.3	(17.5)	104.6	(13.0)	108.9	(12.0)
PDMS at age five						
Number of children[b]	25		49		73	
Age in years	5.8	(0.3)	5.3	(0.3)	5.3	(0.3)
Eye/hand coordination	79.0	(5.6)	79.1	(5.3)	80.7	(3.3)
Balance	56.8	(5.4)	58.7	(4.8)	59.1	(4.3)
Locomotor	100.6	(11.5)	105.2	(8.1)	105.9	(5.4)
Movement ABC at age 14						
Number of children[c]	28		57		77	
Age in years	13.9	(0.2)	14.2	(0.3)	14.2	(0.3)
Manual dexterity	2.5	(3.2)	2.1	(3.1)	1.2	(1.6)
Ball skills	2.7	(2.6)	1.3	(1.5)	1.6	(1.9)
Static/dynamic balance	5.0	(4.4)	3.7	(3.0)	3.4	(2.8)
Total ABC score	10.3	(8.8)	7.1	(5.5)	6.2	(4.2)

VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
[a] Children who were examined at 1 and 14 years of age.
[b] Children who were examined at 5 and 14 years of age.
[c] Total number included in the study (i.e. children who were examined at 1 and 14 and/or 5 and 14 years of age).

3. Results

3.1. Background

Table 1 shows some clinical characteristics of the participating children. The VLBW group had median 1 day (range: 0–35) on mechanical ventilator and length of stay in NICU was median 64 days (range: 1–386). There were two VLBW children with IVH grade I.

Table 2 shows the results of the motor tests for all children included in this study.

3.2. Children with examinations at 1 and 14 years of age

In the VLBW group, ROC curve analyses indicated that 92% of the children were correctly classified by the PDI into those with and those without motor problems at age 14 (AUC: 0.92; CI: 0.78–1.0). In the

Table 3
Proportion of children with a low Psychomotor Development Index (PDI <2SD) of the Bayley Scales of Infant Development at age one and Movement ABC scores <5th centile at age 14 in preterm VLBW, term SGA and control children.

	VLBW ($n=23$)		SGA ($n=45$)		Control ($n=71$)	
	n	(%)	*n*	(%)	*n*	(%)
PDI	4	(17.4)	4	(8.9)	3	(4.2)
Manual dexterity[a]	4	(17.4)	10	(22.2)	3	(4.3)
Ball skills	4	(17.4)	0	(0)	3	(4.2)
Static/dynamic balance[b]	4	(18.2)	6	(13.3)	3	(4.2)
Total ABC[c]	5	(22.7)	8	(17.8)	2	(2.9)

VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
[a] One control had missing data on Manual dexterity.
[b] One VLBW had missing data on Static/dynamic balance.
[c] These two children therefore had missing data on Total ABC.

Table 4
Sensitivity, specificity, positive and negative predictive value with 95% confidence interval of a low Psychomotor Development Index (PDI <2SD) of the Bayley Scales of Infant Development at age one in order to predict motor problems (Movement ABC scores <5th centile) at age 14 in preterm VLBW, term SGA and control children.

PDI <2SD	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)
Total ABC <5th centile								
VLBW	0.80	(0.38–0.96)	1.0	(0.82–1.0)	1.0	(0.51–1.0)	0.94	(0.74–0.99)
SGA	0.13	(0.02–0.47)	0.92	(0.79–0.97)	0.25	(0.05–0.70)	0.83	(0.69–0.91)
Control	0.0	(0.0–0.66)	0.97	(0.90–0.99)	0.0	(0.0–0.66)	0.97	(0.90–0.99)
Manual dexterity <5th centile								
VLBW	1.0	(0.51–1.0)	1.0	(0.83–1.0)	1.0	(0.51–1.0)	1.0	(0.83–1.0)
SGA	0.10	(0.02–0.40)	0.91	(0.78–0.97)	0.25	(0.05–0.70)	0.78	(0.63–0.88)
Control	0.0	(0.0–0.56)	0.97	(0.90–0.99)	0.0	(0.0–0.66)	0.96	(0.88–0.98)
Ball skills <5th centile								
VLBW	0.25	(0.05–0.70)	0.84	(0.62–0.94)	0.25	(0.05–0.70)	0.84	(0.62–0.94)
SGA	[a]		0.91	(0.79–0.96)	[a]		1.0	(0.91–1.0)
Control	0.0	(0.0–0.56)	0.96	(0.88–0.98)	0.0	(0.0–0.56)	0.96	(0.88–0.98)
Static/dynamic balance <5th centile								
VLBW	0.75	(0.30–0.95)	0.94	(0.74–0.99)	0.75	(0.30–0.95)	0.94	(0.74–0.99)
SGA	0.0	(0.0–0.39)	0.90	(0.76–0.96)	0.0	(0.0–0.49)	0.85	(0.72–0.93)
Control	0.0	(0.0–0.56)	0.96	(0.88–0.98)	0.0	(0.0–0.56)	0.96	(0.88–0.98)

PPV = Positive Predictive Value.
NPV = Negative Predictive Value.
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
[a] Sensitivity and PPV cannot be calculated because no children in the SGA group scored <5th centile on Ball skills.

SGA group, the AUC was 0.73 (CI: 0.57–0.90), whereas in the control group AUC was 0.70 (CI: 0.58–0.82).

The proportions of children with low scores among those who were examined at 1 and 14 years of age are shown in Table 3, while Table 4 shows sensitivity, specificity, positive and negative predictive value of a low PDI in predicting motor problems at age 14. A low PDI correctly identified four of five VLBW children with later motor problems, two of whom had CP, while all children with a normal ABC score at 14 years of age had a normal PDI at 1 year of age.

In the SGA group, a low PDI identified only one of eight SGA children with later motor problems, resulting in poor sensitivity and low positive predictive value (Table 4). The one child identified had spastic diplegic CP.

In the control group, a low PDI at 1 year did not identify the two children with motor problems at age 14. However, specificity was high both in the SGA and the control group (Table 4).

Table 4 also shows the results for the different Movement ABC subscores. Manual dexterity was best predicted by a low PDI in the VLBW group, while in the SGA group the diagnostic efficiency measures were essentially the same for all subscores of the Movement ABC (Table 4).

3.3. Children with examinations at 5 and 14 years of age

The AUC for the three PDMS subscales in the VLBW group was 0.75 (CI: 0.47–1.0) for eye-hand coordination, 0.89 (CI: 0.70–1.0) for balance and 0.86 (CI: 0.61–1.0) for locomotor.

In the SGA group, the AUC for the three PDMS subscales at age five was slightly lower than in the VLBW group. For eye-hand coordination it was 0.74 (CI: 0.56–0.91), for balance 0.86 (CI: 0.73–1.0) and for locomotor 0.81 (CI: 0.61–1.0).

In the control group, AUC was 0.84 (CI: 0.73–0.94) for eye-hand coordination, 0.90 (CI: 0.76–1.0) for balance and 0.65 (CI: 0.35–0.95) for locomotor.

Table 5 shows the proportions of children with low scores at 5 and 14 years of age, while Table 6 shows sensitivity, specificity, positive and negative predictive values of a low PDMS score in predicting motor problems at age 14. In the VLBW group, a low PDMS score identified five of six children with motor problems at age 14, two of whom had CP.

In the SGA group, a low PDMS score identified four of eight children who had motor problems at age 14, including the one child with CP.

In the control group, a low PDMS score correctly identified one of the two subjects with motor problems at 14 years of age.

Again, specificity was high in all three groups (Table 6), indicating that most children without motor problems at age 14 had normal scores at age five.

Table 6 also shows the results of the different subscores on the Movement ABC. Again, manual dexterity problems were best predicted by a low PDMS score in the VLBW group, but now also in the SGA group, while static/dynamic balance was best predicted in the control group.

3.4. Children with borderline low scores at 1 and 5 years

Using borderline low PDI or PDMS as cut-offs resulted in better sensitivity for both the PDI (0.50; CI: 0.22–0.78) and the PDMS (0.75; CI: 0.41–0.93) for later motor problems in the SGA group, while sensitivity was unchanged in the VLBW and the control group. However, specificity was lower in all three groups (data not shown).

Regarding the Movement ABC subscores, sensitivity was unchanged in the VLBW group, whereas a borderline low PDMS score identified seven of eight SGA children with manual dexterity problems (sensitivity: 0.88; CI: 0.53–0.98) and four of six SGA children with static/dynamic balance problems (sensitivity: 0.67; CI: 0.30–0.90) at age 14.

Table 5
Proportion of children with low scores (<5th centile) on each of the three subscales of the Peabody Developmental Motor Scales (PDMS) and on at least one of three PDMS subscales at age five and Movement ABC scores <5th centile at age 14 in preterm VLBW, term SGA and control children.

	VLBW ($n=25$)		SGA ($n=49$)		Control ($n=73$)	
	n	(%)	n	(%)	n	(%)
Eye/hand coordination	6	(24.0)	8	(16.3)	1	(1.4)
Balance	3	(12.0)	2	(4.1)	2	(2.7)
Locomotor	5	(20.0)	4	(8.2)	1	(1.4)
PDMS	8	(32.0)	9	(18.4)	4	(5.5)
Manual dexterity[a]	5	(20.0)	8	(16.3)	3	(4.2)
Ball skills	4	(16.0)	0	(0)	2	(2.7)
Static/dynamic balance[b]	5	(20.8)	6	(12.2)	3	(4.1)
Total ABC[c]	6	(25.0)	8	(16.3)	2	(2.8)

VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
[a] One control had missing data on Manual dexterity.
[b] One VLBW had missing data on Static/dynamic balance.
[c] These two children therefore had missing data on Total ABC.

Table 6
Sensitivity, specificity, positive and negative predictive value with 95% confidence interval of a low score on the Peabody Developmental Motor Scales at age five (PDMS; at least one of three subscores <5th centile) in order to predict motor problems (Movement ABC scores <5th centile) at age 14 in preterm VLBW, term SGA and control children.

PDMS <5th centile	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)
Total ABC <5th centile								
VLBW	0.83	(0.44–0.97)	0.83	(0.61–0.94)	0.63	(0.31–0.86)	0.94	(0.72–0.99)
SGA	0.50	(0.22–0.78)	0.88	(0.74–0.95)	0.44	(0.19–0.73)	0.90	(0.77–0.96)
Control	0.50	(0.09–0.91)	0.96	(0.88–0.99)	0.25	(0.05–0.70)	0.99	(0.92–1.0)
Manual dexterity <5th centile								
VLBW	1.0	(0.57–1.0)	0.85	(0.64–0.95)	0.63	(0.31–0.86)	1.0	(0.82–1.0)
SGA	0.63	(0.31–0.86)	0.90	(0.77–0.96)	0.56	(0.27–0.81)	0.93	(0.80–0.97)
Control	0.0	(0.0–0.56)	0.94	(0.86–0.98)	0.0	(0.0–0.49)	0.96	(0.88–0.98)
Ball skills <5th centile								
VLBW	0.50	(0.15–0.85)	0.71	(0.50–0.86)	0.25	(0.07–0.59)	0.88	(0.66–0.97)
SGA	[a]		0.82	(0.69–0.90)	[a]		1.0	(0.91–1.0)
Control	0.0	(0.0–0.66)	0.94	(0.86–0.98)	0.0	(0.0–0.49)	0.97	(0.90–0.99)
Static/dynamic balance <5th centile								
VLBW	0.80	(0.38–0.96)	0.79	(0.57–0.91)	0.50	(0.22–0.78)	0.94	(0.72–0.99)
SGA	0.33	(0.10–0.70)	0.84	(0.70–0.92)	0.22	(0.06–0.55)	0.90	(0.77–0.96)
Control	0.33	(0.06–0.79)	0.96	(0.88–0.99)	0.25	(0.05–0.70)	0.97	(0.90–0.99)

PPV = Positive Predictive Value.
NPV = Negative Predictive Value.
VLBW = Very Low Birth Weight.
SGA = Small for Gestational Age.
[a] Sensitivity and PPV cannot be calculated because no children in the SGA group scored <5th centile on Ball skills.

In the control group, one of three children with manual dexterity problems was identified by borderline low PDI and PDMS. One of three controls with ball skills problems was identified by a borderline low PDI.

3.5. Analyses excluding children with CP

When we excluded the children with CP from the analyses AUC for the PDI in the VLBW group was 0.87 (CI: 0.65–1.0). For the PDMS it was 0.79 (CI: 0.31–1.0) for eye/hand coordination, 0.83 (CI: 0.57–1.0) for balance and 0.79 (CI: 0.43–1.0) for locomotor. In this group, sensitivity of the PDI (both <1 and 2SD) for total motor problems at age 14 was reduced to 0.67 (CI: 0.21–0.94) and sensitivity of the PDMS (both <5th and 15th centile) was reduced to 0.75 (CI: 0.30–0.95).

In the SGA group, AUC for PDI was 0.70 (CI: 0.52–0.97), for PDMS eye/hand coordination 0.70 (CI: 0.52–0.89), for balance 0.84 (CI: 0.70–1.0) and for locomotor 0.79 (CI: 0.56–1.0). A low PDI did not identify any SGA children with later motor problems, while the sensitivity of a low PDMS score and a borderline low PDI was reduced to 0.43 (CI: 0.16–0.75). Sensitivity of a borderline low PDMS score was reduced to 0.71 (CI: 0.36–0.92).

Specificity was unchanged in both groups.

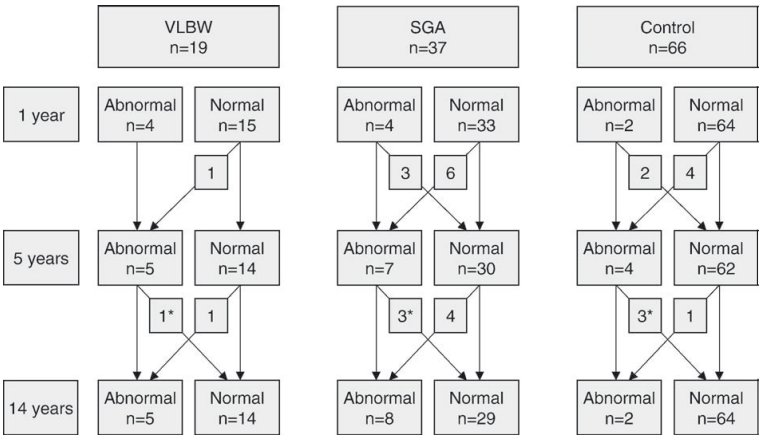


Fig. 1. Proportion of children with 'abnormal' and 'normal' scores at each examination among children with complete test results at all three examination points, illustrating children who changed from 'normal' to 'abnormal' and vice versa. The asterisk indicates children who were classified as 'normal' at age one, 'abnormal' at age five and 'normal' again at age 14.

VLBW Very Low Birth Weight
SGA Small for Gestational Age

'Abnormal':

At 1 year: PDI<2SD;
At 5 years: at least one of the three PDMS subscales <5th centile;
At 14 years: a total Movement ABC score <5th centile.

3.6. Children who were examined at all three examination points

When we restricted analyses to the children who had met at 1, 5 and 14 years of age AUC and sensitivity of a low PDI and PDMS was essentially the same in all three groups (data not shown). In the VLBW group, specificity of a low PDMS score was increased to 0.93 (CI: 0.69–0.99), whereas specificity was essentially the same in the SGA and control group.

Fig. 1 shows that seven (10.6%) controls and two (10.5%) VLBW children changed classification from one to 14 years of age. A total of 13 SGA children (35.1%) ($p = 0.003$ vs controls) changed their classification.

The one VLBW child who changed from 'normal' at age one to 'abnormal' at age five were again classified as 'normal' at age 14. The same was the case for three of six SGA children and three of four controls.

The two children who changed classification in the VLBW group had a higher gestational age and fewer days on mechanical ventilator than those who did not change classification (data not shown). The SGA and control children who changed classification did not differ from those who did not change classification with respect to birth weight, head circumference, gestational age or Apgar scores after 1 and 5 min.

4. Discussion

The main finding of the present study is that regardless of being born prematurely, small for gestational age at term or with normal birth weight (controls), a normal motor examination at 1 and 5 years of age is highly predictive of normal motor skills at 14 years of age. Among VLBW children with motor problems at age 14, a high proportion was identified using either Bayley Scales of Infant Development at age one or the Peabody Developmental Motor Scales at age five. In contrast, SGA and control children with motor problems at age 14 were not identified by the Bayley Scales of Infant Development at 1 year of age, while fifty percent were identified by Peabody Developmental Motor Scales at 5 years of age. In the SGA group, sensitivity increased by including those with borderline low scores at age one and five. In particular, the five year examination identified seven of eight SGA children with later manual dexterity problems.

A strength of the present study is that all motor tests at age 14 were carried out by one physiotherapist (KAIE) who was blinded to group adherence. At 1 and 5 years of age, the assessments were done by one examiner, blinded to neonatal history in the VLBW group, and for group adherence regarding SGA and control children. It may be a weakness that the examiner knew which children were born VLBW at the early examinations, but on the other hand, in daily clinical practice knowledge of whether a child was born preterm or not is the reality.

Although our follow-up rate varied between 70 and 80%, comparable to other long-term follow-up studies [16,52], a higher proportion of non-participants had low scores at the early examinations compared with participants (not statistically significant). If these non-participants with low scores at the early examinations would still have low scores at 14 years of age, this would have resulted in better sensitivity. In contrast, if they would all have normal scores at 14 years of age, specificity would be slightly reduced. However, since there were no major differences in background characteristics between non-participants and participants, the latter assumption seems less probable. Thus, we consider it unlikely that the main results are explained by selection bias. Due to the limited sample size, some of the confidence intervals, especially for sensitivity and positive predictive values, were wide, and the point estimates must therefore be interpreted with caution. However, for specificity and negative predictive values, the confidence intervals were narrower, supporting our main conclusion that a normal motor examination at age one or five is highly predictive of normal motor skills at age 14.

The cut-offs for motor problems used in this study are in accordance with the respective test manuals [28,29,31] with the modification described by Sommerfelt et al. [20] for the PDMS. Percentiles and standard deviations are derived from our own control group.

Although some misclassification cannot be excluded when cut-offs are used [26], the relatively high AUC's of the ROC curve analyses for all groups when the PDI and the PDMS were used as continuous variables, and therefore not affected by cut-off for motor problems at age one and five, support the diagnostic efficiency measures found in this study.

The VLBW children were slightly younger than the control children at the 1 and 14 year follow-up, but older than controls at the five year examination. However, the PDI of the BSID is independent of age at testing, and both the BSID and the PDMS are cumulative scales, i.e. the children are tested up to their ceiling level [28,29]. The outcome measure, the Movement ABC, is not designed to determine basal and ceiling levels, but to identify children with motor problems [31]. However, in this study we do not compare test results between groups, and we therefore consider the small age differences to be unimportant.

Although several authors have studied motor development in low birth weight groups [5,9,10,14,45], we are not aware of others who have examined sensitivity, specificity and predictive values of the BSID and the PDMS with respect to motor outcome in adolescence. However, in children born with extremely low birth weight, a very recent study by Goyen and Lui [53] has examined the predictive value of the PDMS at 3 years of age with regard to developmental coordination disorder at 8 years of age, including ROC curves, sensitivity and specificity. They found that the majority of children with motor problems at 8 years of age could be identified by the PDMS at 3 years of age. Moreover, this study used the 15th centile on the Movement ABC as cut-off for adverse outcome, and the ROC curve analyses yielded a cut-off on the PDMS at the 27th centile for fine and the 41st centile for gross motor function. Our results show that definite motor problems can be identified in VLBW children already at 1 year of age using a stricter cut-off.

Our study suggests that PDI and PDMS predicted later motor problems better in the VLBW group than in the other groups. The reason for this may be linked to the aetiology of motor problems. A number of MRI studies have consistently reported white matter pathology as a consequence of periventricular leukomalacia to be common in VLBW children and adolescents [48,54–58]. Several white matter regions, in particular the corpus callosum, internal capsule and superior fasciculus, have shown less integrity on fractional anisotropy maps in VLBW adolescents compared with controls [58]. Furthermore, studies have shown associations between white matter pathology and motor problems in VLBW children and adolescents [48,54,58]. Thus, it is likely that motor problems in VLBW children may have more severe and focal perinatal causes than in SGA and control children. This could in part explain why the PDI and the PDMS identified children with later motor problems better in the VLBW than in the SGA and control group. The fact that all three children with spastic diplegic CP were correctly identified as having motor problems at 1 and 5 years of age, further supports that the PDI and the PDMS are sensitive to motor problems caused by perinatal brain lesions. Apart from the one child with CP in the SGA group, motor problems in SGA children may be due to more subtle and diffuse brain dysfunctions, which may become more apparent with age. This may explain why we were able to identify more children in this group with later motor problems at age five than at age one. Thus, these children may "grow into" motor problems due to higher demands as they enter kindergarten and school.

Another explanation for our findings in the SGA group may be that the BSID, focusing on the attainment of critical milestones and using a

simple pass/fail assessment [28,59], mainly measures gross motor function. It may therefore be reasonable that the PDI was less predictive of manual dexterity problems, which seems to be a specific finding in this group [15].

The proportion of children who changed classification across the three examinations was higher in the SGA group than in the two other groups. This may suggest a high prevalence of borderline motor problems in the SGA group. However, in all three groups, the children who changed classification from 'abnormal' at age five to 'normal' at age 14 had all been classified as 'normal' at age one. One could therefore speculate that the modified PDMS cut-off was too high. However, this was not supported by other findings in our study, where the proportion of children having motor problems by this definition was 5.5% in the control group, close to the expected proportion, and that PDMS in fact identified 50% of the children with later motor problems both in the SGA and in the control group.

Finally, taking into consideration the continuous development of the child's brain [60], it may be reasonable that a significant proportion of SGA children changed classification and that motor problems were not identified in a high proportion of control and SGA children. Neurodevelopmental changes can result in disappearance of dysfunctions present at early age, but also children without signs of dysfunction at an early age can grow into a functional deficit with increasing age due to the age-related increase in complexity of neural functions [60]. However, reassuring in this study was the high specificity and negative predictive values of the PDI already at 1 year of age.

It is important for physical therapists to use both clinical judgment as well as objective motor test scores when assessing young children [39]. A study by De Kleine et al. [47] has shown that general paediatric examination has limited ability to identify motor problems. Therefore, we argue that systematic evaluation is needed in order to identify children at risk of later motor problems. Early identification of motor problems could also enhance alertness for psychiatric, attentional, social and academic problems often seen in VLBW adolescents [61] and promote subsequent intervention when needed. Some of these problems may also be linked directly to poor motor skills, for instance preventing the children from writing fluently or kicking a ball. This may in turn discourage them from normal playground and school activities [24], and thus reduce their self confidence and social competence [61].

Both BSID and PDMS were primarily developed to discriminate between infants with a deviant neuromotor condition and those falling within the range of typical development and not to predict future motor disorders [62]. However, our results suggest that for VLBW children, being a risk population for later motor problems, these tests may be included in a routine assessment at an early age in order to predict future problems or normality. For SGA children born at term, our results suggest that alertness for later problems seems warranted, since these children were less likely to be identified as early as 1 year of age.

In conclusion, a normal psychomotor development index of the Bayley Scales of Infant Development at age one and normal scores on Peabody Developmental Motor Scales at age five were highly predictive of normal motor skills at age 14 in children born VLBW, SGA and with normal birth weight. Among VLBW children, the Bayley Scales of Infant Development and the Peabody Developmental Motor Scales may be valuable early assessment tools for identifying later motor problems. Including children with borderline motor problems on the Peabody Developmental Motor Scales at age five, most SGA children with later motor problems were identified, in particular those with poor manual dexterity scores.

Acknowledgements

We want to thank the children and their parents for their co-operation and interest in the study. We are grateful to test technician Helle Andersson for providing data on the Bayley Scales of Infant Development at 1 year of age and to Professor of medical statistics Stian Lydersen at the Faculty of Medicine, Norwegian University of Science and Technology, for reviewing the statistical methods.

Financial Support

Part of the study population was recruited from a multicenter study sponsored by the US National Institute of Child Health and Human Development, NIH (NICHD contract No. 1-HD-4-2803 and No. 1-HD-1-3127), and the study was funded by Trondheim University Hospital; St. Olav's Hospital Research Fund, and Department of Child and Adolescent Psychiatry, Norwegian University of Science and Technology.

References

[1] Janssen AJWM, Nijhuis-van der Sanden MWG, Akkermans RP, Oostendorp RAB, Kollée LAA. Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. Dev Med Child Neurol 2008;50:926–31.
[2] Sun J, Mohay H, O'Callaghan M. A comparison of executive function in very preterm and term infants at 8 months corrected age. Early Hum Dev 2009;85:225–30.
[3] Stoelhorst GMSJ, Rijken M, Martens SE, van Zwieten PHT, Feenstra J, Zwinderman AH, et al. Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997. Early Hum Dev 2003;72:83–95.
[4] Wolf MJ, Koldewijn K, Beelen A, Smit B, Hedlund R, de Groot IJM. Neurobehavioral and developmental profile of very low birthweight preterm infants in early infancy. Acta Paediatr 2002;91:930–8.
[5] Erikson C, Allert C, Carlberg EB, Katz-Salamon M. Stability of longitudinal motor development in very low birthweight infants from 5 months to 5.5 years. Acta Paediatr 2003;92:197–203.
[6] The Scottish Low Birthweight Study Group. Mutch L. The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment. Arch Dis Child 1992;67:675–81.
[7] Herrgard E, Luoma L, Tuppurainen K, Karjalainen S, Martikainen A. Neurodevelopmental profile at five years of children born at < or = 32 weeks gestation. Dev Med Child Neurol 1993;35:1083–96.
[8] Torrioli MG, Frisone MF, Bonvini L, Luciano R, Pasca MG, Lepori R, et al. Perceptual-motor, visual and cognitive ability in very low birthweight preschool children without neonatal ultrasound abnormalities. Brain Dev 2000;22:163–8.
[9] Marlow N, Roberts BL, Cooke RWI. Motor skills in extremely low birthweight children at the age of 6 years. Arch Dis Child 1989;64:839–47.
[10] Marlow N, Roberts L, Cooke R. Outcome at 8 years for children with birth weights of 1250 g or less. Arch Dis Child 1993;68:286–90.
[11] Cooke RWI, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child 2003;88:482–7.
[12] Jongmans M, Mercuri E, de Vries L, Dubowitz L, Henderson SE. Minor neurological signs and perceptual-motor difficulties in prematurely born children. Arch Dis Child 1997;76:F9–14.
[13] Michelsson K, Lindahl E, Parre M, Helenius M. Nine-year follow-up of infants weighing 1500 g or less at birth. Acta Paediatr Scand 1984;73:835–41.
[14] Powls A, Botting N, Cooke RW, Marlow N. Motor impairment in children 12 to 13 years old with a birthweight of less than 1250 g. Arch Dis Child Fetal Neonatal Ed 1995;73:F62–6.
[15] Evensen KAI, Vik T, Helbostad JL, Indredavik MS, Kulseng S, Brubakk AM. Motor skills in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed 2004;89:F451–5.
[16] 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;84:343–9.
[17] Gagliardo HGRG, Goncalves VMG, Lima MCMP, Francozo MdFdC, Aranha Netto A. Visual function and fine-motor control in small-for-gestational age infants. Arq Neuropsiquiatr 2004;62:955–62.
[18] Campos D, Santos DCC, Goncalves VMG, Goto MMF, Campos-Zanelli TM. Motor performance of infants born small or appropriate for gestational age: a comparative study. Pediatr Phys Ther 2008;20:340–6.
[19] Neligan GA, Kolvin I, Scott DM, Garside RF. Born too soon or born too small: A follow-up study to seven years of age. London: William Heinemann Medical Books Ltd.; 1976.
[20] Sommerfelt K, Sonnander K, Skranes J, Andersson HW, Ahlsten G, Ellertsen B, et al. Neuropsychologic and motor function in small-for-gestation preschoolers. Pediatr Neurol 2002;26:186–91.
[21] Low JA, Galbraith RS, Muir D, Killen H, Pater B, Karchmar J. Intrauterine growth retardation: a study of long-term morbidity. Am J Obstet Gynecol 1982;142:670–7.
[22] Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational-age babies. Pediatrics 1982;69:296–300.
[23] Markestad T, Vik T, Ahlsten G, Gebre-Medhin M, Skjaerven R, Jacobsen G, et al. Small-for-gestational-age (SGA) infants born at term: growth and development during the first year of life. Acta Obstet Gynecol Scand Suppl 1997;165:93–101.
[24] Jongmans MJ. Early identification of children with Developmental Coordination Disorder. In: Sugden D, Chambers M, editors. Children with Developmental Coordination Disorder. London: Whurr Publishers Ltd; 2005. p. 155–67.

[25] Yoon DY, Scott K, Hill MN, Levitt NS, Lambert EV. Review of three tests of motor proficiency in children. Percept Mot Skills 2006;102:543–51.
[26] Kolobe THA, Bulanda M, Susman L. Predicting motor outcome at preschool age for infants tested at 7, 30, 60, and 90 days after term age using the Test of Infant Motor Performance. Phys Ther 2004;84:1144–56.
[27] Amiel-Tison C, Gosselin J. Neurological development from birth to six years. Guide for Examination and Evaluation. Baltimore: The Johns Hopkins University Press; 2000.
[28] Bayley N. Manual for the Bayley scales of infant development. New York: The Psychological Corporation; 1969.
[29] Folio MR, Fewell RR. Peabody developmental motor scales and activity cards. Manual. Austin, TX: DLM Teaching Resources; 1983.
[30] Bruininks RH. Manual of the Bruininks-Oseretsky test of motor proficiency. Circle Pines, Minnesota, USA: American Guidance Service; 1978.
[31] Henderson S, Sugden D. Movement Assessment Battery for Children. Manual. The Psychological Corporation; 1992.
[32] Miller LJ, Roid GH. The TIME Toddler and Infant Motor Evaluation, a Standardized Assessment. San Antonio, Texas: Therapy Skill Builders; 1994.
[33] Piper MC, Darrah J. Motor Assessment of the Developing Infant. Philadelphia: Saunders; 1994.
[34] Touwen BCL. Neurological Development in Infancy. Philadelphia: Lippincott; 1976. Clinics in Developmental Medicine No. 58.
[35] Einspeiler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants. London: Mac Keith Press; 2004. Clinics in Developmental Medicine No. 167.
[36] Dubowitz L, Dubowitz V. The Neurological Assessment of the preterm and Full-Term Newborn Infant. London: Heinemann; 1981. Clinics in Developmental Medicine No. 79.
[37] Campbell SK, Kolobe TH, Osten ET, Lenke M, Girolami GL. Construct validity of the Test of Infant Motor Performance. Phys Ther 1995;75:585–96.
[38] Geuze RH, Jongmans MJ, Schoemaker MM, Smits-Engelsman BCM. Clinical and research diagnostic criteria for developmental coordination disorder: a review and discussion. Hum Mov Sci 2001;20:7–47.
[39] Provost B, Heimerl S, McClain C, Kim NH, Lopez BR, Kodituwakku P. Concurrent validity of the Bayley Scales of Infant Development II Motor Scale and the Peabody Developmental Motor Scales-2 in children with developmental delays. Pediatr Phys Ther 2004;16:149–56.
[40] Gillberg C, Kadesjö B. Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). Neural Plas 2003;10:59–68.
[41] Low JA, Galbraith RS, Muir DW, Killen HL, Pater EA, Karchmar EJ. Factors associated with motor and cognitive deficits in children after intrapartum fetal hypoxia. Am J Obstet Gynecol 1984;148:533–9.
[42] Palisano RJ. Concurrent and predictive validities of the Bayley Motor Scale and the Peabody Developmental Motor Scales. Phys Ther 1986;66:1714–9.
[43] Siegel LS, Saigal S, Rosenbaum P, Morton RA, Young A, Berenbaum S, et al. Predictors of development in preterm and full-term infants: a model for detecting the at risk child. J Pediatr Psychol 1982;7:135–48.
[44] Darrah J, Piper M, Watt MJ. Assessment of gross motor skills of at-risk infants: predictive validity of the Alberta Infant Motor Scale. Dev Med Child Neurol 1998;40:485–91.
[45] Goyen TA, Lui K. Longitudinal motor development of "apparently normal" high-risk infants at 18 months, 3 and 5 years. Early Hum Dev 2002;70:103–15.
[46] Palisano RJ. Use of chronological and adjusted ages to compare motor development of healthy preterm and fullterm infants. Dev Med Child Neurol 1986;28:180–7.
[47] De Kleine MJK, Nijhuis-van der Sanden MWG, den Ouden AL. Is paediatric assessment of motor development of very preterm and low-birthweight children appropriate? Acta Paediatr 2006;95:1202–8.
[48] Skranes JS, Vik T, Nilsen G, Smevik O, Andersson HW, Brubakk AM. Cerebral magnetic resonance imaging and mental and motor function of very low birth weight children at six years of age. Neuropediatrics 1997;28:149–54.
[49] Vik T, Vatten L, Markestad T, Ahlsten G, Jacobsen G, Bakketeig LS. Morbidity during the first year of life in small for gestational age infants. Arch Dis Child Fetal Neonatal Ed 1996;75:F33–7.
[50] Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther 2000;80:974–85.
[51] Altman DG. Diagnostic tests. In: Altman DG, Machin D, Bryant TN, Gardner MJ, editors. Statistics with confidence. Second edition. London: BMJ Books; 2000. p. 105–19.
[52] Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008;93:458–61.
[53] Goyen TA, Lui K. Developmental coordination disorder in 'apparently normal' school children born extremely preterm. Arch Dis Child 2009;94:298–302.
[54] Mercuri E, Jongmans M, Henderson S, Pennock J, Chung YL, de Vries L, et al. Evaluation of the corpus callosum in clumsy children born prematurely: a functional and morphological study. Neuropediatrics 1996;27:317–22.
[55] Olsén P, Pääkkö E, Vainionpää L, Pyhtinen J, Järvelin MR. Magnetic resonance imaging of periventricular leukomalacia and its clinical correlation in children. Ann Neurol 1997;41:754–61.
[56] Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born preterm. Lancet 1999;353:1653–7.
[57] Cooke RWI, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. Arch Dis Child Fetal Neonatal Ed 1999;81:F116–21.
[58] Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KAI, Martinussen M, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007;130:654–66.
[59] MacCobb S, Greene S, Nugent JK, O'Mahony P. Measurement and prediction of motor proficiency in children using Bayley infant scales and the Bruininks-Oseretsky test. Phys Occup Ther Pediatr 2005;25:59–79.
[60] de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? Early Hum Dev 2006;82:257–66.
[61] Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Brubakk AM. Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires. Eur Child Adolesc Psychiatry 2005;14:226–36.
[62] Heinemann KR, Hadders-Algra M. Evaluation of neuromotor function in infancy — a systematic review of available methods. J Dev Behav Pediatr 2008;29:315–23.

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.

31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.
33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.

66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.

105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.

135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.

164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell Arne Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.

194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.

219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS

247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS

275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY

300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS
324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN
326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION

327. Ingebjørg S. Juel: INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT
350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION
352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY

354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal: EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES
379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM

383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY
410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA
412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS

415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE