ISBN 978-82-326-2486-7 (printed ver.)
ISBN 978-82-326-2487-4 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2017:207

Ingrid Marie Husby Hollund

Long-term consequences of prematurity

Motor skills, mental health, health-related quality of life and white matter microstructure in young adults born preterm with very low birth weight

Ingrid Marie Husby Hollund

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Clinical and
Molecular Medicine

Doctoral theses at NTNU, 2017:207

NTNU

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of
Science and Technology

Ingrid Marie Husby Hollund

Long-term consequences of prematurity

Motor skills, mental health, health-related quality of life and white matter microstructure in young adults born preterm with very low birth weight

Thesis for the Degree of Philosophiae Doctor

Trondheim, August 2017

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the Degree of Philosophiae Doctor

Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

ISBN 978-82-326-2486-7 (printed ver.)
ISBN 978-82-326-2487-4 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2017:207

Printed by NTNU Grafisk senter

LANGTIDSKONSEKVENSER AV FOR TIDLIG FØDSEL

Motoriske ferdigheter, psykisk helse, livskvalitet og integritet av hjernens hvite substans hos unge voksne født for tidlig med veldig lav fødselsvekt

Barn som er født for tidlig har umodne organer som er mer utsatt for skade enn barn født til termin. Hjernen er spesielt sårbar, og diffus skade av hvit substans forekommer hyppig. Risikoen for død og sykelighet øker med lavere fødselsvekt og gestasjonsalder. Barn født med veldig lav fødselsvekt (VLBW;≤1500g) har økt forekomst av vansker med motorikk, kognisjon, atferd, oppmerksomhet og læring. Flere har sosiale utfordringer, og psykiske symptomer og plager blir mer fremtredende i tenårene. I voksen alder er det færre som tar høyere utdanning, har fast partner og lever et selvstendig liv. Det er tidkrevende og kostbart å studere langtidseffektene av VLBW, og få studier har fulgt denne gruppen inn i voksen alder.

Dette doktorgradsarbeidet er en del av et større hovedprosjekt, *Lav fødselsvekt i et livstidsperspektiv,* ved Senter for tidlig hjerneutvikling (CEBRA). I dette prosjektet har vi fulgt for tidlig fødte barn med VLBW og terminfødte barn med fødselsvekt ≥10-persentilen fra fødsel og inn i voksen alder. Disse gruppene har blitt undersøkt på flere tidspunkt med mange ulike tester, spørreskjema og MR av hjernen. I denne avhandlingen undersøkte vi motoriske ferdigheter, psykisk helse, livskvalitet og integritet av hjernens hvite substans ved 23 års alder. Vi undersøkte også utviklingen av motoriske ferdigheter fra 14 til 23 år og studerte potensielle endringer i psykisk helse og livskvalitet i overgangen til selvstendig voksenliv fra 20 til 23 års alder. Dessuten undersøkte vi om motoriske ferdigheter kunne være relatert til psykisk helse og livskvalitet, og om motoriske problemer kunne henge sammen med endringer i hvit substans.

Vi fant at VLBW-gruppen hadde dårligere fin- og grovmotoriske ferdigheter ved 23 år sammenlignet med kontrollgruppen, særlig på oppgaver som krevde motorisk hurtighet. Det var ingen forbedring av motoriske ferdigheter fra 14 til 23 år. Hovedforskjellene bestod da vi ekskluderte deltakere med cerebral parese. VLBW-gruppen rapporterte dårligere psykisk helse enn kontrollgruppen ved 23 år i form av mer oppmerksomhets- og internaliserende problemer, samt en tendens til flere symptomer på angst heller enn depresjon. Det var en økning i psykiske plager fra 20 til 23 år i VLBW-gruppen. Ved 23 år hadde de også en tendens til å rapportere færre og svakere sosiale relasjoner, men et lavere alkoholforbruk enn kontrollgruppen. Videre rapporterte VLBW-gruppen lavere fysisk og psykisk livskvalitet enn kontrollgruppen, inkludert redusert fysisk og sosial fungering som påvirket deres hverdagsroller, samt mer kroppslig smerte. Både fysisk og psykisk livskvalitet ble svekket fra 20 til 23 år i VLBW-gruppen. Reduserte motoriske ferdigheter var relatert til dårligere psykisk helse, mer internaliserende problemer og lavere fysisk og psykisk livskvalitet. Gruppeforskjellene for psykisk helse og livskvalitet ble mindre da vi ekskluderte deltakere med cerebral parese og lav IQ, men hovedforskjellene bestod og det var fremdeles en sammenheng mellom reduserte motoriske ferdigheter og lavere fysisk livskvalitet. I forhold til kontrollgruppen fant vi endringer i hvit substans i alle hjernens sentrale nervebaner hos VLBW-gruppen ved 23 år, og disse gruppeforskjellene syntes å øke i omfang fra 20 til 23 år. Reduserte motoriske ferdigheter var assosiert med endringer i hvit substans i motoriske nervebaner hos VLBW-gruppen ved 23 år.

Vi konkluderte med at unge voksne født med VLBW ikke vokser av seg motoriske problemer og at de rapporterer dårligere og synkende psykisk helse og livskvalitet inn i ung voksen alder sammenlignet med kontrollgruppen. De har fortsatt synlige og mulig økende endringer i hvit substans, og disse endringene var assosiert med reduserte motoriske ferdigheter. Disse funnene indikerer at endringer i hvit substans kan påvirke funksjonen hos unge voksne født med VLBW og at overgangen til voksenlivet synes å være spesielt utfordrende for denne gruppen.

Kandidat: Ingrid Marie Husby Hollund
Institutt: Institutt for klinisk og molekylær medisin
Veiledere: Kari Anne Indredavik Evensen, Jon Skranes, Live Eikenes
Finansieringskilde: Norges forskningsråd og Norges teknisk-naturvitenskapelige universitet

Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden ph.d. i klinisk medisin
Disputasen finner sted i auditoriet ØHA11, Øya Helsehus
Torsdag 24.august 2017 kl. 12.15

Acknowledgements

First, I would like to thank the young adults participating in this study for their patience and interest in the project and joining even one more data collection, thereby expanding the knowledge on long-term outcome of preterm birth.

Kari Anne Indredavik Evensen, my main supervisor: This thesis would not have been possible without you. Thank you for all your patience and valuable time listening, reading, rereading, supervising and guiding me through the jungle of research, making the path walkable and safe. Thank you for sharing of your knowledge in research and life, frustrations and joys. We're a great team and it's been wonderful working with you!

Ann-Mari Brubakk, co-author and mother of the main project "Low birth weight in a life time perspective": Thank you for introducing me to Kari Anne and the project in 2012. Without you being so fast minded and efficient, I would probably not have had the pleasure of spending these years in your research group. Thank you for your energy, wisdom, laughter and never-ending interest and competence in the research field.

Jon Skranes, co-supervisor: Thank you for always listening and quickly replying on my many questions and drafts. Thank you for your humour and for sharing of your broad knowledge in research and medicine.

Live Eikenes, co-supervisor: Thank you for introducing me to MRI and DTI, and for invaluable support with my third paper and thesis. Your knowledge and energy inspire me, working with you is a pleasure.

A great thank you to the rest of my **co-authors**: Alexander Olsen, for your efforts in the design of the study and revising my manuscripts. Marit Sæbø Indredavik, for thorough feedback and profound knowledge on mental health. Stian Lydersen, for guidance through statistical methods, numbers and figures. Kaia Stray, for preparing data, revising manuscripts and uplifting e-mails. Asta Håberg, for vast knowledge on MRI, the brain, the whole picture and intricate details.

I would also like to thank all members of the **Centre for Early Brain Development** and all my **co-workers** in the 6th floor –thank you for the positive working environment, talks around the coffee machine, help when needed, encouragements, smiles in the corridors, uplifting lunch breaks

and meetings, and wonderful journeys around the world. Thank you for sharing of your experience and being so friendly.

Geir Jacobsen: Thank you for the opportunity to attend the Medical Student Research Program, for guidance, support and enthusiasm the whole way from the very beginning to the end of my PhD. To all my fellow students at Forskerlinjekull 12, thank you for knowing how it feels, walking together, sharing ideas and laughing together.

Ingrid Ingeborg Riphagen: Thank you for guidance through searching the literature and reference styling, sharing of ideas, reflections and chocolate. I enjoyed working with you.

Nancy Eik-Nes: Thank you for teaching me about academic writing and communication, for proof reading my thesis and being encouraging and enthusiastic. You have the eye of an eagle.

Lastly, I would like to thank my family and friends for your interest in what I do, but mainly in who I am. Thanks to my father, Tom, for inspiration, encouragement and wisdom in medicine, research and life. Thanks to my mother, Lillian, for backing me up and putting things in perspective. Thanks to my siblings Andreas, Martin and Hilde for actually reading my manuscripts, feedback and computer support. My dear Raymond, thank you for being strong when I am weak.

"My grace is sufficient for you, for power is made perfect in weakness". *2 Corinthians 12:9*

Table of contents

Abbreviations

AD	Axial diffusivity
ASR	Adult Self-Report
BDI	Beck Depression Inventory
CC	Corpus callosum
CP	Cerebral palsy
CST	Corticospinal tract
DCD	Developmental coordination disorder
DOHaD	Developmental origins of health and disease
DOBHaD	Developmental origins of behaviour, health and disease
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
ELBW	Extremely low birth weight
FA	Fractional anisotropy
GMFCS	Gross Motor Function Classification System
HiMAT	High-level Mobility Assessment Tool
HPA	Hypothalamic-pituitary-adrenal
HRQoL	Health-related quality of life
IQ_{est}	Estimated intelligence quotient
IVH	Intraventricular haemorrhage
MD	Mean diffusivity
Movement ABC-2	Movement Assessment Battery for Children-2
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
NTNU	Norwegian University of Science and Technology
QoL	Quality of life
RD	Radial diffusivity
RF	Radio-frequency
ROI	Region-of-interest
SD	Standard deviation
SES	Socioeconomic status
SF-36	Short Form 36 Health Survey
TMT-5	Trail Making Test-5
VLBW	Very low birth weight
WISC-III	Wechsler Intelligence Scale for Children -Third Edition
WHO	World Health Organization

List of Papers

Paper I

Husby IM, Skranes J, Olsen A, Brubakk AM, Evensen KAI

Motor skills at 23 years of age in young adults born preterm with very low birth weight. *Early Human Development 2013;89:747-754*

Paper II

Husby IM, Stray K, Olsen A, Lydersen S, Indredavik MS, Brubakk AM, Skranes J, Evensen KAI

Long-term follow-up of mental health, health-related quality of life and associations with motor skills in the transition to adulthood for young adults born preterm with very low birth weight. *Health and Quality of Life Outcomes 2016;14:56*

Paper III

Hollund IMH, Olsen A, Skranes J, Brubakk AM, Eikenes L, Evensen KAI

White matter alterations and their associations with motor function in very low birth weight young adults. *Submitted.*

Summary

Infants born very preterm have immature organs, vulnerable to damage. The brain is especially vulnerable, and diffuse white matter injury is common. Mortality and morbidity increases with decreasing birth weight and gestational age. Children born with a very low birth weight (VLBW; ≤1500g) have an increased prevalence of motor problems, cognitive impairments, behavioural and attentional problems, and learning difficulties. As VLBW children grow older, social problems and mental health problems emerge. Fewer take higher education, have a partner and live independent lives as grown-ups. It is costly and time-consuming to study long-term effects of being born with a VLBW, and few studies have followed this group into adulthood.

This thesis is part of the main project *Low birth weight in a lifetime perspective* at the Centre for Early Brain Development (CEBRA). In this project, we have followed preterm VLBW children and term-born children with birth weight ≥10th percentile from birth and into adult age. These two groups have been assessed with various test batteries, questionnaires and cerebral MRI at several time-points. In this thesis, we examined motor skills, mental health, health-related quality of life (HRQoL) and white matter microstructure at 23 years of age. We also examined longitudinal changes in motor skills from 14 to 23 years and the development of mental health and HRQoL in the transition to adulthood from 20 to 23 years of age. Furthermore, we investigated potential associations of motor skills with mental health and HRQoL, and if motor problems were related to changes in white matter microstructure.

We found that the VLBW group had poorer fine and gross motor skills at 23 years compared with the control group, especially for tasks involving motor speed. There were no improvements in motor skills from 14 to 23 years. Main differences between groups persisted when we excluded participants with cerebral palsy. The VLBW group reported more mental health problems than controls at 23 years, in terms of more attentional and internalizing problems and a tendency of more symptoms of anxiety rather than depression. There was an increase in mental health problems from 20 to 23 years in the VLBW group. At 23 years, they also reported a tendency of fewer and poorer social relations, but a lower alcohol consume than the control group. Furthermore, the VLBW group reported lower physical and mental HRQoL than the control group at 23 years, including poorer physical and social functioning, role limitations due to physical and emotional problems, and more bodily pain. Physical and mental HRQoL

decreased from 20 to 23 years in the VLBW group. Poorer motor skills were associated with more mental health problems and internalizing problems, as well as lower physical and mental HRQoL. When we excluded participants with cerebral palsy and low IQ, group differences were somewhat reduced, but the main results persisted and poorer motor skills were still associated with physical HRQoL.

The VLBW group showed white matter alterations in all major white matter tracts compared with the control group at 23 years, and these group differences seemed to have increased in extent from 20 to 23 years. Poor motor function was associated with white matter alterations in motor pathways within the VLBW group at 23 years.

In conclusion, VLBW young adults have not outgrown their motor problems and they reported poorer and declining mental health and HRQoL into adulthood compared with young adults born at term with birth weight $\geq 10^{th}$ percentile. Furthermore, VLBW young adults showed persisting and possibly increasing white matter alterations compared with the control group, and these alterations were associated with poorer motor function. These findings indicate that white matter alterations have an impact on outcome in VLBW young adults and that the transition to adulthood seems to be especially challenging for VLBW individuals.

Introduction

Perspective

Globally, about 15 million children are born preterm each year, representing a preterm birth rate of 11.1%[31]. In Norway, 5-6% of all live births are preterm, and 561 children (~1%) were born with a very low birth weight (VLBW: <1500g) in 2015[167]. Preterm birth is now the second most common cause of death after pneumonia in children under five years worldwide and the leading cause of child death in almost all high- and middle-income countries[151]. During the last decades, however, mortality rates have been decreasing along with the great improvements of neonatal medicine[90,210]. Neonatal mortality in Norway fell from 67% in 1967 to 25% in 1987, and further to 10% in 2015 for live born VLBW infants[167]. At St. Olavs Hospital, formerly Regional Hospital in Trondheim, Norway, the VLBW neonatal mortality rate was 22.5% in 1987/1988[239]. A large Norwegian registry study identified interventions that together explained about 50% of this decline in mortality: ventilators, antenatal steroids and surfactant[90].

As more and more immature and vulnerable children survived, concerns about morbidity and long-term consequences increased[68]. Forsdahl[79] and Barker[19] were two of the pioneers who linked foetal and early life milieu with an increased risk of later disease. These hypotheses were the beginning of the foetal programming hypothesis[156] and a new research area called the "Developmental origins of health and disease" (DOHaD)[84]. Large epidemiological studies have found an association between low birth weight and later metabolic risk factors and disease[20,203]. Early in life, VLBW survivors are at an increased risk of brain injury and reduced cerebral growth, likely to be related to later adverse outcomes[183,224]. Major motor deficits, such as cerebral palsy (CP), are present in 5-10% of VLBW children[114,210]. More than half of VLBW survivors show significant cognitive, behavioural, or sensory deficits later in life[210]. Learning difficulties and social problems manifest in school age[1,49], and mental health problems emerge in adolescence[140]. While studies have shown that preterm infants experience many physical, mental health and social difficulties later in life, studies of their quality of life remain sparse.

Already during childhood, preterm birth has public health implications related to paediatric healthcare resources, family support, and school education[166]. If problems emerging in school age persist into adulthood, the need for societal assistance may also be increased later in life[150,172]. To study long-term consequences of prematurity is costly, time-consuming and prone to bias from loss to follow-up. Studies following preterm infants into adulthood, and especially

true longitudinal studies, are therefore few. Nevertheless, in order to alleviate or possibly prevent future challenges, it is of clinical importance to know the prospects of these immature and vulnerable children. The preterm brain is central in the understanding of the origin of later adverse outcome, and inter-relationships of various long-term outcomes might give clues to common causes.

Topic of this thesis

This thesis examines long-term outcomes for young adults born preterm with a VLBW regarding motor skills, mental health, health-related quality of life (HRQoL) and white matter microstructure, compared with a control group born at term with normal birth weight. Outcome at 23 years of age was the main focus of this thesis, but longitudinal data from 14 and 20 years were also included. Furthermore, motor skills were investigated in relation to mental health, HRQoL and white matter microstructure.

Preterm birth and very low birth weight

Definitions and concepts

The World Health Organization (WHO) defines "preterm" as live birth before 37 weeks of pregnancy are completed, with sub-categories based on gestational age: moderate to late preterm (32 to <37 weeks), very preterm (28 to <32 weeks) and extremely preterm (<28 weeks)[284]. There are great individual differences in birth weight at the different gestational ages, and being born with a low birth weight is found to be associated with an increased risk of mortality[151]. WHO defines low birth weight as a birth weight <2500g, which can be further divided into VLBW (<1500g) and extremely low birth weight (ELBW: <1000g). In this thesis, VLBW was defined as a birth weight ≤1500g. Low birth weight is either caused by preterm birth, the infant being small for gestational age or a combination of both. In practice, all VLBW infants are born preterm. Studies of preterm populations use birth weight and/or gestational age as cut-off. The use of gestational age is likely to yield a more homogenous group in terms of maturity. For studies initiated before the introduction of routine ultrasound, birth weight is more precise as a proxy measure of prematurity. However, growth restricted infants with more advanced gestational ages are probably over-represented in such studies.

Risk factors for preterm birth

The causes of preterm birth are multifactorial and numerous risk factors have been established[162]. Most preterm births occur spontaneously, but some are provider-initiated, like early induction of labour and elective caesarean birth on obstetric or foetal indication. Risk factors associated with spontaneous preterm birth include maternal and antenatal factors, such as chronic diseases, low body mass index, smoking, psychosocial stress, multiple gestations, uterine dysfunction and infections[85,205,235]. Premature activation of the maternal or foetal hypothalamic-pituitary-adrenal (HPA) axis is a possible pathogenic process leading to preterm birth[61,139], and a dysfunctional immunological defence within the tissues of the uterus is suggested as the root cause of preterm birth[181]. However, the cause of spontaneous preterm birth remains unknown in up to half of all cases[168]. Provider-initiated preterm birth is increasing in some countries, partly due to more aggressive policies for caesarean section for poor foetal growth[137]. This is contributing to the overall increase in preterm birth rate and the decline in perinatal mortality in the United States[8].

Neonatal complications due to preterm birth

Neonatal complications of prematurity are contributing factors to the higher rate of mortality and morbidity in preterm infants compared with full-term infants, and problems are increasing with decreasing gestational age and birth weight[210]. The immature brain, lungs, sensory organs and intestines are especially vulnerable to damage[210]. External factors from intensive neonatal care, such as mechanical ventilation, medications, pain, stress and sensory exposure, may increase the risk of injury to these immature organs[192].

The most common complication in VLBW infants is respiratory distress syndrome due to surfactant deficiency[237], and some develop the more chronic bronchopulmonary dysplasia[130]. Closure of the ductus arteriosus is delayed in some VLBW infants[70], and the failure of closure is associated with a higher incidence of brain haemorrhage[69] and chronic lung disease[18]. The most severe, but luckily rare intestinal complication is necrotizing enterocolitis with high mortality and long-term morbidity[117,217]. Retinopathy of prematurity may lead to visual impairments and blindness in very preterm born children[32]. The degree of prematurity, the severity of respiratory disease and episodes of infection largely determine the neonatal course and outcome in early childhood[236,237] and are factors associated with diffuse white matter injury of the brain[41].

The preterm brain

VLBW infants are born around week 24 to 32, a critical phase of brain development. This is a phase of maximal brain growth, with the late migration of neurons, formation of axons, dendrites and synapses, and the process of myelination[241]. The germinal matrix and subplate are temporary structures which are active in this phase, and they are sites of neuronal and glial cell proliferation[241]. The developing brain is especially sensitive to hypoxia-ischaemia and infection/inflammation, which are more prevalent in preterm infants due to their immature lungs, poor autoregulation of cerebral perfusion, underdeveloped immune system and increased risk of externally imposed infections. It is therefore not surprising that very premature delivery, followed by prolonged intensive care, may lead to pervasive and wide-ranging disturbances of cortical and white matter development and organisation[11,257]. In the next section, the most common preterm brain injuries and disturbances of brain development will be outlined, with focus on cerebral white matter.

Cerebral haemorrhage and white matter injury

A frequent injury of the preterm brain is intraventricular haemorrhage (IVH), most commonly associated with germinal matrix haemorrhages[16]. This is specific for preterm infants as the germinal matrix is a temporary structure, involuting around week 34 of gestation[241]. The germinal matrix is especially vulnerable to haemorrhage due to its rich and immature microvascular network in combination with episodes of cerebral hyper perfusion due to the impaired auto-regulation of blood flow in the preterm brain[16]. A germinal matrix haemorrhage may influence neuronal and glial cell proliferation, disturbing further brain development[17,257]. A subependymal bleeding (grade I bleeding) can easily rupture into the lateral ventricular system (grade II bleeding). Blood in the ventricular system may hinder resorption of cerebrospinal fluid causing increased intraventricular pressure, hydrocephalus and dilated ventricles (grade III bleeding). The most serious complication of IVH is haemorrhagic infarction within the parenchyma of the periventricular white matter (grade IV), usually resulting in destruction of motor fibres causing unilateral spastic CP. This is fortunately a rare complication today along with the great improvements in neonatal medicine[109].

Periventricular white matter injury may also occur in the absence of haemorrhages, and is the most common preterm brain injury with an incidence ranging from 50% to 70%[125,222]. The white matter adjacent to the posterior part of the lateral ventricles in the so-called watershed area is especially vulnerable to hypoxic-ischaemic episodes. These regions are in close relation

to the corticospinal motor tracts, and consequently the classical presentation of a severe periventricular white matter injury with focal cysts is bilateral spastic CP. This severe injury with focal cysts is also relatively unusual today with an incidence <5% in VLBW infants[103,124]. However, the much more common diffuse white matter injury affects a larger area of the total cerebral white matter and is associated with a high risk of neurodevelopmental impairments[46,169,258]. These white matter abnormalities are likely to be related to a disturbance in myelination and axonal development. Premyelinating oligodendrocytes are in a phase of active development during 23 to 32 weeks of gestation[12], and are especially vulnerable to microglia and free radical attack activated by cerebral ischaemia and intrauterine or neonatal infection and inflammation[11,258]. There is a subsequent increase in oligodendroglial progenitors to compensate for the loss of premyelinating oligodendrocytes. However, these cells do not have the capacity for full differentiation to mature myelin-producing cells, resulting in hypo- and dysmyelination[11,258]. Furthermore, oligodendrocytes are critical for axon survival[146], and abnormalities of cerebral white matter are frequently accompanied by volumetric and microstructural changes in the overlying cortex[121].

The term "Encephalopathy of prematurity" has been proposed by Volpe for the combination of myelin and axonal disease[257], and he describes preterm brain injury as a "complex amalgam of primary destructive disease and secondary maturational and trophic disturbances". Indeed, static lesions may interact with the dynamic processes of brain development and plasticity[163-165], but developmental disturbances may also occur in the absence of localised injury[192]. Hence, the preterm brain seems to be especially vulnerable to hypoxia-ischaemia and infection/inflammation, and preterm brain injury seems to be a combination of dysmaturation and direct injury. The relative contribution of these two mechanisms remains a major area of debate and further investigation[192]. The result is often reduced cerebral growth, involving both grey and white matter, and an altered brain development[13].

Motor skills

Definitions and concepts

Motor skills are an important part of daily life and can be defined as tasks that "require voluntary body and/or limb movement to achieve a specific goal"[161]. Fine motor skills include the use of fingers to grasp and manipulate objects. Gross motor skills include the movement of large limbs or the whole body, as in walking and jumping[161]. Movements provide infants and children with

new opportunities for learning, facilitating development in other domains such as language, cognition and mental health[3].

Motor development can be defined as "changes in children's ability to control their body's movements, from infants' first spontaneous waving and kicking movements to the adaptive control of reaching, locomotion, and complex sport skills"[4]. It is closely related to motor learning: "a set of processes associated with practice or experience leading to relatively permanent changes in the ability to perform motor skills"[214]. There are different theories concerning the basis of motor development. Around 1950, motor development was generally regarded as a gradual unfolding of predetermined patterns in the central nervous system[123]. This is called the "neural-maturationist theory", a concept leaving little place for the interaction with the environment[82]. In the "systems theory" introduced in the late 1990s, the central nervous system is only one part of all subsystems within and outside the body, cooperating and interacting in the complex and dynamic process of motor development[39,243]. These two theories are combined in the "neuronal group selection theory"[62,232], proposing that practice in a given task increases connections within specific areas of the brain, thereby causing selection of the dynamic and variable neuronal groups[101]. According to this theory, normal motor development follows phases of primary and secondary variability[98]. During foetal life and until four months post term, motor activity is characterized by general movements with great variability and complexity involving all parts of the body[100,198]. These general movements are gradually replaced by more goal-directed movements during secondary variability, which is required for the development of motor skills during later preschool age and school age[100,246]. However, the motor repertoire is not fully mature until adolescence, with the ability to adapt movements exactly and efficiently to task-specific conditions[99]. Motor learning continues throughout life; however, only modest changes in motor skills and motor speed are reported after puberty[51,81,144].

The concept of motor problems, or "clumsiness", has been described in various ways through the years. Terms like "minimal brain dysfunction" and "deficits in attention, motor control and perception" have been used, showing that motor problems can be part of a more complex picture[83,143]. However, "clumsiness" has generally included individuals who are delayed and have difficulty in learning motor skills, but are cognitively competent and have no known neuromuscular involvement[261]. Motor problems have the diagnostic label of "developmental coordination disorder" (DCD) today[58]. This is a problematic label for preterm born individuals,

as they have an excess of cognitive delay and behavioural difficulties[80]. In this thesis, the term "motor problems" is confined to low scores on motor tests.

Prevalence and aetiology in the general population

About 6-10% of all children have motor problems corresponding to DCD[219], consistent with studies in Norway[176]. Motor problems may affect the child's total function and are often associated with poor academic, emotional and social problems[155]. Adults with a history of DCD are shown to retain motor difficulties, which can exclude them from important activities of daily living[47]. Motor, cognitive and sensory systems all play a role in the execution of motor skills[39], so the aetiology of motor problems is likely to be multifactorial. Motor problems are suggested to be caused by an immature CNS, cerebral lesions[40], cerebellar dysfunction[128], and/or as a result of problems with sensory processing[219].

Motor cortex and motor pathways

There are many brain structures which are important for motor function, like the motor, sensory and visual cortices, basal ganglia, cerebellum and numerous white matter tracts. I will focus on the motor cortex and some related motor pathways. The primary motor cortex is responsible for the execution of motor movements, while the premotor and supplementary motor cortices are involved in the planning of movements. The supplementary motor cortex is also likely to be involved in bimanual coordination[131]. The corticospinal tract (CST) is the main descending tract leading signals from the motor cortex to the body, while other projection tracts are important for the communication between the motor cortex and other brain structures. The corpus callosum (CC) is also involved in motor function by facilitating interhemispheric communication and bimanual coordination[86,131]. The CC is topographically organised and fibres running to the primary motor and premotor cortices are located in the body and genu, respectively[115]. Both the CST and the CC are especially vulnerable to periventricular white matter injury because of their close relation to the lateral ventricles[179].

Mental health

Definitions and concepts

Mental health is defined by WHO as "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community"[283]. When this state is

disturbed, a psychiatric disorder may develop. There is a continuum of psychiatric symptoms ranging from none to a large burden of symptoms, and it might be difficult to make a distinction between normality and disorder. The assumption that psychological normality is free of pathology is questioned in the book of Offer and Sabshin[185]:

> "A person who labels himself "normal" and is also labelled "normal" by others is far from being free from psychopathology, and indeed may be quite neurotic" (p.33)

Normality in the aspect of mental health is therefore not easily defined, and is dependent on situation, changes throughout history and often involves value judgements. Psychiatric symptoms affect thoughts, feelings, behaviour and interactions with others, and psychiatric disorders range from simple phobias, mild anxiety and depressive disorders to severe illnesses such as schizophrenia. One can also use the term "psychological distress" for psychiatric symptoms that are strenuous, but not characterised as a diagnosis[202]. Psychiatric symptoms and disorders can be viewed either categorically or dimensionally[178]. In the categorical approach, a disorder is classified by the pattern of criteria required for a specific diagnostic label. This approach is used in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[59]. The dimensional approach emphasises the degree of symptoms, and classifies clinical presentations based on quantification of attributes[59]. This can be provided by questionnaires, and has statistical benefits since the burden of symptoms are measured as a continuity between normality and disorder [208]. However, in contrast to the categorical approach, the dimensional approach yields no diagnosis.

Prevalence and aetiology in the general population

In a study from Oslo, the lifetime prevalence of any psychiatric disorder was 52.4%, and the 12-month prevalence was 32.8%[142]. Many psychiatric disorders manifest in adolescence, and about 75% have debuted by the age of 24[140]. It is estimated that every third 16-year-old in Norway will fulfil the criteria of a psychiatric disorder during childhood and adolescence, and that around 10% of the adult population report psychological distress within the last 14 days[175]. These are very high numbers and exemplify the challenge in cut-offs for psychiatric disorders and distress. The most common psychiatric disorders in Norway are anxiety and depressive disorders, and alcohol dependence/abuse, the former dominated by women, the latter by men[175].

The development of a psychiatric disorder is often a combination of the presence of risk factors and the lack of resilience and other protective factors, with great individual differences. Environmental factors may trigger an existing vulnerability to psychiatric disorders, while

others have a genetic heredity[48]. Low socioeconomic status (SES) is associated with a higher risk of psychiatric disorders[174]. Hence, there are genetic and epigenetic factors in the development of psychiatric disorders. It has been proposed that the DOHaD hypothesis be expanded to the "Developmental origins of behaviour, health and disease" (DOBHaD), as clear evidence has been found that prenatal and early postnatal adversity may have a negative impact on brain architecture and circuits, and affect lifelong behaviour and both mental and physical health[249].

Associations with motor skills

In the general population, poorer motor skills in childhood are associated with anxiety in adolescence[220], and psychiatric disorders seem to be more common in children with deficits in attention, motor control and perception[105]. Adults previously diagnosed with DCD report more symptoms of anxiety and depression than peers[110]. Hence, there seems to be an association between mental health and motor skills.

Health-related quality of life

Definitions and concepts

WHO has a well-known definition of health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity"[44]. Quality of life (QoL) is about well-being and functioning in life, about experiencing joy and meaning, vitality and satisfaction, safety and belonging, about using personal strengths and experiencing mastering, interest and engagement. Eiser and Morse[65] have identified three key elements regarding QoL: 1) QoL is subjective and based on the perception of the individual; 2) QoL is a multidimensional construct; and 3) QoL can include objective information and the individual's subjective appraisal of their QoL. The term HRQoL is more restrictive (parameters such as environment, freedom and income are not included), and refers to the impact of health conditions on the person's total well-being, including his or her psychological, social, and physical health status. This brings us back to the definition of health by WHO, where the aspects of physical, mental and social well-being are emphasised. Physical and mental health, social network and support are positively associated with HRQoL. A good HRQoL strengthens the power of resistance towards negative life events and strains.

Among adolescents from 13 to 17 years, HRQoL is found to deteriorate over a three-year period and becoming more stable after puberty[187]. However, for half the adult population, people's evaluations of their general health seem to be dynamic and changing within a two-year period[14]. Research into HRQoL focuses on well-being rather than on ill-being and examines important supplemental dimensions of health, and might therefore be a useful instrument in research.

Associations with motor skills

The QoL in children with DCD remains largely unknown as there are few studies using QoL as an outcome measure[287]. Studies have reported significantly poorer results in physical, psychological and social functioning in children with DCD compared with peers[287], and one study showed that children with DCD and comorbid attention deficit hyperactivity disorder have significantly lower HRQoL than typically developing children[78]. Young adults with DCD and borderline motor problems have been found to report lower QoL[240] and satisfaction[111] compared with controls. Poorer motor skills are therefore likely to be associated with lower HRQoL.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a well-established imaging modality in the evaluation and assessment of normal and abnormal conditions of the brain. MRI is based on magnetic moment and spin of the hydrogen nuclei in a magnetic field[268], and as the body contains much water, soft tissue may be well visualised by MRI. This is possible because the spins of hydrogen nuclei are ½ and are therefore inherently magnetic and will align with a surrounding magnetic field. After the hydrogen nuclei are aligned with the external magnetic field, a radio-frequency (RF) pulse is added to the body part of interest, thereby exciting the nuclei and disturbing the orientation of the spins. When the RF pulse is turned off, the hydrogen nuclei de-excite and return to their original energy level, a process called relaxation. During the relaxation process, the orientations of the spins are again disturbed, and this introduces an electromagnetic signal, which is the basis of the MRI signal[268].

Depending on intrinsic properties of the tissue and image acquisition conditions (extrinsic contrast mechanisms), images with a variety of contrasts can be obtained. Two of the most common forms of contrasts in MRI are based on the intrinsic relaxation rates of protons in the different tissue types, the longitudinal relaxation time T1 and transversal relaxation time T2[268].

MRI can also be obtained by using diffusion of the water molecules, namely diffusion weighted imaging (DWI), and an advanced application of DWI; diffusion tensor imaging (DTI).

Diffusion tensor imaging

Diffusion tensor imaging[21] is a sensitive method for detecting subtle alterations in white matter microstructure by measuring the 3D diffusion of water molecules (Brownian motion). Motion perpendicular to axons entails passing through or around axons, layers of myelin and cellular membranes, whereas motion parallel to axons has fewer obstacles. Thus, water diffusion in white matter is highly anisotropic, and this information can be used to acquire information regarding the white matter microstructure and architecture.

In order to describe the 3D diffusion of the water molecules, we need to measure the diffusion in many directions (minimum 6, normally 30-60). A diffusion tensor can be calculated from the DTI acquisition, describing this 3D diffusion pattern using a Gaussian model. The tensor can also be represented as an ellipsoid, described by three orthogonal eigenvectors and their corresponding eigenvalues (λ_1, λ_2 and λ_3), describing the diffusion in the three main directions. From the three eigenvalues, we can calculate various metrics describing the white matter microstructure. The most commonly used DTI metrics and their biological correlates are summarised in Table 1.

In normal brain development, fractional anisotropy (FA) increases and mean diffusivity (MD) decreases as white matter pathways mature and myelinate through childhood and until early adulthood[145]. The first wave of FA increase occurs before the start of myelination, and may reflect changes in axonal membranes and axonal diameter[278]. The second wave, which lasts at least until early adulthood, is associated with the appearance and subsequent consolidation of myelin, which is required to allow increased axonal conduction speed[121]. Hence, a reduction of FA and an increase of MD may be indicators of poorer white matter "integrity", and possibly lower conduction speed[215]. Based on mouse models, diffusion parallel to the axons (axial diffusivity; AD) has been associated with axonal injury and dysfunction, whereas diffusion perpendicular to the axons (radial diffusivity; RD) has been associated with deficits in myelination[35,230]. However, it is important to bear in mind that DTI metrics are only measures of diffusion, and their relations with tissue microstructure remain hypothetical until autopsy, and will be dependent on both technical parameters (such as magnetic strength on MRI scanner

and DWI sequence parameters), and biological factors (such as fibre coherence, axonal density and number, cell membranes and myelination in nervous fibre tissue)[24,136,270].

Table 1. Description of the most commonly used DTI metrics

	Fractional anisotropy	**Mean diffusivity**	**Axial diffusivity**	**Radial diffusivity**
	A scalar value (0-1) indicating the degree of diffusional restriction	A measure of overall mean diffusion, independent of directionality ($(\lambda_1 + \lambda_2 + \lambda_3)/3$)	Diffusion along the principal eigenvector, parallel to the axons (λ_1)	Diffusion along the second and third eigenvector, perpendicular to the axons ($(\lambda_2 + \lambda_3)/2$)
Grey matter	⇩	-	⇩	⇧
White matter	⇧	-	⇧	⇩
Cerebrospinal fluid	⇩	⇧	⇧	⇧
High myelination	⇧	⇩	-	⇩
Demyelination	⇩	⇧	-	⇧
White matter maturation	⇧	⇩	⇧	⇩
Axonal degeneration	⇩	⇧	⇩	⇧
Dense axonal packing	⇧	⇩	-	⇩

Methods of DTI analysis

There are two main methods for analysing DTI: tractography and voxel-based analyses.

Tractography is a method that traces the main eigenvector in each voxel to form streamlines leading to a visualisation of anatomical white matter tracts[27]. There are many tractography algorithms, which can be performed manually, semi-automatically or fully automatically[200]. The simplest and most common approach is called deterministic tractography. With this method, tracing is performed by starting in one or several predefined regions-of-interest (ROI) or seed points, and following the main eigenvector from voxel to voxel. The algorithm normally uses FA value, length of streamline and angle between eigenvectors in neighbouring voxels as stopping criteria. This algorithm has several limitations, particularly related to crossing fibres, which often lead to a termination in the tracking[27]. This is, however, somewhat improved with

another tractography approach, called probabilistic tractography. With this method, one can estimate the most likely fibre orientations in every voxel and trace the connections (thousands of times) from seed ROIs to target ROIs, each time using slightly different orientations according to their likelihood. The set of all these different paths is then a collective measure of the connection likelihood or probability between two or more predefined ROIs[27]. In all the tractography methods, DTI parameters such as mean FA and MD can be calculated for each tract and be used for group comparisons to investigate structural connectivity, or to seek associations between DTI and neurological, cognitive, or behavioural outcome.

Voxel-based analyses using automated image processing software are specifically suited for whole brain analyses to statistically compare local diffusion metrics within and across groups. There are also many approaches to voxel-based analyses, but tract-based spatial statistics (TBSS)[227] is one of the most commonly used approaches. One of the main advantages with TBSS is the step of skeletonising the white matter, where a mean FA image of all the participants' images is created and then thinned to create a skeletonised mean FA image. This white matter skeleton represents the centres of all white matter tracts common to the participants in the study, and defines the areas where all statistical comparisons are performed[227].

Long-term consequences of prematurity

There is an important transitional phase from adolescence to adulthood involving increasing demands on independency, education and adult roles, which may stress the underlying neuroimpairments in VLBW individuals. Indeed, preterm birth is shown to have an adverse effect on educational level, income and establishment of family[93,172], and the risks of medical and social disabilities in adulthood increase with decreasing gestational age at birth[172].

Motor skills

Motor problems are the most common neurodevelopmental disorder in preterm children[53], and range from mild motor delay to severe CP[231]. Cerebral palsy is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain", and is often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour[207]. The prevalence of CP in Europe has fallen from 8% in 1980 to 3.6% in 2003 among VLBW children[114,218], in contrast to a relatively stable prevalence at

0.1% among normal birth weight children[218]. Both including and excluding participants with CP, there are consistent findings of motor delay in VLBW populations from infancy to adolescence[53,71,129,280]. There seems to be a catch-up in reaching important milestones, while more subtle motor problems are likely to increase by the time these children enter school and experience greater demands in various areas. In school age and adolescence, motor problems are evident in fine and gross motor development, balance, ball skills and manual dexterity[53,72]. VLBW children are found to be six times more likely to have motor problems than peers[63], and 25-35% of VLBW adolescents had motor problems according to the Movement Assessment Battery for Children (Movement ABC)[72,197]. No studies previous to Paper I in this thesis have assessed motor function in preterm born young adults. However, a recent study investigating self-reported motor coordination difficulties in ELBW young adults at 22-26 and 29-36 years of age compared with normal birth weight controls, found that motor coordination remained poorer in ELBW survivors into adulthood[196].

Mental health

Psychiatric symptoms and disorders are frequent among VLBW children and adolescents, and seem to persist into young adulthood. In childhood and adolescence, the increased risk of inattention, anxiety and social problems, including autism spectrum disorders, is most prevalent[1,29,56,66,127,133,250], suggesting a "Preterm behavioural phenotype"[132]. In young adulthood, anxiety and internalizing problems are still prominent[93,112,157,158,199,262], and some studies report increased risk of depression[93,262,269], bipolar disorders[184] and psychiatric disorders requiring hospitalisation[149,184]. A newly published meta-analysis representing data from six longitudinal birth cohorts concluded that VLBW young adults reported more internalizing and avoidant personality problems and fewer externalizing, rule-breaking, intrusive and antisocial personality problems than term controls[199]. However, there are also studies indicating no increased risk of psychiatric morbidity in VLBW young adults, or only in females[45,97,209]. Cognitive function and SES has been found to modify the risk of mental health problems in preterm populations[97,132,147], while a positive family history of mental disorders may increase the psychiatric risk among very preterm young adults[262]. Both Norwegian[172] and Swedish[150] registry studies have reported an increased risk of medical disability among adults born preterm. In the Norwegian study, emotional and behavioural problems as well as an increased risk of autism spectrum disorders were among the causes of disability[172].

Health-related quality of life

Despite increasing evidence of the risk of mental health problems, medical disability and lower educational level among VLBW young adults, most studies of HRQoL and well-being show similar outcomes for this group and controls[5,23,30,50,91,255,286]. However, a recent study found lower HRQoL in very preterm and VLBW young adults compared with term controls as reported by participants and parents[22]. Furthermore, poorer physical functioning as part of HRQoL has been reported[23,45], and one study reported poorer objective QoL based on societal standards for VLBW individuals without disabilities at 18 years[60]. VLBW children and adolescents also report similar HRQoL to their normal birth weight peers; however, parent-reports are typically lower[234,286]. Both positive and negative changes in HRQoL have been reported from 14 to 19 years in a very preterm and/or VLBW cohort[255], while no important changes were reported in HRQoL between 19 and 28 years in the same cohort[252]. The psychological attributes, especially emotion and cognition, were less stable than the physical attributes[252]. A recent study found that adolescents born very preterm or VLBW reported little changes in HRQoL from 13 to 26 years of age, whereas their parents perceived a deterioration at this time of transition into adult roles[22]. In the latter study, both participant- and parent-reported HRQoL were related to economic and social functioning outcomes. Hence, there is evidence of decreased, stable and improved HRQoL as VLBW individuals enter young adulthood.

White matter microstructure

The normal maturation of white matter is disrupted in the preterm brain, and this is normally seen on DTI as lower FA and higher MD in preterm populations compared with term-born controls[148,189]. There is a variation in affected brain areas between different studies, possibly due to the variability in methodology, age at assessment and selection of preterm populations. There are, however, some general traits: In preterm infants, lower FA is seen mainly in white matter tracts in frontal and central brain regions (corpus callosum, fornix, corticospinal tract, optic radiation)[10,121,191,206]. In preterm children and adolescents, association tracts also show reduced FA[43,254]. The relatively few studies of FA in preterm young adults show that central white matter is still affected, and that a greater number of association tracts are affected in young adults than in adolescents[64,141]. Due to the rapid technical advances in MRI and DTI acquisition and analysis techniques, there are few true longitudinal DTI studies. However, white matter regions (number of voxels) with lower FA in the VLBW group compared with controls

seem to increase from adolescence to young adulthood[64], possibly indicating that the extent of disrupted brain development increases over the years.

Diffusion measures of white matter tracts, especially reduced FA, are found to correlate with numerous outcomes in VLBW populations. The majority of such studies have examined the association between FA across the whole brain and cognitive functions[7,64,173,212], while the minority of the studies have investigated the association between FA and motor function. In very preterm infants, a positive correlation has been reported between FA throughout the white matter and fine motor scores[251]. Another study found no relationship between FA values and a motor sub-scale in very preterm individuals without major motor problems or focal lesions at two years[46]. In school-age children, reduced FA values have been found to strongly underpin motor impairment and DCD in very preterm children[54]. Also in adolescence, lower FA has been found to correlate with poorer fine motor function in a VLBW population[224]. In adults, however, no correlation between white matter microstructure at 26 years and motor function at eight years in a very preterm and VLBW population has been found[138]. Hence, the few studies investigating the relationship between white matter microstructure and motor function in preterm populations yield mixed findings.

Possible aetiology of long-term consequences of prematurity

Early insults to the preterm brain are likely to be related to later motor and mental health problems, either through specific injuries or widespread changes throughout the brain[183,224]. Motor pathways like the CST and CC are in close relation to the periventricular white matter and may be particularly vulnerable to long-term injury[64,88]. Consistent with the DOBHaD hypothesis, the immune system and the HPA stress-regulating system are found to be especially vulnerable to long-term alteration in former preterm children[36]. VLBW infants may have been exposed to intrauterine stress, psychosocial stress and infection during pregnancy and early life that may lead to changes in both neurodevelopment and the set point of neuroendocrine systems (including the HPA axis). This may have long-lasting effects on behaviour and mental health[213,249,266]. The increased risk of later neurodevelopmental problems in preterm populations is likely to have an impact on HRQoL, especially when they leave home and enter adult roles and independent living.

What this thesis adds

This study is one of few multidisciplinary longitudinal studies that have followed VLBW children into adulthood. It is the first study to assess motor skills in adulthood using well-known and new motor tests and examine whether motor skills are associated with mental health, HRQoL and/or white matter microstructure in VLBW young adults. Furthermore, this thesis adds to the limited knowledge on white matter abnormalities in VLBW young adults and longitudinal changes in motor skills from adolescence to young adulthood, as well as changes in mental health and HRQoL in the transition to adulthood within a VLBW population. Hopefully, this thesis may provide a small piece in the large puzzle of prematurity.

Aims

The overall aim was to investigate long-term clinical outcome in young adults born preterm with VLBW, focusing on motor skills, mental health, HRQoL and white matter microstructure compared with term-born controls with normal birth weight. Specifically, the objective of each paper was to address the following research questions:

Paper I:

1) How do fine and gross motor skills differ between VLBW and control young adults?
2) Are there longitudinal changes in motor skills from adolescence to young adulthood?

Paper II:

3) Do VLBW young adults have more mental health problems and/or lower HRQoL than controls?
4) Are there longitudinal changes in mental health and HRQoL from 20 to 23 years of age?
5) Are mental health and HRQoL associated with motor skills?

Paper III:

6) Are there differences in white matter microstructure between VLBW and control young adults?
7) Are there longitudinal changes in the extent of group differences regarding white matter microstructure from 20 to 23 years of age?
8) Is motor function related to white matter microstructure of motor pathways in VLBW young adults?

Hypotheses

Based on previous research, we expected to find:

Paper I:

1) Poorer fine and gross motor skills in VLBW young adults compared with controls
2) That motor skills do not improve from adolescence to young adulthood

Paper II:

3) More mental health problems and lower HRQoL for VLBW young adults compared with controls
4) A decrease in mental health and HRQoL from 20 to 23 years in the VLBW group
5) That poorer motor skills are associated with more mental health problems and lower physical HRQoL in the VLBW group

Paper III:

6) Lower fractional anisotropy and higher mean diffusivity in all major white matter tracts in VLBW young adults compared with controls
7) Persisting group differences in white matter microstructure from 20 to 23 years of age
8) An association between poorer motor function and lower fractional anisotropy in motor pathways in VLBW young adults

Material and methods

Study design

This is a geographically-based follow-up study of 23-year-old young adults born preterm with VLBW and a term-born control group with normal birth weight. The VLBW young adults were born in 1986 – 1988 and admitted to the Neonatal Intensive Care Unit (NICU) at St. Olavs Hospital, Trondheim University Hospital, Norway (formerly Regional Hospital in Trondheim). The control young adults were born in the same period to mothers living in the Trondheim region, recruited from a 10% random sample of women selected for follow-up during pregnancy in a multicentre study on causes and consequences of intrauterine growth restriction[15]. The current study is part of a longitudinal follow-up study on long-term consequences of VLBW, and both groups have previously participated in evaluations at 1, 5, 14 and 20 years of age[72,157,225,226,229,256]. We aimed to include all VLBW participants at 23 years of age who had participated in the 14-year follow-up and control participants matched by age and sex in order to compare motor skills longitudinally. Assessments of motor skills and self-evaluating questionnaires on mental health and HRQoL were included as part of a large assessment battery and all participants underwent cerebral MRI. This thesis also includes data on motor skills at 14 years[72] and data on mental health, HRQoL and MRI at 20 years[64,157].

Study population

Flow chart of the study population is presented in Figure 1.

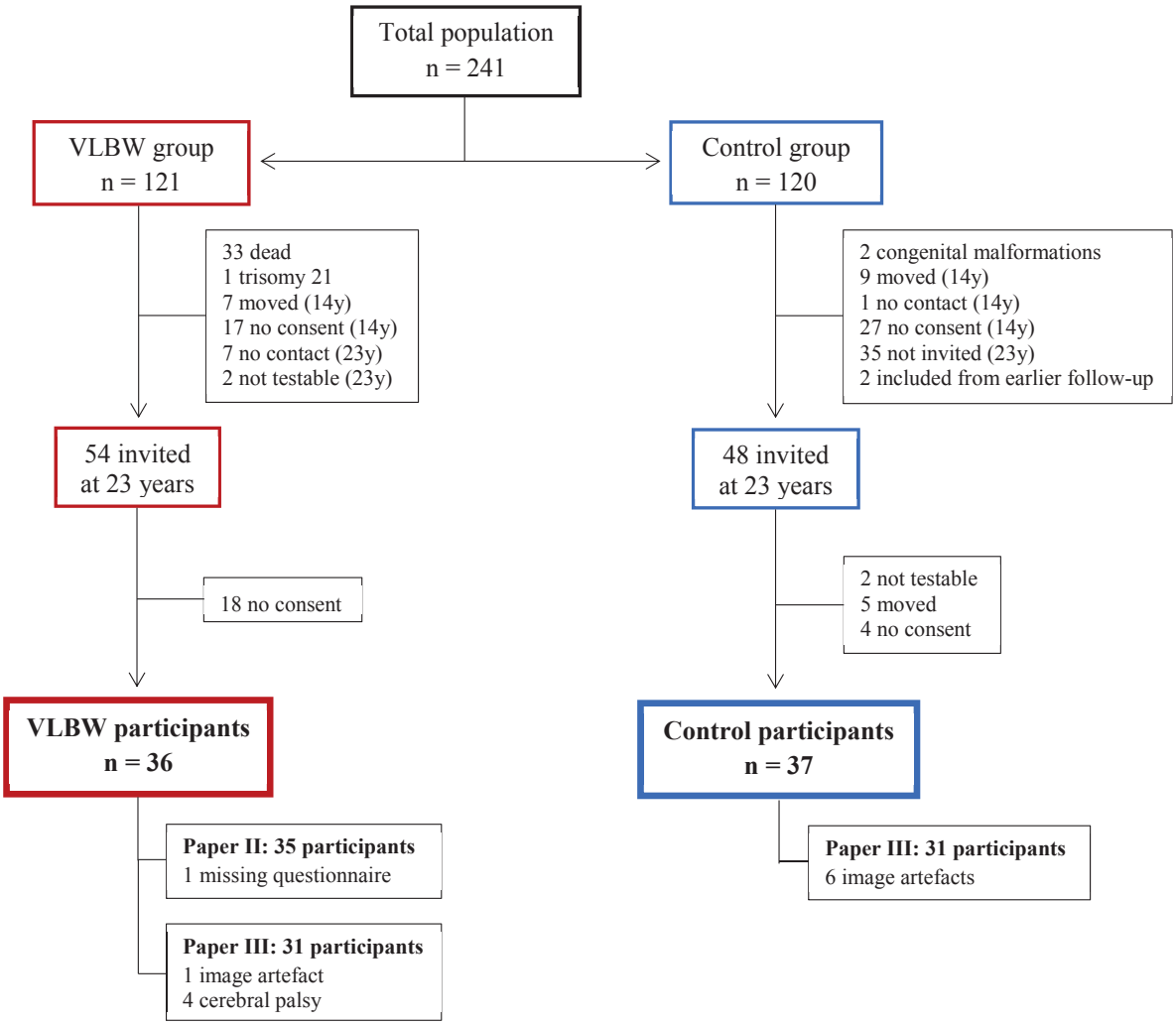

Figure 1 Flow chart of the study population

Abbreviations: VLBW, very low birth weight

VLBW group

The VLBW group comprised 36 young adults (15 males and 21 females) born preterm with a birth weight ≤1500g. At birth, 121 VLBW infants were included in the study. Of these, 33 children died in the neonatal period and one child with trisomy 21 was excluded. At 14 years, seven children had moved out of the region and 17 did not consent to participation, leaving 63 adolescents for examination. At 23 years, seven of these young adults were not contactable and two were excluded due to severe bilateral spastic CP of Gross Motor Function Classification System (GMFCS) level V[188]. Thus, we contacted 54 VLBW young adults at 23 years, of whom 18 (33%) did not consent. Four (11%) participants had CP; one female had unilateral spastic CP of GMFCS level I and three males had bilateral spastic CP of GMFCS level I, II and IV. Eight (23%) VLBW participants had low estimated intelligence quotient (IQ_{est}), of whom two had CP. For Paper II, one participant did not fill out the questionnaires regarding mental health and HRQoL. For Paper III, we excluded one participant with image artefacts on MRI and all four participants with CP because of their obvious motor difficulties and large impact on DTI metrics.

At the 14-year examination, two VLBW participants with bilateral spastic CP did not perform the Movement ABC, and one of these did not perform the Grooved Pegboard Test. Data for longitudinal analyses in Paper I was therefore available for 34 and 35 participants, respectively. At 20 years, mental health and HRQoL had been assessed for 52 VLBW participants, of whom nine were excluded due to missing IQ_{est} at 14 years. Hence, the longitudinal analyses in Paper II included 43 VLBW participants at 20 years and 35 participants at 23 years, of whom 29 were examined at both time-points.

Control group

The control group comprised 37 young adults (15 males and 22 females) born with a birth weight ≥10th percentile for gestational age. At birth, 120 control participants were included in the study. Of these, two with congenital malformations were excluded. At 14 years, nine participants had moved, one was not contactable and 27 did not consent to participation, leaving 81 adolescents for examination. At 23 years, we contacted 48 control participants matched to the VLBW participants by age and sex, of whom 46 had participated at the 14-year examination and two were included from an earlier follow-up. Two of the contacted controls were not testable due to pregnancy, five had moved too far away and four (9%) did not consent. One

control participant had low IQ_{est}. For Paper III, six control participants were excluded due to image artefacts on MRI.

At the 14-year examination, data on Movement ABC and Grooved Pegboard Test were available for 35 controls for longitudinal analyses. At 20 years, mental health and HRQoL had been assessed for 77 controls and were included in longitudinal analyses in Paper II together with 37 control participants at 23 years, of whom 31 were examined at both time-points.

Non-participants

There were no significant differences between those who participated and those who did not consent to participation in the VLBW group in neither of the papers regarding perinatal data (data not shown). In Paper II, parental SES at 14 years was significantly higher among participants than non-participants. In the control group, there were no significant differences between those who participated and those who did not consent to participation or were not invited from previous follow-up in neither of the papers. In Paper I, VLBW non-participants comprised those who were not testable (two participants), not contactable (seven participants) and the 18 who did not consent to participation. However, the control non-participants comprised only those who did not consent to participation or were not invited. Therefore, only the 18 VLBW young adults who did not consent to participation comprised VLBW non-participants in Papers II and III, consistent with the control non-participants in all three papers. Importantly, there were still no significant differences between VLBW participants and non-participants when we included those who were not testable and not contactable as non-participants.

Study methods

Assessments used in this thesis are summarised in Table 2, and a detailed description of the assessments follows in this section.

Table 2 Overview of assessments used in this thesis

Age	Outcome	Assessment tool	Examiner
Birth			
	BW, GA, head circumference, Apgar scores, days at NICU and ventilator, IVH-status, maternal age	Medical records	Paediatrician
14 years			
	Neurological status, including CP	Neurological examination	Paediatrician
	Cognitive abilities	WISC-III	Psychologist
	Parental SES	Hollingshead's two factor index of social position	Self-report
	Motor skills	Movement ABC Grooved Pegboard Test	Physiotherapist Psychologist
20 years			
	Mental health	ASEBA, ASR	Self-report
	Health-related quality of life	SF-36	Self-report
	TBSS	1.5T Siemens Magnetom Symphony	MRI physicist
23 years			
	Weight, height, head circumference	Electronic scale, tape measure	Physiotherapist
	Injury, illness, medication usage, exercise, education	Questionnaires	Self-report
	Pain	Visual analogue scale (0-10)	Self-report
	Handedness	Edinburgh Handedness Inventory	Self-report
	Motor skills	Grooved Pegboard Test Trail Making Test-5 Movement ABC-2 HiMAT	Physiotherapists/ master student in movement science
	Mental health	ASEBA, ASR BDI	Self-report
	Health-related quality of life	SF-36	Self-report
	Probabilistic tractography, TBSS	3T Siemens Trio	MRI physicist

Abbreviations: BW, birth weight; GA, gestational age; NICU, neonatal intensive care unit; IVH, intraventricular haemorrhage; CP, cerebral palsy; WISC-III, Wechsler Intelligence Scales for Children -Third Edition; SES, socioeconomic status; Movement ABC, Movement Assessment Battery for Children; ASEBA, Achenbach System of Empirically Based Assessment; ASR, adult self-report; SF-36, Short Form 36 Health Survey; TBSS, tract-based spatial statistics; MRI, magnetic resonance imaging; HiMAT, High-level Mobility Assessment Tool; BDI, Beck Depression Inventory

Background assessments

Clinical characteristics

Perinatal data included birth weight, gestational age, head circumference, Apgar scores, days in NICU, days on mechanical ventilator, IVH-status and maternal age. At 23 years of age, weight was measured on an electronic scale (to nearest 10 grams). Height was self-reported or measured. Body mass index was calculated from these two measures (kg/m^2). Head circumference (occipital-frontal) was measured to the nearest 0.1 cm.

Handedness was assessed by the Edinburgh Handedness Inventory[186], which gives a laterality index determined by the dominance of a person's right or left hand in 12 everyday activities. The laterality index ranges from -100 for complete left-handedness, to +100 for complete right-handedness. For Paper III, the dominant hand was defined as the writing hand and the dominant foot was self-reported or defined as the preferred foot for one leg stand. The participants answered questionnaires regarding recent injury, recent illness, current medication usage, pain, exercise and education. Pain was reported through a visual analogue scale by indicating a position along a continuous line between 0 and 10. The participants recorded their weekly frequency and duration of exercise and number of exercise activities performed regularly (if any). Education was dichotomized into "high school completion plus higher education admissions" and "incomplete high school plus vocational training".

Socioeconomic status

Parental SES was calculated according to Hollingshead's two factor index of social position[116] at 14 years of age, based on a combination of parents' education and occupation, rated from 1 (lowest) to 5 (highest).

Neurological examination

A clinical neurological examination was performed at age 14 by project paediatricians. Cerebral palsy was classified as spastic hemiplegia (unilateral), diplegia (bilateral, most involvement in lower extremities) or quadriplegia (involvement of all extremities). Functional level was assessed according to the GMFCS[188].

Cognitive abilities

IQ_{est} was calculated at 14 years using two subscales of Wechsler Intelligence Scales for Children, third edition (WISC-III); vocabulary and block design[267]. "Low IQ_{est}" was defined as a score more than two standard deviations below the mean in the control group (IQ_{est} <69).

Assessment of motor skills

Fine and gross motor skills in young adulthood were assessed by two physiotherapists and one master student in movement science. Each participant was tested by one examiner. All examiners were blinded to neonatal history, clinical characteristics and results from previous follow-up.

Grooved Pegboard Test

The Grooved Pegboard Test[89] is a manipulative dexterity test which requires complex visual-motor coordination and measures how quickly the participants can insert pegs into 25 keyhole-shaped holes with various orientations in a 5 x 5 matrix. Time (in seconds) and number of drops are registered for each hand individually. Poor performance was defined as scores >2SD of the mean in the control group in this thesis. One VLBW participant with bilateral spastic CP was not able to perform the Grooved Pegboard Test.

Trail Making Test-5 (TMT-5)

The TMT-5[55] measures motor speed and consists of 32 circles linked with a dotted line on a paper. The task is to draw a line from the first to the last circle following the dotted line as fast as possible, touching all the circles. Time (in seconds) and errors (number of circles missed) are noted. The TMT-5 is one of five subtests of the TMT in the standardised Delis-Kaplan Executive Function System[55]. The other TMT subtests assess executive functions, such as attention, working memory and mental flexibility, which we considered less relevant for the aim of this thesis. The TMT-5 is a basic test for motor speed with less involvement of executive functioning to quantify the influence of motor function on the other subtests. One VLBW participant with bilateral spastic CP was not able to perform the TMT-5.

Movement Assessment Battery for Children-2 (Movement ABC-2)

The Movement ABC-2[107] is the revised version of the widely used and well-validated Movement ABC[106,228,253], which identifies and evaluates children's motor development. There are only minor changes to the original items in the revised version[107], and the Movement ABC-2 is also found to be reliable and valid[67,216,260,285]. The test is divided into three age bands, where the highest age band (up to 16 years and 11 months) was used in this study. The test consists of eight items grouped into three subscales of "manual dexterity" (three items), "aiming and catching" (two items) and "balance" (three items). The raw scores (for instance number of seconds to complete a task) are converted into item standard scores, which add up to a component score for each subscale. The total test score of maximum 108 points is the sum of the three component scores, where a higher score indicates better motor skills. Motor problems were defined as scores <5th percentile in the control group in this thesis. One wheelchair-dependent VLBW participant with bilateral spastic CP was not able to perform the balance items, thus total score could not be calculated for this participant.

High-level Mobility Assessment Tool (HiMAT)

The HiMAT[272] is a new test specifically developed to examine high-level mobility following traumatic brain injury, although the authors claim that the test may also be applicable to other neurological conditions[271,273]. It is one of few motor tests developed for adults and has high validity and responsiveness[271,275,277]. High-level mobility refers to motor performance necessary for many leisure, sporting and social activities, among others. The test assesses 13 items (walk, walk backwards, walk on toes, walk over obstacle, run, skip, hop forward, bound each leg, and walk up/down stairs). The participants are asked to complete the task at their fastest safe speed over a distance of 20 m, whereof the middle 10 m is timed in all items except for the bound item (distance in cm) and stair items (normal walking speed). The raw score (time in seconds and distance in cm) is converted to a score from 0 to 4 for most items, and 0 to 5 for the stair items. The higher score the better performance. The stair items are classified as "dependent" or "independent" based on the use of railings for support and reciprocal walking. A 12-step staircase was used in the current study, and the scoring corrected thereafter (seconds x 14/12) in accordance with the manual[273]. Failure, refusal or inability to perform a test item is given an item score of zero. The maximum total score is 54 points. The Norwegian translation of the test was used in this thesis[171].

The authors of the test have also published a revised version of the HiMAT[274], consisting of eight of the original 13 items, where bound on affected leg and the stair items have been removed with a total 8-item HiMAT score of 32 points. For Paper I, we calculated both the total original HiMAT score and the revised 8-item HiMAT score. One wheelchair-dependent VLBW participant with bilateral spastic CP was not able to perform the HiMAT. One control participant had an ankle sprain during skipping, thus was not testable on the remaining tasks.

Intra- and inter-tester reliability

We performed inter- and intra-tester reliability by scoring video recordings of the Grooved Pegboard Test, TMT-5 and the Movement ABC-2 (except the drawing task which was not possible to score from video recordings). We chose not to include the HiMAT in the reliability-testing due to poor video quality. The author of this thesis scored the video recordings for inter-tester reliability on 51 (70%) participants (27 VLBW, 24 control) and was blinded to group adherence, clinical characteristics and outcome from previous and current follow-up. One of the examiners scored the video recordings for intra-tester reliability on 44 (60%) of the participants (26 VLBW, 18 control). The two-way mixed intra-class correlation (ICC 3.1) is a

measure of inter-rater reliability from 0 to 1 where a value between 0.6 – 0.74 is good and 0.75 – 1 is excellent[42]. ICC (3.1) for inter-tester reliability ranged from 0.913 to 1.000 for 84% of the rated tasks. For the remaining rated tasks, ICC (3.1) was 0.708 and 0.781 for right and left foot zig-zag hopping, and 0.814 for Grooved Pegboard drops with non-dominant hand. ICC (3.1) for intra-tester reliability ranged from 0.952 to 1.000 for 79% of the rated tasks. For the remaining tasks, ICC (3.1) was 0.789 and 0.591 for right and left foot zig-zag hopping, 0.897 for throwing and 0.851 for Grooved Pegboard drops with non-dominant hand.

Assessment of mental health

Two questionnaires were used to assess self-reported mental health: Adult Self-Report (ASR) and Beck Depression Inventory (BDI).

Adult Self-Report

Self-reported mental health was obtained by the ASR[2], which is part of the Achenbach System of Empirically Based Assessment. An authorised Norwegian translation of the ASR was used. The ASR (age range 18-59) comprises 120 problem items (scored 0-2), yielding eight syndrome scales: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior and intrusive. The first three scales comprise the composite scale for internalizing problems, whereas the last three scales comprise the composite scale for externalizing problems. The total problems score is the sum of all problem items. A score for critical items is made by summing scores on 19 problem items evaluated to be the most clinically relevant psychiatric symptoms. Raw scores were used, and higher scores indicate more problems. In addition, the ASR includes items on adaptive functioning, of which we used the scales for friends, family and substance use in this thesis. Questions on friends include number of close friends, frequency of contact with friends, getting along with friends and visits from friends, rated 0-3, with a maximum sum score of 12. Information on family relations include self-perceived quality of relation with parents and/or siblings compared with others, rated 0-2. Higher scores indicate better adaptive functioning. The substance use scales include tobacco, alcohol and drugs, and scores reflect number of cigarettes smoked daily, days being drunk and number of days using drugs during the last six months. T-scores for substance use were used to calculate a mean substance use scale, which is recommended when dealing with outliers. One VLBW participant did not complete the ASR questionnaire.

Beck Depression Inventory

The BDI[25] is among the most used self-rating scales world-wide for measuring depression, and has high validity in differentiating between depressed and non-depressed individuals[201]. Version IA was used in this thesis. The BDI (age range ≥13) consists of 21 questions measuring symptoms and severity of depression during the past week[25]. The scores range from 0-3, with a total score of 63. For the general population, a total score of ≥21 represents depression. One VLBW and two control participants did not complete the BDI.

Assessment of health-related quality of life

Short Form 36 Health Survey (SF-36)

The SF-36 examines self-reported HRQoL. It is a generic measure with high reliability and it has been widely validated for use across a range of health care professions, settings and patients[264], also for the Norwegian translation used in this study[154,263,265]. Version 1.0 was used in this thesis. The questionnaire comprises 36 items across eight domains: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional) and mental health. Raw scores are transformed into an aggregate percentage score for each domain ranging from 0-100%, where higher percentages indicate favourable health outcomes and higher level of functioning. Three of the domains (physical functioning, role limitations due to physical problems and bodily pain) contribute mainly to a physical component summary, while three other domains (social functioning, role limitations due to emotional problems and mental health), contribute mainly to a mental component summary[264]. Three of the domains (general health, vitality and social functioning) have noteworthy correlations with both component summaries[264]. We used the recommended oblique model for calculating the component summaries, found to provide a more universal factor structure without loss of predictive power or reliability[74,104]. We used the Certified Scoring Software 4.0™ to score the questionnaire and calculate component summary scores based on Norwegian normative data[153]. Two control participants did not complete the SF-36. One control had missing scores for vitality and mental health and we could therefore not calculate component summaries for this participant.

Assessment of diffusion tensor imaging

Details of the DTI and MRI acquisition and analyses have been outlined in Paper III, and will be summarised here.

Image acquisition

At 23 years, DTI and T1 weighted MRI were acquired on a 3T Siemens Trio with Quantum gradients (30 mT/m) and a 12-channel head matrix coil (Siemens AG, Erlangen, Germany). DTI was acquired with a single-shot balanced-echo EPI sequence with b = 1000 s/mm^2 in 30 non-collinear directions. A 3D T1 weighted magnetisation prepared rapid acquisition gradient echo (MPRAGE) volume was also acquired. At 20 years, DTI was acquired on a 1.5T Siemens Magnetom Symphony with Quantum gradients (30 mT/m) and a quadrature head coil. Details regarding the DTI acquisition at 20 years are given elsewhere[64].

Image analyses

The DTI analyses were performed with the tools of the FMRIB Software Library (FSL: Oxford Centre for Functional MRI of the Brain, UK: www.fmrib.ox.ac.uk/fsl). The brain was extracted using Brain Extraction Tool (BET, part of FSL). FMRIB's Diffusion Toolbox (FDT) was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxel-wise maps of FA, MD, AD and RD were calculated for the VLBW and control group. FreeSurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu) was used to calculate intracranial volume based on subcortical volumetric analysis of the T1 MPRAGE volume.

Probabilistic tractography

Fibre tractography of the CST and CC was performed using BedpostX, a probabilistic tractography routine implemented in FSL based on a multifibre model[26]. A ROI approach was used to track the CST and CC pathways. The CST was tracked from a seed ROI in the cerebral peduncles to target ROIs in the hand and foot areas in the primary motor cortices (CST_{hand}, CST_{foot}) and premotor cortices ($CST_{premotor}$). The CC_{motor} and $CC_{premotor}$ were tracked from seed ROIs in the CC including motor and premotor fibres[115] to target ROIs in the primary motor and premotor cortices. The thresholded fibre pathways were used to calculate mean FA, MD, AD, RD and volume for the tractography results in all VLBW and control individuals. Relative volume was calculated as mean volume of the tract divided by intracranial volume for each individual. All seed ROIs were manually drawn by the same researcher, blinded to neonatal history, clinical characteristics and results from previous follow-up.

Tract-based spatial statistics (TBSS)

Voxel-wise statistical analysis was performed using TBSS (part of FSL)[227] at 20 years in our cohort[64] and at 23 years in the current study. A detailed description is given elsewhere[64]. Voxel-wise statistics of the skeletonised FA, MD, AD and RD were carried out on the white matter skeleton using Randomise (part of FSL) to test for group differences between the VLBW and control group. Randomise performs non-parametric permutation-based testing and inference using Threshold-Free Cluster Enhancement[180] with a correction for multiple comparisons ($p<0.05$, corrected for sex and age at MRI).

Ethics

The project complies with the principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK number 4.2005.2605). Written informed consent was obtained from all participants through written invitation letters and verbal information upon attendance. Methods used in the study were non-invasive and did not inflict pain. Participants received financial compensation (NOK 1000) for attendance and were referred to medical specialists if indicated.

Statistical analyses

Student's t-test was used for approximately normally distributed data; else the Mann-Whitney U test was applied. Descriptive statistics are reported as mean (SD) where relevant. Normality was judged by visual inspection of Q-Q plots of the residuals. Correlation analyses (Spearman's rho) were performed to investigate relationships between clinical characteristics and outcome variables, in order to identify possible confounding factors. Chi-square test was used to analyse differences in proportions between groups. For Paper I, a two-way mixed ANOVA was performed to calculate intra-class correlation (ICC 3.1) for inter- and intra-tester reliability, and STATA Version 12.1 software was used for analysis of the longitudinal data with the asymptotic McNemar's test. In Paper II, linear mixed models were used to analyse changes in ASR and SF-36 scores from 20 to 23 years. Dependent variables were entered separately for ASR and SF-36 scores, whereas age, group and age x group were entered as independent variables. Analyses were performed both including and excluding participants with CP in Paper I, and CP and/or low IQ_{est} in Paper II. Linear regression was used in Paper II and III to explore associations of mental health, HRQoL and DTI metrics with motor skills. In Paper II, dependent variables were entered separately for critical items, internalizing, externalizing and total problems for ASR, and physical and mental component summaries for SF-36, whereas motor

test scores, group and the interaction motor test scores x group were entered as independent variables. In Paper III, motor test scores were entered separately as dependent variables, whereas FA, group, sex, age and the interaction FA x group were entered as independent variables. The interaction terms were added to test if the effect of motor test scores or FA were different in VLBW and control participants. For motor tests performed with one hand, we performed the association analyses in Paper III with only the contralateral CST in the brain to reduce the number of analyses. Percentage of voxels in the white matter skeleton (from TBSS) with significantly different FA and MD in the VLBW group compared with the control group at 20 at 23 years was calculated to examine whether the extent of FA and MD group differences changed from 20 to 23 years. IBM SPSS Statistics for Windows version 19.0 and 22.0 were used for data analyses and two-sided p-values <0.05 were considered statistically significant.

Results

Clinical characteristics

Clinical characteristics were similar for all three papers despite a small variation in the number of participants (Table 3).

Table 3 Clinical characteristics of study participants

	VLBW (n=36)		**Control** (n=37)		
Background characteristics	Mean	(SD)	Mean	(SD)	p-value
Birth weight (g)	1197	(250)	3608	(361)	<0.001
Gestational age (weeks)	29.1	(2.7)	39.4	(1.1)	<0.001
Birth head circumference (cm)[a]	27.0	(2.4)	35.2	(1.2)	<0.001
Apgar score after 1 min[b]	6.8	(1.9)	8.9	(0.5)	<0.001
Apgar score after 5 min[c]	8.4	(1.6)	9.7	(1.5)	<0.001
Maternal age at birth	28.7	(5.7)	30.1	(4.5)	0.251
Parental SES at 14 years[c]	3.4	(1.2)	3.7	(1.1)	0.575
	n	(%)	n	(%)	
Intraventricular haemorrhage	3	(9)	*NA*	*NA*	
Grade I-II	2				
Grade IV	1				
Cerebral palsy	4	(11)	0		
GMFCS level I-II	3				
GMFCS level IV	1				
Low IQ_{est}[c]	8	(23)	1	(3)	
	Median	(Range)	Median	(Range)	
Stay in NICU (days)[d]	61	(25-386)	*NA*	*NA*	
Mechanical ventilation (days)[d]	1	(0-63)	*NA*	*NA*	
Characteristics at 23 years	Mean	(SD)	Mean	(SD)	p-value
Age at assessment (years)	22.5	(0.7)	22.7	(0.6)	0.236
Body mass index	23.3	(4.2)	24.4	(3.8)	0.271
Weight (kg)	66.6	(14.0)	73.5	(15.7)	0.053
Height (cm)	168.8	(9.4)	173.2	(10.7)	0.066
Head circumference (cm)	56.0	(1.8)	57.4	(1.7)	0.001

[a] Data missing for seven VLBW and two control participants
[b] Data missing for three control participants
[c] Data missing for two control participants
[d] Data missing for two VLBW participants
Mann-Whitney U test was used to analyse Apgar scores and parental SES, else the Student's t-test was applied.

Abbreviations: VLBW, very low birth weight; SES, socioeconomic status; GMFCS, Gross Motor Function Classification System; IQ_{est}, estimated intelligence quotient; NICU, neonatal intensive care unit; NA, not applicable.

Paper I

Motor skills at 23 years of age in young adults born preterm with very low birth weight

In Paper I, we used various motor tests to examine motor skills in VLBW and control young adults. We found that the VLBW group had overall poorer motor skills compared with the control group. This was seen in all tests performed. The VLBW group were slower than controls on Grooved Pegboard Test ($p=0.026$) and TMT-5 ($p<0.001$). Mean total score of the Movement ABC-2 was 69.7 (20.2) in the VLBW group compared with 74.1 (14.4) in the control group ($p=0.017$). Group differences were also seen in the sub-scores of manual dexterity and balance. Additionally, results on HiMAT showed significantly lower total score and lower scores for items involving balance and speed in the VLBW group compared with the control group. Longitudinal analyses indicated that motor skills did not improve from adolescence into early adulthood in the VLBW group, and the proportion of participants with motor problems did not change from 14 to 23 years. After exclusion of participants with CP, group differences were generally slightly reduced, but still significant for TMT-5 and HiMAT, and borderline significant for Grooved Pegboard Test and Movement ABC-2.

Paper II

Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight

In Paper II, we assessed mental health by the ASR and BDI; HRQoL was assessed by the SF-36. The VLBW young adults reported more mental health problems and lower HRQoL compared with controls at 23 years of age. On the ASR, the VLBW young adults reported more total problems, internalizing problems and attention problems, and scored higher on critical items of clinically relevant psychiatric symptoms compared with controls. They also seemed to be less social and reported to drink half as much alcohol as their peers. There was also a tendency of more anxious/depressed symptoms in the VLBW group, while there were no group differences in symptoms or severity of depression according to the BDI. On the SF-36, the physical and mental component summaries were lower in the VLBW group than in the control group, in addition to the domains physical and social functioning, role limitation due to physical and emotional problems, and bodily pain. As hypothesised, mental health and HRQoL decreased from 20 to 23 years in the VLBW group. Poorer results on motor tests at 23 years were associated with both poorer physical and mental HRQoL in VLBW young adults. In addition, a poorer result on TMT-5 was associated with more internalizing problems and total problems on the ASR in the VLBW group. Overall, when we excluded participants with CP and/or low IQ_{est}, many of the group differences were no longer significant. However, mean values in the VLBW group were essentially the same on the ASR and somewhat higher on the SF-36, especially for the physical component summary. Longitudinal changes and associations with motor skills were similar when we excluded participants with CP and/or low IQ_{est}, except mental HRQoL only being associated with TMT-5.

Paper III

White matter alterations and their associations with motor function in young adults born preterm with very low birth weight

In Paper III, cerebral white matter was examined with DTI. Motor pathways of the CST and CC in the VLBW and control group were analysed with probabilistic tractography; whole brain white matter was analysed with TBSS. Association analyses were performed between specific motor tests and FA in CST and CC. Tractography of the CST and CC showed that the VLBW group had higher diffusion (MD, AD and RD) and lower CC volume than the control group, but FA did not differ significantly. In the VLBW group, poorer performance on TMT-5 and Movement ABC-2 Triangle was significantly associated with higher FA in CST and CC ($p<0.005$). Poorer performance on Grooved Pegboard Test was associated with higher FA in CST ($p<0.02$), and poorer performance on HiMAT was associated with higher FA in CC ($p<0.03$). There were no associations between motor function and FA in the control group. In the TBSS analysis, the VLBW group had lower FA and higher MD compared with controls in all major white matter tracts, and these group differences were more widespread at 23 years than at 20 years of age.

Discussion

Main findings

In this thesis, we found that at 23 years of age, VLBW young adults had poorer fine and gross motor skills and reported more mental health problems and lower HRQoL compared with term-born controls. Furthermore, the VLBW group showed white matter alterations in all major white matter tracts compared with the control group. Longitudinal findings indicated that motor skills did not improve from adolescence into adulthood, and that mental health and HRQoL worsened from 20 to 23 years in the VLBW group. Group differences in white matter alterations seemed to increase in extent from 20 to 23 years. Poorer motor function was associated with white matter alterations in motor pathways of the CST and CC. Poorer motor skills were also associated with more mental health problems and lower physical and mental HRQoL. The effect of VLBW on motor skills, mental health and physical HRQoL seemed to be weaker when we excluded participants with CP and/or low IQ_{est}.

Validity of the study

Several issues should be addressed when considering the validity of a study. In the following, I will first address the internal validity of the study in terms of methodological considerations, chance, bias and confounding. I will then address the external validity of the study in terms of generalisability.

Methodological considerations

Motor assessments

The Grooved Pegboard Test[89] and the TMT-5[55] are valid and reliable tests, developed for use on children and adults. We chose to use the Movement ABC-2[107], a revised version of the widely used Movement ABC[106], because of its improvements and extended age range up to 16 years and 11 months. The participants in our study groups were older than the test was designed for, which can yield ceiling effects, and true differences between groups may not be revealed. However, there are not many motor tests for adults and only modest changes in motor skills are reported after puberty[51,144]. Moreover, we used raw scores instead of the age converted scores, and the VLBW group was compared with our control group instead of the normative sample.

The HiMAT has high validity and responsiveness in the examination of high-level gross mobility primarily in patients with traumatic brain injury[275-277]. The HiMAT was used for the

first time in a preterm population in this thesis. Despite different injury mechanisms (perinatal brain injury versus later acquired traumatic brain injury), both populations show diffuse white matter injury[64,122] and a range of motor difficulties[9,53,113]. Moreover, the test developers state that the HiMAT is applicable to other neurological conditions, especially in young adults[271,273]. This may be supported by the analyses of the raw scores in our study, which gave essentially the same results as the converted item scores. The HiMAT involves items such as running and jumping, similar to other tests used in VLBW populations[33,92,242]. The items reflect gross motor activities in daily life better than items of the Movement ABC-2, and the HiMAT may therefore be useful as a supplementary test in adults born preterm.

Mental health and HRQoL

We used well-known, valid and reliable self-report questionnaires to examine mental health and HRQoL, simplifying comparisons of findings with other studies of VLBW young adults. Self-reports give the participants an opportunity to describe their own perspective of life. The inclusion of data from multiple informants is generally recommended. However, most clinical evaluations in this age group are based on reports by the young adults themselves, and one could argue that their own reports are more important for their well-being than are the parent reports. Questionnaires like the ASR enable the assessment of mental health as a continuum, emphasising the degree of symptoms (dimensional approach). Diagnostic interviews would have been useful for diagnosis setting (categorical approach) and are objective complements to self-reports, but are very time- and resource-consuming. We were not able to identify rare conditions or detect small differences between groups, to which registry studies would have been advantageous.

As for SF-36, it is important to note that the role scales have displayed substantial floor and ceiling effects in the general population[153]. In our study, the control group had mean scores above 94 out of 100 for physical functioning, role-physical, social functioning and role-emotional, possibly introducing a ceiling effect that may have caused an underestimation rather than an overestimation of group differences.

Diffusion tensor imaging

Diffusion tensor imaging is a widely used technique in clinic and research due to its simplicity in terms of sequencing and analyses. However, there are limitations to the diffusion tensor model, especially considering the tracking of non-dominant fibres through crossing fibre

regions[245]. This may be improved with the use of other models and sequences, like high-angular resolution diffusion imaging[247] and constrained spherical deconvolution[244]. However, these techniques put more demand on MRI sequences and analyses. The quality of the DTI measures depends on acquisition parameters, sequencing and methods of analysis, which might affect the final results[135,245]. It is not within the scope of this thesis to address all these; however, some comments about the specific analysing methods used in this thesis are warranted.

For our DTI analyses, we applied a whole-brain voxel-based approach (TBSS) and a ROI-based probabilistic tractography approach. These are complementary approaches that may yield somewhat different results. As TBSS yields voxel-based results, differences in parts of a tract may be detected, as compared to our tractography method that relies on average measures within the whole tract. Furthermore, tractography traces the whole width of the selected tract, including more peripheral parts with more spurious and less dense tracts, likely to result in a lower FA than TBSS, tracing the inner core of tracts where axons are more coherent and dense. Hence, analysing a tract's entire width and length may even out the typical finding of reduced FA by TBSS in VLBW populations compared with controls, thereby yielding no group differences in FA for the whole tract by tractography, as seen in this thesis. It should be noted that FA values from TBSS and in the resulting streamlines of the probabilistic tractography are thresholded to include only relevant tissue, i.e. white matter. However, this might also lead to deviations from the actual underlying anatomy. Although only large tracts like the CST and CC were tracked in our study, FA will nevertheless be influenced by voxels containing crossing fibres, which is important to bear in mind when interpreting the results.

Chance

The role of chance may occur any time a sample of a population is examined[108]. The p-value is defined as the probability that the effect observed in the study could have occurred by chance alone, given that there is no relationship between the exposure and disease. The p-value is a composite measure reflecting both the magnitude of the difference between the groups, and the sample size. Therefore, a large effect may not achieve statistical significance if the sample size is insufficient, which should be considered in this thesis, especially when interpreting results when participants with CP and/or low IQ_{est} are excluded. When interpreting the role of chance, group differences and confidence intervals or standard deviations should also be considered. A wide confidence interval or large standard deviations may be compatible with a true effect even if the sample size was not adequate to yield sufficient statistical power[108].

Our main findings are not likely to be due to chance because of p-values <0.05 and consistent findings. The VLBW group had significantly poorer motor skills than controls for all tests performed, and scores were still lower when we excluded participants with CP, although some findings were borderline significant (p<0.1). This may be caused by a combination of the obvious motor problems in participants with CP and the reduction in sample size. The findings of more mental health problems were shown in several scales of the ASR, and lower HRQoL were found in almost all domains of the SF-36. The DTI findings were also consistent. Lower FA and higher MD in the VLBW group compared with the control group were seen in all major white matter tracts. The associations between motor function and FA were all in the same direction and found in the VLBW group only, reducing the risk of these findings being caused by chance alone.

Bias

If some aspect of the design or the conduct of a study has introduced a systematic error into the results, this is called bias. There are many sources of bias in a study, and I will discuss the two most relevant types of bias in this thesis more closely: information bias and selection bias.

Information bias

Information bias may arise either from the investigators eliciting or interpreting the information differentially, or from the study participants themselves reporting events in a non-comparable manner. In Papers I and III, examiners were unfortunately not blinded to group adherence. However, examiners were blinded to neonatal history and previous test-result. In Paper I, inter-tester reliability assessed by a blinded independent tester from video recordings showed generally high intra-class correlation, indicating minimal variation in the measurements between examiners. Thus, information bias in the motor assessments are unlikely. In Paper III, some operator bias may have been introduced in the manual drawing of ROIs, but this method is generally more precise than automatically placed ROIs. The self-report questionnaires used in Paper II are prone to social desirability bias, meaning that participants tend to give socially acceptable answers rather than being completely accurate. In addition, recall bias may be introduced since the participants were to answer questions based on the last six months for the ASR, the last four weeks for the SF-36 and the last week for the BDI. Since IQ may affect the ability of self-perception and understanding a questionnaire, we also performed analyses excluding VLBW participants with low IQ_{est} in Paper II.

Selection bias

If study participants are not randomly enrolled, selection bias may occur. This study was geographically based and prospective, which minimises selection bias. All VLBW infants born at St. Olavs Hospital in 1986-88 were enrolled in the study. Control participants were recruited from a 10% random sample of women selected for follow-up during pregnancy in another study, investigating causes and consequences of intrauterine growth restriction[15]. Hence, the control group does not include infants small-for-gestational-age (birth weight <10th percentile) and may therefore represent a group with better long-term outcome than the general population[204]. The use of birth weight as a proxy for prematurity introduces a risk of including children with advanced gestational ages and severe growth restriction. This is important to bear in mind when interpreting the results as growth restriction and prematurity are likely to pose different risks for long-term outcome[102].

At long-term follow-up, cohort studies are prone to selection bias due to loss to follow-up. Due to limited resources, we aimed at including the VLBW participants who were examined at 14 years and an equal number of controls, matched by age and sex. This is likely to have reduced the potential sample size from the initial birth cohort, thereby reducing study power, and possibly introducing selection bias. The sample size for longitudinal analyses in Paper II was less affected since the statistical method allowed for inclusion of all available data at each time-point. Participants with poorer outcome may have a stronger tendency to drop out[193], resulting in a greater risk of underestimation of problems rather than an overestimation in the VLBW group. VLBW non-participants in Paper II had lower parental SES than participants, which may have underestimated mental health problems in this group since lower SES is associated with more mental health problems[37]. Except from this, there were no significant differences in clinical characteristics between participants and non-participants in either of the study groups, indicating that we included a representative sample of our initial cohort. Rates of 50-80% participation have been suggested to be acceptable in cohort studies[77]. Of the VLBW young adults we invited to the study, 67% participated. Of the invited controls, 89% consented to participation. Our rate of participation is comparable to other studies of similar length of follow-up[23,50,94].

Confounding

Confounding provides an alternative explanation for an association between exposure (VLBW) and outcome (results of this study). The confounder must be related to both the exposure and

the outcome without being affected by them (Figure 2). Controls were matched to the VLBW participants by age and sex to minimise confounding by these factors. However, we adjusted for age and sex in DTI analyses in Paper III since even small variations within and between groups in these variables may influence DTI metrics. Furthermore, we adjusted for intracranial volume when comparing tract volumes between groups. The higher prevalence of CP and low IQ_{est} in the VLBW group affects the results. However, when studying preterm populations, CP and low IQ_{est} could be considered as mediators rather than confounders, since they are likely to represent factors in the causal chain between exposure (VLBW) and outcome (Figure 2).

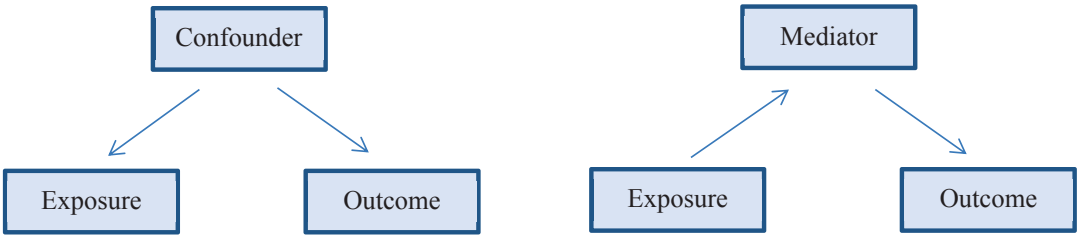

Figure 2 Directed acyclic graph showing the effect of a confounder (left) and a mediator (right) on exposure and outcome

Nonetheless, analyses were performed both including and excluding participants with CP in Paper I, and CP and/or low IQ_{est} in Paper II, since this distinction may be of clinical relevance. The main results persisted when we excluded participants with CP and/or low IQ_{est}. In Paper III, participants with CP were excluded due to the large impact CP has on the white matter microstructure. In sum, known confounders or mediators are not likely to have affected the main findings in this thesis. However, we cannot exclude that we have overlooked other possibly important factors which may have influenced our results.

Generalisability

In sum, the internal validity of the study is likely to be acceptable because chance, bias and confounding were not likely to explain the association between VLBW and poorer motor skills, more mental health problems, lower HRQoL and white matter alterations. However, for this study to be applicable to other similar populations, the external validity should also be acceptable. Generalisation of our results to younger VLBW cohorts may be inappropriate because the quality of intensive care in neonates has improved during the latest decades.

Survival of VLBW infants has increased, but neonatal and short-term morbidity among VLBW children has remained relatively unchanged[73]. In sum, this reflects an increase in the number of VLBW survivors at risk of later adverse outcomes. Our findings provide the best estimate of long-term outcome of VLBW survivors today until more contemporary data is available. As VLBW infants were at the limit of viability in the late 1980s, and ELBW infants are at the limit of viability today, the long-term outcomes found in this thesis may be especially relevant to today's ELBW survivors.

Causality

In this thesis, our aim was to investigate the association between being born with a VLBW and later motor skills, mental health, HRQoL and white matter microstructure. The primary objective in epidemiological studies is to judge whether an association between exposure and outcome is causal[108]. However, the presence of an association does not in any way imply causality. The result of any single study is only one component in the totality of evidence leading towards a judgment of the existence of cause and effects. Hence, judging whether the associations in this thesis are causal extends beyond the validity of the results, and includes considerations of strength of the association, biological credibility of the findings and consistency with other studies[108]. These three issues will be discussed in the following.

Strength of the association

We found a strong association between VLBW and motor problems. At 23 years, 29.4% of the VLBW participants had motor problems according to the Movement ABC-2; this is a prevalence around three to four times higher than in the general population[176]. Group differences were highly significant for motor speed measured by TMT-5, also when we excluded participants with CP ($p<0.001$). Reduced balance was found on two different tests (Movement ABC-2 and HiMAT), strengthening the association between VLBW and poor balance in young adulthood. Clinically important changes are found to be 1.21 points on the Movement ABC-2 total score[285] and 2.66 points on the HiMAT total score[273]. The VLBW group scored 10.5 points lower than the control group on the Movement ABC-2 total score (6.1 points when participants with CP were excluded) and 4.7 points lower than the control group on the HiMAT total score (3.0 points when participants with CP were excluded). Thus, these findings indicate large differences of clinical importance, strengthening the association between VLBW and motor problems.

Group differences in mental health by ASR were generally not highly significant. However, this may be explained by the small sample size and high SD in both groups, indicating a large variability in scores. For the ASR total problems score, the VLBW group scored 9.6 points higher than the control group (p=0.048), reflecting an increase of 33% or 0.5SD from the mean score in the control group. The higher total problems score was mainly due to more internalizing problems, where the VLBW group scored 4.3 points higher than the control group (p=0.042), reflecting an increase of 50% or 0.6 SD from the mean score in the control group. These differences are likely to be of clinical importance. Longitudinal analyses of mental health problems from 20 to 23 years showed a highly significant increase in the VLBW group for internalizing problems (p=0.001) and total problems (p=0.002), showing a strong association between VLBW and declining mental health into young adulthood, likely to be of clinical importance.

The physical and mental component summaries of HRQoL in the VLBW group were more than 0.5 SD lower than the mean score in the control group (3.4 points, p=0.009 and 4.5 points, p=0.013) respectively), a difference likely to be of clinical significance[75]. The statistical significant change in HRQoL from 20 to 23 years was seen in the VLBW only, supporting an association between VLBW and poor HRQoL.

For DTI metrics, group differences were seen by TBSS in all major white matter tracts, after adjusting for multiple comparisons. These adjustments are strict, strengthening the association between VLBW and white matter alterations. We also found strong associations between FA and fine motor function in the VLBW group with p-values ranging from 0.001 to 0.01 for most of the analyses. The associations between FA and gross motor function were weaker and less likely to be of clinical importance.

Biological credibility

Poorer motor skills and mental health in addition to widespread white matter alterations in VLBW young adults compared with controls suggest a comprehensive and general deficit. The preterm brain is susceptible to a cascade of adverse events, often referred to as the "Encephalopathy of prematurity"[259], which is likely to affect both white matter microstructure, motor function and mental health. Indeed, both motor and mental health problems were associated with white matter alterations in the VLBW group in our cohort at age 15[126,224]. In this thesis, poorer motor skills were associated with mental health problems in Paper II, and an

association between poorer fine motor function and white matter alterations was confirmed in VLBW young adults in Paper III. The association was found in motor pathways close to the lateral ventricles, the CST and CC. Due to an increased risk of germinal matrix haemorrhages[16] and injury to and loss of periventricular white matter in the preterm brain[223,259], these pathways may be especially vulnerable to alterations. Structural-functional associations may be caused directly or indirectly by focal brain lesions, a reduced or aberrant myelination and/or axonal abnormalities in the preterm brain, reducing connectivity. Further explanations may be that the plastic changes that allow function to be broadly spared in very preterm individuals are incomplete, or that the altered brain architecture that results from plasticity is less efficient[183]. The negative association we found between motor function and FA was somewhat contra intuitive, as higher FA often is interpreted as improved white matter integrity. However, this is not always true as FA is only an indirect measure of white matter integrity. An example of this is FA in crossing fibre regions. Since crossing fibres in general reduce the apparent AD and thereby reduce the FA value in a voxel, and healthy controls are likely to have more crossing fibres with higher FA than VLBW individuals, voxels in regions of crossing fibres are likely to show lower FA in controls than VLBW individuals. This has been seen in the corona radiata[138] and centrum semiovale[88], where the CST, CC and association fibres are crossing. VLBW individuals with poor motor function are likely to have a more widespread and severe injury of white matter, and thereby fewer crossing fibres and seemingly higher FA in crossing fibre regions, which might explain the association between poorer motor function and higher FA in the VLBW group found in this thesis.

Potential underlying mechanisms for the increased risk of internalizing problems and the characteristic preterm behavioural phenotype are naturally multi-aetiological. As the development of a psychiatric disorder is often a combination of the presence of risk factors and the lack of resilience and other protective factors, I will discuss this specifically for preterm individuals. The altered brain development is found to be associated with behavioural, mental and social problems[152,182,190,224], constituting a biological risk factor. These associations may also be mediated by problems with cognition and executive functioning[281]. Poor executive functioning with difficulties holding information in mind and switching between mental sets is related to behavioural functioning[1], and might also partly explain the social difficulties of VLBW individuals. Furthermore, the functioning of the HPA axis may be altered by intrauterine stress, early distress at the NICU, infections or through parental separation and distress[34,36,279]. Alterations of the HPA axis may have long-lasting effects on behaviour and

mental health in VLBW individuals[213,249]. These biological risk factors may also cause lack of resilience and other biological protective factors, and show that biological and environmental risk factors are closely related. Other environmental risk factors for adverse mental health may be the increased risk of bullying in preterm children[87,282], and not succeeding in life as peers in terms of education and family life[150,172,177]. Parental psychological well-being may be negatively affected by a preterm birth[221], and may further have an impact on later mental health problems in the preterm individual[120]. Resilience factors preventing development of later adverse mental health have also been documented. As an example, maternal sensitivity may be a long-term resilience factor preventing the development of internalizing problems in very preterm born adolescents[76].

We speculate that the lower HRQoL in VLBW young adults in our study could be partly due to the transition to independent living. To move away from home, start to study or work, finding a partner and live more independent and social lives are challenges that may stress the underlying physical, mental, cognitive and social difficulties of VLBW individuals. This speculation is supported by a recent study demonstrating that the lower HRQoL in very preterm and VLBW young adults compared with controls could be partly explained by economic and social functioning problems[22].

Consistency with other studies

Motor skills

To our knowledge, there are no other studies assessing motor skills in young adults born with VLBW. However, our findings of poorer motor skills among VLBW young adults compared with controls in Paper I are consistent with the existing knowledge of poorer motor skills in VLBW children and adolescents[53,72,224,242]. A recent study investigating self-reported motor coordination difficulties in ELBW young adults at 22-26 and 29-36 years of age compared with normal birth weight controls, found that motor coordination remained poorer in ELBW survivors into adulthood[196]. A meta-analysis[53] found that motor problems in VLBW children and adolescents were evident in balance skills, ball skills, manual dexterity, and fine and gross motor skills. We found poorer balance and manual dexterity according to the Movement ABC-2, but no differences in ball skills. Poorer manual dexterity persisting into young adulthood was also confirmed by the Grooved Pegboard Test and the TMT-5 in our study. When we excluded participants with CP, mean values for the Movement ABC-2 were still poorer than for controls on most of the items, however no longer statistically significant. We found that 29.4% in the

VLBW group had motor problems at both 14 and 23 years, defined as a score <5th percentile on the Movement ABC-2. This is comparable to a study finding that 34% in the preterm group with a birth weight <1250g had scores <5th percentile on the Movement ABC at 12-13 years of age[197]. No other studies have examined motor skills in VLBW populations using the HiMAT. The poorer total score of the HiMAT indicates poorer gross motor function in the VLBW group, both including and excluding participants with CP. Furthermore, most of the significantly poorer item scores on the HiMAT involved balance, such as "hop forward" (hopping on one leg) and "bound" both legs (jumping once from one leg to the other). This supports the finding of poorer balance by Movement ABC-2. Hence, our findings of poorer motor skills in young adulthood are well in accordance with other studies in adolescence.

Mental health

Our findings of more internalizing and attention problems, and the tendency of more anxious symptoms and poorer social relations in VLBW young adults in Paper II are consistent with the literature[1,5,93,112,157,199]. These findings support the suggested "Preterm behavioural phenotype"[132], characterised by anxiety, inattention and social difficulties. This is in accordance with the personality type reported among young adults born VLBW or very preterm (<33 weeks' gestation), including less sensation seeking, extraversion and openness to experience, and higher conscientiousness, neuroticism and shyness[5,6,194]. A newly published meta-analysis including data from six cohorts of VLBW young adults support these findings[199]. They concluded that VLBW young adults have more internalizing and avoidant personality problems and fewer externalizing, rule-breaking, intrusive, and antisocial personality problems than term controls[199]. Lower alcohol consumption among VLBW young adults as found in our study and other studies[95,238], may be explained by this personality type or the fact that they are less social[112,157]. Other studies have also found that cognitive function modifies the risk of mental health problems in preterm born populations[97,132,157].

There are few studies reporting on longitudinal changes in mental health in VLBW populations. In VLBW females, internalizing problems at eight years of age was found to predict the same problems in young adulthood[96]. We have previously reported a trend towards an increase of mental health problems from 14 to 20 years of age in this cohort[159], and the further increase from 20 to 23 years found in the current study is worrying. This increase in mental health problems seemed to persist to 26 years in our recent follow-up, as the probability of psychiatric disorders based on diagnostic interviews increased from 28% at 20 years to 36% at 26 years in

the VLBW group vs 8% to 13% in the control group[160]. These findings are disturbing, and call for further examination.

Associations between mental health and motor skills

Adults previously diagnosed with DCD have reported more symptoms of anxiety and depression[110,111]. Both in adults with normal birth weight and ELBW, self-reported childhood coordination problems were associated with elevated levels of inattention and symptoms of anxiety and depression[195]. These studies indicate that the association between mental health and motor skills is independent of birth weight.

Health-related quality of life

Findings on HRQoL in VLBW populations are conflicting. In Paper II, we found lower HRQoL in VLBW young adults, in accordance with other VLBW studies[22,45,60] and ELBW studies[38,211]. In contrast to our findings, two systematic reviews[5,286] concluded that VLBW young adults were as satisfied with their HRQoL as their peers, and that differences seen in their younger years seemed to diminish over time. This conclusion was supported by two more recent studies examining HRQoL using SF-36 among young adults born with a VLBW[50] or with a birth weight <1250g[23]. There are possibly considerable cultural differences in factors influencing HRQoL, complicating comparison between countries. Furthermore, as some subscales of the SF-36 are prone to floor and ceiling effects, this may reduce the chance of capturing group differences[153].

There are few longitudinal studies investigating changes in HRQoL into adulthood in preterm populations. One study found a worsening in HRQoL from 13 to 26 years of age as reported by parents of very preterm and VLBW young adults, whereas the participants themselves reported no change[22]. Both positive and negative changes in HRQoL have been reported from 14 to 19 years in a very preterm and/or VLBW cohort[255], while no important changes were reported in HRQoL between 19 and 28 years in the same cohort[252]. A recent study of HRQoL trajectories of ELBW survivors into adulthood (age 12 to 36 years) found modest nonsignificant declines in HRQoL scores over time in ELBW and control individuals, with differences among trajectories becoming most prominent in adulthood[211]. Our findings showed a decline in self-reported physical and mental HRQoL in the VLBW group in the transition to adulthood (20 to 23 years) that may not have been captured by the other studies with larger intervals of assessment.

Associations between health-related quality of life and motor skills

Results in Paper II showed that poorer motor skills were associated with lower physical and mental HRQoL, which remained significant for fine motor speed when we excluded participants with CP and/or low IQ_{est}. A distinct low trajectory of HRQoL has been found in ELBW individuals with neurosensory impairments[211] and a strong association has been found between physical impairments and HRQoL in a group of VLBW young adults[255]. However, even mild motor difficulties are shown to impact on children's ability to perform daily self-care, social, academic and leisure tasks[170]. Adults previously diagnosed with DCD have reported lower QoL satisfaction compared with peers[111,240]. An association between motor skills and HRQoL is therefore likely to exist, but more studies are needed to examine this association in VLBW populations, especially in participants without neurosensory impairments.

White matter microstructure

Lower FA and higher MD are common findings in major white matter tracts throughout the preterm brain[148,189], supporting our TBSS findings. These changes are already evident in infancy[10,191,206], and persist in childhood[43,46], adolescence[254] and young adulthood[7,64,141]. To our knowledge, there are no true longitudinal DTI studies due to the rapid development of MRI techniques. We were not able to analyse within-group longitudinal changes, due to different MRI scanner type and strength. However, we found that the group differences in white matter diffusion seemed to increase in extent (number of voxels) from 20 to 23 years. A similar increase was seen between 14 to 19 years in our cohort[64]. The finding of equal FA between the VLBW and control group in motor pathways by tractography was somewhat surprising, but may be explained by methodological differences. However, the tractography results showed group differences in axial, radial and mean diffusion, supporting white matter alterations in motor pathways as seen in other studies[64,141]. A similar discrepancy in results by TBSS and tractography in CST has also been found in another study of VLBW young adults[138].

Associations between white matter microstructure and motor function

The negative association we found between motor function and FA was opposite from what we expected based on earlier findings. A positive association between motor function and FA in VLBW populations has been found in infancy[251], childhood[54], adolescence[224] and young adulthood[233]. There are also studies that do not indicate any association between motor function and FA[46,138]. However, these studies included only VLBW infants without major motor

problems or focal brain lesions[46], or they assessed motor function in childhood and DTI in adulthood[138], possibly reducing the likelihood of finding an association. Furthermore, it is difficult to compare results between studies due to large differences in age at examination, motor assessments, DTI sequencing and analyses. The negative association we found may be explained by regional group differences in crossing fibres, but further research is needed to explore these associations and crossing fibre regions more closely.

Clinical implications

Poor manual dexterity combined with reduced motor speed may have a negative influence on writing skills and computer-typing, which again can interfere with academic achievement, work and independent living. Reduced balance and gross motor function may interfere with sports and various leisure activities and reduce the chances of an active life with friends. The continuation of motor problems into adulthood strengthens the importance of early intervention or helping parents choose alternative activities and sports more adapted to the child's motor skills to ensure an active lifestyle. Motor problems in VLBW young adults are likely to be related to the "Encephalopathy of prematurity", emphasising the importance of continuation in efforts to enhance normal brain development.

As motor problems were associated with mental health problems and low physical and mental HRQoL, awareness of the coexistence of problems is needed, and special attention should be given to individuals with multiple risks. Poor motor skills, mental health and HRQoL may influence self-esteem, increase risk of bullying and lead to social isolation, which may further worsen the problems[52,87,282]. An increased focus on resilience factors preventing the development of adverse mental health and HRQoL in preterm individuals is warranted. Assessments of mental health should include a cognitive examination since mental health problems were modified by IQ. As mental health and HRQoL declined in the transition to adulthood, there is reason to be observant of problems that might become more visible as the VLBW young adults enter independent living and encounter the demands of adulthood.

Future research

As it may seem that the transition to adulthood is especially challenging for VLBW individuals, we encourage more research into adulthood, including association analyses of possible coexisting factors to identify especially vulnerable individuals. Further follow-up is needed to see how motor and mental health problems, HRQoL and white matter alterations change further into adulthood. It will be equally important to identify early risk factors for adverse outcome in order to possibly prevent problems in adulthood by environmental adaptation. A new follow-up at 26 years in our cohort was completed recently, assessing HRQoL and mental health, including self-report questionnaires and psychiatric diagnostic interviews. MRI was also performed, and one aim is to investigate possible mental health correlates in the brain.

Further research on the brain and inflammation is important to detect possible biological correlates and early biomarkers to later neurodevelopmental difficulties. More advanced MRI techniques such as hybrid/simultaneous PET/MRI and fMRI, as well as quantitative EEG may be increasingly important in future research on brain connectivity. Higher field-strength magnets in MRI scanners and an integration of DTI and fMRI may improve the accuracy of anatomical localisation of microstructural changes. There is also a lack of genuinely longitudinal studies of brain development in preterm populations, using DTI and other imaging modalities.

Early interventions may be effective as the brain is highly plastic early in life[134]. Early interventions have been found to improve short-term motor function[119,248], but long-term follow-up is lacking. Interventions continuing after hospital discharge and including parents seem to be most beneficial for motor and cognitive function[119]. Motor practice in childhood and adulthood has been found to improve white matter integrity in musicians[28], possibly because electrical activity by axons can stimulate myelination[57]. It would be of great interest to investigate if this may apply to preterm populations and have positive effects for other domains than motor function. The study of genetic and environmental influences on brain and white matter may be more relevant in the future to examine the interactions between perinatal brain injury, genetics and white matter structure in preterm individuals.

To advance the knowledge on long-term outcomes after preterm birth, our research group is a member of "Adults Born Preterm International Collaboration" (APIC), that includes several research groups around the world, and which enables us to share data and perform pooled analyses for joint publications. Two papers have already been published as a result of this collaboration[118,199], with more to come. Furthermore, NTNU is a partner through our research group in an EU project: Research on European Children and Adults born Preterm (RECAP). This project aims at harmonising and combining European follow-up data to promote health and well-being for children and adults born preterm and to study underlying factors of risk and resilience.

Conclusions

In conclusion, VLBW young adults had poorer fine and gross motor skills compared with a term-born control group at 23 years, and they did not show any improvements in motor skills from adolescence into young adulthood. At 23 years of age, the VLBW group reported more mental health problems and lower health-related quality of life (HRQoL) than the control group. They seemed to have a cautious lifestyle with a tendency of less alcohol use and restricted social network, and more internalizing problems. Longitudinal findings indicated that mental health and HRQoL worsened from 20 to 23 years in the VLBW group. Poorer motor skills were associated with more mental health problems and especially lower physical HRQoL, the cause of which is likely to be of shared aetiology. The VLBW young adults showed white matter alterations in all major white matter tracts compared with controls; these group differences seemed to increase in extent from 20 to 23 years. White matter alterations in motor pathways of the corticospinal tract and the corpus callosum were associated with poorer motor function in the VLBW group only. These findings indicate that white matter alterations have an impact on outcome in VLBW young adults and that the transition to adulthood seems to be especially challenging for VLBW individuals.

References

1. 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(2):717-28.
2. Achenbach TM, Rescorla LA. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont; 2003.
3. Adolph KE, Joh AS. Motor development: How infants get into the act. In: Slater A, Lewis M, editors. Introduction to infant development. 2nd ed. New York: Oxford University Press; 2007. p. 63-80.
4. Adolph KE, Weise I, Marin L. Motor development. In: Nadel L, editor. Encyclopedia of Cognitive Science. London: Macmillan; 2003.
5. Allen MC, Cristofalo E, Kim C. Preterm birth: Transition to adulthood. Developmental Disabilities Research Reviews. 2010;16(4):323-35.
6. Allin M, Rooney M, Cuddy M, Wyatt J, Walshe M, Rifkin L, et al. Personality in young adults who are born preterm. Pediatrics. 2006;117(2):309-16.
7. Allin MP, Kontis D, Walshe M, Wyatt J, Barker GJ, Kanaan RA, et al. White matter and cognition in adults who were born preterm. PloS one. 2011;6(10):e24525.
8. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol. 2006;195(6):1557-63.
9. Andelic N, Sigurdardottir S, Schanke AK, Sandvik L, Sveen U, Roe C. Disability, physical health and mental health 1 year after traumatic brain injury. Disability and Rehabilitation. 2010;32(13):1122-31.
10. Anjari M, Srinivasan L, Allsop JM, Hajnal JV, Rutherford MA, Edwards AD, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. Neuroimage. 2007;35(3):1021-7.
11. Back SA. Brain Injury in the Preterm Infant: New Horizons for Pathogenesis and Prevention. Pediatr Neurol. 2015;53(3):185-92.
12. Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci. 2001;21(4):1302-12.
13. Back SA, Miller SP. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? Ann Neurol. 2014;75(4):469-86.
14. Bailis DS, Segall A, Chipperfield JG. Two views of self-rated general health status. Soc Sci Med. 2003;56(2):203-17.
15. 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.
16. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010;67(1):1-8.
17. Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol. 2014;41(1):47-67.

18. Bancalari E, Claure N, Gonzalez A. Patent ductus arteriosus and respiratory outcome in premature infants. Biol Neonate. 2005;88(3):192-201.

19. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;1(8489):1077-81.

20. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of Growth among Children Who Have Coronary Events as Adults. N Engl J Med. 2005;353(17):1802-09.

21. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B. 1996;111(3):209-19.

22. Baumann N, Bartmann P, Wolke D. Health-related quality of life into adulthood after very preterm birth. Pediatrics. 2016;137(4).

23. Baumgardt M, Bucher HU, Arlettaz Mieth R, Fauchère J-C. Health-related quality of life of former very preterm infants in adulthood. Acta Paediatr. 2012;101(2):e59-e63.

24. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 2002;15(7-8):435-55.

25. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71.

26. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage. 2007;34(1):144-55.

27. Behrens TE, Sotiropoulos SN, Jbabdi S. MR Diffusion Tractography. In: Johansen-Berg H, Behrens TE, editors. Diffusion MR. 2nd ed. San Diego, USA: Academic Press; 2014. p. 430-40.

28. Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci. 2005;8(9):1148-50.

29. 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(6):728-37.

30. Bjerager M, Steensberg J, Greisen G. Quality of life among young adults born with very low birthweights. Acta Paediatr. 1995;84(12):1339-43.

31. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

32. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74 Suppl 1:35-49.

33. Bruininks RH. Bruininks-Oseretsky test of motor proficiency: Examiner's Manual Circle Pines: American Guidance Service; 1978.

34. Brummelte S, Chau CM, Cepeda IL, Degenhardt A, Weinberg J, Synnes AR, et al. Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress. Psychoneuroendocrinology. 2015;51:151-63.

35. Budde MD, Kim JH, Liang HF, Schmidt RE, Russell JH, Cross AH, et al. Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. Magn Reson Med. 2007;57(4):688-95.

36. Buske-Kirschbaum A, Krieger S, Wilkes C, Rauh W, Weiss S, Hellhammer DH. Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. J Clin Endocrinol Metab. 2007;92(9):3429-35.

37. Bøe T, Øverland S, Lundervold A, Hysing M. Socioeconomic status and children's mental health: results from the Bergen Child Study. Soc Psychiatry Psychiatr Epidemiol. 2012;47(10):1557-66.

38. Båtsvik B, Vederhus BJ, Halvorsen T, Wentzel-Larsen T, Graue M, Markestad T. Health-related quality of life may deteriorate from adolescence to young adulthood after extremely preterm birth. Acta Paediatr. 2015.

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

40. Campbell SK, Vander Linden DW, Palisano RJ. Developmental coordination disorder. In: Campbell SK, Vander Linden DW, Palisano RJ, editors. Physical therapy for children. 3rd ed. St.Louis: Sauders Elsevier; 2006. p. 559-89.

41. Chau V, Brant R, Poskitt KJ, Tam EW, Synnes A, Miller SP. Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. Pediatr Res. 2012;71(3):274-9.

42. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychological Assessment. 1994;6(4):284-90.

43. Constable RT, Ment LR, Vohr BR, Kesler SR, Fulbright RK, Lacadie C, et al. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. Pediatrics. 2008;121(2):306-16.

44. Constitution of the World Health Organization. Geneva, Switzerland: World Health Organization; 1948.

45. Cooke RW. Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child. 2004;89(3):201-6.

46. Counsell SJ, Edwards AD, Chew ATM, Anjari M, Dyet LE, Srinivasan L, et al. Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. Brain. 2008;131(12):3201-08.

47. Cousins M, Smyth MM. Developmental coordination impairments in adulthood. Hum Mov Sci. 2003;22(4-5):433-59.

48. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013;381(9875):1371-79.

49. Dahl LB, Kaaresen PI, Tunby J, Handegard BH, Kvernmo S, Ronning JA. Emotional, behavioral, social, and academic outcomes in adolescents born with very low birth weight. Pediatrics. 2006;118(2):e449-59.

50. Darlow BA, Horwood LJ, Pere-Bracken HM, Woodward LJ. Psychosocial Outcomes of Young Adults Born Very Low Birth Weight. Pediatrics. 2013;132(6):e1521-e28.

51. Davies PL, Rose JD. Motor skills of typically developing adolescents: awkwardness or improvement? Phys Occup Ther Pediatr. 2000;20(1):19-42.

52. Day KL, Van Lieshout RJ, Vaillancourt T, Saigal S, Boyle MH, Schmidt LA. Long-term effects of peer victimization on social outcomes through the fourth decade of life in individuals born at normal or extremely low birthweight. Br J Dev Psychol. 2016.

53. de Kieviet JF, Piek JP, Aarnoudse-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(20):2235-42.

54. de Kieviet JF, Pouwels PJ, Lafeber HN, Vermeulen RJ, van Elburg RM, Oosterlaan J. A crucial role of altered fractional anisotropy in motor problems of very preterm children. Eur J Paediatr Neurol. 2014;18(2):126-33.

55. Delis DC, Kaplan E, Kramer JH. The Delis-Kaplan Executive Function System: D-KEFS. Stockholm: Pearson Assessment; 2005.

56. Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M, et al. Behavioral Problems and Cognitive Performance at 5 Years of Age After Very Preterm Birth: The EPIPAGE Study. Pediatrics. 2009;123(6):1485-92.

57. Demerens C, Stankoff B, Logak M, Anglade P, Allinquant B, Couraud F, et al. Induction of myelination in the central nervous system by electrical activity. Proc Natl Acad Sci U S A. 1996;93(18):9887-92.

58. Developmental coordination disorder. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 1994. p. 53-55.

59. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 2000.

60. Dinesen SJ, Greisen G. Quality of life in young adults with very low birth weight. Arch Dis Child Fetal Neonatal Ed. 2001;85(3):F165-F69.

61. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal stress and preterm birth. Am J Epidemiol. 2003;157(1):14-24.

62. Edelman GM. Bright air, brilliant fire. New York: Basic Books; 1992.

63. Edwards J, Berube M, Erlandson K, Haug S, Johnstone H, Meagher M, et al. Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: a systematic review. J Dev Behav Pediatr. 2011;32(9):678-87.

64. Eikenes L, Løhaugen GC, Brubakk AM, Skranes J, Håberg AK. Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. Neuroimage. 2011;54(3):1774-85.

65. Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr. 2001;22(4):248-56.

66. 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(2):F128-32.

67. Ellinoudis T, Evaggelinou C, Kourtessis T, Konstantinidou Z, Venetsanou F, Kambas A. Reliability and validity of age band 1 of the Movement Assessment Battery for Children--second edition. Res Dev Disabil. 2011;32(3):1046-51.

68. Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. Arch Dis Child. 1991;66(2):204-11.

69. Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. Arch Dis Child Fetal Neonatal Ed. 1996;75(3):F183-6.

70. Evans NJ, Archer LN. Postnatal circulatory adaptation in healthy term and preterm neonates. Arch Dis Child. 1990;65(1 Spec No):24-6.

71. Evensen KA. Born too soon or too small: Motor problems in adolescence. Trondheim: Department of Laboratory Medicine, Children's and Women's Health; Norwegian University of Science and Technology; 2010.

72. Evensen KAI, Vik T, Helbostad J, Indredavik MS, Kulseng S, Brubakk AM. Motor skills in adolescents with low birth weight. Arch Dis Child. 2004;89(5):F451-F55.

73. 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(2):147 e1-8.

74. Farivar S, Cunningham W, Hays R. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.1. Health Qual Life Outcomes. 2007;5(1):54.

75. Farivar SS, Liu H, Hays RD. Half standard deviation estimate of the minimally important difference in HRQOL scores? Expert Rev Pharmacoecon Outcomes Res. 2004;4(5):515-23.

76. Faure N, Habersaat S, Harari MM, Muller-Nix C, Borghini A, Ansermet F, et al. Maternal Sensitivity: a Resilience Factor against Internalizing Symptoms in Early Adolescents Born Very Preterm? J Abnorm Child Psychol. 2016.

77. 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(6):458-61.

78. Flapper BC, Schoemaker MM. Effects of methylphenidate on quality of life in children with both developmental coordination disorder and ADHD. Dev Med Child Neurol. 2008;50(4):294-9.

79. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med. 1977;31(2):91-5.

80. Foulder-Hughes LA, Cooke RWI. Motor, cognitive, and behavioural disorders in children born very preterm. Dev Med Child Neurol. 2003;45(2):97-103.

81. Gasser T, Rousson V, Caflisch J, Jenni OG. Development of motor speed and associated movements from 5 to 18 years. Dev Med Child Neurol. 2010;52(3):256-63.

82. Gesell A, Amatruda CS. Developmental Diagnosis. Normal and Abnormal Child Development. 2nd ed. New York: Harper & Row; 1947.

83. Gillberg C. Deficits in attention, motor control, and perception: a brief review. Arch Dis Child. 2003;88(10):904-10.

84. Gluckman PD, Hanson MA, Buklijas T. A conceptual framework for the developmental origins of health and disease. J Dev Orig Health Dis. 2010;1(1):6-18.

85. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

86. Gooijers J, Swinnen SP. Interactions between brain structure and behavior: The corpus callosum and bimanual coordination. Neurosci Biobehav Rev. 2014;43:1-19.

87. Grindvik AS, Hodøl JS, Vik T, Evensen KAI, Skranes J, Brubakk A-M, et al. Bullying among adolescents with very low birth weight. Acta Paediatr. 2009;98(6):1049-51.

88. Groeschel S, Tournier JD, Northam GB, Baldeweg T, Wyatt J, Vollmer B, et al. Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. Neuroimage. 2014;87:209-19.

89. Grooved Pegboard Test. User instructions. Lafayette, IN: Lafayette Instrument Company, Inc; 2002.

90. Grytten J, Monkerud L, Skau I, Eskild A, Sorensen RJ, Saugstad OD. Saving Newborn Babies - The Benefits of Interventions in Neonatal Care in Norway over More Than 40 Years. Health Econ. 2016.

91. Gäddlin PO, Finnström O, Sydsjö G, Leijon I. Most very low birth weight subjects do well as adults. Acta Paediatr. 2009;98(9):1513-20.

92. 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(5):343-9.

93. Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr. 2009;30(5):460-70.

94. Hack M, Cartar L, Schluchter M, Klein N, Forrest CB. Self-perceived health, functioning and well-being of very low birth weight infants at age 20 years. J Pediatr. 2007;151(6):635-41, 41 e1-2.

95. 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(3):149-57.

96. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor GH, Flannery DJ, et al. Predictors of internalizing symptoms among very low birth weight young women. J Dev Behav Pediatr. 2005;26(2):93-104.

97. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor HG, Flannery D, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. Pediatrics. 2004;114(4):932-40.

98. Hadders-Algra M. The neuronal group selection theory: a framework to explain variation in normal motor development. Dev Med Child Neurol. 2000;42(8):566-72.

99. Hadders-Algra M. The neuronal group selection theory: promising principles for understanding and treating developmental motor disorders. Dev Med Child Neurol. 2000;42(10):707-15.

100. Hadders-Algra M, Van Eykern LA, Klip-Van den Nieuwendijk AW, Prechtl HF. Developmental course of general movements in early infancy. II. EMG correlates. Early Hum Dev. 1992;28(3):231-51.

101. Haga M, Pedersen AV, Sigmundsson H. Interrelationship among selected measures of motor skills. Child Care Health Dev. 2008;34(2):245-8.

102. Hall J, Wolke D. A comparison of prematurity and small for gestational age as risk factors for age 6-13 year emotional problems. Early Hum Dev. 2012;88(10):797-804.

103. Hamrick SE, Miller SP, Leonard C, Glidden DV, Goldstein R, Ramaswamy V, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. J Pediatr. 2004;145(5):593-9.

104. Hann M, Reeves D. The SF-36 scales are not accurately summarised by independent physical and mental component scores. Qual Life Res. 2008;17(3):413-23.

105. Hellgren L, Gillberg IC, Bagenholm A, Gillberg C. Children with deficits in attention, motor control and perception (DAMP) almost grown up: psychiatric and personality disorders at age 16 years. J Child Psychol Psychiatry. 1994;35(7):1255-71.

106. Henderson SE, Sugden DA. The Movement Assessment Battery for Children, Manual. London: The Psychological Corporation; 1992.

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

108. Hennekens CH, Buring J. Epidemiology in Medicine. 1st ed. Little: Brown and Co.; 1987.

109. Heuchan AM, Evans N, Henderson Smart DJ, Simpson JM. Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand Neonatal Network, 1995-97. Arch Dis Child Fetal Neonatal Ed. 2002;86(2):F86-90.

110. Hill EL, Brown D. Mood impairments in adults previously diagnosed with developmental coordination disorder. J Ment Health. 2013;22(4):334-40.

111. Hill EL, Brown D, Sorgardt SK. A Preliminary Investigation of Quality of Life Satisfaction Reports in Emerging Adults With and Without Developmental Coordination Disorder. J Adult Dev. 2011;18(3):130-34.

112. Hille ETM, Dorrepaal C, Perenboom R, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Social Lifestyle, Risk-taking Behavior, and Psychopathology in Young Adults Born Very Preterm or with a Very Low Birthweight. J Pediatr. 2008;152(6):793-800.e4.

113. Hillier SL, Sharpe MH, Metzer J. Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Inj. 1997;11(9):661-75.

114. Himmelmann K. Epidemiology of cerebral palsy. Handb Clin Neurol. 2013;111:163-7.

115. Hofer S, Frahm J. Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage. 2006;32(3):989-94.

116. Hollingshead AB. Two factor index of social position. New Haven, CT: Yale University; 1957.

117. Holman RC, Stoll BJ, Clarke MJ, Glass RI. The epidemiology of necrotizing enterocolitis infant mortality in the United States. Am J Public Health. 1997;87(12):2026-31.

118. Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, et al. Blood Pressure in Young Adults Born at Very Low Birth Weight: Adults Born Preterm International Collaboration. Hypertension. 2016;68(4):880-7.

119. Hughes AJ, Redsell SA, Glazebrook C. Motor development interventions for preterm infants: A systematic review and meta-analysis. Pediatrics. 2016;138(4).

120. Huhtala M, Korja R, Lehtonen L, Haataja L, Lapinleimu H, Rautava P. Parental psychological well-being and behavioral outcome of very low birth weight infants at 3 years. Pediatrics. 2012;129(4):e937-44.

121. Hüppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol. 1998;43(2):224-35.

122. Håberg AK, Olsen A, Moen KG, Schirmer-Mikalsen K, Visser E, Finnanger TG, et al. White matter microstructure in chronic moderate-to-severe traumatic brain injury: Impact of acute-phase injury-related variables and associations with outcome measures. J Neurosci Res. 2015;93(7):1109-26.

123. Illingworth RS. The development of the infant and young child: normal and abnormal. Baltimore: Williams and Wilkins Co.; 1966. 378 p.

124. Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. AJNR Am J Neuroradiol. 2003;24(5):805-9.

125. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. J Pediatr. 2003;143(2):171-9.

126. Indredavik MS, Skranes JS, Vik T, Heyerdahl S, Romundstad P, Myhr GE, et al. Low-Birth-Weight Adolescents: Psychiatric Symptoms and Cerebral MRI Abnormalities. Pediatr Neurol. 2005;33(4):259-66.

127. 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.

128. Ivry RB. Cerebellar involvement in clumsiness and other developmental disorders. Neural Plast. 2003;10(1-2):141-53.

129. Janssen AJ, Nijhuis-van der Sanden MW, Akkermans RP, Oostendorp RA, Kollee LA. Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. Dev Med Child Neurol. 2008;50(12):926-31.

130. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr. 2011;23(2):167-72.

131. Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, Paus T. Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. Neuroimage. 2007;36 Suppl 2:T16-21.

132. Johnson S, Marlow N. Preterm Birth and Childhood Psychiatric Disorders. Pediatr Res. 2011;69(5 Part 2):11R-18R.

133. Johnson S, Wolke D. Behavioural outcomes and psychopathology during adolescence. Early Hum Dev. 2013;89(4):199-207.

134. Johnston MV. Plasticity in the developing brain: implications for rehabilitation. Dev Disabil Res Rev. 2009;15(2):94-101.

135. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed. 2010;23(7):803-20.

136. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage. 2013;73:239-54.

137. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. Semin Perinatol. 2002;26(4):250-9.

138. Jurcoane A, Daamen M, Scheef L, Bauml JG, Meng C, Wohlschlager AM, et al. White matter alterations of the corticospinal tract in adults born very preterm and/or with very low birth weight. Hum Brain Mapp. 2016;37(1):289-99.

139. Kelly R, Holzman C, Senagore P, Wang J, Tian Y, Rahbar MH, et al. Placental vascular pathology findings and pathways to preterm delivery. Am J Epidemiol. 2009;170(2):148-58.

140. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602.

141. Kontis D, Catani M, Cuddy M, Walshe M, Nosarti C, Jones D, et al. Diffusion tensor MRI of the corpus callosum and cognitive function in adults born preterm. Neuroreport. 2009;20(4):424-8.

142. Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. Am J Psychiatry. 2001;158(7):1091-8.

143. Landgren M, Kjellman B, Gillberg C. Attention deficit disorder with developmental coordination disorders. Arch Dis Child. 1998;79(3):207-12.

144. Largo RH, Catlisch JA, Hug F, Muggli K, et al. Neuromotor development from 5 to 18 years. Part 1: Time performance. Dev Med Child Neurol. 2001;43(7):436-43.

145. Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage. 2008;40(3):1044-55.

146. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487(7408):443-8.

147. 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(1):63-78.

148. Li K, Sun Z, Han Y, Gao L, Yuan L, Zeng D. Fractional anisotropy alterations in individuals born preterm: a diffusion tensor imaging meta-analysis. Dev Med Child Neurol. 2014.

149. Lindström K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. Pediatrics. 2009;123(1):e47-53.

150. Lindström K, Winbladh B, Haglund B, Hjern A. Preterm Infants as Young Adults: A Swedish National Cohort Study. Pediatrics. 2007;120(1):70-77.

151. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.

152. Loe IM, Lee ES, Feldman HM. Attention and internalizing behaviors in relation to white matter in children born preterm. J Dev Behav Pediatr. 2013;34(3):156-64.

153. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med. 1998;26(4):250-8.

154. Loge JH, Kaasa S, Hjermstad MJ, Kvien TK. Translation and performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability, and construct validity. J Clin Epidemiol. 1998;51(11):1069-76.

155. 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(1):55-68.

156. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ. 1999;319(7204):245-9.

157. Lund LK, Vik T, Lydersen S, Løhaugen GC, Skranes J, Brubakk AM, et al. Mental health, quality of life and social relations in young adults born with low birth weight. Health Qual Life Outcomes. 2012;10:146.

158. Lund LK, Vik T, Skranes J, Brubakk AM, Indredavik MS. Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. Acta Paediatr. 2011;100(4):598-604.

159. Lund LK, Vik T, Skranes J, Lydersen S, Brubakk AM, Indredavik MS. Low birth weight and psychiatric morbidity; stability and change between adolescence and young adulthood. Early Hum Dev. 2012;88(8):623-9.

160. Lærum AM, Reitan SK, Evensen KA, Lydersen S, Brubakk AM, Skranes J, et al. Psychiatric Disorders and General Functioning in Low Birth Weight Adults: A Longitudinal Study. Pediatrics. 2017;139(2).

161. Magill RA. Motor learning: Concepts and applications. 6th ed. New York: McGraw-Hill Companies; 2001.

162. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Howson CP, Kinney MV, Lawn JE, editors. Geneva: World Health Organization; 2012.

163. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. I: Hemorrhagic lesions of neocortex. J Neuropathol Exp Neurol. 1996;55(7):758-73.

164. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. II: white matter lesions of the neocortex. J Neuropathol Exp Neurol. 1997;56(3):219-35.

165. Marin-Padilla M. Developmental neuropathology and impact of perinatal brain damage. III: gray matter lesions of the neocortex. J Neuropathol Exp Neurol. 1999;58(5):407-29.

166. McCormick MC, Litt JS, Smith VC, Zupancic JAF. Prematurity: An Overview and Public Health Implications. Annu Rev Public Health. 2011;32(1):367-79.

167. Medical Birth Registry of Norway. Norwegian Institute of Public Health.

168. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand. 2008;87(6):590-600.

169. Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. The Lancet Neurology. 2009;8(11):1042-55.

170. Missiuna C. Childhood motor impairment is associated with male anxiety at 11 and 16 years. Evid Based Ment Health. 2003;6(1):18.

171. Moen KT, Kleffelgård I. High-level Mobility Assessment Tool for Traumatic Brain Injury. Norsk Versjon2011. 12 p.

172. Moster D, Lie RT, Markestad T. Long-Term Medical and Social Consequences of Preterm Birth. N Engl J Med. 2008;359(3):262-73.

173. Mullen KM, Vohr BR, Katz KH, Schneider KC, Lacadie C, Hampson M, et al. Preterm birth results in alterations in neural connectivity at age 16 years. Neuroimage. 2011;54(4):2563-70.

174. Muntaner C, Eaton WW, Miech R, O'Campo P. Socioeconomic position and major mental disorders. Epidemiol Rev. 2004;26:53-62.

175. Mykletun A, Knudsen AK, Mathiesen KS. Psykiske lidelser i Norge: et folkehelseperspektiv. Oslo: Nasjonalt folkehelseinstitutt; 2009. Report No.: 2009:8.

176. Mæland AF. Identification of children with motor coordination problems. Adapt Phys Activ Q. 1992;9(4):330-42.

177. Männistö T, Vääräsmäki M, Sipola-Leppänen M, Tikanmäki M, Matinolli HM, Pesonen AK, et al. Independent living and romantic relations among young adults born preterm. Pediatrics. 2015;135(2):290-97.

178. Möller H-J. The forthcoming revision of the diagnostic and classificatory system: perspectives based on the European psychiatric tradition. Eur Arch Psychiatry Clin Neurosci. 2008;258(5):7-17.

179. Nagae LM, Hoon AH, Jr., Stashinko E, Lin D, Zhang W, Levey E, et al. Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts. AJNR Am J Neuroradiol. 2007;28(7):1213-22.

180. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp. 2002;15(1):1-25.

181. Norwitz ER, Bonney EA, Snegovskikh VV, Williams MA, Phillippe M, Park JS, et al. Molecular Regulation of Parturition: The Role of the Decidual Clock. Cold Spring Harb Perspect Med. 2015.

182. Nosarti C. Structural and functional brain correlates of behavioral outcomes during adolescence. Early Hum Dev. 2013;89(4):221-7.

183. Nosarti C, Giouroukou E, Healy E, Rifkin L, Walshe M, Reichenberg A, et al. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. Brain. 2008;131(Pt 1):205-17.

184. Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, et al. Preterm birth and psychiatric disorders in young adult life. Arch Gen Psychiatry. 2012;69(6):E1-8.

185. Offer D, Sabshin M. Normality: Theoretical and Clinical Concepts of Mental Health. 1st ed: Basic Books; 1966.

186. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113.

187. Palacio-Vieira JA, Villalonga-Olives E, Valderas JM, Espallargues M, Herdman M, Berra S, et al. Changes in health-related quality of life (HRQoL) in a population-based sample of children and adolescents after 3 years of follow-up. Qual Life Res. 2008;17(10):1207-15.

188. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214-23.

189. Pandit AS, Ball G, Edwards AD, Counsell SJ. Diffusion magnetic resonance imaging in preterm brain injury. Neuroradiology. 2013;55 Suppl 2:65-95.

190. Papini C, White TP, Montagna A, Brittain PJ, Froudist-Walsh S, Kroll J, et al. Altered resting-state functional connectivity in emotion-processing brain regions in adults who were born very preterm. Psychol Med. 2016;46(14):3025-39.

191. Partridge SC, Mukherjee P, Henry RG, Miller SP, Berman JI, Jin H, et al. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. Neuroimage. 2004;22(3):1302-14.

192. Penn AA, Gressens P, Fleiss B, Back SA, Gallo V. Controversies in preterm brain injury. Neurobiol Dis. 2016;92(Pt A):90-101.

193. 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(6):643-45.

194. Pesonen AK, Räikkönen K, Heinonen K, Andersson S, Hovi P, Järvenpää AL, et al. Personality of young adults born prematurely: the Helsinki study of very low birth weight adults. J Child Psychol Psychiatry. 2008;49(6):609-17.

195. Poole KL, Schmidt LA, Missiuna C, Saigal S, Boyle MH, Van Lieshout RJ. Motor coordination and mental health in extremely low birth weight survivors during the first four decades of life. Res Dev Disabil. 2015;43–44:87-96.

196. Poole KL, Schmidt LA, Missiuna C, Saigal S, Boyle MH, Van Lieshout RJ. Motor Coordination Difficulties in Extremely Low Birth Weight Survivors Across Four Decades. J Dev Behav Pediatr. 2015;36(7):521-8.

197. 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.

198. Prechtl HFR, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;349(9062):1361-63.

199. Pyhälä R, Wolford E, Kautiainen H, Andersson S, Bartmann P, Baumann N, et al. Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-Analysis. Pediatrics. 2017.

200. Reichenbach A, Hlawitschka M, Tittgemeyer M, Scheuermann G. Choosing a Tractography Algorithm: On the Effects of Measurement Noise. In: Schultz T, Nedjati-Gilani G, Venkataraman A, O'Donnell L, Panagiotaki E, editors.

Computational Diffusion MRI and Brain Connectivity: MICCAI Workshops, Nagoya, Japan, September 22nd, 2013. Cham: Springer International Publishing; 2014. p. 115-28.

201. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology. 1998;31(3):160-8.

202. Ridner SH. Psychological distress: concept analysis. J Adv Nurs. 2004;45(5):536-45.

203. Risnes KR, Pape K, Bjørngaard JH, Moster D, Bracken MB, Romundstad PR. Premature Adult Death in Individuals Born Preterm: A Sibling Comparison in a Prospective Nationwide Follow-Up Study. PloS one. 2016;11(11):e0165051.

204. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. Int J Epidemiol. 2011;40(3):647-61.

205. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760-5.

206. Rose SE, Hatzigeorgiou X, Strudwick MW, Durbridge G, Davies PS, Colditz PB. Altered white matter diffusion anisotropy in normal and preterm infants at term-equivalent age. Magn Reson Med. 2008;60(4):761-7.

207. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.

208. Rutter M. Categories, dimensions, and the mental health of children and adolescents. Ann N Y Acad Sci. 2003;1008:11-21.

209. Räikkönen K, Pesonen AK, Heinonen K, Kajantie E, Hovi P, Järvenpää AL, et al. Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. Arch Gen Psychiatry. 2008;65(3):290-6.

210. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-9.

211. Saigal S, Ferro MA, Van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH. Health-Related Quality of Life Trajectories of Extremely Low Birth Weight Survivors into Adulthood. J Pediatr. 2016;179:68-73.e1.

212. Salvan P, Froudist Walsh S, Allin MP, Walshe M, Murray RM, Bhattacharyya S, et al. Road work on memory lane--functional and structural alterations to the learning and memory circuit in adults born very preterm. Neuroimage. 2014;102 Pt 1:152-61.

213. Schlotz W, Phillips DI. Fetal origins of mental health: evidence and mechanisms. Brain Behav Immun. 2009;23(7):905-16.

214. Schmidt RA. Motor learning principles for physical therapy. Contemporary management of motor problems Proceedings of the II STEP conference 1990. Alexandria, VA: Foundation for Physical Therapy; 1991. p. 49-63.

215. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp. 2005;26(2):139-47.

216. Schulz J, Henderson SE, Sugden DA, Barnett AL. Structural validity of the Movement ABC-2 test: factor structure comparisons across three age groups. Res Dev Disabil. 2011;32(4):1361-9.

217. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. Arch Pediatr Adolesc Med. 2007;161(6):583-90.

218. Sellier E, Platt MJ, Andersen GL, Krageloh-Mann I, De La Cruz J, Cans C. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol. 2016;58(1):85-92.

219. Sigmundsson H. Disorders of motor development (clumsy child syndrome). J Neural Transm Suppl. 2005(69):51-68.

220. Sigurdsson E, Van Os J, Fombonne E. Are impaired childhood motor skills a risk factor for adolescent anxiety? Results from the 1958 U.K. birth cohort and the National Child Development Study. Am J Psychiatry. 2002;159(6):1044-6.

221. Singer LT, Salvator A, Guo S, Collin M, Lilien L, Baley J. Maternal psychological distress and parenting stress after the birth of a very low-birth-weight infant. JAMA. 1999;281(9):799-805.

222. Skiold B, Horsch S, Hallberg B, Engström M, Nagy Z, Mosskin M, et al. White matter changes in extremely preterm infants, a population-based diffusion tensor imaging study. Acta Paediatr. 2010;99(6):842-9.

223. 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(8):758-65.

224. Skranes JS, 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(3):654-66.

225. 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(3):149-54.

226. 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(05):256-62.

227. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31(4):1487-505.

228. Smits-Engelsman BC, Fiers MJ, Henderson SE, Henderson L. Interrater reliability of the Movement Assessment Battery for Children. Phys Ther. 2008;88(2):286-94.

229. 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(1):25-30.

230. Song S-K, Sun S-W, Ju W-K, Lin S-J, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 2003;20(3):1714-22.

231. Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. Semin Fetal Neonatal Med. 2014;19(2):84-89.

232. Sporns O, Edelman GM. Solving Bernstein's problem: a proposal for the development of coordinated movement by selection. Child Dev. 1993;64(4):960-81.

233. Sripada K, Løhaugen GC, Eikenes L, Bjørlykke KM, Håberg AK, Skranes J, et al. Visual-motor deficits relate to altered gray and white matter in young adults born preterm with very low birth weight. Neuroimage. 2015;109:493-504.

234. Stahlmann N, Eisemann N, Thyen U, Herting E, Rapp M. Long-Term Health Outcomes and Health-Related Quality of Life in Adolescents from a Cohort of Extremely Premature Infants Born at Less Than 27 Weeks of Gestation in Northern Germany. Neuropediatrics. 2016;47(6):388-98.

235. Steer P. The epidemiology of preterm labour. BJOG. 2005;112 Suppl 1:1-3.

236. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357-65.

237. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443-56.

238. Strang-Karlsson S, Räikkönen K, Pesonen AK, Kajantie E, Paavonen EJ, Lahti J, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. Am J Psychiatry. 2008;165(10):1345-53.

239. Støen R, Vik T, Brubakk AM. [Mortality and functional disabilities among children with birth weight lower than 1500 g. Changes during 1983-88 at the neonatal unit of the Trondheim regional hospital]. Tidsskr Nor Laegeforen. 1992;112(6):745-9.

240. Tal-Saban M, Ornoy A, Parush S. Young adults with developmental coordination disorder: a longitudinal study. Am J Occup Ther. 2014;68(3):307-16.

241. Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology. 2010;35(1):147-68.

242. Taylor HG, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: neuropsychological findings. J Int Neuropsychol Soc. 2004;10(2):149-63.

243. Thelen E. Motor development. A new synthesis. Am Psychol. 1995;50(2):79-95.

244. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. Neuroimage. 2007;35(4):1459-72.

245. Tournier JD, Mori S, Leemans A. Diffusion tensor imaging and beyond. Magn Reson Med. 2011;65(6):1532-56.

246. Touwen BCL. How normal is variable, or how variable is normal? Early Hum Dev. 1993;34(1–2):1-12.

247. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn Reson Med. 2002;48(4):577-82.

248. Ustad T, Evensen KAI, Campbell SK, Girolami GL, Helbostad J, Jørgensen L, et al. Early Parent-Administered Physical Therapy for Preterm Infants: A Randomized Controlled Trial. Pediatrics. 2016;138(2).

249. Van den Bergh BR. Developmental programming of early brain and behaviour development and mental health: a conceptual framework. Dev Med Child Neurol. 2011;53 Suppl 4:19-23.

250. van der Pal-de Bruin KM, van der Pal SM, Verloove-Vanhorick SP, Walther FJ. Profiling the preterm or VLBW born adolescent; implications of the Dutch POPS cohort follow-up studies. Early Hum Dev. 2015;91(2):97-102.

251. van Kooij BJ, de Vries LS, Ball G, van Haastert IC, Benders MJ, Groenendaal F, et al. Neonatal tract-based spatial statistics findings and outcome in preterm infants. AJNR Am J Neuroradiol. 2012;33(1):188-94.

252. van Lunenburg A, van der Pal SM, van Dommelen P, van der Pal-de Bruin KM, Bennebroek Gravenhorst J, Verrips GH. Changes in quality of life into adulthood after very preterm birth and/or very low birth weight in the Netherlands. Health Qual Life Outcomes. 2013;11:51.

253. Van Waelvelde H, De Weerdt W, De Cock P, Smits-Engelsman BCM. Aspects of the validity of the Movement Assessment Battery for Children. Hum Mov Sci. 2004;23(1):49-60.

254. Vangberg TR, Skranes J, Dale AM, Martinussen M, Brubakk AM, Haraldseth O. Changes in white matter diffusion anisotropy in adolescents born prematurely. Neuroimage. 2006;32(4):1538-48.

255. Verrips G, Brouwer L, Vogels T, Taal E, Drossaert C, Feeny D, et al. Long term follow-up of health-related quality of life in young adults born very preterm or with a very low birth weight. Health Qual Life Outcomes. 2012;10:49.

256. 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(1):F33-7.

257. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110-24.

258. Volpe JJ. Cerebral white matter injury of the premature infant-more common than you think. Pediatrics. 2003;112(1 Pt 1):176-80.

259. Volpe JJ. The Encephalopathy of Prematurity—Brain Injury and Impaired Brain Development Inextricably Intertwined. Semin Pediatr Neurol. 2009;16(4):167-78.

260. Wagner MO, Kastner J, Petermann F, Bos K. Factorial validity of the Movement Assessment Battery for Children-2 (age band 2). Res Dev Disabil. 2011;32(2):674-80.

261. Wall AE, Reid G, Paton J. The syndrome of physical awkwardness. In: Reid G, editor. Problems in movement control. Amsterdam: North-Holland: Elsevier science publishers; 1990. p. 283-316.

262. Walshe M, Rifkin L, Rooney M, Healy E, Nosarti C, Wyatt J, et al. Psychiatric disorder in young adults born very preterm: Role of family history. Eur Psychiatry. 2008;23(7):527-31.

263. Ware JE, Jr. SF-36 Health Survey Update. Spine. 2000;25(24):3130-39.

264. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51(11):903-12.

265. Ware JE, Jr., Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, et al. The Factor Structure of the SF-36 Health Survey in 10 Countries: Results from the IQOLA Project. J Clin Epidemiol. 1998;51(11):1159-65.

266. Waxman JA, Lieshout RJ, Boyle MH, Saigal S, Schmidt LA. Linking extremely low birth weight and internalizing behaviors in adult survivors: Influences of neuroendocrine dysregulation. Dev Psychobiol. 2015;57(4):486-96.

267. Wechsler D. Wechsler Intelligence Scale for Children – Third Edition, Manual. Stockholm: Psykologiförlaget AB; 1999.

268. Westbrook C, Roth CK, Talbot J. MRI in Practice. West Sussex, UK: John Wiley & Sons; 2011.

269. Westrupp EM, Northam E, Doyle LW, Callanan C, Anderson PJ. Adult psychiatric outcomes of very low birth weight survivors. Aust N Z J Psychiatry. 2011;45(12):1069-77.

270. Wheeler-Kingshott CA, Cercignani M. About "axial" and "radial" diffusivities. Magn Reson Med. 2009;61(5):1255-60.

271. Williams G, Hill B, Pallant JF, Greenwood K. Internal validity of the revised HiMAT for people with neurological conditions. Clin Rehabil. 2012;26(8):741-7.

272. Williams G, Morris ME. High-level mobility outcomes following acquired brain injury: a preliminary evaluation. Brain Inj. 2009;23(4):307-12.

273. Williams G, Morris ME, Greenwood KM, Goldie PA, Robertson V. High-Level Mobility Assessment Tool for Traumatic Brain Injury: User Manual Melbourne: La Trobe University; 2004.

274. Williams G, Pallant J, Greenwood K. Further development of the High-level Mobility Assessment Tool (HiMAT). Brain Inj. 2010;24(7-8):1027-31.

275. Williams G, Robertson V, Greenwood K, Goldie P, Morris ME. The concurrent validity and responsiveness of the high-level mobility assessment tool for measuring the mobility limitations of people with traumatic brain injury. Arch Phys Med Rehabil. 2006;87(3):437-42.

276. Williams G, Robertson V, Greenwood K, Goldie P, Morris ME. The high-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 1: Item generation. Brain Inj. 2005;19(11):925-32.

277. Williams G, Robertson V, Greenwood KM, Goldie PA, Morris ME. The high-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 2: content validity and discriminability. Brain Inj. 2005;19(10):833-43.

278. Wimberger DM, Roberts TP, Barkovich AJ, Prayer LM, Moseley ME, Kucharczyk J. Identification of "premyelination" by diffusion-weighted MRI. J Comput Assist Tomogr. 1995;19(1):28-33.

279. Winchester SB, Sullivan MC, Roberts MB, Granger DA. Prematurity, Birth Weight, and Socioeconomic Status Are Linked to Atypical Diurnal Hypothalamic-Pituitary-Adrenal Axis Activity in Young Adults. Res Nurs Health. 2016;39(1):15-29.

280. Wolf MJ, Koldewijn K, Beelen A, Smit B, Hedlund R, de Groot IJ. Neurobehavioral and developmental profile of very low birthweight preterm infants in early infancy. Acta Paediatr. 2002;91(8):930-8.

281. Wolfe KR, Vannatta K, Nelin MA, Yeates KO. Executive functions, social information processing, and social adjustment in young children born with very low birth weight. Child Neuropsychol. 2015;21(1):41-54.

282. Wolke D, Baumann N, Strauss V, Johnson S, Marlow N. Bullying of preterm children and emotional problems at school age: cross-culturally invariant effects. J Pediatr. 2015;166(6):1417-22.

283. World Health Organization. Mental health. Geneva, Switzerland; 2016.

284. World Health Organization. Preterm birth. Geneva, Switzerland; 2016.

285. Wuang YP, Su JH, Su CY. Reliability and responsiveness of the Movement Assessment Battery for Children-Second Edition Test in children with developmental coordination disorder. Dev Med Child Neurol. 2012;54(2):160-5.

286. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. Pediatrics. 2008;121(2):e366-76.

287. Zwicker JG, Harris SR, Klassen AF. Quality of life domains affected in children with developmental coordination disorder: a systematic review. Child Care Health Dev. 2013;39(4):562-80.

Appendix

Paper I-III

Paper I

Early Human Development 89 (2013) 747–754

Contents lists available at SciVerse ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Motor skills at 23 years of age in young adults born preterm with very low birth weight

Ingrid Marie Husby [a,*], Jon Skranes [a,b], Alexander Olsen [c,d], Ann-Mari Brubakk [a,e], Kari Anne I. Evensen [a,f,g]

[a] Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway
[b] Department of Pediatrics, Sørlandet Hospital, Arendal, Norway
[c] MI Lab and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway
[d] Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[e] Department of Pediatrics, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[f] Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway
[g] Department of Physiotherapy, Trondheim Municipality, Norway

ARTICLE INFO

Article history:
Received 20 December 2012
Received in revised form 23 May 2013
Accepted 28 May 2013

Keywords:
Fine motor skills
Gross motor skills
Grooved Pegboard test
High-level Mobility Assessment Tool
Long-term outcome
Motor speed
Movement Assessment Battery for Children-2
Prematurity
Trail Making Test-5

ABSTRACT

Background: Motor skills have previously not been reported in young adults born with very low birth weight (VLBW), although they are commonly reported in children and adolescents.
Aim: To compare fine and gross motor skills in VLBW young adults with matched term-born controls, and to study longitudinal changes in the VLBW group.
Study design: A geographically based follow-up study of a VLBW group and a control group.
Subjects: Thirty-six VLBW (birth weight ≤ 1500 g) young adults, including four participants with cerebral palsy (CP), and 37 matched controls (birth weight ≥ 10th centile) were examined at 14 and 23 years of age.
Outcome measures: Fine and gross motor skills were assessed using Grooved Pegboard test (GP), Trail Making Test-5 (TMT-5), Movement Assessment Battery for Children-2 (Movement ABC-2) and High-level Mobility Assessment Tool (HiMAT).
Results: VLBW young adults were slower than controls on GP ($p = 0.026$) and TMT-5 ($p < 0.001$). Mean total Movement ABC-2 score was 69.7 ± 20.2 in the VLBW group compared with 74.1 ± 14.4 in the control group ($p = 0.017$). Differences were also seen in manual dexterity and balance. Additionally, HiMAT showed reduced balance and speed in gross motor skills in the VLBW group. The proportion of participants with motor problems did not change between age 14 and 23. After exclusion of participants with CP, scores were essentially the same.
Conclusion: VLBW young adults had overall poorer fine and gross motor skills compared with controls. Reduced speed seemed to be an underlying problem. Longitudinal findings indicate that VLBW children have not outgrown their motor problems when entering adulthood.

1. Introduction

Long-term disability as a consequence of prematurity has been increasing during the last decades, as more of these infants survive [1–3]. In very low birth weight children (VLBW; birth weight ≤ 1500 g), the rate of brain injury is high [4], and cognitive, neurosensory and neuromotor disabilities, including cerebral palsy (CP), are common [1,5–7]. Signs of perinatal white matter injury that influences white matter development and maturation are seen on magnetic resonance imaging of the brain in VLBW populations from birth to young adulthood [8–10], which also have been shown to correlate with motor problems in VLBW children and adolescents [11–15]. Myelination deficits also affect connectivity, and may lead to slower signalling in the brain. A meta-analysis of 41 studies on motor outcome, have documented poorer fine and gross motor skills in very preterm and VLBW children from childhood to adolescence [16]. This was most pronounced for balance skills, then manual dexterity and to some extent, ball skills [16]. To our knowledge, none have yet reported on motor skills in adulthood. Both fine and gross motor skills influence leisure and social activities, daily tasks, work and academic achievement, which may be increasingly important as young adults enter independent living.

The aim of this study was to compare fine and gross motor skills in VLBW young adults with matched term-born controls, using well known motor tests and a new assessment tool measuring gross motor skills. Additionally, we wanted to study longitudinal changes from adolescence to adulthood. Based on previous research, we hypothesized that young adults born preterm with VLBW have poorer

* Corresponding author at: Norwegian University of Science and Technology, Faculty of Medicine, Department of Laboratory Medicine, Children's and Women's Health, P.O. Box 8905, 7491, Trondheim, Norway. Tel.: +47 48 13 25 90; fax: +47 73 86 77 08.
E-mail address: ingrihu@stud.ntnu.no (I.M. Husby).

0378-3782/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.earlhumdev.2013.05.009

fine and gross motor skills than controls, especially regarding balance, manual dexterity and timed performances, and that performance does not improve with time.

2. Methods

2.1. Study design

This is a matched case control study of 23-year-old adults born preterm with very low birth weight (VLBW) and a control group born at term with normal birth weight. The VLBW children had been admitted to the Neonatal Intensive Care Unit (NICU) at St. Olavs Hospital, Trondheim University Hospital, Norway, in 1986 88. These same VLBW children have previously participated in a longitudinal follow-up study at the Norwegian University of Science and Technology, Trondheim with evaluations at 1, 5 and 14 years of age [17 19]. The controls were from the same geographical area as the VLBW children, born in the same period at the same hospital, and were originally recruited through a multicenter study on causes and consequences of intrauterine growth restriction. This group has served as controls in the follow-up study at all time points. At 23 years of age, fine and gross motor skills were assessed as part of a larger assessment battery, also including MRI and mental health questionnaires.

2.2. Study groups

2.2.1. VLBW group

The VLBW group comprised 36 young adults (15 males and 21 females) born preterm (before 37th week of gestation) with birth weight ≤1500 g. At 14 years of age, 63 adolescents met for examination. At 23 years, seven of these young adults were non-traceable and two were not testable due to severe quadriplegic CP. Thus, we contacted 54 VLBW young adults, thereof 18 (33%) did not consent, leaving 36 (67%) young adults for examination. Four (11%) of these had CP; one female had spastic hemiplegia with functional level I and three males had spastic diplegia with functional levels I, II and IV according to the Gross Motor Function Classification System (GMFCS) [20].

2.2.2. Control group

The control group comprised 37 young adults (15 males and 22 females) born with a birth weight ≥10th centile for gestational age. We contacted 48 controls matched to the VLBW participants by age and sex. Of these, 46 had met at the 14 year examination. Two of the contacted controls were not testable due to pregnancy, five had moved too far away and four did not consent.

2.2.3. Non-participants

There were no significant differences regarding data collected around birth; birth weight, gestational age, head circumference, Apgar scores, days in NICU, days on mechanical ventilator, proportion of infants with intraventricular haemorrhage (IVH) and maternal age, or parental socioeconomic status (SES) and motor skills at 14 years of age between those who participated at follow-up at 23 years of age and those who did not give their consent to participate in the VLBW group. In the control group, we did not find any differences between those who participated at 23 years of age and those who did not consent or were not contacted from previous follow-up (Table 1).

2.3. Methods

2.3.1. Clinical characteristics

Data collected around birth included birth weight, gestational age, head circumference, Apgar scores, days in NICU, days on mechanical ventilator, IVH and maternal age. Parental SES was calculated according to Hollingshead's Two factor index of social position [21] at 14 years of age, based on a combination of parents' education and occupation. CP was diagnosed in childhood, and classified as spastic hemiplegia (unilateral), diplegia (bilateral, most involvement in lower extremities) or quadriplegia (involvement of all extremities). Functional level was assessed according to the GMFCS [20].

At 23 years of age, weight was measured on an electronic scale (to nearest 10 g). Height was self-reported or measured if the participant did not know. Body mass index (BMI) was calculated from these two measures (kg/m^2). Head circumference (occipital frontal circumference) was measured to the nearest 0.1 cm. Handedness was assessed by the Edinburgh Handedness Inventory [22], which gives a laterality index determined by the dominance of a person's right or left hand in 12 everyday activities. The laterality index ranges from −100 for complete left-handedness, to +100 for complete right-handedness. The participants answered questionnaires regarding recent injury, recent illness, current medication usage, pain, exercise and education. Pain was reported with VAS (Visual Analogue Scale). The participants recorded their weekly frequency and duration of exercise (if any) and number of exercise activities performed regularly. Education was dichotomized into high school completion plus higher education admissions and incomplete high school plus vocational training .

2.3.2. Motor examination

Fine and gross motor skills in young adults were assessed by three examiners; two physiotherapists and one master student in movement science. All testers were blinded to neonatal history, clinical characteristics and results from previous follow-up, but not to group adherence.

2.3.3. Grooved Pegboard test (GP)

The GP [23] is a manipulative dexterity test which requires complex visual motor coordination and measures how quickly the participants can insert pegs into 25 keyhole-shaped holes with various orientations in a 5 × 5 matrix. Time (in seconds) and number of drops are registered for each hand individually. In the current study, one VLBW participant with spastic diplegic CP was not able to perform this test due to attention problems. Poor performance was defined as scores >2SD of the mean in the control group.

2.3.4. Trail Making Test-5 (TMT-5)

The TMT-5 measures motor speed and consists of 32 circles linked with a dotted line on a paper. The task is to draw a line between the circles in the order directed as fast as possible, touching all the circles. Time (in seconds) and errors (number of circles missed) are measured. The TMT-5 is one of five TMT subtests in the standardized Delis Kaplan Executive Function System (D KEFS) [24]. The other TMT subtests measure visual scanning, attention, working memory and number letter sequencing, which we considered less relevant for the aim of this study because they are more related to executive functions than to motor skills.

2.3.5. Movement Assessment Battery for Children-2 (Movement ABC-2)

The Movement ABC-2 [25] is the revised version of the standardized Movement ABC which identifies and evaluates children's motor development. The test is divided into three age bands, where the highest age band (up to 16 years and 11 months) was used in this study. The test consists of eight items grouped into three subscales of manual dexterity (three items), aiming and catching (two items), and balance (three items). The raw scores (for instance number of seconds to complete a task) are converted into item standard scores, which add up to a component score for the three subscales. The total test score of maximum 108 points is the sum of the three component scores, where a higher score indicates better motor skills. Motor problems were defined as scores <5th centile in the control group.

2.3.6. High-level Mobility Assessment Tool (HiMAT)

The HiMAT [26] is a new test specifically developed to examine high-level mobility following traumatic brain injury (TBI), although

Table 1
Clinical characteristics for participants met versus not met in the VLBW group and the control group.

	VLBW					Control				
	Met (n = 36)		Not met (n = 27)			Met (n = 37)		Not met (n = 39)		
	Mean	(SD)	Mean	(SD)	p-value	Mean	(SD)	Mean	(SD)	p-value
Clinical characteristics										
Birth weight (g)	1197	(250)	1167	(217)	0.441	3608	(361)	3714	(491)	0.290
Gestational age (weeks)	29.1	(2.7)	29.0	(2.5)	0.955	39.4	(1.1)	39.8	(1.3)	0.185
Head circumference at birth (cm)[a]	27.0	(2.4)	27.3	(2.4)	0.671	35.2	(1.2)	35.4	(1.0)	0.429
Apgar score after 1 min[b]	6.8	(1.9)	6.7	(2.8)	0.689	8.9	(0.5)	9.0	(0.0)	0.067
Apgar score after 5 min[c]	8.4	(1.6)	8.6	(1.6)	0.519	9.7	(1.5)	9.9	(0.3)	0.916
Days in NICU[d]	80.7	(63.2)	61.1	(31.4)	0.253	0.2	(1.5)	0.1	(0.3)	0.955
Days on ventilator[d]	5.4	(12.9)	3.6	(7.7)	0.662					
Maternal age at birth (years)	28.7	(5.7)	26.8	(3.7)	0.216	30.1	(4.5)	29.7	(4.4)	0.713
Parental SES at 14 years[e]	3.4	(1.2)	2.9	(1.3)	0.087	3.7	(1.1)	3.8	(1.2)	0.559
Total Movement-ABC score at 14 years[f]	11.9	(8.1)	10.6	(8.5)	0.449	6.1	(4.6)	6.4	(3.9)	0.765

VLBW = Very Low Birth Weight.
SD = Standard Deviation.
NICU = Neonatal Intensive Care Unit.
SES = Socioeconomic Status.
Movement-ABC = Movement Assessment Battery for Children.
Mann Whitney *U* test was used to analyse non-parametric data and Student's *t*-test was used to analyse parametric data.
[a] Data for head circumference was missing for eight VLBW met, six VLBW not met, three controls met and two controls not met.
[b] Apgar scores after 1 min were missing for one VLBW not met, three controls met and two controls not met.
[c] Apgar scores after 5 min were missing for two VLBW not met, two controls met and two controls not met.
[d] Data from the NICU including days on ventilator was missing for one VLBW met.
[e] Parental SES was missing for two controls met.
[f] Total score Movement-ABC at 14 years was missing for two VLBW met, four VLBW not met, two controls met and one control not met.

the authors claim that the test may also be applicable to other neurological conditions [27]. High-level mobility refers to motor performance necessary for many leisure, sporting and social activities, among others. The test assesses 13 items (walk, walk backwards, walk on toes, walk over obstacle, run, skip, hop forward, bound, and walk up/down stairs). The participants are asked to complete the task at their fastest safe speed over a distance of 20 m, whereof the middle 10 m is timed in all items except for the bound item (distance in cm) and stair items (normal walking speed). The raw score (time in seconds and distance in cm) is converted to a score from 0 to 4, except the stair items, which yield 0 to 5 points each, the higher the better. Failure, refusal or inability to perform a test item is given an item score of zero, and the maximum total score is 54 points. The stair items are classified as dependent or independent based on the use of railings for support and reciprocal walking. A 12-steps staircase was used in the current study, and the scoring corrected thereafter (seconds × 14 / 12) in accordance to the manual [27]. The Norwegian translation of the test was used in the current study [28].

The authors of the test have also published a revised version of the HiMAT [29], consisting of eight of the original 13 items, where bound on affected leg and the stair items have been removed with a total 8-item HiMAT score of 32 points. In the present study, we calculated both the total original HiMAT score and the revised 8-item HiMAT score. One wheelchair-dependent VLBW participant with CP was not able to perform any of the HiMAT items in our study.

2.3.7. Inter- and intra-tester reliability

We assessed inter- and intra-tester reliability by scoring video-recordings of the GP, TMT-5 and the Movement ABC-2 (except the drawing task which is not possible to score from video recordings). We chose not to include the HiMAT in the reliability-testing due to poor video quality. An independent tester (IMH), blinded to group adherence in addition to clinical characteristics and outcome from previous and current follow-up, scored the video-recordings for inter-tester reliability on 51 (70%) participants (27 VLBW, 24 controls). One of the examiners scored the video-recordings for intra-tester reliability on 44 (60%) of the participants (26 VLBW, 18 controls).

2.3.8. Longitudinal data

Longitudinal data from 14 years of age were available for the GP and for the previous version of the Movement ABC [30]. Poor performance on the GP was defined as scores >2SD of the mean in the control group. Motor problems on the Movement ABC were defined as scores <5th centile in the control group.

2.4. Ethical considerations

The project complies with the principles laid down in the Declaration of Helsinki and was approved by the Ethical Committee for Medical Research in Mid-Norway. Written informed consent was achieved through written invitation letters and verbal information upon attendance. Methods used in the study were non-invasive and did not inflict pain. Participants received financial compensation (NOK 1000) for attendance.

2.5. Statistical analyses

IBM SPSS Statistics for Windows version 19.0 was used for data analysis, and two-sided p-values less than 0.05 were considered statistically significant. Mann Whitney *U* test was used to analyse differences in ordinal variables and non-parametric data. Student's *t*-test was used for normally distributed data. Chi-square test was used to analyse differences in proportions between groups. Correlation analyses (Spearman's rho) were performed to investigate relationships between clinical characteristics and outcome variables, in order to identify possible confounding factors. A two-way mixed ANOVA was performed to calculate intra-class correlation (ICC (3.1)) for inter- and intra-tester reliability. STATA Version 12.1 software was used for analysis of the longitudinal data with the asymptotic McNemar's test.

3. Results

3.1. Clinical characteristics

Clinical characteristics are described in Table 2. By definition, there were significant differences in data from birth such as birth

Table 2
Clinical characteristics from previous and current follow-up for the VLBW group, the non-CP VLBW group and the control group.

	VLBW (n = 36)			Non-CP VLBW (n = 32)			Control (n = 37)	
	Mean	(SD)	p-value (vs controls)	Mean	(SD)	p-value (vs controls)	Mean	(SD)
Previous follow-up								
Birth weight (g)	1197	(250)	<0.001	1237	(216)	<0.001	3608	(361)
Gestational age (weeks)	29.1	(2.7)	<0.001	29.3	(2.6)	<0.001	39.4	(1.1)
Head circumference at birth (cm)[a]	27.0	(2.4)	<0.001	27.3	(2.3)	<0.001	35.2	(1.2)
Apgar score after 1 min[b]	6.8	(1.9)	<0.001	6.8	(1.9)	<0.001	8.9	(0.5)
Apgar score after 5 min[b]	8.4	(1.6)	<0.001	8.4	(1.7)	<0.001	9.7	(1.5)
Maternal age (years)	28.7	(5.7)	0.251	29.2	(5.5)	0.455	30.1	(4.5)
Parental SES (14 years)[c]	3.4	(1.2)	0.575	3.4	(1.2)	0.503	3.7	(1.1)
Current follow-up (23 years)								
Age	22.5	(0.7)	0.236	22.5	(0.7)	0.201	22.7	(0.6)
BMI	23.3	(4.2)	0.271	23.4	(4.1)	0.336	24.4	(3.8)
Weight (kg)	66.6	(14.0)	0.053	67.4	(14.2)	0.095	73.5	(15.7)
Height (cm)	168.8	(9.4)	0.066	169.2	(9.5)	0.108	173.2	(10.7)
Head circumference (cm)	56.0	(1.8)	0.001	56.1	(1.8)	0.003	57.4	(1.7)
Laterality index	58.6	(66.4)	0.466	66.3	(59.5)	0.803	86.2	(15.8)

VLBW = Very Low Birth Weight.
CP = Cerebral Palsy.
SD = Standard Deviation.
NICU = Neonatal Intensive Care Unit.
SES = Socioeconomic Status.
BMI = Body Mass Index.
Mann Whitney *U* test was used to analyse non-parametric data and Student's *t*-test was used to analyse parametric data.
[a] Data for head circumference were missing for eight VLBW participants and three controls.
[b] Apgar scores after 1 and 5 min were missing for three and two controls, respectively.
[c] Parental SES was missing for two controls.

weight, gestational age and head circumference between the groups. Median stay in the NICU was 61 days (range: 25 386 days). The VLBW group had a median of one day on mechanical ventilator (range: 0 63 days) and three (9%) developed IVH (one of these was later diagnosed with CP). At 23 years of age, the VLBW group had smaller mean head circumference and was borderline lighter and shorter than the control group, whereas BMI did not differ between the groups. There was no significant difference in laterality index between the groups.

The median number of physical activities of the VLBW group was 1.0 (range: 1.0 2.0) compared to 3.0 (range: 0.0 3.0) in the control group ($p < 0.001$). However, there was no association between the number of physical activities and outcome of any of the tests.

There were no statistical differences in other clinical characteristics, such as recent injury, recent illness, medication, pain, exercise (yes/no and duration of exercise) or education, where 20 (56%) in the VLBW group and 27 (73%) in the control group had general university and college admissions certification. There were no associations between any of the other clinical characteristics and the outcomes.

3.2. Grooved Pegboard test (GP)

The VLBW group was significantly slower than the control group on the GP, with both dominant hand and non-dominant hand at 23 years of age (Table 3). However, there was no difference in number of drops. When excluding participants with CP, mean time in seconds was slightly reduced for the dominant hand ($p = 0.064$), and for the non-dominant hand ($p = 0.061$). There were no differences in the number of drops or errors after exclusion of the young adults with CP.

When comparing with the results at 14 years of age, the VLBW group improved their scores with 5.5 ± 22.3 s for the dominant hand compared with an improvement of 4.0 ± 11.1 s in the control group ($p = 0.727$). For the non-dominant hand, the difference was 10.2 ± 25.6 s for the VLBW group compared with 6.4 ± 12.4 s in the control group ($p = 0.434$). At 14 years of age, seven (20.0%) VLBW participants had poor performance (>2SD) with the dominant hand, compared with five (14.3%) at 23 years of age ($p = 0.414$). The proportion of VLBW participants with poor performance with the non-dominant hand increased from four (11.8%) at 14 years of age to ten (29.4%) at 23 years of age ($p = 0.034$). The results were unchanged when participants with CP were excluded.

3.3. Trail Making Test-5 (TMT-5)

The VLBW group was significantly slower on the TMT-5, but there was no difference between the groups in terms of number of errors (Table 3). When we excluded the young adults with CP, the mean time in seconds to complete the TMT-5 barely changed, and the group difference remained highly significant ($p < 0.001$).

3.4. Movement Assessment Battery for Children-2 (Movement ABC-2)

Table 4 shows the results of the Movement ABC-2. The VLBW group had significantly lower total Movement ABC-2 score (indicating poorer performance) than the control group. They also had significantly poorer score for manual dexterity and balance, while the score for aiming and catching was borderline different between the groups. When the four participants with CP were excluded, the difference in total Movement ABC-2 score between the groups was borderline significant, whereas the component scores were no longer significantly different from the control group.

We also analysed the raw scores for the individual items which gave similar results as the item scores, yielding significant results for turning pegs , catching with one hand , walking toe-to-heel backwards and zig-zag hopping .

At 14 and 23 years of age, ten (29.4%) VLBW participants had motor problems, defined as <5th centile, whereof seven (20.6%) VLBW participants had motor problems at both time points ($p = 1.000$). There were no differences in proportion of participants with problems on the subscores or when the participants with CP were excluded.

Table 3
Results of the *Grooved Pegboard test* and the *Trail Making Test-5* at age 23 in the VLBW group, the non-CP VLBW group and the control group.

	VLBW (n = 35)			Non-CP VLBW (n = 32)			Control (n = 37)	
	Mean	(SD)	p-value (vs controls)	Mean	(SD)	p-value (vs controls)	Mean	(SD)
Grooved Pegboard test								
Dominant hand								
Time (s)	70.7	(19.0)	0.025	68.5	(16.9)	0.064	62.2	(9.5)
Drops (no)	0.3	(0.8)	0.169	0.3	(0.8)	0.205	0.1	(0.4)
Non-dominant hand								
Time (s)	80.6	(35.1)	0.026	73.9	(13.4)	0.061	68.3	(10.6)
Drops (no)	0.3	(0.5)	0.450	0.3	(0.5)	0.517	0.2	(0.4)
Trail Making Test-5								
Time (s)	28.6	(10.8)	<0.001	28.2	(11.1)	<0.001	19.9	(5.6)
Errors (no)	0.1	(0.4)	0.791	0.1	(0.4)	0.603	0.3	(1.2)

VLBW = Very Low Birth Weight.
CP = Cerebral Palsy.
SD = Standard Deviation.
Mann Whitney *U* test was used to analyse all data.

3.5. High-level Mobility Assessment Tool (HiMAT)

The total HiMAT score and the 8-item HiMAT score were significantly lower in the VLBW group compared with the control group (Table 5). In the non-CP VLBW group, the total HiMAT score was still significantly lower, while the 8-item HiMAT score was no longer significantly lower than in the control group. Both including and excluding participants with CP, differences were seen in the items walk backwards , hop forward and bound (both legs).

Analyses of the raw scores for the VLBW group showed essentially the same results, the only change was that the items skip and run were borderline significant in these analyses (data not shown). In the non-CP VLBW group, the raw score for the item bound less affected leg was significantly lower than in the control group (data not shown).

3.6. Inter- and intra-tester reliability

Inter-tester reliability was examined in 51 (70%) participants. The two-way mixed intra-class correlation (ICC (3.1)), ranged from 0.913 to 1.000 for 84% of the rated tasks. The result for the remaining rated tasks deviated from these results with an ICC (3.1) of 0.708 and 0.781 for right and left foot zig-zag hopping and 0.814 for GP drops non-dominant hand. Intra-tester reliability was examined in 44 (60%) participants. ICC (3.1) ranged from 0.952 to 1.000 for 79% of the rated tasks. For the remaining tasks, ICC (3.1) was 0.789 and 0.591 for right and left foot zig-zag hopping, 0.851 for GP drops non-dominant hand and 0.897 for throwing.

4. Discussion

This is the first study to report on motor skills in young adulthood. Our longitudinal data indicate that the poorer motor skills documented in VLBW adolescents do persist into early adulthood. We found that VLBW young adults had overall poorer motor skills compared to matched controls. This was seen in all the tests performed. When we excluded the young adults with CP from the analyses, the VLBW group still had significantly poorer performances on the Trail Making Test-5 (TMT-5), the High-level Mobility Assessment Tool (HiMAT), as

Table 4
Results of the *Movement ABC-2* with item scores, component scores and total score in the VLBW group, the non-CP VLBW group and the control group of 23 years of age.

	VLBW (n = 36)			Non-CP VLBW (n = 32)			Control (n = 37)	
	Mean	(SD)	p-value (vs controls)	Mean	(SD)	p-value (vs controls)	Mean	(SD)
Turning pegs								
Preferred hand	7.0	(3.1)	0.030	7.5	(2.7)	0.107	8.4	(2.5)
Non-preferred hand	7.0	(3.2)	0.018	7.6	(2.8)	0.079	8.9	(2.2)
Triangle with nuts and bolts	7.8	(4.3)	0.096	8.3	(4.1)	0.292	9.3	(2.6)
Drawing trial	9.8	(3.9)	0.491	10.4	(3.3)	0.967	10.4	(3.2)
Manual dexterity	24.5	(8.6)	0.049	26.1	(7.2)	0.179	28.2	(5.4)
Catching with one hand								
Best hand	8.3	(3.8)	0.056	8.8	(3.6)	0.168	10.1	(2.9)
Other hand	9.1	(3.3)	0.014	9.5	(3.2)	0.055	10.9	(2.3)
Throwing at wall target	8.5	(3.3)	0.610	8.8	(3.2)	0.854	8.9	(3.2)
Aiming and catching	17.1	(5.0)	0.066	17.9	(4.3)	0.173	19.3	(4.6)
Two-board balance[a]	9.8	(3.8)	0.087	10.3	(3.4)	0.250	11.2	(3.0)
Walking toe-to-heel backwards[a]	8.7	(3.9)	0.031	9.3	(3.5)	0.112	10.5	(2.9)
Zig-zag hopping [a]								
Right leg	9.6	(3.6)	0.018	10.4	(2.5)	0.126	11.0	(0.0)
Left leg	9.7	(3.4)	0.018	10.5	(2.1)	0.126	11.0	(0.0)
Balance [a]	28.1	(9.4)	0.050	30.1	(7.0)	0.159	32.6	(3.9)
Total score [a]	69.7	(20.2)	0.017	74.1	(14.4)	0.061	80.2	(8.7)

Movement ABC-2 = Movement Assessment Battery for Children-2.
VLBW = Very Low Birth Weight.
CP = Cerebral Palsy.
SD = Standard Deviation.
Mann Whitney *U* test was used to analyse all data.
[a] One wheelchair-dependent VLBW participant was not able to perform the balance items, thus total score could not be calculated for this participant.

Table 5
Results of the *HiMAT* with item scores, 8-item HiMAT score and total HiMAT score in the VLBW group, the non-CP VLBW group and the control group of 23 years of age.

	VLBW (n = 35)			Non-CP VLBW (n = 32)			Control (n = 37)	
	Mean	(SD)	p-value (vs controls)	Mean	(SD)	p-value (vs controls)	Mean	(SD)
Walk	3.6	(0.5)	0.804	3.7	(0.5)	0.700	3.7	(0.5)
Walk backwards	3.5	(0.7)	0.004	3.6	(0.6)	0.020	3.9	(0.3)
Walk on toes	3.5	(1.0)	0.266	3.7	(0.5)	0.507	3.8	(0.4)
Walk over obstacle	3.5	(0.7)	0.210	3.6	(0.6)	0.519	3.7	(0.5)
Run	2.9	(0.9)	0.150	3.0	(0.8)	0.372	3.1	(0.6)
Skip[a]	2.9	(1.3)	0.041	3.1	(1.0)	0.128	3.4	(1.0)
Hop forward (more affected leg)[a]	3.0	(1.2)	0.002	3.2	(1.0)	0.010	3.7	(0.6)
Bound (less affected leg)[a]	3.2	(0.9)	<0.001	3.4	(0.8)	0.001	3.9	(0.3)
8-item HiMAT score[a]	26.0	(6.1)	0.037	27.3	(4.5)	0.119	29.3	(2.5)
Bound (more affected leg)[a]	3.2	(0.9)	0.003	3.4	(0.6)	0.013	3.8	(0.4)
Up stairs dependent[a]	4.9	(0.2)	0.526	5.0	(0.2)	0.918	5.0	(0.2)
Up stairs independent[a]	2.8	(1.1)	0.089	2.8	(1.0)	0.122	3.2	(0.9)
Down stairs dependent[a]	4.9	(0.3)	0.600	5.0	(0.2)	0.882	5.0	(0.2)
Down stairs independent[a]	3.1	(1.3)	0.260	3.2	(1.2)	0.395	3.4	(1.1)
Total HiMAT score[a]	44.9	(7.9)	0.006	46.6	(5.4)	0.023	49.6	(3.4)

HiMAT = High-level Mobility Assessment Tool.
VLBW = Very Low Birth Weight.
CP = Cerebral Palsy.
SD = Standard Deviation.
Mann Whitney *U* test was used to analyse all data.
[a] One control had an ankle sprain during skipping, thus was not testable on the remaining tasks.

well as borderline significantly poorer performances on the Grooved Pegboard test (GP) and the Movement Assessment Battery for Children-2 (Movement ABC-2). The reduction of sample size after the exclusion of participants with CP may explain the non-significant p-values, and thus one should put more emphasis on the actual scores when interpreting the results.

Loss to follow-up may have reduced the power to detect differences between the groups in our study [31]. The reason why 18 (33%) of the invited VLBW young adults did not want to participate is not known. However, we did not find any differences in clinical characteristics from previous follow-up between the VLBW young adults who participated and those who did not. We found no differences between the control young adults who participated and non-participants. We therefore consider it unlikely that the main results are explained by selection bias. The VLBW group engaged in a lower number of physical activities than the control group, but this was not related to results on motor tests. There were no differences in other clinical characteristics from the current follow-up between the groups. Thus, the association between the VLBW group and poorer motor skills is unlikely to be explained by confounding factors.

Even though examiners were not blinded to group adherence, inter-tester reliability assessed by a blinded independent tester showed generally high intra-class correlation (ICC (3.1)), indicating minimal variation in the measurements between examiners. In addition, the ICC (3.1) was high for intra-tester reliability assessed by one of the examiners. Both for inter- and intra-tester reliability, the lowest ICC (3.1) was found for zig-zag hopping and GP drops non-dominant hand. This might be due to a different visual angle on the video tape compared to real life.

We chose to use the Movement ABC-2, even though our participants were older than those for whom the test was designed. There are not many motor tests for adults, and only modest changes in motor skills are reported after puberty [32,33]. Moreover, analyses of the raw scores indicated similar differences between the groups when we did not use the age-converted scores. A recent study on reliability and responsiveness of the Movement ABC-2 [34] in Taiwanese children aged 6 12 years has documented a change of 1.21 points in the total score (before and after intervention) to represent a true change in overall motor function. Even though our participants differ from this study group, the difference between VLBW and control participants in our study was 10.5 points (6.1 points when participants with CP were excluded), which is therefore likely to reflect a clinically significant difference between the groups.

The HiMAT is a new test, with high validity and responsiveness, developed to examine high-level gross mobility primarily in patients with traumatic brain injury (TBI) [35,36]. The test has never been used in VLBW populations. Despite different injury mechanisms in VLBW young adults and TBI patients (perinatal injury versus later acquired traumatic injury), both groups may have white matter injury [9,37,38] and show a range of motor difficulties [39,40]. Moreover, the test developers state that the HiMAT is applicable to other neurological conditions [27,41]. This may be supported by the analyses of the raw scores in our study, which gave essentially the same results as the converted item scores. The HiMAT involves items such as running and jumping, which are similar to items in other tests used in VLBW populations, like the BOTMP [42 44]. The items are more similar to daily life activities than those in the Movement ABC-2, and the HiMAT may therefore be useful as a supplementary test. According to the HiMAT manual [27], a change of 2.66 points reflects a clinically important change. Thus, the difference of 4.7 points between the VLBW and control group (3.0 points when participants with CP were excluded) in our study is likely to be of clinical significance.

In accordance with the meta-analysis by de Kieviet [16] for VLBW children up to adolescence, we found poorer balance and manual dexterity skills for the VLBW young adults compared to the control group. The scores for balance, including the items walking toe-to-heel backwards and zig-zag hopping both legs, were significantly poorer in the VLBW group compared to the control group. These item scores were virtually the same for the non-CP VLBW group, however, no longer significantly lower than the control group. Most of the significantly poorer item scores on the HiMAT in the non-CP VLBW group involved balance more than the other item scores, such as hop forward (hopping on one leg) and bound both legs (jumping once from one leg to the other). This may indicate that the non-CP VLBW young adults have difficulties especially with items involving balance, and supports the findings of reduced balance in the Movement ABC-2.

Our results show reduced speed in fine motor skills, seen in both GP and TMT-5, the latter still significant in the non-CP VLBW group. Reduced speed was also seen on the Movement ABC-2, both including and excluding participants with CP in the VLBW group, with lower scores on the turning pegs item, but not on the drawing trial , where there is no time limit and only the number of errors is registered.

Thus, the VLBW young adults seem to be accurate, but slow. The overall gross motor skills measured by the HiMAT are mainly timed performances, and the lower total HiMAT score in the non-CP VLBW group may confirm that motor speed is a general problem among the VLBW young adults in this study, also when excluding the participants with CP.

The GP and the Movement ABC were used at age 14 in this cohort, showing reduced fine motor speed [45] and increased prevalence of motor problems [17] in the VLBW group. When comparing the GP results from 23 years of age with the results from 14 years, we found that the differences between VLBW participants and controls remained the same between the two time points. Furthermore, the proportion of VLBW participants with poor performance with the dominant hand was stable, while the proportion with poor performance with the non-dominant hand actually increased between the two time points. On the Movement ABC, the proportion of VLBW participants with motor problems did not change between 14 years and 23 years of age. These longitudinal findings were the same both including and excluding participants with CP, and show that fine and gross motor problems in VLBW adolescents do persist into adulthood.

The poorer motor skills and the reduced speed found among the VLBW participants in the current study, are likely to be explained by perinatal brain injury. The brain of VLBW infants is especially vulnerable to focal and diffuse periventricular leukomalacia (PVL) [46]. The former may cause cerebral palsy, especially of spastic diplegic type, while the latter may cause milder motor impairments [47,48]. Several neuroimaging studies have confirmed that these perinatal injuries persist into adolescence and adulthood, resulting in dilated ventricles, reduced white matter, thinning of corpus callosum, periventricular gliosis, deviations in white matter microstructure and decreased brain volumes [8 10,49]. Studies have shown associations between motor problems and white matter pathology in VLBW children and adolescents [11 14,48]. At 14 years in this cohort, white matter pathology was associated with impairments in fine motor function evaluated with the Movement ABC and the GP [14]. We speculate that the reduced motor speed, found in both fine and gross motor tests in this study, and the reduced motor skills may be caused primarily by reduced connectivity in motor networks. Including HiMAT in the examination protocol adds and enhances the dimension of reduced gross motor skills in the VLBW group. Both reduced speed and balance may contribute to the reduction in gross motor function as demonstrated by using the HiMAT. For a comprehensive motor assessment of VLBW young adults, Movement ABC-2, GP, TMT-5 and HiMAT in combination seem to be useful.

Reduced balance and gross motor function may interfere with sports and various leisure activities and reduce the chances of an active life with friends. Poor manual dexterity combined with reduced motor speed may have a negative influence on writing skills and computer-typing, which again can interfere with academic achievement, work and independent living. This study indicates that motor problems continue into adulthood, which supports the importance of early intervention or helping parents choose alternative activities and sports more adapted to the child's motor skills.

In conclusion, VLBW young adults had overall poorer fine and gross motor skills compared with matched term-born controls, which is likely to be of clinical importance. Reduced speed seemed to be an underlying problem. Longitudinal findings indicate that VLBW children have not outgrown their problems when entering adulthood. Using a broad spectrum of tests may add to the understanding of motor skills in VLBW populations, which may be important for intervention and efforts to optimise inclusion in daily life activities and work.

Financial support

The study was funded by the Research Council of Norway and was independent of commercial interest.

Conflict of interest statement

None of the authors have any conflicts of interest.

Acknowledgements

We want to thank the young adults for their participation and interest in the study. We are grateful to Inger Helene Hamborg and Sigrun Flekken for help in data collection.

References

[1] McCormick MC. The outcomes of very low birth weight infants: are we asking the right questions? Pediatrics 1997;99(6):869 76.
[2] Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115(4):997 1003.
[3] O'Brien F, Roth S, Stewart A, Rifkin L, Rushe T, Wyatt J. The neurodevelopmental progress of infants less than 33 weeks into adolescence. Arch Dis Child 2004;89(3): 207 11.
[4] 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(2):e249 57.
[5] Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. Future Child 1995;5(1):176 96.
[6] McCormick MC, Litt JS, Smith VC, Zupancic JAF. Prematurity: an overview and public health implications. Annu Rev Public Health 2011;32(1):367 79.
[7] 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(3): 149 57.
[8] 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(8):758 65.
[9] Vangberg TR, Skranes J, Dale AM, Martinussen M, Brubakk AM, Haraldseth O. Changes in white matter diffusion anisotropy in adolescents born prematurely. Neuroimage 2006;32(4):1538 48.
[10] Eikenes L, Lohaugen GC, Brubakk AM, Skranes J, Haberg AK. Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. Neuroimage 2011;54(3):1774 85.
[11] 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(3):149 54.
[12] 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(5 Pt 1):939 48.
[13] Rademaker KJ, Uiterwaal CS, Beek FJ, 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(6):F489 93.
[14] 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(3):654 66.
[15] Volpe JJ. The encephalopathy of prematurity brain injury and impaired brain development inextricably intertwined. Semin Pediatr Neurol 2009;16(4):167 78.
[16] de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis.J Am Med Assoc 2009;302(20):2235 42 [Review].
[17] Evensen KAI, Vik T, Helbostad J, Indredavik MS, Kulseng S, Brubakk AM. Motor skills in adolescents with low birth weight. Arch Dis Child 2004;89(5):F451 5.
[18] Evensen KA, 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(1):47 56.
[19] Evensen KA, Skranes J, Brubakk AM, Vik T. Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children. Early Hum Dev 2009;85(8):511 8.
[20] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39(4):214 23 [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.].
[21] Hollingshead AS. Two factor index of social status. New Haven: Yale University; 1958.
[22] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97 113.
[23] Lafayette I. Lafayette Instrument Grooved Pegboard Test. User's manual. Lafayette Instrument Company, Inc.; 2002
[24] Delis D, Kaplan E, Kramer J. D-KEFS Executive Function System. Norsk manual supplement; 2005.
[25] Henderson S, Sugden D, Barnett A. Movement Assessment Battery for Children-2. Examiner's manual. 2nd ed. London: Pearson Assessment; 2007.
[26] Williams GP, Morris ME. High-level mobility outcomes following acquired brain injury: a preliminary evaluation. Brain Inj 2009;23(4):307 12.
[27] Williams GP, Morris M, Greenwood K, Goldie P, Robertson V. High-level mobility assessment tool for traumatic brain injury. La Trobe University, User Manual Melbourne; 2004.

[28] Moen KT, Kleffelg rd I. HiMAT. High-level mobility assessment tool for traumatic brain injury. Norsk Versjon; 2011 12.
[29] Williams G, Pallant J, Greenwood K. Further development of the High-level Mobility Assessment Tool (HiMAT). Brain Inj 2010;24(7 8):1027 31.
[30] Henderson SE, Sugden DA. The movement assessment battery for children. Psychological Corporation; 1992.
[31] 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(6):458 61.
[32] Davies PL, Rose JD. Motor skills of typically developing adolescents: awkwardness or improvement? Phys Occup Ther Pediatr 2000;20(1):19 42.
[33] Largo RH, Caflisch JA, Hug F, Muggli K, Molnar AA, Molinari L, et al. Neuromotor development from 5 to 18 years. Part 1: time performance. Dev Med Child Neurol 2001;43(7):436 43.
[34] Wuang YP, Su JH, Su CY. Reliability and responsiveness of the Movement Assessment Battery for Children-Second Edition Test in children with developmental coordination disorder. Dev Med Child Neurol 2012;54(2):160 5.
[35] Williams G, Robertson V, Greenwood K, Goldie P, Morris ME. The concurrent validity and responsiveness of the high-level mobility assessment tool for measuring the mobility limitations of people with traumatic brain injury. Arch Phys Med Rehabil 2006;87(3):437 42.
[36] Williams GP, Robertson V, Greenwood KM, Goldie PA, Morris ME. The high-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 2: content validity and discriminability. Brain Inj 2005;19(10):833 43.
[37] Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am J Neuroradiol 2002;23(5): 794 802.
[38] Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. J Neurosurg 2010;113(3):556 63.
[39] Hillier SL, Sharpe MH, Metzer J. Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Inj 1997;11(9): 661 75.
[40] Andelic N, Sigurdardottir S, Schanke AK, Sandvik L, Sveen U, Roe C. Disability, physical health and mental health 1 year after traumatic brain injury. Disabil Rehabil 2010;32(13):1122 31.
[41] Williams G, Hill B, Pallant JF, Greenwood K. Internal validity of the revised HiMAT for people with neurological conditions. Clin Rehabil 2012;26(8):741 7.
[42] Bruininks R. Bruininks Oseretsky test of motor proficiency: examiner's manual. Circle Pines: American Guidance Service; 1978.
[43] Taylor HG, Minich NM, Klein N, Hack M. Longitudinal outcomes of very low birth weight: neuropsychological findings. J Int Neuropsychol Soc 2004;10(2):149 63.
[44] Gaddlin PO, Finnstrom 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(5):343 9.
[45] Skranes J, L haugen GCC, Evensen KAI, Indredavik MS, Haraldseth O, Dale AM, et al. Entorhinal cortical thinning affects perceptual and cognitive functions in adolescents born preterm with very low birth weight (VLBW). Early Hum Dev 2012;88(2):103 9.
[46] Volpe JJ. Neurology of the newborn. 5th ed. Book; 2008.
[47] Bracewell MN. Patterns of motor disability in very preterm children.Ment Retard Dev Disabil Res Rev 2002;8(4):241 8 [Article].
[48] Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8(1):110 24.
[49] Nosarti C, Al-Asady MH, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. Brain 2002;125(Pt 7): 1616 23.

Paper II

Husby et al. Health and Quality of Life Outcomes (2016) 14:56
DOI 10.1186/s12955-016-0458-y

Health and Quality of Life Outcomes

RESEARCH Open Access

Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight

Ingrid Marie Husby[1*], Kaia Mølbach-Thellefsen Stray[2], Alexander Olsen[3,4,5], Stian Lydersen[6], Marit Sæbø Indredavik[6,7], Ann-Mari Brubakk[1], Jon Skranes[1,8] and Kari Anne I. Evensen[1,9,10]

Abstract

Background: Being born with very low birth weight (VLBW: ≤1500 g) is related to long-term disability and neurodevelopmental problems, possibly affecting mental health and health-related quality of life (HRQoL). However, studies in young adulthood yield mixed findings. The aim of this study was to examine mental health and HRQoL at 23 years, including changes from 20 to 23 years and associations with motor skills in VLBW young adults compared with controls.

Methods: In a geographically based follow-up study, 35 VLBW and 37 term-born young adults were assessed at 23 years by using Achenbach Adult Self-Report (ASR), Short Form 36 Health Survey (SF-36), Beck Depression Inventory (BDI) and various motor tests. The ASR and SF-36 were also used at 20 years. Longitudinal changes in ASR and SF-36 from 20 to 23 years were analysed by linear mixed models and associations with motor skills at 23 years by linear regression.

Results: At 23 years, total ASR score was 38.6 (SD: 21.7) in the VLBW group compared with 29.0 (SD: 18.6) in the control group ($p = 0.048$). VLBW participants had higher scores for attention problems, internalizing problems and critical items, and they reported to drink less alcohol than controls. BDI total score did not differ between groups. On SF-36, VLBW participants reported significantly poorer physical and social functioning, more role-limitations due to physical and emotional problems, more bodily pain and lower physical and mental component summaries than controls. In the VLBW group, total ASR score increased by 9.0 (95 % CI: 3.3 to 14.7) points from 20 to 23 years ($p = 0.009$ vs controls), physical and mental component summaries of SF-36 decreased by 2.9 (95 % CI: -4.8 to -1.1) and 4.4 (95 % CI: -7.1 to -1.7) points, respectively ($p = 0.012$ and $p = 0.022$ vs controls). Among VLBW participants, more mental health problems and lower physical and mental HRQoL were associated with poorer motor skills at 23 years.

Conclusions: VLBW young adults reported poorer and declining mental health and HRQoL in the transitional phase into adulthood. They seemed to have a cautious lifestyle with more internalizing problems and less alcohol use. The associations of mental health problems and HRQoL with motor skills are likely to reflect a shared aetiology.

Keywords: Prematurity, Very low birth weight, Long-term outcome, Mental health, Health-related quality of life, Young adulthood, ASEBA, BDI, SF-36, Motor skills

* Correspondence: ingridmhusby@gmail.com
[1]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway
Full list of author information is available at the end of the article

Background

As neonatal medicine has been improving for the last decades, more very low birth weight (VLBW; birth weight ≤1500 g) infants survive. The preterm brain is especially vulnerable to injury and developmental disturbances [1], increasing the risk of later neurodevelopmental problems [2, 3]. This may have an impact on mental health and health-related quality of life (HRQoL); however, studies on long-term effects of VLBW into adulthood are sparse and yield mixed findings.

Children and adolescents born preterm with VLBW are reported to have more mental health problems than full-term controls, with an increased occurrence of attention deficits, internalizing symptoms and social problems in particular [2, 4]. There is an important transitional phase from adolescence to adulthood involving increasing demands on independency, education and adult roles [5], which may stress the underlying neuroimpairments in VLBW individuals. Indeed, preterm birth is shown to have an adverse effect on educational attainment, income and establishment of a family [6], and mental health problems tend to persist or even increase into young adulthood [7–9].

The concept of HRQoL refers to the impact of health conditions on a person's total well-being, including psychological, social, and physical aspects [10]. Measuring HRQoL gives valuable insight into the person's perception of his or her own health status, complementing more objectively collected data, and should therefore be addressed when assessing long-term consequences of VLBW. Although self-reports of HRQoL in VLBW children and adolescents seem to be similar to their normal birth weight peers, parent-reports are typically lower [11]. Some studies of VLBW young adults have revealed lower HRQoL based on societal standards [12] and lower scores on HRQoL domains of mental health [13] and physical functioning [14, 15]. Other studies report similar HRQoL [14, 16, 17] and well-being [18] for VLBW young adults compared with controls. Longitudinal studies on changes of HRQoL in VLBW populations are sparse, but receive growing attention [11, 19].

Developmental disturbances in the preterm brain are global and likely to affect both mental health and other areas of neurodevelopment, such as motor problems. Poorer fine and gross motor skills are prevalent in childhood, adolescence and young adulthood in VLBW individuals [3, 20]. Both among adults with normal birth weight and <1000 g, self-reported childhood coordination problems have been associated with elevated levels of inattention and symptoms of anxiety and depression [21]. Lower quality of life has been reported among adults with developmental coordination disorder [22]. However, no previous studies have investigated associations of mental health and HRQoL with motor skills in VLBW young adults. As motor skills are often assessed in childhood, and we have previously reported stability of motor problems from early childhood to young adulthood [20, 23], it may be possible to identify children at risk for later mental health problems and low HRQoL.

In this study, we aimed to investigate the effects of VLBW on mental health and HRQoL in young adults at 23 years of age, including changes from 20 to 23 years and whether mental health and HRQoL were associated with motor skills. We hypothesized that VLBW young adults at age 23 would have more mental health problems and lower HRQoL compared with controls. Due to increased demands following the transition to adulthood, we predicted a decrease in mental health and HRQoL from 20 to 23 years in the VLBW group. Based on previous findings, we hypothesized that more mental health problems and lower physical HRQoL would be associated with poorer motor skills at age 23.

Methods

Study design

This is a geographically based follow-up study of young adults born preterm with VLBW and a control group born at term with normal birth weight at 23 years. The VLBW children were born in 1986-1988 and admitted to the Neonatal Intensive Care Unit (NICU) at St. Olavs Hospital, Trondheim University Hospital, Norway. The control children were born in the same period to mothers living in the Trondheim region (total population approximately 135.000), recruited from a 10 % random sample of women selected for follow-up during pregnancy in a multicentre study on causes and consequences of intrauterine growth restriction [24]. Both groups had previously participated in the study with evaluations at 1, 5, 14 and 20 years of age [13, 23, 25]. At 23 years, we aimed to include all VLBW participants from the 14-year follow-up and a selection of control participants, matched by age and sex, due to lack of resources. Self-report questionnaires on mental health and HRQoL were included as part of a large assessment battery, which also covered executive tests, motor tests and cerebral magnetic resonance imaging. Data on mental health and HRQoL were also available from the 20-year follow-up, and results have been published previously [13].

Study groups

Figure 1 shows a flow chart of the study groups.

VLBW group

At 14 years, 63 VLBW adolescents with birth weight ≤1500 g had been examined. At 23 years, seven of these were non-traceable and two were excluded due to severe bilateral spastic cerebral palsy (CP) of Gross Motor Function Classification System (GMFCS) level V [26].

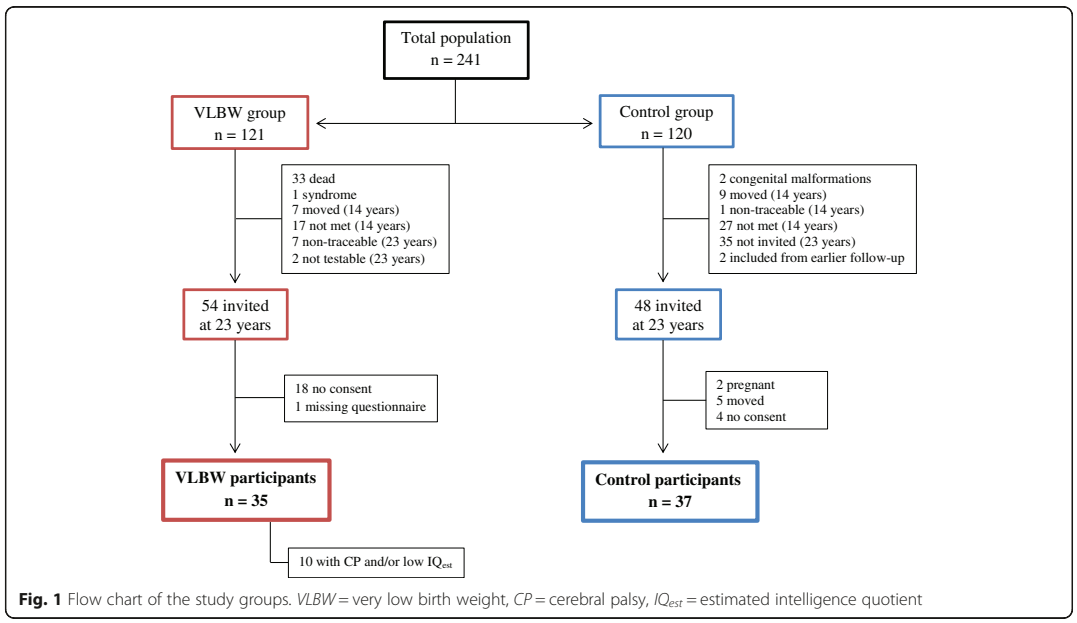

Fig. 1 Flow chart of the study groups. *VLBW* = very low birth weight, *CP* = cerebral palsy, IQ_{est} = estimated intelligence quotient

Thus, we contacted 54 VLBW young adults, whereof 18 (33 %) did not consent and one did not fill out the questionnaires, leaving 35 participants (14 males and 21 females) in the VLBW group (Fig. 1). At 20 years, mental health and HRQoL had been assessed in 52 VLBW participants, whereof nine were excluded from this paper due to missing data on estimated intelligence quotient (IQ_{est}). Hence, 43 VLBW participants with mean age 19.7 (0.8) were included in longitudinal analyses at 20 years, whereof 29 were examined at both time-points.

Control group

At 14 years, 81 control adolescents born at term with birth weight ≥10th percentile for gestational age had been examined. At 23 years, we contacted 48 controls matched to the VLBW participants by age and sex, of which 46 were examined at the 14-year follow-up. Two were not testable due to pregnancy, five had moved and four (9 %) did not consent, leaving 37 participants (15 males and 22 females) in the control group (Fig. 1). At 20 years, mental health and HRQoL were examined for 77 controls with mean age 19.7 (0.5), whereof 31 were examined at both time-points.

Non-participants

In the VLBW group, there were no significant differences between those who participated and those who did not consent to participation at age 23 regarding perinatal data (data not shown). Parental socioeconomic status (SES) at 14 years was 3.5 (1.1) among participants compared with 2.8 (1.3) among non-participants ($p = 0.045$, Mann Whitney *U* test). In the control group, there were no significant differences between those who participated and those who did not consent to participation or were not contacted from previous follow-up (data not shown). Furthermore, there were no significant differences in motor skills at 14 years [20] or summary scores for mental health or HRQoL at 20 years between participants and non-participants at the 23-year follow-up in either group (data not shown).

Data collection

Clinical characteristics

Perinatal data included birth weight, gestational age, head circumference, Apgar scores, days in NICU, days on mechanical ventilator, intraventricular haemorrhage status and maternal age. CP was diagnosed in childhood, and classified as spastic hemiplegia (unilateral spastic CP), diplegia (bilateral spastic CP, mainly involvement of lower extremities) and quadriplegia (bilateral spastic CP with involvement of all extremities). Functional level was assessed according to the GMFCS [26]. At 14 years, IQ_{est} was calculated at using two subscales of Wechsler Intelligence Scales for Children, third edition; vocabulary and block design [27]. Low IQ_{est} was defined as a score more than two standard deviations below the mean in the control group (IQ_{est} <69). Parental SES was calculated according to Hollingshead s two factor index of social position [28], rated from 1

(lowest) to 5 (highest) based on a combination of parents education and occupation at the 14-year follow-up.

Follow-up at 23 years

The self-report questionnaires and the motor tests were carried out at the same day and at the same location. For one participant with unilateral spastic CP and low IQ_{est}, the self-report was carried out as an interview by one of the researchers.

Mental health: Adult Self-Report (ASR)

Mental health was measured by the Adult Self-Report (ASR) [29], which is part of the Achenbach System of Empirically Based Assessment (ASEBA), a worldwide used instrument shown to be reliable and valid [29]. An authorized Norwegian translation of the ASEBA was applied. The ASR (age range 18 59) comprises 120 problem items (scored 0 2), yielding eight syndrome scales (score range): anxious/depressed (0 36), withdrawn (0 18), somatic complaints (0 24), thought problems (0 20), attention problems (0 30), aggressive behaviour (0 30), rule-breaking behaviour (0 28) and intrusive (0 12). The first three scales comprise the composite scale for internalizing problems whereas the last three comprise the composite scale for externalizing problems. The sum of all problem items yields a total problems score (range: 0 240). A score for critical items is made by summing the scores on 19 problem items evaluated to be the most clinically relevant psychiatric symptoms. Raw scores are used, and higher scores indicate more problems. In addition, the ASR includes items on adaptive functioning, of which we used scales for friends, family and substance use. The scale for friends yield a total score based on number of close friends, frequency of contact with friends, getting along with friends and visits from friends, each scored 0 3, with a maximum of 12 points. The scale for family relations yield a mean score based on self-perceived quality of relation with parents and/or siblings compared with others, each scored 0 2. Higher scores for friends and family indicate better adaptive functioning. Substance use includes tobacco (number of cigarettes smoked daily), alcohol (number of days being drunk last 6 months) and drugs (number of days using drugs last 6 months). T-scores are recommended when having extreme outliers [29], and are also used to calculate a mean substance use scale. One VLBW participant did not complete the ASR at 23 years. For one VLBW participant, reliable data on alcohol use was missing at age 20 and excluded in the analysis for longitudinal change in alcohol use.

Mental health: Beck Depression Inventory (BDI), Version IA

The BDI [30] is among the most used self-rating scales for measuring depression, and has high validity in differentiating between depressed and non-depressed participants [31]. The BDI (age ≥13) consists of 21 questions measuring symptoms and severity of depression during the past week, including today. Values range from 0 to 3 and are summed into a total score, where a score ≥21 indicates depression in the general population [30]. One VLBW and two control participants did not complete the BDI at 23 years. The BDI was not used at 20 years.

Health-related quality of life: Short Form 36 Health Survey (SF-36), Version 1.0

The SF-36 is a generic measure of HRQoL with high reliability and it has been validated for use across a range of health care professions, settings and patients [32], also for the Norwegian translation applied in this study [33, 34]. The questionnaire comprises 36 items across eight domains: physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional) and mental health. Raw scores are transformed into an aggregate percentage score for each domain ranging from 0 to 100 %, where higher percentage indicate favourable health outcome and higher level of functioning. The two domains role-physical and role-emotional have dichotomised response choices, while the other domains have a Likert-type response with three to six choices. The recall period is 4 weeks, except for physical functioning and general health, which address current status. Three of the domains (physical functioning, role-physical and bodily pain) contribute mainly to a physical component summary, while three other domains (social functioning, role-emotional and mental health) contribute mainly to a mental component summary. Three of the domains (general health, vitality and social functioning) have noteworthy correlations with both components [32]. We applied an oblique model for calculating the component summaries after recommendation from Hann and Reeves [35]. We used a Certified Scoring Software 4.0™ to score the questionnaire and the official calculator at the home page of SF-36 to calculate the component summaries [36] based on Norwegian normative data [37] with average of 50 points and a standard deviation of 10 points. One control had missing domain scores for vitality and mental health because of too many missing items, and we could therefore not calculate component summaries for this participant. Two controls did not complete the SF-36 at 23 years.

Motor examination

Motor skills were examined by using four different motor tests, described in detail in a previous paper on motor skills in the same study population [20]. The Grooved Pegboard (GP) [38] is a manipulative dexterity

test giving a score for each hand separately, which we calculated into a mean score for both hands. The Trail Making Test-5 (TMT-5) is one of five subtests in the standardized Delis-Kaplan Executive Function System [39] measuring motor speed of the dominant hand. The Movement Assessment Battery for Children-2 (Movement ABC-2) [40] consists of three components (manual dexterity, aiming and catching, and balance) yielding a total score. The High-Level Mobility Assessment Tool (HiMAT) [41] assesses 13 gross motor items (walk, walk backwards, walk on toes, walk over obstacle, run, skip, hop forward, bound, and walk up/down stairs) yielding a total score. For the GP and TMT-5, higher scores indicate poorer function and for Movement ABC-2 and HiMAT, higher scores indicate better function.

Ethical approval and consent

The project complies with the principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway. Written informed consent was obtained from all participants.

Statistical analyses

Student s *t*-test was used for approximately normally distributed data; else the Mann Whitney *U* test was applied. Descriptive statistics are reported as mean (SD) where relevant. To limit the number of statistical tests, we only included the summary scores of ASR (critical items, internalizing, externalizing and total problems) and SF-36 (physical and mental component summaries) for longitudinal changes and associations with motor skills. Linear mixed models were used to analyse changes in summary scores from 20 to 23 years. Summary scores were entered separately as dependent variables, whereas age, group and the interaction age x group were entered as independent variables in analyses, both unadjusted and adjusted for sex. Linear regression was applied to explore associations of mental health and HRQoL with motor skills. Summary scores of ASR and SF-36 were entered separately as dependent variables, whereas motor test, group and the interaction motor test x group were entered as independent variables. The interaction terms were added to test if the effect of time or motor skills were different in VLBW and control participants. Normality was judged by visual inspection of Q-Q plots of the residuals. If outliers were observed, sensitivity analyses excluding the outlier were carried out. Two-sided p-values <0.05 were considered statistically significant. Analyses were performed both including and excluding participants with CP and/or low IQ_{est}. SPSS 22.0 was used for data analyses.

Results

Clinical characteristics

Clinical characteristics are shown in Table 1. Age at current follow-up was 22.5 (0.7) years in the VLBW group and 22.7 (0.6) years in the control group ($p = 0.234$, Student s *t*-test). Maternal age at birth and parental SES at age 14 did not differ between groups ($p = 0.165$, Student s *t*-test and $p = 0.580$, Mann Whitney *U* test, respectively). Four VLBW participants had CP; one female had unilateral spastic CP of GMFCS level I and three males had bilateral spastic CP with GMFCS level I, II and IV. One control and eight VLBW participants had low IQ_{est} at age 14, whereof two had CP.

Mental health: Adult Self-Report (ASR) at 23 years

The results from the ASR are shown in Table 2. The VLBW group had significantly higher scores (indicating more problems) than the control group for the scales attention problems, internalizing problems, total problems and critical items. Aggressive behaviour was also higher in the VLBW group when we

Table 1 Clinical characteristics

	VLBW ($n = 35$)		Control ($n = 37$)	
	Mean	(SD)	Mean	(SD)
Birth weight (g)	1198	(254)	3608	(361)
Gestational age (weeks)	29.0	(2.7)	39.4	(1.1)
Birth head circumference (cm)[a]	26.9	(2.4)	35.2	(1.2)
Apgar score after 1 min[b]	6.8	(1.9)	8.9	(0.5)
Apgar score after 5 min[c]	8.4	(1.7)	9.7	(1.5)
Maternal age at birth (years)	28.4	(5.6)	30.1	(4.5)
Parental SES (at 14 years)[c]	3.5	(1.1)	3.7	(1.1)
Age at current follow-up	22.5	(0.7)	22.7	(0.6)
	Median	(Range)	Median	(Range)
Stay in NICU (days)[d]	63	(25 386)	0	(0 9)
Mechanical ventilation (days)[d]	1	(0 63)	-	
	n	(%)	n	(%)
Intraventricular haemorrhage[d]	3	(9)	-	
Grade I-II	2			
Grade IV	1			
Cerebral palsy	4	(11)	0	
GMFCS level I-II	3			
GMFCS level IV	1			
Low IQ_{est}	8	(23)[e]	1	(3)

[a]Data missing for eight VLBW and three control participants
[b]Data missing for three control participants
[c]Data missing for two control participants
[d]Data missing for one VLBW participant
[e]Two VLBW participants with low IQ_{est} had cerebral palsy
VLBW = very low birth weight, *SES* = socioeconomic status, *NICU* = neonatal intensive care unit, *GMFCS* = Gross Motor Function Classification System, IQ_{est} = estimated intelligence quotient
Group differences for maternal age, SES and age at follow-up were non-significant

excluded one outlier in the control group ($p = 0.032$, Student s t-test). The VLBW group had significantly lower alcohol use than controls. For the scales alcohol, tobacco and drugs, results did not change using T-scores (data not shown). When we excluded VLBW participants with CP and/or low IQ_{est}, mean scores were still higher than for controls on nearly all scales, but only the scales critical items and alcohol use showed a significant group difference (Table 2).

Mental health: Beck Depression Inventory (BDI) at 23 years

Mean total BDI score was 3.3 (5.0) in the VLBW group and 4.0 (6.5) in the control group ($p = 0.796$, Mann Whitney U test). Results were similar when we excluded VLBW participants with CP and/or low IQ_{est}. One VLBW participant with low IQ_{est} and one control were clinically depressed according to a cut-off ≥21.

Health-related quality of life: Short Form 36 Health Survey (SF-36) at 23 years

The results from the SF-36 are shown in Table 3. The VLBW group had significantly lower scores than controls on the physical and mental component summaries and five of the eight domains: physical functioning, role-physical, bodily pain, social functioning and role-emotional. When we excluded VLBW participants with CP and/or low IQ_{est}, mean scores were still lower than for controls, although mean differences between groups were reduced and no longer significant (Table 3).

Changes in mental health and health-related quality of life from 20 to 23 years

Longitudinal changes in mental health and HRQoL from 20 to 23 years are shown in Table 4, visualized for ASR total problems score in Fig. 2, and physical and mental component summaries of SF-36 in Figs. 3 and 4, respectively. There were significant between-group differences with time for internalizing and total

Table 2 Results of the *ASEBA Adult Self-Report* at 23 years

	VLBW ($n = 34$)			VLBW ($n = 24$) without CP and/or low IQ_{est}			Control ($n = 37$)	
	Mean	(SD)	p-value vs control	Mean	(SD)	p-value vs control	Mean	(SD)
Syndrome scales								
Anxious/depressed	7.0	(6.1)	0.096	7.3	(6.2)	0.095	4.6	(5.7)
Withdrawn	2.4	(3.0)	0.325	2.1	(2.6)	0.669	1.8	(2.3)
Somatic complaints	3.4	(3.4)	0.081	3.0	(2.7)	0.220	2.2	(1.9)
Thought problems	1.8	(1.8)	0.371	1.5	(1.6)	0.861	1.4	(1.8)
Attention problems	7.7	(4.6)	0.013	7.0	(4.3)	0.081	5.2	(3.5)
Aggressive behaviour	3.8	(3.3)	0.205	3.4	(3.3)	0.447	2.7	(3.7)
Rule-breaking behaviour	2.9	(3.1)	0.188	3.0	(3.6)	0.243	2.0	(2.3)
Intrusive	1.7	(1.3)	0.544	1.5	(1.4)	0.386	1.9	(2.0)
Critical items	4.6	(3.4)	0.013	4.6	(3.5)	0.037	2.8	(2.7)
Internalizing problems	12.9	(9.4)	0.042	12.3	(9.1)	0.098	8.6	(7.7)
Externalizing problems	8.3	(6.0)	0.232	8.0	(6.6)	0.412	6.6	(5.7)
Total problems	38.6	(21 .7)	0.048	36.3	(22.2)	0.173	29.0	(18.6)
Adaptive functioning								
Friends	10.0	(2.1)	0.059	10.2	(2.0)	0.170	10.8	(1.4)
Family	1.5	(0.4)	0.756	1.5	(0.4)	0.955	1.5	(0.4)
Substance use								
Tobacco	3.3	(4.8)	0.688	3.2	(5.2)	0.673	3.9	(6.3)
Alcohol[a]	5.5	(5.0)	0.008	6.3	(5.5)	0.036	10.6	(9.8)
Drugs	3.7	(17.3)	0.359	4.9	(20.5)	0.366	1.0	(4.2)
Mean substance use[a]	54.1	(2.7)	0.067	54.2	(2.6)	0.119	55.5	(3.3)

[a]Data missing for one VLBW and two control participants

Raw scores are given for all scales, except mean substance use which is given as T-score. Higher scores indicate more problems on syndrome scales and substance use, while higher scores on adaptive functioning indicate better functioning

ASEBA = Achenbach System of Empirically Based Assessment, *VLBW* = very low birth weight, *CP* = cerebral palsy, IQ_{est} = estimated intelligence quotient

Analyses performed with Students t-test

Table 3 Results of the *Short Form 36 Health Survey* at 23 years

	VLBW ($n = 35$)			VLBW ($n = 25$) without CP and/or low IQ_{est}			Control ($n = 35$)	
	Mean	(SD)	*p*-value vs control	Mean	(SD)	*p*-value vs control	Mean	(SD)
Domains								
Physical functioning	90.4	(13.6)	0.018	94.6	(8.3)	0.286	96.6	(5.9)
Role-physical	80.0	(30.8)	0.005	86.0	(24.0)	0.051	96.4	(10.7)
Bodily pain	68.7	(28.3)	0.022	74.5	(23.8)	0.193	82.0	(18.3)
General health	72.1	(18.9)	0.260	70.5	(18.5)	0.477	66.8	(20.0)
Vitality[a]	49.2	(14.2)	0.091	50.5	(13.7)	0.227	54.9	(13.2)
Social functioning	86.1	(16.5)	0.025	88.5	(13.0)	0.099	94.3	(13.3)
Role-emotional	78.1	(33.3)	0.012	82.7	(29.1)	0.069	95.2	(20.0)
Mental health[a]	70.6	(16.8)	0.067	73.4	(14.1)	0.272	77.4	(13.2)
Physical component summary[a]	47.8	(5.9)	0.009	49.4	(5.2)	0.160	51.2	(4.1)
Mental component summary[a]	45.2	(8.4)	0.013	46.6	(7.4)	0.087	49.7	(6.4)

[a]Data missing for one control participant
Domain scores are given in percentage (range 0–100) and higher scores indicate better health-related quality of life
Component summaries are given as T-scores with average of 50 points and a standard deviation of 10 points
VLBW = very low birth weight, *CP* = cerebral palsy, IQ_{est} = estimated intelligence quotient
Analyses performed with Students *t*-test

problems. In the VLBW group, ASR scores increased significantly with time (indicating more mental health problems) for internalizing, externalizing and total problems. There were significant between-group differences with time for the physical and mental component summaries. In the VLBW group, there was a significant reduction in scores with time (indicating lower HRQoL) for both the physical and mental component summaries. There were no significant changes in the control group. Adjusting for sex in the analyses did not affect the longitudinal changes (data not shown). Results for ASR were essentially the same when we excluded VLBW participants with CP and/or low IQ_{est}, but for SF-36 only the mental component summary reached a statistical significant reduction with time (data not shown).

Associations with motor skills at 23 years

For the ASR, more internalizing and total problems were associated with lower motor speed on the TMT-5 (B = 0.41; 95 % CI: 0.14 to 0.67; $p = 0.004$ and B = 0.75; 95 % CI: 0.10 to 1.39; $p = 0.024$, respectively) in the VLBW group. Results were no longer significant when we excluded VLBW participants with CP and/or low IQ_{est} (data not shown). There were no significant associations of externalizing problems and critical items with motor skills.

Table 4 Estimated changes from 20 to 23 years in scores for *ASEBA Adult Self-Report* and *Short Form 36 Health Survey*

	VLBW ($n = 49$)			Control ($n = 83$)			
	B	(95 % CI)	*p*-value	B	(95 % CI)	*p*-value	*p*-value (age x group)[b]
Adult Self-Report							
Critical items	0.73	(-0.47 to 1.93)	0.228	−0.38	(-1.42 to 0.66)	0.470	0.167
Internalizing problems	4.94	(1.63 to 6.24)	0.001	0.40	(-1.67 to 2.46)	0.704	0.025
Externalizing problems	1.87	(0.02 to 3.71)	0.047	−0.45	(-2.08 to 1.18)	0.583	0.064
Total problems	9.00	(3.30 to 14.71)	0.002	−1.35	(-6.46 to 3.76)	0.600	0.009
Short Form 36 Health Survey[a]							
Physical component summary	−2.94	(-4.83 to -1.06)	0.003	0.46	(-1.39 to 2.30)	0.623	0.012
Mental component summary	−4.37	(-7.07 to -1.67)	0.002	0.08	(-2.57 to 2.73)	0.952	0.022

[a]Data missing for one control participant at both time-points
[b]p-value for between-group differences in longitudinal changes from 20 to 23 years
ASEBA = Achenbach System of Empirically Based Assessment, *VLBW* = very low birth weight, *CI* = confidence interval
Regression coefficient B per 3 years, in a linear mixed models with scores as dependent variables, and age, group and age x group as independent variables

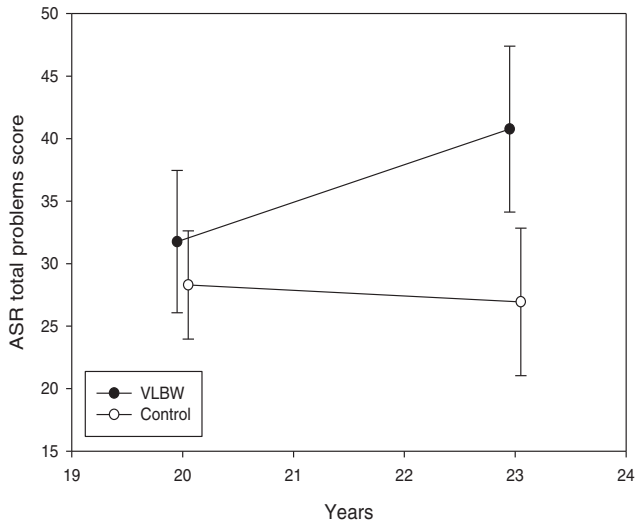

Fig. 2 Adult Self-Report (ASR) total problems score with 95 % confidence interval at 20 and 23 years. Raw scores are given. A higher score indicates more mental health problems. *VLBW* = very low birth weight

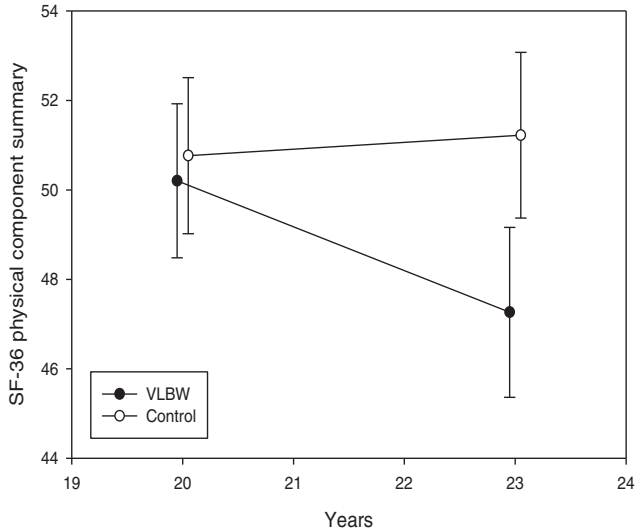

Fig. 3 Short Form 36 Health Survey (SF-36) physical component summary with 95 % confidence interval at 20 and 23 years. T-scores are given. A higher score indicates higher physical health-related quality of life. *VLBW* = very low birth weight

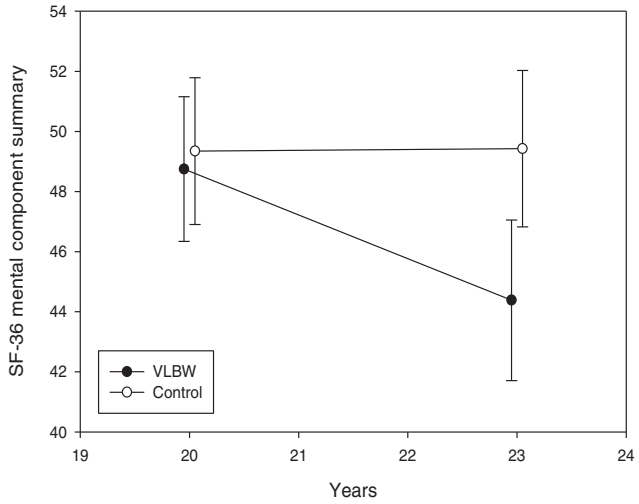

Fig. 4 Short Form 36 Health Survey (SF-36) mental component summary with 95 % confidence interval at 20 and 23 years. T-scores are given. A higher score indicates higher mental health-related quality of life. *VLBW* = very low birth weight

Associations of physical and mental component summaries of SF-36 with motor skills are shown in Table 5. There was a significant between-group difference for the association of physical component summary with TMT-5. In the VLBW group, lower physical and mental component summaries were associated with poorer performance on all motor tests. When we excluded VLBW participants with CP and/or low IQ_{est}, lower physical component summary was still associated with poorer performance on TMT-5 and HiMAT, while lower mental component summary was only associated with poorer performance on TMT-5 (data not shown).

Table 5 Associations of *Short Form 36 Health Survey* physical and mental component summaries with motor skills at 23 years

	VLBW ($n = 35$)			Control ($n = 34$)			
	B	(95 % CI)	*p*-value	B	(95 % CI)	*p*-value	*p*-value (motor test x group)[e]
Physical component summary							
Grooved Pegboard[a,b]	−0.09	(-0.16 to -0.02)	0.010	−0.05	(-0.23 to 0.13)	0.596	0.679
Trail Making Test-5[a]	−0.31	(-0.46 to -0.16)	0.000	0.02	(-0.25 to 0.30)	0.862	0.038
MABC-2 total score[c]	0.13	(0.04 to 0.21)	0.003	0.15	(-0.04 to 0.33)	0.125	0.847
HiMAT total score[c,d]	0.39	(0.18 to 0.59)	0.000	0.06	(-0.46 to 0.58)	0.823	0.244
Mental component summary							
Grooved Pegboard[a,b]	−0.15	(-0.25 to -0.06)	0.002	−0.04	(-0.30 to 0.22)	0.767	0.420
Trail Making Test-5[a]	−0.40	(-0.62 to -0.18)	0.001	0.00	(-0.42 to 0.42)	0.998	0.094
MABC-2 total score[c]	0.15	(0.02 to 0.27)	0.024	0.00	(-0.29 to 0.28)	0.985	0.349
HiMAT total score[c,d]	0.36	(0.04 to 0.68)	0.026	0.04	(-0.78 to 0.85)	0.928	0.462

[a]Data missing for one VLBW participant with unilateral spastic cerebral palsy
[b]Mean score for both hands
[c]Data missing for one VLBW participant with bilateral spastic cerebral palsy
[d]Data missing for one control participant
[e]p-values for between-group differences in associations of physical and mental component summaries with motor skills
HRQoL = health-related quality of life, *VLBW* = very low birth weight, *CI* = confidence interval
MABC-2 = Movement Assessment Battery for Children-2, *HiMAT* = High-level Mobility Assessment Tool
Higher scores on the Grooved Pegboard and Trail Making Test-5 indicate poorer function and higher scores on the MABC-2 and HiMAT indicate better function
Regression coefficient B for motor test, in linear regression with physical component summary and mental component summary as dependent variable, and motor test, group, and motor test x group as independent variables

Discussion

In this study, VLBW young adults reported more mental health problems and lower HRQoL compared with controls at 23 years of age. In the VLBW group, mental health and HRQoL decreased from 20 to 23 years. Furthermore, in this group, more internalizing and total mental health problems as well as lower physical and mental HRQoL were associated with poorer performance on motor tests at 23 years, especially lower motor speed. When we excluded VLBW participants with CP and/or low IQ_{est}, several group differences were no longer significant, but for the ASR, mean values and longitudinal changes were essentially the same, whereas associations with motor skills became weaker.

Strengths of this study are the longitudinal and multidisciplinary design and the use of reliable and valid methods [29, 31, 32]. However, sample size was limited, especially when we excluded participants with CP and/or low IQ_{est}, resulting in reduced power in our analyses. Results and especially non-significant group differences should therefore be carefully interpreted, and one should focus more on means and standard deviations than *p*-values. Furthermore, our limited sample size did not give the possibility to study sub groups. Loss to follow-up may result in selection bias. The reason why 18 (33 %) of the invited VLBW young adults at 23 years did not want to participate and one did not fill out the questionnaires is not known. Our participants did not differ from non-participants on perinatal data or previous examinations of motor skills [20], mental health or HRQoL. The only difference in clinical characteristics between participants and non-participants was lower parental SES for VLBW non-participants. Low parental SES is associated with more mental health problems in childhood and adolescence [42], thus our results are more likely to be an underestimation than an overestimation of problems.

Self-report questionnaires like the ASR and SF-36 give participants the opportunity to describe their own perspective of their lives. However, self-reports are prone to social desirability bias, and cognitive function may influence the ability of self-perception and understanding questionnaires. We therefore performed analyses also when excluding VLBW participants with CP and/or low IQ_{est}. In this VLBW cohort at 20 years, we found more symptoms of psychiatric disorders with diagnostic assessment by a psychiatrist than self-reported mental health problems on the ASR [43], and poorer executive functions on neuropsychiatric testing than on self-reports [44], which might indicate that the VLBW individuals underreported or had adjusted to their problems. Even though objective evaluations add valuable insights; how the young adults rate their own health, and especially their HRQoL, might be more important to them.

Our findings of more mental health problems in VLBW young adults, with emphasis on internalizing and attention problems are consistent with the literature [2, 9, 13, 45 47]. In our study, the VLBW young adults also had a tendency of reporting more anxious/depressed problems and social problems than the control group, supporting the suggested Preterm behavioural phenotype characterized by anxiety, inattention and social difficulties [4]. The VLBW young adults did not seem to be more depressed than controls according to BDI, in line with the findings of R ikk nen et al. [48]. However, Westrupp et al. [49] found that VLBW young adults in their late twenties were five times more likely to be diagnosed with depression. We speculate that depression may become more prevalent when our VLBW participants grow older. We also found that VLBW young adults reported less substance use with regard to alcohol, consistent with other studies [15, 50, 51], where some also describe less risk-taking behaviour [15, 18, 46]. These findings are in accordance with the personality type reported among young adults born with VLBW or very preterm (<33 weeks gestation), including less sensation seeking, extraversion and openness to experience, and higher conscientiousness, neuroticism and shyness [52, 53]. Even though increased parental monitoring and protectiveness cannot be excluded [47], Harrison [54] suggests that VLBW children and young adults have cognitive and behavioural deficits that isolate them from both their peers and their peers risk-taking behaviour, and that the isolation and withdrawal are caused by a lack of social and intellectual resilience. Cognitive function has been found to modify the risk of mental health problems of VLBW young adults in some studies [45]. In our study, group differences in mental health problems were no longer significant when we excluded VLBW participants with CP and/or low IQ_{est}, however scores were essentially the same. It is of concern that the VLBW young adults scored significantly higher for critical items of clinically relevant psychiatric symptoms, also when we excluded participants with CP and/or low IQ_{est}. We have previously reported a trend towards an increase of mental health problems from 14 to 20 years of age in this cohort [7], and the further increase from 20 to 23 years found in the current study is worrying and needs to be confirmed by other studies.

Findings on HRQoL in VLBW populations are conflicting. In contrast to our findings, the systematic reviews of Zwicker and Harris [11] and Allen et al. [9] concluded in four studies [12, 15, 18, 55] that VLBW young adults around age 20 have similar HRQoL to controls. However, poorer physical functioning [15] and lower objective quality of life [12] were reported. More recent studies from Switzerland [14] and New Zealand [16] also reported similar HRQoL to controls according to the SF-36 among young adults born with birth weight <1250 g or with

VLBW at age 23. A Norwegian study by B tsvik et al. [8] found lower scores for the SF-36 domains of bodily pain, vitality, social functioning, role-emotional and mental health among young adults born before week 28 or with a birth weight ≤1000 g compared with term-born controls at age 24. When they excluded participants with disabilities, group differences were significant for social functioning, role-emotional and mental health. When we excluded VLBW participants with CP and/or low IQ_{est} in our study, group differences on SF-36 were reduced and no longer significant, but mean scores where still lower for all domains in the VLBW group compared with the control group. Cooke [15] found poorer physical functioning on SF-36 in VLBW young adults able to attend mainstream schools, and Dinesen and Greisen [12] reported lower objective quality of life based on societal standards for VLBW individuals without disabilities at 18 years. Hence, both preterm born young adults with and without disabilities might be at risk for lower HRQoL than controls.

We speculate that the lower HRQoL among VLBW young adults found in our study could be partly due to challenges related to the transition to young adulthood. The underlying neuroimpairments of VLBW individuals may become more evident with these challenges, such as moving away from home, starting to study or work, finding a partner and living more independent and social lives [5]. In Norway, only 29 % of 20 to 24-year-olds live with their parents, in contrast to 83 % in Switzerland (Additional file 1), and parent-support might to some extent explain the discrepancy from the Swiss study [14]. In New Zealand, the proportion of 20 to 24-year-olds living with their parents was 32 % in 2006 (Additional file 2), similar to that in Norway. However, Darlow et al. [16] only used the component summaries of the SF-36 relative to 18 to 24-year norms, and their control group was recruited at 23 years among peers to the VLBW group. Our control group was followed from birth, and may therefore be more representative of the general population. The lower HRQoL found among extremely preterm young adults by B tsvik et al. [8] supports our findings and might be more comparable as it is a Norwegian study. However, they studied young adults born before week 28 or with a birth weight ≤1000 g, a group that may be more vulnerable than VLBW individuals.

The increase in mental health problems found in our study may also have an impact on the reduction of HRQoL from 20 to 23 years in the VLBW group. In children and adolescents, HRQoL may decrease with time if mental health problems increase [56], and in VLBW young adults, internalizing problems are found to be strongly correlated to low HRQoL [57]. Longitudinal studies of HRQoL in VLBW populations are sparse and show few changes from adolescence to young adulthood. In one study, HRQoL from 14 to 19 years were stable in the VLBW group, however clinically important changes in psychological attributes of HRQoL were reported [57]. Van Lunenburg et al. [58] did not find any changes in HRQoL among VLBW young adults from 19 to 28 years of age. This may indicate that the lower HRQoL we found at age 23 may stabilize and improve over the next years. However, the methods and cultural settings in these studies are not directly comparable. Both the VLBW and control group in our study reported a reduction in general health from 20 to 23 years, which might be a general change during this life period. People s evaluations of their general health are found to be dynamic and changing within a two-year period for half the adult population [59]. More studies are needed to understand the changes in HRQoL in preterm populations with time.

We have previously reported that VLBW young adults had poorer motor skills than controls at 23 years [20]. The current study shows that internalizing and total mental health problems as well as lower physical and mental HRQoL were associated with poorer motor skills, especially motor speed, also when we excluded VLBW participants with CP and/or low IQ_{est}. Studies of adults with developmental coordination disorder showed that they reported more symptoms of anxiety and depression [60] and lower quality of life than peers [22]. Both among adults with normal birth weight and <1000 g, self-reported childhood coordination problems were associated with elevated levels of inattention and symptoms of anxiety and depression [21]. Our study confirms and extends the existing knowledge by using clinically assessed motor skills in young adulthood to establish the associations of mental health and HRQoL with motor skills in VLBW young adults.

There is reason to believe that the motor and mental health problems in preterm populations share a common cause. The preterm brain is susceptible to a cascade of adverse events, often referred to as the Encephalopathy of prematurity [1], likely to affect both motor skills and mental health. The altered brain development continues into young adulthood [61, 62], and we have previously reported changes in brain white matter that were associated with cognitive, motor and mental health impairments among VLBW adolescents [63]. Poor executive functioning with difficulties holding information in mind and switching between mental sets is related to behavioural functioning [2], and might also partly explain the social difficulties of VLBW individuals. There is emerging evidence that stressful prenatal and neonatal factors, such as preterm birth, may imprint a pattern of physiological activity in the developing brain, known as foetal programming [64]. The immune system and the hypothalamus-pituitary-adrenal stress-regulating system are found to be especially vulnerable to long-term alteration in children born preterm [65]. We therefore speculate that an altered stress-response might contribute

to more mental health problems among the VLBW young adults.

Clinical implications

This study adds to the knowledge of mental health and HRQoL in VLBW young adults. In HRQoL studies, a difference or change of 0.5SD is suggested to reflect a clinical important difference [66], and the finding of more mental health problems and lower HRQoL is therefore likely to impact the daily life of these young adults. The reduction of mental health and HRQoL in the transition to adulthood emphasizes the importance of long-term follow-up and performing longitudinal analyses. Awareness of the association of mental health and HRQoL with motor skills may be important as motor problems are easily identified in early childhood. This makes selection for early intervention possible. There is reason to be observant of and encourage research on problems that might become more visible as the VLBW young adults enter independent living and encounter the demands of adulthood.

Conclusions

In conclusion, VLBW young adults reported poorer and declining mental health and HRQoL in the transitional phase into adulthood compared with matched term-born controls. They seemed to have a cautious lifestyle with more internalizing problems and less alcohol use. Poorer motor skills were associated with more mental health problems and especially lower physical HRQoL, the cause of which is likely to be of shared aetiology.

Additional files

Additional file 1: Share of young people living with their parents in Europe. (XLS 30 kb)

Additional file 2: Proportion (%) of young people living with their parents in New Zealand, 1981 2006. (DOCX 14 kb)

Abbreviations

ASR: Adult Self-Report; BDI: Beck Depression Inventory; CI: confidence interval; CP: cerebral palsy; GMFCS: Gross Motor Function Classification System; GP: Grooved Pegboard Test; HiMAT: High-Level Mobility Assessment Tool; HRQoL: health-related quality of life; IQ_{est}: estimated intelligence quotient; Movement ABC-2: Movement Assessment Battery for Children-2; NICU: neonatal intensive care unit; SD: standard deviation; SES: socioeconomic status; SF-36: Short Form 36 Health Survey; VLBW: very low birth weight.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IMH prepared data for analyses, performed the statistical analyses and drafted the manuscript; KMTS prepared data for analyses and helped drafting the manuscript; AO participated in the design and coordination of the study and helped drafting the manuscript; SL supervised the statistical analyses; MSI helped interpreting results and drafting the manuscript; JS helped interpreting results and drafting the manuscript; AMB conceived of the study and participated in the design of the study; KAIE participated in the design and coordination of the study and helped performing the statistical analyses and drafting the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all the young adults for their participation and interest in this study. We are grateful to Inger Helene Hamborg, Sigrun Fl kken, Alexandra Maria Costache and Gunnar Gotaas for their contribution in data collection and assistance in pre-processing self-report data.

Author details

[1]Department of Laboratory Medicine, Children s and Women s Health, Norwegian University of Science and Technology, Trondheim, Norway. [2]Stamina Helse, Lillestr m, Norway. [3]Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway. [4]Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [5]MI Lab and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway. [6]Regional Centre for Child and Youth Mental Health and Child Welfare, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway. [7]Department of Child and Adolescent Psychiatry, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [8]Department of Pediatrics, S rlandet Hospital, Arendal, Norway. [9]Department of Public Health and General Practice, Norwegian University of Science and Technology, Trondheim, Norway. [10]Department of Physiotherapy, Trondheim Municipality, Trondheim, Norway.

Received: 13 October 2015 Accepted: 29 March 2016
Published online: 07 April 2016

References

1. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110 24. doi:10.1016/s1474-4422(08)70294-1.
2. Aarnoudse-Moens CSH, 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(2):717 28. doi:10.1542/peds.2008-2816.
3. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor Development in Very Preterm and Very Low-Birth-Weight Children From Birth to Adolescence A Meta-analysis. Jama-J Am Med Assoc. 2009;302(20):2235 42.
4. Johnson S, Marlow N. Preterm Birth and Childhood Psychiatric Disorders. Pediatr Res. 2011;69(5 Part 2):11R-8R.
5. Jekielek S, Brown B. The Transition to Adulthood: Characteristics of Young Adults Ages 18 to 24 in America. The Annie E. Casey Foundation, Population Reference Bureau, and Child Trends; 2005.
6. Moster D, Lie RT, Markestad T. Long-Term Medical and Social Consequences of Preterm Birth. N Engl J Med. 2008;359(3):262 73. doi:10.1056/NEJMoa0706475.
7. Lund LK, Vik T, Skranes J, Lydersen S, Brubakk AM, Indredavik MS. Low birth weight and psychiatric morbidity; stability and change between adolescence and young adulthood. Early Hum Dev. 2012;88(8):623 9. doi:10.1016/j.earlhumdev.2012.01.006.
8. B tsvik B, Vederhus BJ, Halvorsen T, Wentzel-Larsen T, Graue M, Markestad T. Health-related quality of life may deteriorate from adolescence to young adulthood after extremely preterm birth. Acta Paediatr. 2015. doi:10.1111/apa.13069.
9. Allen MC, Cristofalo E, Kim C. Preterm birth: Transition to adulthood. Developmental Disabilities Res Rev. 2010;16(4):323 35. doi:10.1002/ddrr.128.
10. Bowling A. The concept of quality of life in relation to health. Med Secoli. 1995;7(3):633 45.
11. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. Pediatrics. 2008;121(2):e366 76. doi:10.1542/peds.2007-0169.
12. Dinesen SJ, Greisen G. Quality of life in young adults with very low birth weight. Arch Dis Child Fetal Neonatal Ed. 2001;85(3):F165 9. doi:10.1136/fn.85.3.F165.
13. Lund LK, Vik T, Lydersen S, L haugen GC, Skranes J, Brubakk AM, et al. Mental health, quality of life and social relations in young adults born with low birth weight. Health Qual Life Outcomes. 2012;10:146. doi:10.1186/1477-7525-10-146.
14. Baumgardt M, Bucher HU, Arlettaz Mieth R, Fauch re J-C. Health-related quality of life of former very preterm infants in adulthood. Acta Paediatr. 2012;101(2):e59 63. doi:10.1111/j.1651-2227.2011.02422.x.

15. Cooke RW. Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child. 2004;89(3):201 6.
16. Darlow BA, Horwood LJ, Pere-Bracken HM, Woodward LJ. Psychosocial Outcomes of Young Adults Born Very Low Birth Weight. Pediatrics. 2013;132(6):e1521 8. doi:10.1542/peds.2013-2024.
17. G ddlin PO, Finnstr m O, Sydsj G, Leijon I. Most very low birth weight subjects do well as adults. Acta Paediatr. 2009;98(9):1513 20. doi:10.1111/j.1651-2227.2009.01368.x.
18. Hack M, Cartar L, Schluchter M, Klein N, Forrest CB. Self-perceived health, functioning and well-being of very low birth weight infants at age 20 years. J Pediatr. 2007;151(6):635 41. doi:10.1016/j.jpeds.2007.04.063. 41 e1-2.
19. Saigal S. Quality of life of former premature infants during adolescence and beyond. Early Hum Dev. 2013;89(4):209 13. doi:10.1016/j.earlhumdev.2013.01.012.
20. Husby IM, Skranes J, Olsen A, Brubakk A-M, Evensen KAI. Motor skills at 23years of age in young adults born preterm with very low birth weight. Early Hum Dev. 2013;89(9):747 54.
21. Poole KL, Schmidt LA, Missiuna C, Saigal S, Boyle MH, Van Lieshout RJ. Motor coordination and mental health in extremely low birth weight survivors during the first four decades of life. Res Dev Disabil. 2015;43 44: 87 96. doi:10.1016/j.ridd.2015.06.004.
22. Tal-Saban M, Ornoy A, Parush S. Young adults with developmental coordination disorder: a longitudinal study. Am J Occup Ther. 2014;68(3): 307 16. doi:10.5014/ajot.2014.009563.
23. Evensen KA, Skranes J, Brubakk AM, Vik T. Predictive value of early motor evaluation in preterm very low birth weight and term small for gestational age children. Early Hum Dev. 2009;85(8):511 8. doi:10.1016/j.earlhumdev.2009.04.007.
24. Bakketeig LS, Jacobsen G, Hoffman HJ, Lindmark G, Bergsj 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.
25. 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. doi:10.1136/adc.2003.038943.
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214 23.
27. Wechsler D. Wechsler Intelligence Scale for Children Third Edition, Manual. Stockholm: Psykologif rlaget AB; 1999.
28. Hollingshead AS. Two factor index of social status. New Haven: Yale University; 1958.
29. Achenbach T, Rescorla L. Manual for the ASEBA Adult Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003.
30. Beck AT, Steer RA. Manual of the Beck Depression Inventory. San Antonio: TX: The Psychological Corporation; 1987.
31. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology. 1998;31(3):160 8.
32. Ware Jr JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51(11):903 12. doi:10.1016/S0895-4356(98)00081-X.
33. Loge JH, Kaasa S, Hjermstad MJ, Kvien TK. Translation and performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability, and construct validity. J Clin Epidemiol. 1998;51(11):1069 76.
34. Ware Jr JE, Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, et al. The Factor Structure of the SF-36 Health Survey in 10 Countries: Results from the IQOLA Project. J Clin Epidemiol. 1998;51(11):1159 65. doi:10.1016/S0895-4356(98)00107-3.
35. Hann M, Reeves D. The SF-36 scales are not accurately summarised by independent physical and mental component scores. Qual Life Res. 2008; 17(3):413 23. doi:10.1007/s11136-008-9310-0.
36. SF-36 . PCS, MCS and NBS Calculator. 2015. http://www.sf-36.org/nbscalc/index.shtml. Accessed 01 Feb 2015.
37. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med. 1998;26(4):250 8.
38. Lafayette I. Lafayette Instrument Grooved Pegboard Test. User's manual. Lafayette Instrument Company, Inc; 2002.
39. Delis D, Kaplan E, Kramer J. D-KEFS Executive Function System. Norwegian Manual Supplement. Stockholm: Pearson Assessment; 2005.
40. Henderson S, Sugden D, Barnett A. Movement Assessment Battery for Children-2. Examiner s manual. 2nd ed. London: Pearson Assessment; 2007.
41. Williams GP, Morris M, Greenwood K, Goldie P, Robertson V. High-Level Mobility Assessment Tool for Traumatic Brain Injury: User Manual Melbourne: La Trobe University. 2004.
42. B e T, verland S, Lundervold A, Hysing M. Socioeconomic status and children s mental health: results from the Bergen Child Study. Soc Psychiatry Psychiatr Epidemiol. 2012;47(10):1557 66. doi:10.1007/s00127-011-0462-9.
43. Lund LK, Vik T, Skranes J, Brubakk AM, Indredavik MS. Psychiatric morbidity in two low birth weight groups assessed by diagnostic interview in young adulthood. Acta Paediatr. 2011;100(4):598 604. doi:10.1111/j.1651-2227.2010.02111.x.
44. S lsnes AE, Skranes J, Brubakk AM, L haugen GC. Executive functions in very-low-birth-weight young adults: a comparison between self-report and neuropsychological test results. J Int Neuropsychol Soc. 2014;20(5):506 15. doi:10.1017/S1355617714000332.
45. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor HG, Flannery D, et al. Behavioral outcomes and evidence of psychopathology among very low birth weight infants at age 20 years. Pediatrics. 2004;114(4):932 40. doi:10.1542/peds.2003-1017-L.
46. Hille ETM, Dorrepaal C, Perenboom R, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Social Lifestyle, Risk-taking Behavior, and Psychopathology in Young Adults Born Very Preterm or with a Very Low Birthweight. J Pediatr. 2008;152(6):793 800.e4. doi:10.1016/j.jpeds.2007.11.041.
47. Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr. 2009;30(5):460 70.
48. R ikk nen K, Pesonen AK, Heinonen K, Kajantie E, Hovi P, J rvenp AL, et al. Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. Arch Gen Psychiatry. 2008;65(3):290 6. doi:10.1001/archgenpsychiatry.2007.40.
49. Westrupp EM, Northam E, Doyle LW, Callanan C, Anderson PJ. Adult psychiatric outcomes of very low birth weight survivors. Aust N Z J Psychiatry. 2011;45(12):1069 77. doi:10.3109/00048674.2011.620561.
50. 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(3):149 57. doi:10.1056/NEJMoa010856.
51. Strang-Karlsson S, R ikk nen K, Pesonen AK, Kajantie E, Paavonen EJ, Lahti J, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. AJ Psychiatry. 2008;165(10):1345 53. doi:10.1176/appi.ajp.2008.08010085.
52. Pesonen AK, R ikk nen K, Heinonen K, Andersson S, Hovi P, J rvenp AL, et al. Personality of young adults born prematurely: the Helsinki study of very low birth weight adults. J Child Psychol Psychiatry. 2008;49(6):609 17. doi:10.1111/j.1469-7610.2007.01874.x.
53. Allin M, Rooney M, Cuddy M, Wyatt J, Walshe M, Rifkin L, et al. Personality in young adults who are born preterm. Pediatrics. 2006;117(2):309 16. doi:10.1542/peds.2005-0539.
54. Harrison H. Outcomes in Young Adulthood for Very-Low-Birth-Weight Infants (letter to the editor). N Engl J Med. 2002;347(2):141 3. doi:10.1056/NEJM200207113470214.
55. Bjerager M, Steensberg J, Greisen G. Quality of life among young adults born with very low birthweights. Acta Paediatr. 1995;84(12):1339 43.
56. Rajmil L, Palacio-Vieira J, Herdman M, L pez-Aguil S, Villalonga-Olives E, Valderas J, et al. Effect on Health-related Quality of Life of changes in mental health in children and adolescents. Health Qual Life Outcomes. 2009;7(1):103.
57. Verrips G, Brouwer L, Vogels T, Taal E, Drossaert C, Feeny D, et al. Long term follow-up of health-related quality of life in young adults born very preterm or with a very low birth weight. Health Qual Life Outcomes. 2012;10:49. doi:10.1186/1477-7525-10-49.
58. van Lunenburg A, van der Pal SM, van Dommelen P, van der Pal-de Bruin KM, Bennebroek Gravenhorst J, Verrips GH. Changes in quality of life into adulthood after very preterm birth and/or very low birth weight in the Netherlands. Health Qual Life Outcomes. 2013;11:51. doi:10.1186/1477-7525-11-51.
59. Bailis DS, Segall A, Chipperfield JG. Two views of self-rated general health status. Soc Sci Med. 2003;56(2):203 17. doi:10.1016/S0277-9536(02)00020-5.
60. Hill EL, Brown D. Mood impairments in adults previously diagnosed with developmental coordination disorder. J Ment Health. 2013;22(4):334 40. doi:10.3109/09638237.2012.745187.
61. Allin M, Henderson M, Suckling J, Nosarti C, Rushe T, Fearon P, et al. Effects of very low birthweight on brain structure in adulthood. Dev Med Child Neurol. 2004;46(1):46 53.

62. Eikenes L, L haugen GC, Brubakk AM, Skranes J, H berg AK. Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. NeuroImage. 2011;54(3):1774 85. doi:10.1016/j.neuroimage.2010.10.037.
63. 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(3):654 66. doi:10.1093/brain/awm001.
64. Schlotz W, Phillips DI. Fetal origins of mental health: evidence and mechanisms. Brain Behav Immun. 2009;23(7):905 16. doi:10.1016/j.bbi.2009.02.001.
65. Buske-Kirschbaum A, Krieger S, Wilkes C, Rauh W, Weiss S, Hellhammer DH. Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. J Clin Endocrinol Metab. 2007;92(9): 3429 35. doi:10.1210/jc.2006-2223.
66. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582 92. doi:10.1097/01.mlr.0000062554.74615.4c.

Additional file 1: Share of young people living with their parents in Europe

Last update	09.04.15
Extracted on	20.09.15
Source of data	Eurostat
HHSTATUS	Person living with parents
UNIT	Percentage of total population
SEX	Total
AGE	From 20 to 24 years

GEO/TIME	2013
European Union (28 countries)	73,4
Norway	28,7
Switzerland	82,6
Belgium	78,9
Bulgaria	81,7
Czech Republic	85,2
Denmark	16,2
Germany (until 1990 former territory	78,4
Estonia	64,5
Ireland	74,7
Greece	75,7
Spain	87,9
France	58,2
Croatia	88,9
Italy	91,2
Cyprus	87,4
Latvia	78,5
Lithuania	78,2
Luxembourg	85,3
Hungary	82,6
Malta	92,5
Netherlands	60,6
Austria	70,5
Poland	87
Portugal	83,6
Romania	84,8
Slovenia	89,2
Slovakia	93,9
Finland	28,5
Sweden	38,1
United Kingdom	56,5
Iceland	55,2
Former Yugoslav Republic of Maced	:
Serbia	85,9
Turkey	:

Special value:

:	not available

Additional file 2: Proportion (%) of young people living with their parents in New Zealand, 1981–2006

Census year	15–19 years	20–24 years	15–24 years
1981	71	28	51
1986	77	31	54
1991	77	36	57
1996	76	35	55
2001	76	32	55
2006	79	**32**	56

Source: 1981, 1991: Statistics New Zealand (1994) p 59-60;

1986, 1996, 2001, 2006: Statistics New Zealand, unpublished census data

Paper III

White matter alterations and their associations with motor function in young adults born preterm with very low birth weight

Ingrid Marie Husby Hollund[a]*, Alexander Olsen[b,c], Jon Skranes[a,d], Ann-Mari Brubakk[a], Asta K. Håberg[e,f], Live Eikenes[g,1] and Kari Anne I. Evensen[a,h,i,1]

[a] Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

[b] Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway

[c] Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[d] Department of Pediatrics, Sørlandet Hospital, Arendal, Norway

[e] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

[f] Department of Radiology and Nuclear Medicine, MR-center, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

[g] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

[h] Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

[i] Department of Physiotherapy, Trondheim Municipality, Norway

*Corresponding author at: Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, 7491 Trondheim, Norway.
E-mail address: ingridmhusby@gmail.com (I.M.H. Hollund)

[1] Shared last authorship

Abbreviations: AD, axial diffusivity; CC, corpus callosum; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; HiMAT, high-level mobility assessment tool; MABC-2, movement assessment battery for children-2; MD, mean diffusivity; MNI, Montreal neurological institute; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; RD, radial diffusivity; ROI, region-of-interest; TBSS, tract-based spatial statistics; SES, socioeconomic status; TMT-5, trail making test-5; VLBW, very low birth weight

ABSTRACT

Very low birth weight (VLBW: ≤1500g) individuals have an increased risk of white matter alterations and neurodevelopmental problems, including fine and gross motor problems. In this hospital-based follow-up study, the main aim was to examine white matter microstructure and its relationship to fine and gross motor function in 31 VLBW young adults without cerebral palsy compared with 31 term-born controls, at mean age 22.6±0.7 years. The participants were examined with tests of fine and gross motor function (Grooved Pegboard, Trail Making Test-5: TMT-5, Triangle from Movement Assessment Battery for Children-2: MABC-2 and High-Level Mobility Assessment Tool: HiMAT) and diffusion tensor imaging (DTI). Probabilistic tractography of motor pathways of the corticospinal tract (CST) and corpus callosum (CC) was performed, and fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD, RD) and volume were calculated as mean values across the entire tracts, and tested for group differences. Associations between motor test scores and FA in CST and CC were investigated with linear regression. Tract-based spatial statistics (TBSS) was used to examine differences in DTI metrics in all major white matter tracts and changes in the extent of group differences in FA and MD from 20 to 23 years of age. The VLBW group had lower scores on all motor tests compared with controls, however, only statistical significant for TMT-5. Based on tractography, MD, AD and RD were higher and CC volume reduced in the VLBW group compared with the control group, but FA did not differ significantly. Within the VLBW group, poorer performance on TMT-5 and MABC-2 Triangle was significantly associated with higher FA in CST and CC ($p<0.005$). Poorer performance on Grooved Pegboard was associated with higher FA in CST ($p<0.02$), and poorer performance on HiMAT was associated with higher FA in CC ($p<0.03$). There were no associations between motor function and FA within the control group. In the TBSS analysis, the VLBW group had lower FA and higher MD compared with controls in all major white matter tracts, and these group differences were more widespread at 23 years than at 20 years of age. Our findings indicate that individual variability in motor function has structural correlates among VLBW young adults and that white matter abnormalities in the VLBW group increase with age.

Keywords

Preterm, Brain, Diffusion tensor imaging, Tractography, Motor function, Young adulthood

1.1 INTRODUCTION

Being born preterm with very low birth weight (VLBW: ≤1500g) is associated with increased risk of disturbances in perinatal brain development (Volpe, 2009) and later neurodevelopmental problems (Aarnoudse-Moens et al., 2009; de Kieviet et al., 2009). Fine and gross motor problems are common and have been found to persist into young adulthood, also when excluding participants with cerebral palsy (Husby et al., 2013).

The preterm brain is particularly susceptible to diffuse white matter injury, related to a disrupted maturation of pre-oligodendrocytes into oligodendrocytes, important for axonal myelination (Volpe, 2009). Myelination deficits may affect structural and functional connectivity, leading to slower signalling in the brain. In normal brain development, diffusion tensor imaging (DTI) (Basser & Pierpaoli, 1996) shows that fractional anisotropy (FA) increases and mean diffusivity (MD) decreases as white matter pathways mature and myelinate, starting during gestation and continuing into adulthood (Cascio et al., 2007; Lebel et al., 2008). Preterm birth disrupts the normal maturation of white matter, and the preterm brain typically exhibits lower FA and higher MD compared with term-born controls at birth. These DTI changes persist into adolescence and young adulthood (Li et al., 2014; Pandit et al., 2013). Several white matter tracts are affected, including motor pathways, like the corticospinal tract (CST) and the corpus callosum (CC) (Eikenes et al., 2011; Groeschel et al., 2014).

To find a structural explanation for the commonly seen fine and gross motor problems in VLBW individuals, some studies have searched for microstructural correlates to motor problems in the whole brain and in specific motor tracts. Better fine motor performance at two years have been found to correlate with higher FA in the major white matter tracts by TBSS in very preterm infants at term equivalent age (van Kooij et al., 2012). Another study did not find any correlation between motor function and FA at two years of age in very preterm children without major motor problems and focal lesions (Counsell et al., 2008). In older VLBW children and adolescents, reduced FA in several white matter tracts has been shown to be associated with motor problems (de Kieviet et al., 2014; Li et al., 2014; Skranes et al., 2007). However, FA in the CST of VLBW adults was not associated with motor problems at eight years (Jurcoane et al., 2016). Hence, the few existing studies investigating structural white matter correlates to motor problems yield mixed findings, possibly due to variation in

DTI analysis and motor assessments. Furthermore, there are no studies examining associations between fine and gross motor function and DTI metrics in specific motor tracts in young adulthood.

In the current study, we aimed specifically to investigate associations between fine and gross motor function and FA in CST and CC by probabilistic tractography in VLBW young adults without cerebral palsy compared with a term-born control group. Moreover, we wanted to examine group differences in DTI metrics of the CST and CC by tractography and in the whole brain by tract-based spatial statistics (TBSS). Thirdly, we wanted to investigate whether the extent of FA reductions and MD increases seen by TBSS in the VLBW group compared with controls at 20 years in this cohort (Eikenes et al., 2011) were similar at 23 years. We hypothesized that poorer basic fine motor function was associated with lower FA in the CST from the primary motor cortex and that poorer complex fine motor function was associated with lower FA in the CST from the primary and premotor cortices. Furthermore, we hypothesized that poorer bimanual coordination was associated with lower FA in the CC connecting the primary motor and premotor cortices in addition to FA in the CST from the primary and premotor cortices. For gross motor function, we hypothesized that lower scores on automatic tasks were associated with lower FA in the CST from the primary motor cortex, while lower scores on tasks involving planning were associated with lower FA in the CST from the premotor cortex. As for group differences in DTI metrics, we hypothesized that VLBW young adults had lower FA and higher MD in CST and CC by tractography and in all major white matter tracts by TBSS compared with controls.

2. MATERIALS AND METHODS

2.1. Study design

The present study is part of a prospective hospital-based study of a preterm born VLBW group (birth weight ≤ 1500g) and a term-born control group (gestational age ≥ 37 weeks). Clinical tests and cerebral magnetic resonance imaging (MRI) have been carried out at 1, 5, 14 and 20 years of age (Eikenes et al., 2011; Skranes et al., 2007; Skranes et al., 1997; Skranes et al., 1993). The VLBW children were born in 1986-1988 and admitted to the Neonatal Intensive Care Unit (NICU) at St. Olavs Hospital, Trondheim University Hospital, Norway. The control children were included at birth in the same period. They were born to a 10% random sample of women living in the Trondheim region, originally selected for follow-up during pregnancy in a multicentre study (Bakketeig et al., 1993). At 23 years, we aimed to include the VLBW and control participants from the 14-year follow-up in order to compare motor function longitudinally (Husby et al., 2013).

2.2. Participants

2.2.1 VLBW group

At age 23, we contacted 54 VLBW young adults, whereof 18 (33%) did not consent, leaving 36 (67%) VLBW young adults for motor and MRI examinations. Four (11%) of these had cerebral palsy and were therefore excluded from the study. Additionally, one VLBW participant was excluded due to image artefacts, leaving data from 31 VLBW participants suitable for analyses.

2.2.2 Control group

At age 23, we contacted 48 controls matched to the VLBW participants by age and sex. Two of the contacted controls were not testable due to pregnancy, five had moved too far away and four did not consent. Thus, 37 (77%) controls underwent motor and MRI examinations, whereof six were excluded due to image artefacts, leaving data from 31 control participants suitable for analyses.

2.2.3. Non-participants

There were no significant differences between those who participated and those who did not consent to or were not contacted for participation at age 23 in either group with regard to

perinatal data, parental socioeconomic status (SES) or motor skills at 14 years (data not shown).

2.3. Clinical characteristics

Perinatal data included birth weight, gestational age, birth head circumference, Apgar scores, days in NICU, days on mechanical ventilator, proportion of infants with intraventricular haemorrhage and maternal age. At 14 years, parental SES was calculated according to Hollingshead's Two factor index of social position (Hollingshead, 1958), rated from 1 (lowest) to 5 (highest) based on a combination of parents' education and occupation.

2.4. Motor assessments

The motor assessments were carried out by experienced examiners, blinded to neonatal history, clinical characteristics and results from previous follow-up. The dominant hand was defined as the writing hand and the dominant foot was self-reported or defined as the preferred foot for one leg stand.

2.4.1. Trail Making Test-5 (TMT-5)

TMT-5 is part of the standardized Delis-Kaplan Executive Function System and measures motor speed (Delis et al., 2001). The task is to draw a line as fast as possible (time in seconds) between 32 circles in the order directed by a dotted line. The test is performed with the dominant hand only and we considered it as a test of basic fine motor function.

2.4.2. Grooved Pegboard

Grooved Pegboard requires complex visual-motor coordination and measures how quickly (time in seconds) the participants can insert pegs into 25 keyhole-shaped holes with various orientations in a 5 x 5 matrix with each hand separately (Lafayette, 2002). We considered this test as a test of complex fine motor function.

2.4.3. Triangle from Movement Assessment Battery for Children-2 (MABC-2)

MABC-2 is a comprehensive motor test battery that identifies and evaluates children’s motor development (Henderson et al., 2007). We used the item Triangle as a test for bimanual

coordination. The task is to form a triangle out of three strips, nuts and bolts with both hands as fast as possible. Raw scores (time in seconds) were used in this study.

2.4.4. High-Level Mobility Assessment Tool (HiMAT)

HiMAT examines gross motor function (G. Williams et al., 2005; G. P. Williams et al., 2005) and raw scores of the seven timed items (in seconds) were used in this study (Walk, Walk backwards, Walk on toes, Walk over obstacle, Run, Skip and Hop forward). We grouped these items in two categories based on the involvement of automatic or planned movements; HiMAT automatic (Walk, Walk on toes, Run) and HiMAT planned (Walk backwards, Walk over obstacle, Skip, Hop forward).

2.5. Image acquisition

At 23 years, DTI and T1 weighted MRI were acquired on a 3T Siemens Trio with Quantum gradients (30 mT/m) and a 12-channel head matrix coil (Siemens AG, Erlangen, Germany) at St. Olavs Hospital, Trondheim University Hospital, Norway. To reduce movement, foam pads were placed around the participants' heads. DTI was acquired with a single-shot balanced-echo EPI sequence with b = 1000 s/mm^2 in 30 non-collinear directions using the following parameters: TR = 6800 ms, TE = 84 ms, FOV = 240 × 240 mm, slice thickness 2.5 mm, acquisition matrix 96 × 96, giving isotropic voxels of 2.5 mm. Full brain coverage was obtained with 55 transversal slices with no gap. For each slice, six images without diffusion weighting (b = 0) were acquired. The DTI sequence was repeated two times for increased signal-to-noise ratio. To correct for image distortion caused by magnetic susceptibility artefacts (Holland et al., 2010), two additional b0 images were acquired with opposite phase-encode polarity. A 3D T1 weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) volume was acquired using the following parameters: TR = 2300 ms, TE = 30 ms, FOV = 256, slice thickness = 1.2 mm, matrix = 256 x 256, giving an in-plane resolution of 1 x 1 mm.

At 20 years, DTI was acquired on a 1.5 T Siemens Magnetom Symphony with Quantum gradients (30 mT/m) and a quadrature head coil. Details regarding the DTI acquisition at 20 years are given elsewhere (Eikenes et al., 2011).

2.6. Image analyses

The DTI analyses were performed with the tools of the FMRIB Software Library (FSL; Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl). Image artefacts due to motion and eddy current distortions were minimized by registration of all DTI acquisitions to the mean b = 0 image using affine registration. Image distortion caused by magnetic susceptibility artefacts was minimized with a nonlinear B0-unwarping method using paired images with opposite phase-encode polarities (Holland et al., 2010). The brain was extracted using Brain Extraction Tool (BET, part of FSL). FMRIB's Diffusion Toolbox (FDT) was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxel-wise maps of FA, MD, axial (AD; λ_1) and radial diffusivity (RD; $(\lambda_2+\lambda_3)/2$), were calculated for the VLBW and control group. Freesurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu) was used to calculate intracranial volume based on subcortical volumetric analysis of the T1 MPRAGE volume.

2.6.1. Probabilistic tractography

Fibre tractography of the CST and CC was performed using BedpostX, a probabilistic tractography routine implemented in FSL based on a multifibre model (Behrens et al., 2007). The following parameters were used: 5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2.

2.6.1.1. Corticospinal tract (CST)

A region-of-interest (ROI) approach was used to track the CST fibres connecting from a seed ROI in the cerebral peduncles to three different target ROIs in the primary motor and premotor cortices. The seed ROI was placed manually in three contiguous slices in the cerebral peduncle on each individual's colour-coded FA map based on anatomical landmarks in the FA map (Figure 1).

For the primary motor cortex, we wanted to select the hand and foot areas specifically as target ROIs for tracking of CST_{hand} and CST_{foot}. Due to the difficulty of depicting the foot area of the primary motor cortex based on anatomy or template based atlases, both foot and hand ROIs were based on functional ROIs obtained in a group of young healthy adults (Berntsen et al., 2008).

For the $CST_{premotor}$ tracking, the target ROI was placed in the premotor cortex as defined by the Juelich Histological atlas in FSL (Eickhoff et al., 2005). The target ROIs in the primary motor and premotor cortices were transformed from the Montreal Neurological Institute (MNI) space to each individual's FA space using linear registration (FLIRT, FMRIB's Linear Image Registration Tool) between each individual's FA map and the MNI FA-template (FMRIB58_FA_1mm).

Only streamlines passing through the seed ROI and the target ROI were included in the analyses. The CST tracking was performed separately for the left and right hemispheres. An exclusion mask (not shown) was included in the midline of the brain dividing the two hemispheres, and streamlines were discarded if they entered the exclusion mask.

2.6.1.2. Corpus callosum (CC)

For tracking of the CC, a three ROI approach was used to select the CC fibres connecting the primary motor (CC_{motor}) and the premotor ($CC_{premotor}$) cortices (Figure 2). The seed ROIs were placed manually in three contiguous sagittal slices on the colour-coded FA map of CC region number II and III according to Hofer and Frahm (2006), comprising premotor and motor fibres, respectively (Hofer & Frahm, 2006). The target ROIs were placed in the primary motor and the premotor cortices in the left and right cerebral hemispheres, as defined by the Juelich Histological atlas in FSL (Eickhoff et al., 2005). The target ROIs were given in MNI space, and were linearly transformed from MNI to each individual's FA space using FLIRT. Only streamlines passing through the seed ROI and the target ROIs were included in the analyses. An exclusion mask (not shown) was included in the axial slice inferior to the sagittal seed ROIs, and streamlines were discarded if entering the exclusion mask. We chose to use the whole primary motor cortex instead of the hand and foot areas in the CC tracking, because pilot testing showed that few streamlines passed through the CC to the hand area lateral in the primary motor cortices. The difficulty of resolving lateral projections of the CC has been described earlier (Hofer & Frahm, 2006).

2.6.1.3. Quality control and summary DTI measures

The resulting fibre tracts were visually inspected for each individual, and the tractography results were thresholded (50 for the CST and 300 for the CC) in order to include only anatomical plausible pathways. The thresholded fibre pathways were used to calculate mean FA, MD, AD, RD and volume for the left and right CST_{hand}, CST_{foot} and $CST_{premotor}$ and for

the CC_{motor} and $CC_{premotor}$ tractography results in all VLBW and control individuals. Relative volume was calculated as mean volume of the tract divided by intracranial volume for each individual. All manually placed ROIs were drawn by the same researcher, blinded to neonatal history, clinical characteristics and results from previous follow-up.

2.6.2. Tract-based spatial statistics (TBSS)

Voxel-wise statistical analysis was performed using TBSS (part of FSL) at 20 years in Eikenes et al. (2011) and at 23 years in the current study (Smith et al., 2006). A detailed description is given elsewhere (Eikenes et al., 2011). Voxel-wise statistics of the skeletonized FA, MD, AD and RD were carried out on the white matter skeleton using Randomise (part of FSL) to test for group differences between the VLBW and control group. Randomise performs non-parametric permutation-based testing and inference using Threshold-Free Cluster Enhancement (Nichols & Holmes, 2002) with a correction for multiple comparisons ($p<0.05$, corrected for sex and age at MRI).

2.7. Statistical analyses

Student's t-test was used for approximately normally distributed data; else the Mann–Whitney U test was applied. Normality was assessed by visual inspection of Q-Q plots of the residuals. Linear regression was applied to explore associations between motor test scores and FA in CST and CC, adjusted for sex and age. Motor test scores were entered separately as dependent variables, whereas FA, group, sex, age and the interaction FA x group were entered as independent variables. The interaction term was added to test if the effect of FA were different in VLBW and control participants. For motor tests performed with one hand, we performed the association analyses only with the contralateral CST in the brain to reduce the number of analyses. We therefore re-categorized the left and right CST into contralateral CST to the dominant (CST dominant) and non-dominant (CST non-dominant) hand (Figure 3). Percentage of voxels in the white matter skeleton (from TBSS) with significantly different FA and MD in the VLBW group compared with the control group at 20 at 23 years was calculated and compared to examine whether the extent of FA and MD group differences changed from 20 to 23 years. Two-sided *p*-values <0.05 were considered statistically significant. Given the relatively small sample size, no correction for multiple comparisons was applied for linear regression and analyses of group differences in DTI metrics by tractography. SPSS 22.0 was used for statistical analyses.

2.8. Ethics

The project complies with the principles of the Declaration of Helsinki and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK number 4.2005.2605). Written informed consent was obtained from the participants.

3. RESULTS

3.1. Clinical characteristics

Table 1 shows the clinical characteristics of the VLBW and the control group. Birth weight and gestational age differed by definition between the groups and, as expected, head circumference and Apgar scores at birth were lower in the VLBW group. There were no statistically significant group differences in maternal age, parental SES, age at follow-up or sex distribution.

3.2. Motor function

Table 2 shows fine and gross motor test scores in the VLBW and the control group. The VLBW group used longer time than controls on all fine motor tests, however only significant for TMT-5 (Table 2). On gross motor tests, there were no significant group differences for HiMAT automatic and HiMAT planned. However, VLBW young adults were significantly slower than controls on the items Run and Hop forward (Table 2).

3.3. Probabilistic tractography

Table 3 shows that mean FA of the various tracts did not differ significantly between groups when performing probabilistic tractography. However, mean MD, AD and RD were significantly higher for most tracts in the VLBW group compared with controls. Absolute volumes were significantly smaller for most tracts in the VLBW group, while only the volumes of CC_{motor}, $CC_{premotor}$ and CST_{foot} dominant were significantly smaller when adjusting for total intracranial volume.

3.4. Associations between motor function and fractional anisotropy of CST and CC by probabilistic tractography

There were significant between-group differences for several of the associations between fine motor test scores and FA in CST and CC (Table 4). There were no significant associations within the control group, but there was a positive association between longer time on motor tests (indicating poorer function) and higher FA in CST and CC within the VLBW group. Time to complete TMT-5 was positively associated with FA in the contralateral CST_{hand} and $CST_{premotor}$, and with FA in $CC_{primary}$ and $CC_{premotor}$. Time to complete Grooved Pegboard for each hand was only positively associated with FA in the contralateral CST_{hand} and $CST_{premotor}$.

Time to complete MABC-2 Triangle was positively associated with FA in the contralateral CST_{hand} and $CST_{premotor}$ for both hands and with FA in $CC_{premotor}$.

There were significant between-group differences for the association between HiMAT automatic and FA in $CC_{premotor}$ and between HiMAT planned and FA in CC_{motor} (Table 4). Within the VLBW group, time to complete HiMAT automatic and planned was significantly associated with higher FA in CC_{motor}. Within the control group, there were no significant associations between gross motor test scores and FA in CST or CC.

3.5. Tract-based spatial statistics (TBSS)

TBSS analysis demonstrated lower FA and higher MD in the VLBW group compared with controls in all major white matter tracts (Figure 4). FA was lower in 34% and MD higher in 45% of the total voxels on the white matter skeleton at the group level. Lower FA was mainly caused by higher RD (83% of the voxels with lower FA) (data not shown). No area with higher FA and/or lower MD was found in the VLBW group compared with the control group.

At 20 years, TBSS analysis demonstrated lower FA in 18% and higher MD in 20% of the total voxels on the white matter skeleton in the VLBW group compared with the control group. From 20 to 23 years, the number of voxels with lower FA increased by 59% and the number of voxels with higher MD increased by 92%.

4. DISCUSSION

In this study, poorer fine and gross motor function was associated with higher FA in motor pathways of the CST and CC in VLBW young adults without cerebral palsy. Moreover, probabilistic tractography, yielding mean values across the entire CST and CC, demonstrated higher diffusion (MD, AD, RD) and lower CC volumes in VLBW young adults compared with controls, but no statistically significant group differences in FA. Based on the voxel-wise TBSS analysis, VLBW young adults had lower FA and higher MD in all major white matter tract cores compared with controls. Importantly, these changes were more widespread at 23 years than at 20 years, demonstrating that the white matter alterations persisted and even increased in adulthood.

The VLBW group had poorer motor scores than controls for most tests, but only TMT-5, HiMAT Run and Hop forward reached statistical significance, possibly due to lack of statistical power. Time to complete Grooved Pegboard, MABC-2 Triangle and HiMAT planned in the VLBW group was approximately 0.5 SD above the mean in the control group, corresponding to a medium effect size by Cohen's d (Cohen, 1992). Even though TMT-5 is considered a specific test of motor speed (Delis et al., 2001), it was not only associated with FA in the CST from the primary hand motor cortex as hypothesized, but also with FA in the other tracts examined ($CST_{premotor}$, CC_{motor}, $CC_{premotor}$). The more complex fine motor test, Grooved Pegboard, was as hypothesized only associated with FA in the CST from the primary hand and premotor cortices contralateral to the dominant hand. This may indicate that the association between unilateral motor tests and FA in CC is not clear, and as motor function is complex, it may be difficult to localise specific tests to specific regions in the brain. The test for bimanual coordination, Triangle from MABC-2, was as hypothesized associated with FA in contralateral CST from the primary hand and premotor cortices for both hands and with FA in CC connecting the premotor cortices. The supplementary motor cortex (included in our ROI of premotor cortex) is more involved in bimanual coordination and may explain the lack of association with FA in CC connecting the primary motor cortices (Johansen-Berg et al., 2007). As timed fine motor performance was associated with FA, this may support our former speculations that reduced motor speed is one of the key issues in preterm populations and is related to white matter structure in the preterm brain (Husby et al., 2013).

For gross motor function, there were only associations with FA in the CC connecting the primary motor cortices. Coordination of both sides of the body is needed for gross motor tasks involving the whole body, like items of the HiMAT. Furthermore, as these items involve the whole body and not only the legs, an association with FA in the CST from the primary foot motor cortex might have been masked. There were no associations with FA in CST or CC from the premotor cortices, possibly indicating that the items did not place high demands on planning, and/or that there is no clear association between gross motor function and FA in motor pathways of CST and CC.

The associations we found between motor functions and FA in motor pathways of CST and CC in the VLBW group were in the opposite direction than expected, i.e. increasing FA with poorer motor performance. Other studies have found a positive association between motor function and FA in VLBW populations at different ages (de Kieviet et al., 2014; Skranes et al., 2007; Sripada et al., 2015; van Kooij et al., 2012), while some studies have not found any association between motor function and FA (Counsell et al., 2008; Jurcoane et al., 2016). However, it is difficult to compare the results from the various studies due to large differences in methodologies and age at examination. The relationship between motor function and FA might change during the course of development, and two of the studies did not assess motor function and DTI at the same time (Jurcoane et al., 2016; van Kooij et al., 2012). Furthermore, a big variety of motor assessments were used, possibly affecting the associations with FA. The use of different DTI analysis might also explain some of the discrepancy in findings. The former studies have used different tractography and whole-brain voxel-based methods, thereby incorporating a different selection and extent of the white matter studied. Our study shows that group differences in FA in CST and CC may be affected by the methods used, as we found lower FA in the VLBW group compared with controls by TBSS, but no significant group differences in FA by tractography. A similar discrepancy in group differences of FA in CST by TBSS and tractography was seen in another study of VLBW and very preterm young adults (Jurcoane et al., 2016). This could be caused by the fact that TBSS traces the inner core of the tract, while tractography analyses the whole tract. In general, the inner core of a tract is more coherent and has higher density of axons leading to higher FA, while the periphery of a tract is less coherent and includes more spurious and less dense tracts. This could lead to a lower mean FA when the entire width of the tract is taken into consideration. We speculate that the discrepancy in group differences by TBSS and tractography group differences and the negative associations with motor function in the

VLBW group may have common explanations. The preterm brain does not only show reduced and aberrant myelination, but also axonal abnormality (Volpe, 2009), leading to a loss of axons and fewer crossing fibres. Since crossing fibres in general reduce the apparent AD and thereby reduce the FA value in a voxel, and healthy controls are likely to have more crossing fibres with higher FA than VLBW individuals, voxels in regions of crossing fibres are likely to show lower FA in controls than VLBW individuals. This is shown in studies examining CST tractography results slice-wise, where regions with a high degree of crossing fibres (like the corona radiata and centrum semiovale) have higher FA in the VLBW group compared with controls (Groeschel et al., 2014; Jurcoane et al., 2016). Similar effects may exist for the CC as the lateral parts of the CC close to the centrum semiovale are more likely to contain crossing fibres than the body of the CC (Groeschel et al., 2014). Hence, analyzing a tract's entire width and length may even out the typical finding of reduced FA by TBSS in VLBW populations compared with controls, thereby yielding no group differences in FA for the whole tract. Our finding of increased AD by tractography in the VLBW group compared with controls may also explain the lack of group differences in FA as we found both increased AD and increased RD in the CST and CC. Moreover, increased AD in the VLBW group supports the notion of fewer crossing fibres along the CST and CC in VLBW individuals. Also, absolute volumes of the CST and CC tracts were smaller in the VLBW group compared with controls. When adjusting for intracranial volume, only the CC volumes and CST_{foot} remained significantly smaller in the VLBW group, comparable to other studies (Pandit et al., 2013). This finding further strengthens the possibility that the increased AD is due to a loss of axons. These regional differences in crossing fibres between VLBW individuals and healthy controls might explain the structural-functional association between poorer motor function and higher FA seen in the VLBW group. To be able to study such associations in more detail, DTI sequences more sensitive to crossing fibres may be useful, like high-angular resolution diffusion imaging (Tuch et al., 2002) and constrained spherical deconvolution (Tournier et al., 2007).

The TBSS analysis was used to test for voxel-wise group differences in diffusion measures within the core of the brain's major white matter tracts. The finding of reduced FA and increased MD in all major white matter tracts in VLBW young adults compared with controls is in line with earlier findings in this cohort at age 15 and 20 years (Eikenes et al., 2011; Vangberg et al., 2006), as well as other studies of preterm born individuals at different ages

(Li et al., 2014; Meng et al., 2016). The reduction of FA was related to a significant increase in RD, possibly indicating reduced and aberrant myelination or poor axonal packing (Beaulieu, 2002; Song et al., 2005). Hence, these alterations may be related to the "encephalopathy of prematurity", involving diffuse periventricular leukomalacia with a disturbed maturation of myelin-producing oligodendrocytes and injury of axons and subplate neurons (Volpe, 2009). However, other explanations for reduced anisotropy, like decreased fibre organization and increased membrane permeability, may not be excluded (Beaulieu, 2002).

When comparing the TBSS results at 23 years with those at 20 years of age (Eikenes et al., 2011), the number of voxels with lower FA and higher MD compared with controls increased markedly in the VLBW group, indicating that the white matter changes not only persisted into adulthood, but also increased. It is important to note that the 20-year follow-up was conducted on a 1.5T MRI scanner, while the current study was conducted on a 3T MRI scanner. However, as the differences in FA and MD are relative differences at the two time-points, the change of scanner from 1.5T to 3T should influence both groups equally and probably do not explain the longitudinal change.

Strengths of this study are the long-term follow-up of the two study groups, which were recruited at birth and equivalent in terms of maternal age and parental socioeconomic status. The groups have been followed prospectively with comprehensive multidisciplinary clinical, cognitive and MRI assessments at different ages. At 23 years, motor assessments were performed by experienced examiners and manual ROIs were drawn by the same researcher, all of whom were blinded to neonatal history and clinical outcome, thus reducing the risk of information bias. Only participants from the 14-year follow-up were invited, potentially increasing the risk of selection bias due to loss to follow-up from the original cohort. However, we found no differences in clinical characteristics at birth or motor skills at 14 years between those who participated and those who did not participate or were not invited to follow-up at 23 years in either of the groups. Due to the limited sample size, we chose not to correct for multiple comparisons for the association and tractography analyses to avoid potential type II errors. By using linear regression to examine associations between motor function and FA, both the VLBW and control group are included in the analysis, thereby increasing statistical power. The main findings were consistent, indicating that they were not due to chance.

4.1. Conclusion

Our findings showed that individual variability in motor function has structural correlates in VLBW young adults. Higher FA in the motor pathways of the corticospinal and callosal tracts was associated with poorer performance on fine and gross motor tests in the VLBW group. This tractography finding complements previous voxel-based studies, and may be related to an increased sensitivity to the effects of crossing fibres on FA when performing tractography. Furthermore, TBSS analysis showed that white matter abnormalities in the core of all major white matter tracts in the VLBW group increased from age 20 to 23.

Acknowledgements

We would like to thank all the participants for their engagement in the project. We are grateful to Sigrun Flækken and Inger Helene Hamborg for assistance with motor assessments and Erik Magnus Berntsen for access to the functional ROIs.

Funding

The study was funded by the Research Council of Norway and was independent of commercial interest.

REFERENCES

Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-Analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children. *Pediatrics, 124*(2), 717-728. doi:10.1542/peds.2008-2816

Bakketeig, L. S., Jacobsen, G., Hoffman, H. J., Lindmark, G., Bergsjø, P., Molne, K., & Rødsten, J. (1993). Pre-pregnancy risk factors of small-for-gestational age births among parous women in Scandinavia. *Acta Obstet Gynecol Scand, 72*(4), 273-279. doi:10.3109/00016349309068037

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance. Series B, 111*(3), 209-219.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine, 15*(7-8), 435-455. doi:10.1002/nbm.782

Behrens, T. E., Berg, H. J., Jbabdi, S., Rushworth, M. F., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage, 34*(1), 144-155. doi:10.1016/j.neuroimage.2006.09.018

Berntsen, E. M., Samuelsen, P., Lagopoulos, J., Rasmussen, I. A., Jr., Haberg, A. K., & Haraldseth, O. (2008). Mapping the primary motor cortex in healthy subjects and

patients with peri-rolandic brain lesions before neurosurgery. *Neurological Research, 30*(9), 968-973. doi:10.1179/016164108x323753
Cascio, C. J., Gerig, G., & Piven, J. (2007). Diffusion Tensor Imaging: Application to the Study of the Developing Brain. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(2), 213-223. doi:10.1097/01.chi.0000246064.93200.e8
Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155-159.
Counsell, S. J., Edwards, A. D., Chew, A. T. M., Anjari, M., Dyet, L. E., Srinivasan, L., . . . Cowan, F. M. (2008). Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm. *Brain, 131*(12), 3201-3208. doi:10.1093/brain/awn268
de Kieviet, J. F., Piek, J. P., Aarnoudse-Moens, C. S., & Oosterlaan, J. (2009). Motor Development in Very Preterm and Very Low-Birth-Weight Children From Birth to Adolescence A Meta-analysis. *Jama-Journal of the American Medical Association, 302*(20), 2235-2242. doi:10.1001/jama.2009.1708
de Kieviet, J. F., Pouwels, P. J., Lafeber, H. N., Vermeulen, R. J., van Elburg, R. M., & Oosterlaan, J. (2014). A crucial role of altered fractional anisotropy in motor problems of very preterm children. *Eur J Paediatr Neurol, 18*(2), 126-133. doi:10.1016/j.ejpn.2013.09.004
Delis, D., Kaplan, E., & Kramer, J. (2001). Examiner's Manual.
Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*(4), 1325-1335. doi:10.1016/j.neuroimage.2004.12.034
Eikenes, L., Løhaugen, G. C., Brubakk, A. M., Skranes, J., & Håberg, A. K. (2011). Young adults born preterm with very low birth weight demonstrate widespread white matter alterations on brain DTI. *Neuroimage, 54*(3), 1774-1785. doi:10.1016/j.neuroimage.2010.10.037
Groeschel, S., Tournier, J. D., Northam, G. B., Baldeweg, T., Wyatt, J., Vollmer, B., & Connelly, A. (2014). Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. *Neuroimage, 87*, 209-219. doi:10.1016/j.neuroimage.2013.10.034
Henderson, S., Sugden, D., & Barnett, A. (2007). Movement Assessment Battery for Children-2. Examiner's manual. 2 ed. (2 ed.). London: Pearson Assessment.
Hofer, S., & Frahm, J. (2006). Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage, 32*(3), 989-994. doi:10.1016/j.neuroimage.2006.05.044
Holland, D., Kuperman, J. M., & Dale, A. M. (2010). Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. *Neuroimage, 50*(1), 175-183. doi:10.1016/j.neuroimage.2009.11.044
Hollingshead, A. S. (1958). *Two factor index of social status*. New Haven: Yale University.
Husby, I. M., Skranes, J., Olsen, A., Brubakk, A.-M., & Evensen, K. A. I. (2013). Motor skills at 23years of age in young adults born preterm with very low birth weight. *Early Human Development, 89*(9), 747-754. doi:10.1016/j.earlhumdev.2013.05.009
Johansen-Berg, H., Della-Maggiore, V., Behrens, T. E., Smith, S. M., & Paus, T. (2007). Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage, 36 Suppl 2*, T16-21. doi:10.1016/j.neuroimage.2007.03.041
Jurcoane, A., Daamen, M., Scheef, L., Bauml, J. G., Meng, C., Wohlschlager, A. M., . . . Boecker, H. (2016). White matter alterations of the corticospinal tract in adults born

very preterm and/or with very low birth weight. *Human Brain Mapping, 37*(1), 289-299. doi:10.1002/hbm.23031

Lafayette, I. (2002). *Lafayette Instrument Grooved Pegboard Test. User's manual*: Lafayette Instrument Company, Inc.

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage, 40*(3), 1044-1055. doi:10.1016/j.neuroimage.2007.12.053

Li, K., Sun, Z., Han, Y., Gao, L., Yuan, L., & Zeng, D. (2014). Fractional anisotropy alterations in individuals born preterm: a diffusion tensor imaging meta-analysis. *Developmental Medicine and Child Neurology*. doi:10.1111/dmcn.12618

Meng, C., Bauml, J. G., Daamen, M., Jaekel, J., Neitzel, J., Scheef, L., . . . Sorg, C. (2016). Extensive and interrelated subcortical white and gray matter alterations in preterm-born adults. *Brain Struct Funct, 221*(4), 2109-2121. doi:10.1007/s00429-015-1032-9

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping, 15*(1), 1-25. doi:10.1002/hbm.1058

Pandit, A. S., Ball, G., Edwards, A. D., & Counsell, S. J. (2013). Diffusion magnetic resonance imaging in preterm brain injury. *Neuroradiology, 55 Suppl 2*, 65-95. doi:10.1007/s00234-013-1242-x

Skranes, J. S., Vangberg, T. R., Kulseng, S., Indredavik, M. S., Evensen, K. A. I., Martinussen, M., . . . Brubakk, A.-M. (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain, 130*(3), 654-666. doi:10.1093/brain/awm001

Skranes, J. S., Vik, T., Nilsen, G., Smevik, O., Andersson, H. W., & Brubakk, A. M. (1997). Cerebral magnetic resonance imaging and mental and motor function of very low birth weight children at six years of age. *Neuropediatrics, 28*(3), 149-154. doi:10.1055/s-2007-973692

Skranes, J. S., Vik, T., Nilsen, G., Smevik, O., Andersson, H. W., Rinck, P., & Brubakk, A. M. (1993). Cerebral Magnetic Resonance Imaging (MRI) and Mental and Motor Function of Very Low Birth Weight Infants at One Year of Corrected Age. *Neuropediatrics, 24*(05), 256-262. doi:10.1055/s-2008-1071553

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505. doi:10.1016/j.neuroimage.2006.02.024

Song, S. K., Yoshino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage, 26*(1), 132-140. doi:10.1016/j.neuroimage.2005.01.028

Sripada, K., Løhaugen, G. C., Eikenes, L., Bjørlykke, K. M., Håberg, A. K., Skranes, J., & Rimol, L. M. (2015). Visual-motor deficits relate to altered gray and white matter in young adults born preterm with very low birth weight. *Neuroimage, 109*, 493-504. doi:10.1016/j.neuroimage.2015.01.019

Tournier, J. D., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage, 35*(4), 1459-1472. doi:10.1016/j.neuroimage.2007.02.016

Tuch, D. S., Reese, T. G., Wiegell, M. R., Makris, N., Belliveau, J. W., & Wedeen, V. J. (2002). High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magnetic Resonance in Medicine, 48*(4), 577-582. doi:10.1002/mrm.10268

van Kooij, B. J., de Vries, L. S., Ball, G., van Haastert, I. C., Benders, M. J., Groenendaal, F., & Counsell, S. J. (2012). Neonatal tract-based spatial statistics findings and outcome in preterm infants. *AJNR. American Journal of Neuroradiology, 33*(1), 188-194. doi:10.3174/ajnr.A2723

Vangberg, T. R., Skranes, J., Dale, A. M., Martinussen, M., Brubakk, A. M., & Haraldseth, O. (2006). Changes in white matter diffusion anisotropy in adolescents born prematurely. *Neuroimage, 32*(4), 1538-1548. doi:10.1016/j.neuroimage.2006.04.230

Volpe, J. J. (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *The Lancet Neurology, 8*(1), 110-124. doi:10.1016/s1474-4422(08)70294-1

Williams, G., Robertson, V., Greenwood, K., Goldie, P., & Morris, M. E. (2005). The high-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 1: Item generation. *Brain Inj, 19*(11), 925-932. doi:10.1080/02699050500058687

Williams, G. P., Robertson, V., Greenwood, K. M., Goldie, P. A., & Morris, M. E. (2005). The high-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 2: content validity and discriminability. *Brain Inj, 19*(10), 833-843. doi:10.1080/02699050500058711

Table 1. Clinical characteristics of the VLBW group compared with the control group at 23 years of age.

	VLBW (n=31)		Control (n=31)		
	Mean	(SD)	Mean	(SD)	p-value
Birth weight (g)	1238	(219)	3603	(364)	<0.001
Gestational age (weeks)	29.4	(2.7)	39.5	(1.1)	<0.001
Birth head circumference (cm)[a]	27.4	(2.3)	35.3	(1.2)	<0.001
Apgar score after 1 min[b]	6.7	(1.9)	8.9	(0.4)	<0.001
Apgar score after 5 min[c]	8.4	(1.7)	9.7	(1.7)	0.005
Maternal age	28.8	(5.2)	30.2	(4.2)	0.262
Parental SES at 14 years[c]	3.4	(1.2)	3.7	(1.0)	0.462
Age at follow-up	22.5	(0.7)	22.7	(0.7)	0.253
	n	(%)	n	(%)	
Boys	11	(35.5)	14	(42.2)	0.437
Intraventricular haemorrhage[d]	2	(6.7)	*NA*	*NA*	
	Median	(Range)	Median	(Range)	
Stay in NICU (days)[e]	60	(25-386)	*NA*	*NA*	
Mechanical ventilation (days)[e]	1	(0-44)	*NA*	*NA*	

[a] Data missing for seven VLBW and two control participants

[b] Data missing for three control participants

[c] Data missing for two control participants

[d] Grade I and II

[e] Data missing for two VLBW participants

Analyses performed with Student's t-test and Mann-Whitney U test.

Abbreviations: VLBW, very low birth weight; SES, socioeconomic status; NICU, neonatal intensive care unit; NA, not applicable.

Table 2. Scores for motor tests in the VLBW group compared with the control group at 23 years of age.

	VLBW (n=31)		Control (n=31)		
	Mean	(SD)	Mean	(SD)	p-value
Fine motor tests (sec)					
Trail Making Test-5	28.5	(11.1)	19.7	(5.7)	<0.001
Grooved Pegboard dom. hand	68.6	(17.2)	63.5	(9.9)	0.161
Grooved Pegboard non-dom. hand	73.6	(13.5)	68.1	(11.0)	0.080
MABC-2: Triangle	36.5	(12.0)	32.8	(7.4)	0.152
Gross motor tests (sec)					
HiMAT Automatic	10.6	(1.8)	10.1	(1.6)	0.247
Walk	3.9	(0.7)	3.9	(0.6)	0.614
Walk on toes	4.8	(1.0)	4.5	(1.0)	0.234
Run	1.9	(0.3)	1.7	(0.2)	0.045
HiMAT Planned	16.6	(3.5)	15.3	(2.4)	0.088
Walk backwards	5.4	(1.8)	4.8	(0.8)	0.071
Walk obstacle	4.1	(0.7)	4.0	(0.7)	0.377
Skip	3.0	(0.6)	2.9	(0.6)	0.227
Hop forward	4.7	(2.7)	3.6	(0.8)	0.039

Analyses performed with Student's t-test.

Abbreviations: VLBW, very low birth weight; MABC-2, Movement Assessment Battery for Children-2; HiMAT, High-level Mobility Assessment Tool.

Table 3. Mean FA, MD, AD, RD and volumes of the corticospinal tract (CST)[a] and the corpus callosum (CC)[b] in the VLBW group compared with the control group at 23 years of age.

		VLBW (n=31)		Control (n=31)		
		Mean	(SD)	Mean	(SD)	p-value
CST_{hand} dominant	FA	0.617	(0.015)	0.619	(0.011)	0.601
	MD	0.688	(0.027)	0.670	(0.017)	0.002
	AD	1.246	(0.044)	1.215	(0.032)	0.003
	RD	0.409	(0.023)	0.397	(0.015)	0.018
	Vol.	6.6	(2.7)	7.8	(2.3)	0.057
	Rel. vol.	4.4	(1.6)	4.9	(1.3)	0.159
CST_{hand} non-dominant	FA	0.618	(0.014)	0.621	(0.012)	0.378
	MD	0.683	(0.025)	0.669	(0.015)	0.011
	AD	1.239	(0.043)	1.215	(0.027)	0.013
	RD	0.405	(0.020)	0.396	(0.014)	0.048
	Vol.	7.2	(2.7)	8.3	(1.7)	0.062
	Rel. vol.	4.8	(1.5)	5.2	(9.3)	0.208
CST_{foot} dominant	FA	0.616	(0.015)	0.620	(0.012)	0.233
	MD	0.693	(0.024)	0.679	(0.017)	0.008
	AD	1.250	(0.038)	1.229	(0.029)	0.018
	RD	0.415	(0.022)	0.404	(0.015)	0.025
	Vol.	6.5	(2.1)	7.9	(1.6)	0.005
	Rel. vol.	4.4	(1.1)	5.0	(0.9)	0.024
CST_{foot} non-dominant	FA	0.621	(0.015)	0.623	(0.011)	0.618
	MD	0.690	(0.031)	0.676	(0.017)	0.029
	AD	1.252	(0.053)	1.227	(0.027)	0.023
	RD	0.409	(0.024)	0.400	(0.015)	0.100
	Vol.	67.1	(20.2)	77.8	(11.7)	0.014
	Rel. vol.	4.5	(1.3)	4.9	(0.8)	0.109
$CST_{premotor}$ dominant	FA	0.608	(0.012)	0.610	(0.009)	0.359
	MD	0.679	(0.025)	0.665	(0.014)	0.012
	AD	1.216	(0.039)	1.194	(0.027)	0.013
	RD	0.410	(0.021)	0.401	(0.011)	0.038
	Vol.	11.8	(3.6)	13.8	(2.8)	0.017
	Rel. vol.	7.9	(2.0)	8.7	(1.6)	0.100
$CST_{premotor}$ non-dominant	FA	0.608	(0.011)	0.611	(0.010)	0.274
	MD	0.673	(0.022)	0.665	(0.013)	0.094
	AD	1.207	(0.036)	1.193	(0.022)	0.096
	RD	0.406	(0.018)	0.401	(0.012)	0.170
	Vol.	13.5	(3.9)	15.6	(2.9)	0.017
	Rel. vol.	9.0	(2.2)	9.8	(1.6)	0.123
CC_{motor}	FA	0.612	(0.018)	0.618	(0.013)	0.208
	MD	0.726	(0.028)	0.705	(0.015)	0.001
	AD	1.313	(0.048)	1.280	(0.025)	0.002
	RD	0.433	(0.026)	0.417	(0.016)	0.005
	Vol.	6.6	(2.3)	9.1	(2.2)	<0.001
	Rel. vol.	4.4	(1.3)	5.7	(1.3)	<0.001
$CC_{premotor}$	FA	0.623	(0.010)	0.626	(0.010)	0.225
	MD	0.716	(0.026)	0.699	(0.016)	0.003
	AD	1.313	(0.048)	1.285	(0.029)	0.008
	RD	0.418	(0.017)	0.406	(0.014)	0.005
	Vol.	11.7	(3.0)	14.0	(2.8)	0.002
	Rel. vol.	7.8	(1.5)	8.9	(1.8)	0.016

[a] CST_{hand}, CST from hand area in primary motor cortex; CST_{foot}, CST from foot area in primary motor cortex; $CST_{premotor}$, CST from premotor cortex

[b] CC_{motor}, CC connecting the primary motor cortices; $CC_{premotor}$, CC connecting the premotor cortices

CST dominant and non-dominant corresponds to the contralateral CST for the dominant and non-dominant hand. MD, AD and RD are given in 10^{-3} mm^2/sec; Volume is given in ml; Rel. vol. = volume/total intracranial volume, given in 10^{-3}. Analyses performed with Student's t-test.

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; CST, corticospinal tract; CC, corpus callosum; VLBW, very low birth weight; Vol., volume; Rel. vol., relative volume.

Table 4. Associations between motor tests and mean FA of the corticospinal tract (CST)[a] and corpus callosum (CC)[b] in the VLBW group and the control group at 23 years of age.

		VLBW (n=31)			Control (n=31)			FA x group
	Mean FA of motor tracts	B	(95% CI)	p-value	B	(95% CI)	p-value	p-value
Fine motor tests								
Trail Making Test-5	CST_{hand}	293.5	(105.3 to 481.6)	0.003	-178.0	(-440.4 to 84.4)	0.180	0.005
dominant hand	$CST_{premotor}$	418.7	(179.1 to 658.3)	0.001	-11.8	(-340.2 to 316.6)	0.943	0.038
	CC_{motor}	252.6	(82.4 to 422.7)	0.004	-10.6	(-227.6 to 206.5)	0.923	0.058
	$CC_{premotor}$	530.5	(230.9 to 830.0)	0.001	27.7	(-242.0 to 297.3)	0.838	0.016
Grooved Pegboard	CST_{hand}	363.5	(27.5 to 699.5)	0.034	-312.6	(-781.2 to 156.1)	0.187	0.022
dominant hand	$CST_{premotor}$	550.4	(122.7 to 978.1)	0.013	-204.1	(-790.3 to 382.2)	0.488	0.042
	CC_{motor}	145.0	(-152.1 to 442.1)	0.332	-5.5	(-384.6 to 373.7)	0.977	0.528
	$CC_{premotor}$	338.4	(-196.1 to 872.8)	0.210	90.0	(-391.2 to 571.3)	0.709	0.493
Grooved Pegboard	CST_{hand}	448.3	(129.7 to 766.9)	0.007	-340.4	(-698.9 to 18.0)	0.062	0.002
non-dominant hand	$CST_{premotor}$	693.8	(301.1 to 1086.5)	0.001	-312.8	(-737.4 to 111.8)	0.146	0.001
	CC_{motor}	204.2	(-65.4 to 473.9)	0.135	81.1	(-262.9 to 425.2)	0.638	0.570
	$CC_{premotor}$	400.6	(-84.2 to 885.4)	0.103	171.8	(-264.7 to 608.4)	0.434	0.486
MABC-2: Triangle	CST_{hand} dominant	434.0	(224.7 to 643.3)	<0.001	-202.0	(-493.9 to 90.0)	0.171	0.001
	CST_{hand} non-dominant	543.8	(315.6 to 771.9)	<0.001	-139.6	(-396.3 to 117.0)	0.280	<0.001
	$CST_{premotor}$ dominant	569.0	(299.0 to 838.9)	<0.001	-71.5	(-441.5 to 298.6)	0.700	0.007
	$CST_{premotor}$ non-dominant	707.1	(422.5 to 991.7)	<0.001	-150.3	(-458.0 to 157.5)	0.332	<0.001
	CC_{motor}	70.9	(-145.5 to 287.2)	0.514	47.5	(-228.5 to 323.5)	0.732	0.893
	$CC_{premotor}$	594.5	(235.7 to 953.3)	0.002	77.8	(-245.3 to 400.8)	0.631	0.037
Gross motor tests								
HiMAT Automatic	CST_{foot} dominant	6.1	(-35.0 to 47.2)	0.766	26.5	(-26.6 to 79.6)	0.322	0.553
	CST_{foot} non-dominant	14.9	(-27.7 to 57.5)	0.488	-19.4	(-73.5 to 34.7)	0.476	0.325
	$CST_{premotor}$ dominant	15.3	(-37.9 to 68.5)	0.567	-19.3	(-92.3 to 53.6)	0.597	0.445
	$CST_{premotor}$ non-dominant	29.8	(-28.9 to 88.6)	0.313	-7.4	(-70.8 to 56.1)	0.817	0.394

	CC_{motor}	43.9	(9.0 to 78.9)	0.015	-9.4	(-54.1 to 35.3)	0.675	0.060
	$CC_{premotor}$	46.4	(-16.7 to 109.5)	0.147	-44.7	(-102.9 to 13.5)	0.130	0.037
HiMAT Planned[c]	CST_{foot} dominant	-58.3	(-134.8 to 18.2)	0.267	45.2	(-42.7 to 133.1)	0.307	0.139
	CST_{foot} non-dominant	-23.4	(-95.7 to 48.8)	0.519	-42.0	(-133.0 to 48.9)	0.358	0.750
	$CST_{premotor}$ dominant	-37.8	(-138.4 to 62.9)	0.455	-37.2	(-161.7 to 87.2)	0.551	0.995
	$CST_{premotor}$ non-dominant	-20.1	(-125.0 to 84.7)	0.702	-11.1	(-121.1 to 98.9)	0.841	0.906
	CC_{motor}	64.6	(6.0 to 123.1)	0.031	-49.9	(-131.3 to 213.2)	0.224	0.024
	$CC_{premotor}$	42.4	(-65.6 to 150.4)	0.434	-94.7	(-169.1 to 6.6)	0.066	0.068

[a] CST_{hand}, CST from hand area in primary motor cortex; CST_{foot}, CST from foot area in primary motor cortex; $CST_{premotor}$, CST from premotor cortex

[b] CC_{motor}, CC connecting the primary motor cortices; $CC_{premotor}$, CC connecting the premotor cortices

[c] Data missing for one participant in each group

Regression coefficient B for FA in a linear regression with motor tests as dependent variables and FA, group and FA x group (indicating between-group differences) as independent variables. Adjusted for sex and age. For motor tests performed with one hand, FA in the contralateral CST was used in the analyses. For Triangle and HiMAT, FA in the contralateral CST to the dominant and non-dominant hand/foot was used in the analyses.

Abbreviations: FA, fractional anisotropy; CST, corticospinal tract; CC, corpus callosum; VLBW, very low birth weight; MABC-2, Movement Assessment Battery for Children-2; HiMAT, High-level Mobility Assessment Tool

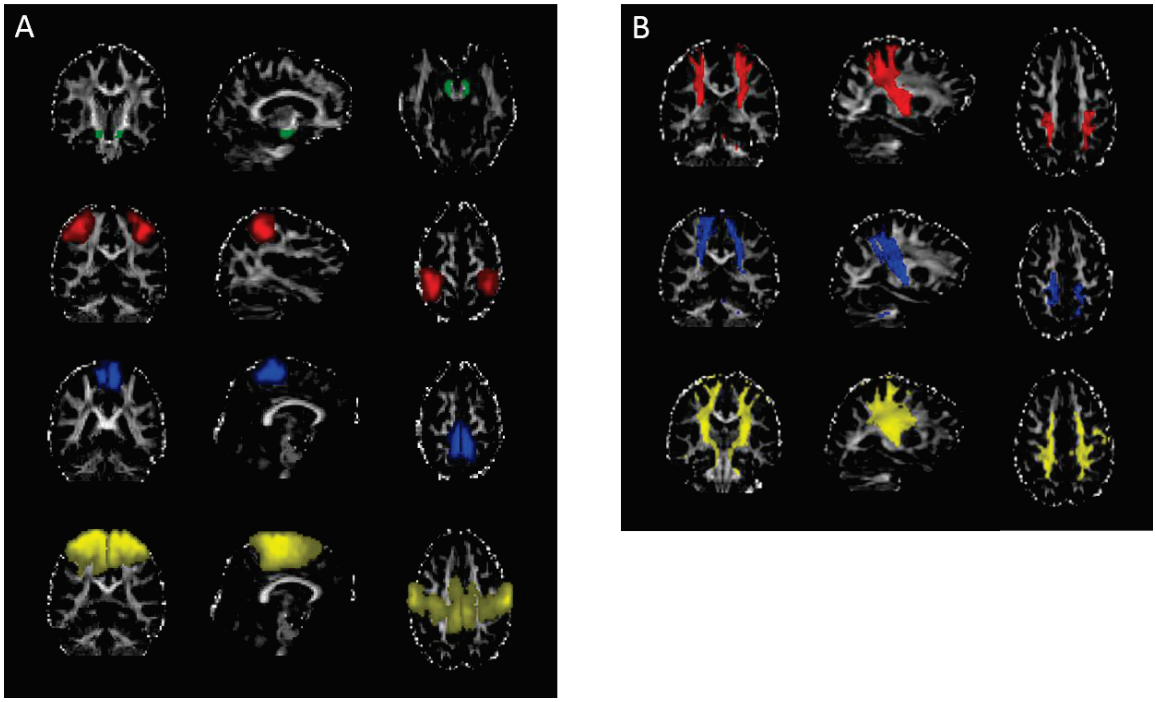

Figure 1. A) ROIs used for the probabilistic tractography of the left and right corticospinal tract (CST): Seed ROI in the cerebral peduncles (green) and target ROIs in the hand area in the primary motor cortex (red), foot area in the primary motor cortex (blue) and premotor cortex (yellow). B) Probabilistic tractography results of the CST_{hand} (red), CST_{foot} (blue) and $CST_{premotor}$ (yellow). Underlying coronal, sagittal and axial grey scaled image is the FA map for one of the individuals in the study.
Abbreviations: ROI, region-of-interest; CST, corticospinal tract; FA, fractional anisotropy

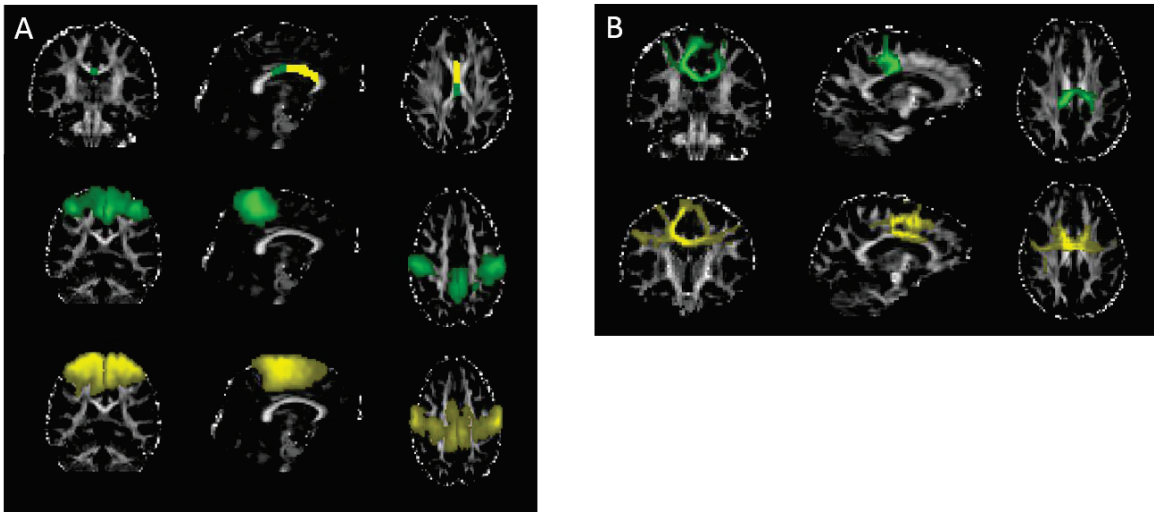

Figure 2. A) ROIs used for probabilistic tractography of the corpus callosum (CC): Seed ROIs in the CC corresponding to areas connecting the primary motor (green) and premotor cortices (yellow), target ROIs in the primary motor cortex (green) and premotor cortex (yellow). B) Probabilistic tractography results of the CC_{motor} (green) and $CC_{premotor}$ (yellow). Underlying coronal, sagittal and axial grey scaled image is the FA map for one of the individuals in the study.
Abbreviations: ROI, region-of-interest; CC, corpus callosum; FA, fractional anisotropy

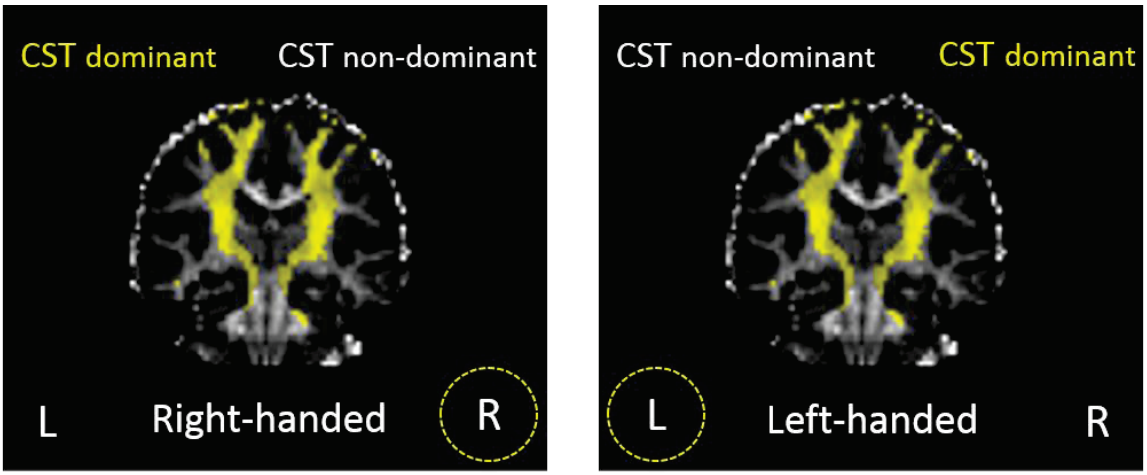

Figure 3. Re-categorization of the left and right corticospinal tract (CST) into the contralateral CST of the dominant and non-dominant hand. CST dominant correspond to the left CST for right-handed participants and the right CST for left-handed participants. Vice versa for CST non-dominant.

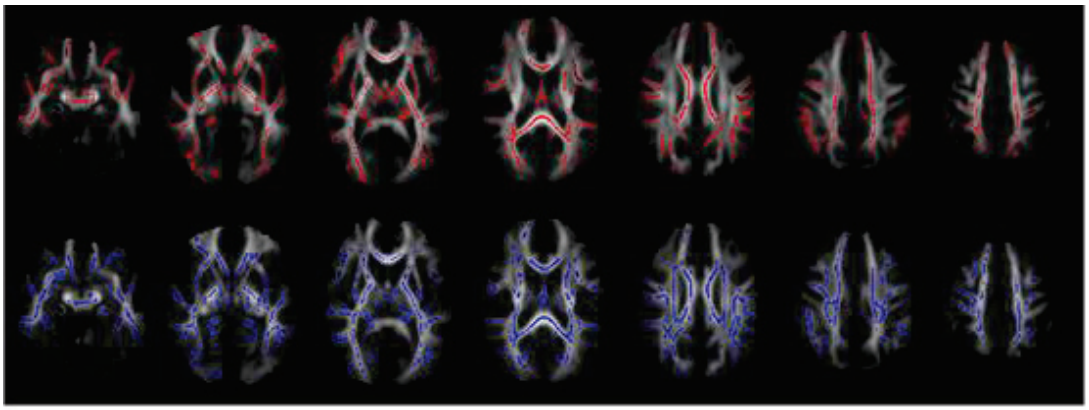

Figure 4. TBSS analysis demonstrated significantly lower fractional anisotropy (in red) and higher mean diffusivity (blue) in the VLBW group compared with the control group ($p<0.05$, nonparametric permutation test, corrected for multiple comparisons, sex and age at MRI).