Mental health and cerebral magnetic resonance imaging in adolescents with low birth weight

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1 Acknowledgements

This work was carried out at the Regional Centre for Child and Adolescent Mental Health, Department of Neuroscience, Norwegian University of Science and Technology (NTNU), in close collaboration with the Department of Laboratory Medicine, Children's and Women's Health, NTNU. The study was funded by Regional Centre for Child and Adolescent Mental Health, and Research Funds at St. Olav's Hospital, Trondheim University Hospital. Part of the study population was recruited from a multicentre study sponsored by the US National Institute of Child Health and Human Development.

The University Clinic for Child and Adolescent Psychiatry, St. Olav's Hospital, gave me the opportunity to take a pause from clinical work. For this goodwill, I wish to thank Chief Physician Thomas Jozefiak and Head of Clinic Odd Sverre Westbye, as well as Head of Administration Arve Winsnes and Professor Graham Clifford at the Regional Centre for Child and Adolescent Mental Health. This unit has provided excellent facilities. I would like to thank the staff for their support throughout the study, and Head of Department of Neuroscience, Professor Are Holen for his encouragement.

In particular I am indebted to the participants for their vital contribution; their trust, effort and willingness to give personal information. I am left with remembrance of fine adolescents and devoted parents, eager to expand the knowledge on the effects of low birth weight.

I am privileged to be surrounded by people who are thoughtful and willing to share knowledge, time and effort with me. I wish to express my gratitude to:

- My main supervisor, Professor Ann-Mari Brubakk, Department of Laboratory Medicine, Children's and Women's Health, NTNU, who made my work possible by inviting me to participate in a follow-up study. She has given invaluable support in planning and carrying out the study, and in completion of this thesis.
- Vice Dean Professor Torstein Vik, Department of Public Health and General Practice, NTNU, who has taught me the procedures of research. I am especially grateful for the guidance in writing the papers, an art he represents with distinction.
- Research Director Sonja Heyerdahl, Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, for valuable supervision throughout the study.

- My co-workers in the research group, for all kinds of on-the-way support: Research Fellows Siri Kulseng, Kari Anne I. Evensen, Susanne Lindqvist, and Associate Professors Jon Skranes and Marit Martinussen. I would like to thank our colleagues at the Department of Circulation and Medical Imaging, NTNU, and Center of Magnetic Resonance Imaging, St. Olav's Hospital: Professors Olav Haraldseth and Henrik Larsson, Associate Professor Kjell Arne Kvistad, Radiologists Gunnar Myhr and Olaug Smevik, and their co-workers.
- MSc-PhD Pål Romundstad, Department of Public Health and General Practice, and Professor Peter Fayers, Department of Cancer Research and Molecular Medicine, NTNU, for vital help with statistics and proper interpretation of results.
- Child and Adolescent Psychiatrists Mari Jordet Bruheim and Sigrun Opsal Vilsvik for their effort performing interviews and diagnostic assessment.
- My colleagues at the University Clinic for Child and Adolescent Psychiatry, St. Olav's Hospital, for their unreserved support. I know they have paid a price for this thesis, attending to the clinical work in my absence.
- Associate Professor, Anna M. Bofin, Department of Laboratory Medicine, Children's and Women's Health, NTNU, for linguistic assistance.

Finally, I will thank my family for their support, encouragement and joy;
Bent, Bård, Kari Anne, Jan-Tore, and Mathea, each of them far more important to me than this thesis.

2 List of papers

Paper I: Indredavik M S, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk A-M. Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F445-50

Paper II: Indredavik M S, Vik T, Heyerdahl S, Kulseng S, Brubakk A-M. Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires. *Eur Child Adolesc Psychiatry* 2005;14:226-36

Paper III: Indredavik M S, Vik T, Heyerdahl S, Romundstad P, Brubakk A-M. Low birth weight adolescents: Quality of life and parent-child relations. *Acta Paediatr;* in press

Paper IV: Skranes J, Martinussen M, Smevik O, Myhr G, Indredavik M, Vik T, Brubakk A-M. Cerebral MRI findings in very-low-birth-weight and small-for-gestational-age children at 15 years of age. *Pediatr Radiol* 2005;35:758-65

Paper V: Indredavik M S, Skranes J, Vik T, Heyerdahl S, Romundstad P, Brubakk A-M. Low birth weight adolescents: Psychiatric symptoms and cerebral MRI abnormalities. *Pediatr Neurol;* in press

3 Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ASEBA	Achenbach System of Empirically Based Assessment
ASSQ	Autism Spectrum Screening Questionnaire
CBCL	Child Behaviour Check List
CGAS	Children's Global Assessment Scale
CI	Confidence interval
DAMP	Deficits in attention, motor control and perception
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ELBW	Extremely low birth weight
fMRI	Functional magnetic resonance imaging
IQ_{est}	Intelligence quotient estimated
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IUGR	Intrauterine growth retardation
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children
LBW	Low birth weight
MCDD	Multiple complex developmental disorder
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
OR	Odds ratio
PDD	Pervasive developmental disorder
PET	Positron emission tomography
PR	Prevalence ratio
PVL	Periventricular leukomalacia
QoL	Quality of life
SCL-90-R	Symptom Checklist-90-Revised
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SES	Socioeconomic status
SGA	Small for gestational age
TRF	Teacher Report Form
VLBW	Very low birth weight
YSR	Youth Self Report

4 Introduction

"Not everything that can be measured counts and not everything that counts can be measured" *Albert Einstein*

4.1 Topic of the thesis

Progress in medical technology has reached a point where it is possible to rescue newborn infants at the border of viability.[65] This entails an obligation to seek knowledge on the consequences of these medical advances. How do preterm children manage? Do they have more physical or mental health problems than others? How do they perceive their own health and well-being? Do they experience problems that matter: with peers, in school and in leisure time activities? And if they do, how do they cope? Are possible developmental difficulties long-lasting? These questions are relevant also for infants born at term, but small for gestational age.

Up to now, the majority of the literature reporting an increased risk of emotional and behavioural problems has focused on preterm very low birth weight children, whereas psychiatric outcome for those born small for gestational age at term is less clear. Studies performed in adolescence are fewer, as are reports on quality of life, parent-child relations, and possible associations between psychiatric symptoms and brain abnormalities in these groups. Therefore, the special feature of this study is overall long-term outcome of low birth weight in adolescence, adding knowledge to the literature on:

- Psychiatric symptoms and disorders
- Quality of life
- Family relations, impact on parents and the parents' mental health
- Cerebral MRI abnormalities
- Associations between psychiatric symptoms and structural brain abnormalities

4.2 Why?

"Why should a child psychiatrist engage in research on low birth weight children, who constitute a very small group of child psychiatric patients?" This question has been

asked. And in fact, the question offers the answer. Low birth weight children, traditionally a paediatric group of patients, may well have psychiatric symptoms and disorders, but do not necessarily receive psychiatric services. From my point of view, they meet with the dichotomy of our health system, dividing somatic and psychiatric disorders. Low birth weight children may be prone to develop disabilities within both areas, with increased risk of experiencing psychiatric consequences on the basis of divergent brain biology.[157] For a child psychiatrist, it is a great challenge to delve into the relations between biology and emotions, trying to bridge the gap between body and mind. "Nature and nurture stand in reciprocity, not in opposition." (Eisenberg)[44] An integrated approach addressing both mental and physical health may make a difference for low birth weight children and their families.

4.3 Theoretical framework

In assessing and treating child psychiatric disorders, we need knowledge on aetiological, maintaining and curative factors. There is a broad spectrum of theories on child development and mental health disorders.

Biological theories include the effects of genetic factors, brain damage and dysfunction, and other physical influences. The presence of brain dysfunction may lead to physical disorders such as cerebral palsy or epilepsy, learning difficulties, and has a non-specific effect on liability to show emotional or behavioural problems.[61]

Behaviour or learning theories have described mechanisms for learning; classical and operant conditioning. Cognitive theories have shed light upon cognitive development throughout childhood, based on the stages proposed by Jean Piaget, subsequently refined and nuanced by research on children's learning abilities.

Family theories have provided conceptualisation of processes within families, which can promote or hamper the psychosocial development of a child. These theories focus on the family system, structure and communication.

Psychoanalytic theories, founded by Sigmund Freud, comprise the development of the child's personality and mental function, and have been the basis for psychoanalytic treatment. The modern form of dynamically oriented psychotherapy is the result of further development of psychoanalytic theories, focusing strongly on relational aspects. Attachment theories, originally developed by John Bowlby, describe

the child's early attachment to the caretaker(s) based on both biological and emotional components. Today, attachment is viewed as an interaction process between the child and the caretaker(s) where both parts are active in developing the pattern of attachment. These theories have been especially useful in understanding disorders of social relationships and anxiety states.[61]

All the above mentioned theories provide at least some useful way of comprehending the development of a child facing different life events and psychosocial experiences. Knowledge of risk factors and resilience supplement the picture. Irrespective of other etiological factors, children's development is closely bound up with the quality of care given by their parents.[61]

The framework of today's child and adolescent psychiatry comprises all these theories, acknowledging that biological, psychological and social factors interact in the development of psychiatric disorders.

4.4 Normality and disorder

In research on mental health, the concepts of normality and disorder need to be accounted for. Normality generally covers the condition of being typical, usual or expected.[130] Psychiatric symptoms can be emotional, behavioural and a wide range of other traits. As emotions and behaviour are universal qualities, normality includes certain characteristics of these qualities. Most psychiatric symptoms can be regarded as occurring along a continuum ranging from none to a large burden of symptoms. Deviation from normality can be measured either categorically or dimensionally.[140]

The categorical approach uses the concept of disorder, defined by a certain degree of abnormal state of health. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines mental disorder as "clinically significant behavioural or psychological syndrome or pattern that occurs in an individual and that is associated with present distress or disability or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom".[6] At the same time, the authors admit that no definition adequately specifies precise boundaries for the concept of "mental disorder".[6] A disorder is classified by the pattern of criteria required for a specific diagnostic label. In a clinical setting, diagnosis opens the doorway to treatment. In research, it is needed in order to explore the prevalence and characteristics of

disorders in a population. The set of criteria for a clinical diagnosis is not the ultimate and everlasting truth, as the currently used diagnostic systems are based on consensus reflecting clinical practice.[61] Semi-structured interviews are designed to assess criteria for the various psychiatric disorders, and are widely used in diagnostic assessment.

The dimensional approach emphasizes the degree of symptoms, and classifies clinical presentations based on quantification of attributes.[6] This approach may comprise more clinical information, including attributes that might be sub-threshold in a categorical system.[6] Questionnaires provide such quantifications. Cut-off scores between normal, borderline and clinical-range scores, based on normative samples, can be used to guide selection of individuals who may need clinical intervention, but questionnaires do not provide diagnostic assessment. Hence, psychiatric interviews and questionnaires give supplementary information; the former by categorical and the latter by dimensional approach. For both approaches the information you obtain is dependent on the source. For example, adolescents' self-reports may differ from parents' reports.[16,68] Therefore, multiple informants are generally used to gather information in child and adolescent psychiatry.

An important characteristic of child psychiatric disorders lies in the degree to which they affect the child's functional capacity at home, at school and in leisure time activities. For most disorders, reduced level of function is an additional criterion for diagnosis. But even with a psychiatric disorder, level of function may vary. Therefore, measuring overall functional capacity provides complementary information about the impact of a psychiatric disorder. Multiaxial systems of classification incorporate this and other aspects relevant to the child, and are widely used in child and adolescent psychiatry. Measuring aspects of quality of life also supplement the picture.

4.5 Epidemiology of psychiatric disorders

This section will be limited to epidemiological data relevant for the study. In a review of 49 studies published between 1965 and 1993, the median prevalence rate of general child and adolescent psychiatric dysfunction was found to be 12.3 % (3 – 18 years).[144] However, the prevalence varies with strictness in criteria and the degree of impairment required for diagnosis. In a Dutch national sample of adolescents (13 – 18 years) where disorders were diagnosed only in the presence of a significant degree of social

impairment (DSM-III-diagnoses), the prevalence was 7.9 %.[145] Rates of general psychiatric disorders remain relatively stable in pre-school and school age children, but there are some suggestions of an increase during adolescence, especially of internalizing disorders.[61] Pre-pubertal boys are more frequently referred to child psychiatric services than girls, because of a higher rate of behavioural problems. Referral of girls increases during adolescence due to a greater tendency to develop depressive and anxiety disorders.[61]

Prevalence rates for children with Attention-deficit/hyperactivity disorder (ADHD) are reported to be 0.5 – 1.0 % in the United Kingdom, and 3 – 5 % in the United States.[61] Prevalence is highest in school-age and lower in adolescence, with a preponderance of boys.[121] Co-morbid disorders are common: Oppositional/defiant disorder in 35 – 50 %, conduct disorder in 25 %, depressive disorder in 15 %, anxiety disorder in 25 % and learning disability in 15 – 40 %.[121] Co-morbitity rates may be affected by referral bias and overlapping diagnostic criteria.

A fair estimate of current prevalence of any anxiety disorder with impairment is 5 – 10 % for children and adolescents, with an over-representation of girls.[80] Co-morbidity is high between different anxiety disorders and between anxiety and depressive disorders.[80] Depression is found in 2 – 5 % of school-aged children, the rates are markedly increased in adolescence, with some evidence that this is greater among girls.[60]

Asperger's disorder is reported to occur in 3 – 4 per 1000 children, and is about four times more common in boys than in girls.[61]

4.6 Concepts and definitions

Some significant concepts used in this thesis need to be defined:

- Very low birth weight (VLBW) is defined by a birth weight ≤ 1500 g, with the subgroup: Extremely low birth weight (ELBW) ≤ 1000 g. These terms do not include a specification of gestational age, but practically all VLBW infants are born pre-term. In 2002, the number of VLBW infants born in Norway was 890 (1.6 % of all births), of whom 564 were ELBW infants (1.0 % of all births).[92] VLBW adolescents constitute one of the groups in our study.

- The concept of small for gestational age (SGA) is used to identify those low birth weight infants who may have been growth-retarded *in utero*. SGA is usually defined as birth weight below the 10th percentile, adjusted for gestational age, gender and parity.[148] They may be born pre-term; before the 37th week of pregnancy, or at term; ≥ the 37th week. In order to increase the specificity of growth retarded infants, SGA may be defined as birth weight below 2 SD, or below the 5th or the 3rd percentile.[146] Using the 10th percentile as cut-off, the number of term SGA infants born in Norway was roughly 5600 in 2002 (10 % of all births).[92] Term SGA adolescents constitute the second group in our study.
- Intrauterine growth retardation (IUGR) is used to describe a process which inhibits normal foetal growth, and is said to occur in 2 – 10 % of foetuses.[146] However, this concept lacks clear criteria for detection. Although SGA and IUGR are defined differently, and may not include the same infants, the two concepts are often used as synonymous terms in the literature.
- "Quality of life" (QoL) is a multidimensional concept which usually covers physical, emotional and social functioning, often including the notion of well-being, happiness and satisfaction.[50] The World Health Organization has launched a unifying and transcultural definition of QoL as: "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment."[156] Different instruments place emphasis on different aspects of QoL, some are disease-specific, and others are generic; that is, intended for general use irrespective of illness.[50] For measuring QoL in adolescents, important dimensions are emotional well-being, behaviour, self-esteem, family and social functioning. Even though QoL is a very subjectively oriented concept, proxy assessment by parents are often used to supplement the self-reports.

4.7 Low birth weight: Risk factors

The aetiology of preterm birth is heterogeneous, and may include both life style factors and biological components. Infection of intrauterine tissues and/or the foetus has been

suggested as a substantial factor.[113] Abnormal programming of the hormonal regulation of pregnancy or abnormal setting of the "placental clock", has also been postulated as a possible cause. These potential causes may be heavily influenced by psychoneuroimmune factors; that is, interactions between psychological state, the neuroendocrine system, and the immune system.[113] A study in New Zealand demonstrated increasing preterm birth rates from 1980 to 1999 with disappearance of a socioeconomic gradient that had existed earlier,[34] suggesting a change in the aetiology of preterm births from socioeconomic to other factors.

The VLBW infant is at risk of developing complications of prematurity: Respiratory disease, hypothyroxemia, hyperbilirubinemia, nutritional deficiencies, glucocorticoid exposure, neonatal infection and multiple medications.[106] The premature brain is vulnerable to injury, including focal or diffuse periventricular leukomalacia (PVL), intraventricular hemorrhage, and several patterns of neuronal injury.[106,150] Focal PVL is characterized by localized necrosis located deep in the cerebral white matter, and is related to severe ischemia, due to incomplete vascular supply or impaired regulation of cerebral blood flow.[150] Diffuse PVL is characterized by injury to oligodendroglial precursor cells, caused by ischemia and its secondary mechanisms, with intraventricular hemorrhage and maternal/foetal infection as contributing factors. The oligodendroglial precursor cells are destined to develop into mature cells forming myelin of the cerebral white matter. Hence, the principal neuropathologic sequela of PVL is diminution of white matter volume and ventriculomegaly, secondary to the deficiency of myelin.[150] Furthermore, organizational events in brain development may be disrupted, and the basal ganglia and hippocampus may be injured secondary to hypoxia-ischemia.[106]

The stay in a Neonatal intensive care unit (NICU) may provide sources of stress, including painful events, medical and nursing procedures, noise and bright light.[106,125] In addition, early attachment may be difficult in a NICU due to reduced parent-child interaction, and the premature infants may be less responsive and provide fewer distinct cues to guide caregivers in the early attachment process.[84] A preterm birth may also affect the mental state of the parents, as families of VLBW children may experience increased emotional impact.[36]

The aetiology and risk factors for term SGA infants are slightly different. A certain proportion of them are simply genetically small normal infants. Others have

been growth-retarded, either throughout the whole pregnancy, or only in the third trimester. If the growth retardation has started early, there may be a number of specific causes, including maternal malnutrition, tobacco smoking, alcohol or drug abuse, and intrauterine infections.[146] Growth retardation in the third trimester is thought to be caused mainly by placental insufficiency or pre-eclampsia,[146] and hypotheses claim that the brain might be spared from the insufficient nutrition.[64] Still, term SGA infants may be at risk of perinatal asphyxia and pulmonary complications, hypoglycaemia, hypothermia, hypocalcaemia and meconium aspiration syndrome.[146] But overall they are less immature than VLBW infants. Many of them manage without an incubator or admission to a NICU. Hence, the physical environmental conditions for early attachment are less extraordinary, and we may hypothesize that parental stress should be less than for VLBW infants. Yet, research reports suggest that psychosocial risk factors may be present, and that ongoing socio-environmental deprivation may play a much greater role in determining outcome than any potential effect of intrauterine growth retardation on the developing nervous system.[64] Also, exposure to tobacco smoke and other maternal life style factors which may be present during pregnancy are suspected to be risk factors for developing ADHD symptoms in children.[86]

4.8 Low birth weight: Long-term outcome

Studies on VLBW children have documented cognitive and learning disadvantages,[22,74,157] as well as increased prevalence of neurodevelopmental disabilities; cerebral palsy, minor motor and visuomotor problems.[49,84,90,109] Psychiatric symptoms and disorders are reported to be frequent,[21,46,84,158] especially attention problems.[21,23,46,110,132,134,141] Anxiety disorders, depression and thought problems may also occur, but the results differ between studies.[21,23,46,119,155,158] Furthermore, there are reports on deficits in social skills.[46,71,138] Socioeconomic status is reported to influence psychological outcome in VLBW children as those with disadvantaged settings may have poorer outcome.[85,129] Still, biological factors are by far the best predictors of cognitive and behavioural functioning in school-age. Furthermore, these factors may reduce the ability to take advantage of environmental offers.[157]

Term SGA children may have a slightly increased risk of cerebral palsy, visual and minor motor difficulties.[49,57] Studies on cognitive and psychiatric problems have

displayed conflicting results. Some have found lower cognitive and academic skills and others have not.[73,82,99,105,135] A few studies have reported a possible risk of mental health problems within the domains of attention deficit and behaviour[73,99,157] but long term psychiatric outcome is not clear.[64,157] There is some suggestion that low birth weight SGA infants are more vulnerable to the effects of the environment than normal birth weight babies.[62]

Varying results on the prevalence of psychiatric disorders may be due to a number of factors; differences in study design, inclusion criteria, assessment age and methods. Most studies are based on questionnaires only,[71,84,99,110,119,134,135,141,158] while a few include psychiatric interview.[21,23,46,154]

There is a growing interest in how low birth weight adolescents perceive their own functioning.[20,25,40,41,117-119,143] VLBW adolescents and young adults are reported to give high value to their QoL, even though they may have a great burden of morbidity,[20,25,40,117] while proxy reports by their parents may indicate reduced QoL.[40] In a study of term SGA as young adults, no social or emotional consequences were found.[135]

Parent-child relations and parenting are mostly studied in VLBW children in early childhood.[33,111] Even though hypotheses claim that disruption of normal parental care and high levels of family stress may predispose towards less optimal caregiving, it is controversial whether or not these possible difficulties in parent-child interaction persist beyond early childhood.[84] One study on parental mental health showed that unresponsiveness of the infant and the severity of the baby's physical health problems during the first year were associated with mental health problems for the mother.[153] Increased long-term family impact was found in a study of ELBW adolescents,[116] but we are not aware of reports on the mental health of parents with low birth weight adolescents.

4.9 Brain and mental health

4.9.1 Brain and mental health in general

This section is confined to psychiatric disorders relevant for the study. In a neuroimaging study of children and adolescents (5 – 18 years), ADHD was associated with a decrease in cerebral and cerebellar volumes.[29] Results were comparable for male

and female patients.[28] Patients with ADHD were found to have developmental growth patterns for nearly all brain regions that paralleled growth curves for controls, but on a lower track.[29] Others have described a moderate size reduction in the frontal lobes, basal ganglia, and some regions of the corpus callosum, which links frontal and parietal brain regions, in male ADHD adolescents.[52] Poor sustained attention performance was found to be related to smaller volume of the right-hemispheric white matter in ADHD males (8 – 17 years).[123] A study of ADHD boys (5 – 13 years) examining the relationship between frontostriatal structures and performance on response inhibition tasks, showed associations of prefrontal regions with attentional control and the basal ganglia with motor control.[27] In a review, Lou discussed evidence of a disturbed function of the striatum and the cingulo-striato-thalamo-cortical loop in ADHD.[87] Furthermore, a distributed neural system involving association cortices in prefrontal, temporal and parietal regions may subserve attention and behavioural inhibition, and cortical abnormalities are reported in these regions in children and adolescents with ADHD.[131] The neurophysiological mechanisms of ADHD are thought to involve dysfunction of dopamine, and possibly other transmitters and neuromodulators as well.[55]

Social behaviour and processing of emotional cues may be linked to a specialized circuit centred on the amygdala, involving the orbital frontal cortex, anterior cingulate and temporal cortex.[1,35] An fMRI study of social intelligence demonstrated activation of the amygdala in social tasks in the normal brain, whereas the amygdala was not activated in the autistic brain.[15] A diffusion tensor imaging study of autistic adolescents showed disrupted white matter tracts between regions implicated in social cognition (in and adjacent to the anterior cingulate, corpus callosum and prefrontal areas).[14] Thus, social intelligence may involve extended networks comprising cortex, subcortical structures and white matter circuits.

The amygdala is also an important component of the system involved in acquisition, storage, and expression of fear memory, which might be important processes in anxiety disorders.[83] If a danger is perceived, a fear reaction is evoked and the amygdala mediates inhibition of sosial behaviour. Amaral suggests (based on animal studies) that hyperactivity of the amygdala may be associated with anxiety and contribute to disorders such as social phobia.[5]

4.9.2 Low birth weight: Brain and mental health

Brain research in low birth weight children has applied different cerebral MRI-techniques. Reduced brain volume, both regionally and in total, has been reported in VLBW children.[17,32,98,107,133] Increased PVL and dilated ventricles may occur[98,101,102] as well as reduced size of the corpus callosum.[32,93,107] These findings fit with the principal neuropathologic sequela of prematurity described by Volpe, with diminution of white matter volume, and ventricular dilatation.[150] Allin et al. found increased lateral ventricular volume, and an increase in the ratio of grey to white matter in VLBW young adults.[3] In this study, increased ventricular volume predicted decreased grey matter in subcortical nuclei and limbic cortical structures, and decreased periventricular white matter.

There are few reports on the relationship between MRI findings and behavioural symptoms in VLBW children. In one study of VLBW adolescents, more than half had abnormal MRI scans, especially ventricular dilatation, thinning of the corpus callosum and abnormal white matter signals.[133] These adolescents had more reading-, adjustment- and neurological impairments than controls, and their behaviour, measured by questionnaire, was significantly related to MRI abnormality. Although another study of VLBW adolescents demonstrated thinning of the corpus callosum, there was no significant association to ADHD, diagnosed by interview.[32] In a tensor imaging study, white matter disturbance in the internal capsules bilaterally and the posterior corpus callosum was associated with attention deficit, scored on a neuropsychological assessment scale.[97] A recent positron emission tomography (PET) study of six adolescents born preterm with subsequent ADHD, demonstrated a link between neonatal cerebral ischemia (low cerebral blood flow), attention deficit and insufficient dopaminergic neurotransmission.[88] This study points to one possible pathway connecting neonatal ischemic events in premature infants to the neurophysiological mechanisms of ADHD.

In term SGA children, studies on cerebral MRI-findings have only focused on the pituitary gland in children with short stature.[9,78] To our knowlege, there have been no reports on associations between brain pathology and psychiatric symptoms in term SGA children.

5 Aims of the thesis

The general aim was to assess the prevalence of psychiatric symptoms and disorders at 14 years of age in two groups of low birth weight adolescents compared with a control group, to evaluate the global outcome for low birth weight adolescents, their quality of life and parent-child relations, and to explore whether psychiatric symptoms can be related to cerebral abnormalities in adolescents with low birth weight.

The aims were specified by the following study hypotheses:
For VLBW and term SGA adolescents compared with controls, we expected to find

- higher prevalence of psychiatric symptoms and disorders
- higher symptom scores on self-, mother-, father- and teacher-rated questionnaires
- reduced quality of life
- affected parent-child-relations
- higher emotional burden and more mental health problems for the parents
- higher frequency of cerebral MRI abnormalities
- associations between psychiatric symptoms and cerebral MRI abnormalities

These aims are addressed in papers I - IV as follows:
Aims of paper I: To evaluate the prevalence of psychiatric symptoms and disorders associated with low birth weight, and describe the characteristics of psychiatric symptoms and disorders in these groups.

Aims of paper II: To explore whether two commonly used questionnaires could confirm and further elaborate our previous findings obtained by psychiatric interview, and to assess whether the information given by the adolescents themselves, their mothers, fathers and teachers gave corresponding results.

Aims of paper III: To explore the effect of low birth weight on quality of life for the adolescents, evaluate the parent-child relationship, emotional burden on the parents, and the parent's mental health.

Aims of paper IV: To assess cerebral MRI abnormalities in two groups of low birth weight adolescents, compared with a control group.

Aims of paper V: To explore associations between psychiatric symptoms and qualitatively assessed cerebral MRI abnormalities in two groups of low birth weight adolescents, compared with a control group.

6 Material and methods

6.1 Study design

This study is a population-based follow-up of two groups of adolescents with low birth weight; VLBW and term SGA, compared with a control group of normal birth weight carried out at 14 years of age. The VLBW children were admitted to the NICU at the University Hospital in Trondheim (the referral hospital) in 1986 – 1988. Children born in 1988 were assessed thoroughly at one and six years of age.[126,127] The SGA and control children were born to mothers living in the Trondheim region. They were enrolled before week 20 of pregnancy in a multicentre study between January 1986 and March 1988.[11,148] A 10 % random sample of women (with one or two previous pregnancies) was selected for follow-up during pregnancy. At birth, all the children born to mothers in the random sample and all the SGA children were included for follow-up.[147] The present study was carried out between November 2000 and October 2002, and included a psychiatric assessment, an evaluation of cognitive abilities, a neuropaediatric examination and cerebral MRI. Further assessment, which is not a part of this thesis, included evaluation of motor abilities and neurocognitive performance, and an ophthalmological examination.

In paper IV and V, we included VLBW participants outside the original cohort. These infants were transferred to the University Hospital of Trondheim from the county of Møre og Romsdal, either close to delivery or after birth.

6.2 Study population

VLBW adolescents

VLBW was defined by a birth weight ≤ 1500 g. Ninety-nine children were admitted to the NICU in the period 1986 – 1988. Of these 23 died. Syndromes affecting the central nervous system were excluded, involving one child with trisomi 21. Of the remaining 75, six had moved and 13 did not consent to participate at follow-up. Thus, 56 (30 boys, 26 girls) were examined (Figure 1). Twelve had birth weight ≤ 1000 g. Ten participants were twins, of whom six were in twin-pairs. The response rate was 81 % of the 69 available for the study and 75 % of the 75 living, non-excluded adolescents.

SGA adolescents

Of 1200 eligible women, 104 (9 %) gave birth to an SGA child at term, defined by a birth weight < 10^{th} percentile of all infants in the multicentre study, adjusted for gestational age, gender and parity.[148] At follow-up, 12 had moved and 32 did not consent, leaving 60 (28 boys, 32 girls) for assessment (Figure 1). The response rate was 65 % of the 92 available for the study and 58 % of all 104 adolescents.

Control adolescents

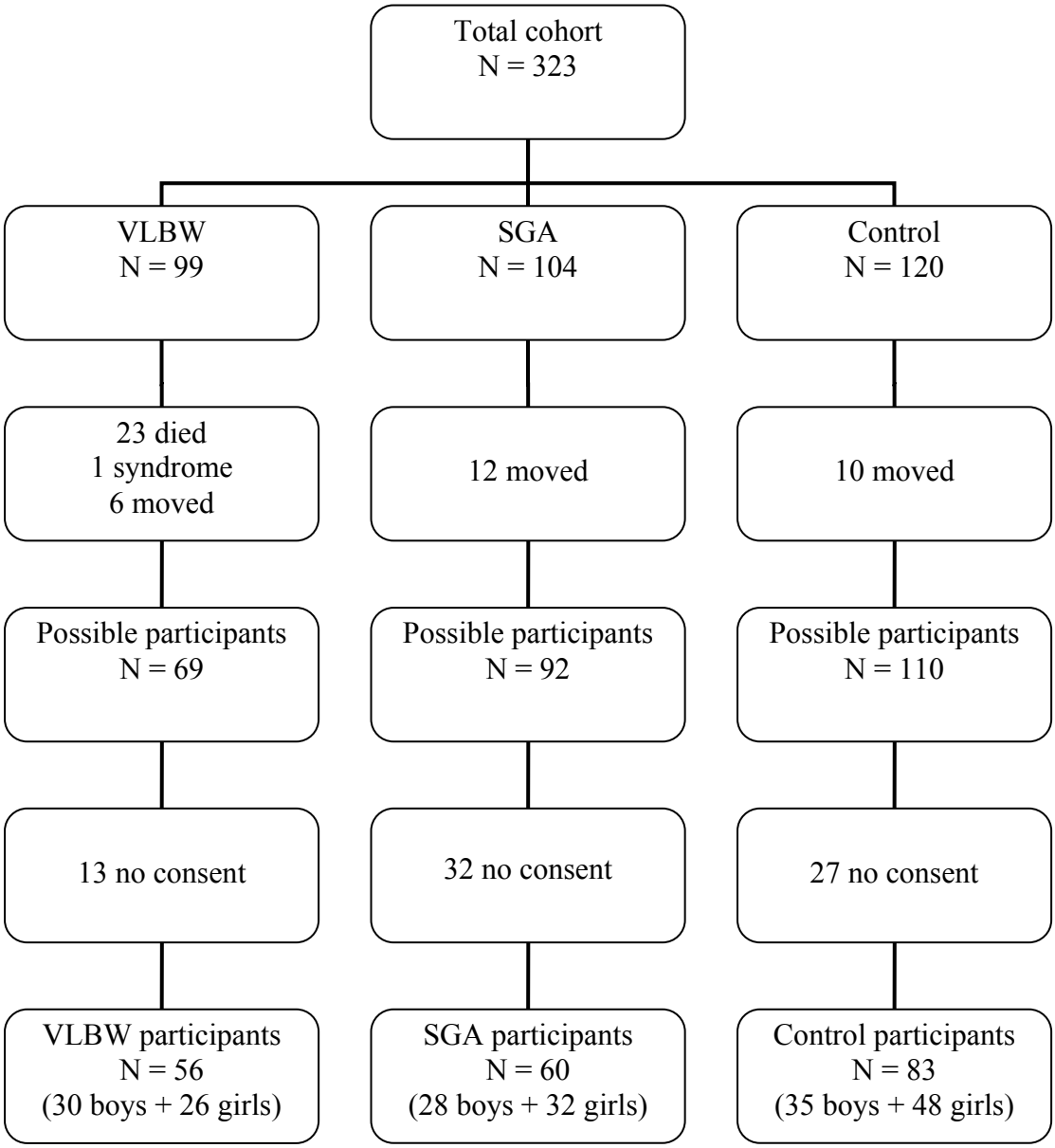
The control group comprised 120 children with a birth weight ≥ 10^{th} percentile for gestational age, born at term to mothers in the 10 % random sample. At follow-up, ten had moved and 27 did not consent, while 83 participated (35 boys, 48 girls) (Figure 1). The response rate was 76 % of the 110 available for the study and 69 % of all 120 adolescents.

Non-participants

There were no differences in mothers' age at childbirth, duration of pregnancy, or the infants' birth weight, body length, and head circumference between those who participated and those who did not consent in any of the groups.

In paper IV-V, numbers differed due to inclusion of VLBW participants outside the original cohort, and the papers are confined to those who completed both psychiatric and cerebral MRI examination: 55 VLBW, 54 SGA and 66 control adolescents.

Figure 1 Flow chart of study population (paper I-III)



6.3 Methods

Psychiatric assessment

Psychiatric symptoms and disorders (in paper I and V) were diagnosed using the semi-structured interview: Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS),[77] performed separately with parents and adolescents. Conclusions were drawn according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[6] The child psychiatrist, who was blinded to birth weight status, differentiated between diagnosis, symptoms ≥ 75 % level of diagnostic criteria, or no clinically significant problems. Autism Spectrum Screening Questionnaire (ASSQ)[42] was used as part of the interview with parents, and the adolescents' overall functioning was scored by the interviewer on Children's Global Assessment Scale (CGAS).[124]

Of the 199 adolescents in paper I, the first author carried out 171 interviews and another child psychiatrist carried out the remaining 28. The first 27 interviews with adolescents were videotaped and scored to test inter-rater reliability. The Intra Class Correlation Coefficient was 0.91 for total symptoms, 0.86 for anxiety symptoms and 0.86 for ADHD symptoms. A third senior child psychiatrist, blinded to the first evaluation, performed a second diagnostic assessment based on the written interviews. Subsequently, diagnostic consensus was obtained.

The psychiatric interview was supplemented with screening questionnaires (described further in the papers):

- ADHD-Rating Scale IV[12] rated by mothers, fathers and teachers. (Paper I and V)
- The Achenbach System of Empirically Based Assessment (ASEBA),[2] with Youth Self Report (YSR), Child Behaviour Checklist (CBCL) age 4 – 18 years, rated separately by mothers and fathers, and Teacher Report Form (TRF). (Paper II)
- Strengths and Difficulties Questionnaire (SDQ)[58] age 4 – 16 years completed by the adolescents, mothers, fathers and teachers. (Paper II)

Quality of life and parent-child relations

- Child Health Questionnaire (CHQ)[81] was used to assess functional health, self esteem and well-being. The adolescents completed the 87 items Child Form (CHQ–

CF87) age 10 – 17 years, and parents completed the 50 items Parent Form (CHQ–PF50).

- The adolescents, mothers and fathers completed the short version of Parental Bonding Instrument (PBI)[103,104] which measures the perceptions of ongoing parental practices.[79]

These questionnaires are described further in paper III.

Cognitive abilities

An estimate of the adolescents' intelligence quotient (IQ_{est}) was calculated using four of Wechsler Intelligence Scales (WISC-III):[152] Vocabulary, Arithmetic, Block Design and Picture Arrangement.[76] We defined "low IQ_{est}" below 2 SD of the mean value in the control group.

Neuropaediatric examination

A medical examination was performed to assess the prevalence of cerebral palsy and other neuropaediatric disabilities.

Magnetic resonance Imaging

Cerebral MRI was performed on a 1.5 Tesla Siemens Symphony. Every examination included sagittal T1-weighted spin echo (SE) images, axial proton density weighted and T2-weighted SE images and axial inversion recovery T1-weighted images. Two experienced radiologists qualitatively assessed the images independently and thereafter in consensus. They were blinded to the neonatal histories, earlier MRI results as well as results of the psychiatric assessment. Ventricular size, periventricular white matter reduction, corpus callosum thinning, white matter gliosis, and grey matter abnormalities were reported.

Criteria for ventricular dilatation included localized and diffuse dilatation of the lateral ventricles, as well as angulation of the occipital horns. White matter thickness was qualitatively judged, and gliosis was reported as focal or diffuse. Criteria for thinning of the corpus callosum included focal posterior and diffuse thinning compared with normal mature corpus callosum in the same age group, described by Barkovich and Truwit.[13] (Paper IV and V)

Parents' mental health and socioeconomic status

Mothers and fathers stated their own mental health on Symptom Checklist-90-R (SCL-90-R).[39] Socioeconomic status was calculated according to Hollingshead's Two Factor Index of Social Position, based on a combination of parents' education and occupation.[72]

6.4 Ethics

The Regional Committee for Medical Research Ethics (Health Region IV) approved the study protocol May 5th 2000. Written informed consent was obtained from both adolescents and parents prior to examination. The Data Inspectorate assigned a license for establishing and maintaining the register containing personal data.

6.5 Statistical analysis

The Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL) was used for data analysis. Three-group comparisons were made using one-way ANOVA for variables with a normal distribution, and Kruskal-Wallis for ordinal data. If these tests indicated differences between groups (defined by an alpha level < 0.05), two-group comparisons were made using Scheffe's post hoc test for normally distributed variables, and Mann-Whitney U-test for variables with a non-normal distribution.[112] Differences in proportions between groups were analysed by the Chi-square test. In paper I, odds ratio (OR) with 95 % confidence interval (CI) was calculated as an estimate of the relative risk that a child with low birth weight had psychiatric symptoms and disorders, compared with the control group. In paper IV, OR with 95 % CI was used as an estimate of the relative risk that VLBW adolescents had specific MRI abnormalities, compared with the SGA group and the control group. In paper V, prevalence ratios (PR) with exact 95 % CI's were calculated to estimate the prevalence of psychiatric symptoms in VLBW adolescents with MRI abnormalities relative to those without MRI abnormalities, using the Epitab procedure in STATA version 8 (Statacorp 2003. Stata Statistical Software: Release 8.0 College Station, TX: Stata Corporation, USA).

To compare results on questionnaires with psychiatric diagnoses assessed by interview (paper II), we calculated sensitivity and specificity based on cut-off values defining clinical range at $\geq 90^{th}$ percentile in the control group.[2] We also applied

Receiver Operating Characteristic curve with calculation of Area Under Curve and 95 % CI.[4] Kappa statistics (κ with 95 % CI) was used to evaluate whether the same adolescents were classified within the clinical range by different informants and on the two questionnaires. By convention, $\kappa \leq 0.20$ may suggest poor agreement; 0.21 – 0.40: fair; 0.41 – 0.60: moderate; 0.61 – 0.80: good; and 0.81 – 1.00: very good agreement.[4]

In order to control for possible confounders in paper I and II, we used logistic regression[112] to calculate adjusted odds ratios, first as univariate analysis, followed by multivariate analysis for covariates altering the unadjusted OR > 10 %. Linear regression was done in order to analyze the influence of adolescent and parental factors on the parents' emotional impact (ln-transformed) in paper III. Furthermore, linear regression was used to analyze the influence of cerebral MRI-findings on the ADHD-Rating Scale total score in paper V. This score, assessed on an ordinal scale, did not show a completely Normal distribution. Therefore, regression was done both with raw and ln-transformed data. As the results were mainly unchanged, we presented the raw data.

7 Main results

Group characteristics

Family and child characteristics, including mean birth weight and gestational age, are shown in table 1 (paper I-III). There were no significant differences between groups regarding mothers' or fathers' education or socioeconomic status (table 1). Mothers in the SGA group were younger than the mothers in the control group. The proportion of boys and girls in each group did not differ. Low IQ_{est} was found in ten (18 %) VLBW adolescents (one boy, nine girls), four SGA (boys) and three control adolescents (two boys, one girl). Cerebral palsy was diagnosed in seven (13 %) VLBW adolescents (five diplegic, one hemiplegic, one quadriplegic) and one SGA adolescent (diplegic). One VLBW and one control adolescent had epilepsy. There were no major visual or hearing impairments.

Table 1. Family and child characteristics for sample in paper I-III

	VLBW N = 56		**SGA N = 60**		**Control N = 83**	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Family characeristics						
Maternal						
Age (years)	42.3	(5.0)	42.1	(3.6)*	44.0	(4.5)
Education (years)	13.5	(3.4)	12.9	(3.1)	14.2	(2.9)
Paternal						
Age (years)	45.7	(5.9)	44.4	(3.6)	46.0	(4.8)
Education (years)	13.1	(3.7)	13.4	(2.8)	14.1	(3.1)
Socioeconomic status	3.3	(1.3)	3.4	(1.3)	3.8	(1.1)
Child characteristics						
Birth weight (g)	1174	(233)†	2921	(211)†	3691	(459)
Gestational age (weeks)	28.8	(2.7)†	39.5	(1.1)	39.6	(1.2)
Assessment age (years)	14.1	(0.3)	14.2	(0.3)	14.2	(0.3)

*$p < 0.05$ vs. controls
†These were the selection criteria, and differed by definition vs. controls ($p \leq 0.001$)

In the sample assessed in paper IV-V (55 VLBW, 54 SGA, 66 controls), mean birth weight and gestational age were essentially the same as in the cohort sample. There were no group differences in mothers' or fathers' age, maternal education or socio-economic status. The level of paternal education was lower in the VLBW group

than in the control group (12.8 vs. 14.2 years). The proportion of boys and girls in each group did not differ. Low IQ_{est} was found in eleven (20 %) VLBW, three SGA and three control adolescents. Cerebral palsy was diagnosed in six (11 %) VLBW adolescents (five diplegic, one hemiplegic) and one SGA adolescent (diplegic). One VLBW adolescent had epilepsy.

Paper I

Psychiatric symptoms and disorders in adolescents with low birth weight

We found increased prevalence of psychiatric symptoms and disorders in the VLBW group compared with the control group; 46 % had psychiatric symptoms (above 75 % of diagnostic criteria) and 25 % had a psychiatric diagnosis, according to K-SADS interview. Anxiety disorders were most prevalent (14 %). Attention deficit problems were acknowledged in 25 %, but only a minority (7 %) fulfilled the diagnostic criteria of ADHD. The VLBW adolescents had higher mean attention and total score (not hyperactivity score) than controls on the ADHD-Rating Scale (teacher-report). Moreover, higher mean sum score on Autism Spectrum Screening Questionnaire suggested relational problems and deficits in social skills, and four (7 %) had symptoms of Asperger's disorder (assessed by interview). We did not record increased prevalence of depression. The CGAS results indicated that the psychiatric problems affected the overall functioning of the VLBW adolescents. The results were mainly unchanged when we excluded those with low IQ_{est}, except for reduced prevalence of anxiety symptoms ($p = 0.09$ vs. controls) and disorders ($p = 0.07$ vs. controls). There were no gender differences. The increased risk of symptoms persisted after controlling for psychosocial factors.

In the SGA group, 23 % had psychiatric symptoms and 10 % had a psychiatric disorder, which did not differ significantly from controls (13 % and 7 % respectively). The sum scores on ADHD-Rating Scale and Autistic Spectrum Screening Questionnaire did not differ from controls. Reduced CGAS score (below 80) was found in 40 % of SGA adolescents, which gave an increased odds ratio of 2.6 (95 % CI 1.2 – 5.4) compared with controls, indicating an increased risk of subnormal functioning.

Paper II

Psychiatric symptoms in low birth weight adolescents, assessed by screening questionnaires

The VLBW and SGA adolescents themselves did not report more symptoms than controls on ASEBA and SDQ. However, mothers, fathers and teachers reported higher symptom scores for VLBW than for control adolescents, especially emotional symptoms, social problems and attention deficit. In addition, the questionnaires revealed more aggressive and rule-breaking behaviour observed by parents, which was not observed by teachers. Low academic performance appeared in the VLBW group, and teachers also reported thought problems. One third of the VLBW adolescents received special educational services at school, and one of ten had received specialized health services.

The SGA adolescents seemed to have more behavioural problems than controls, lower social competence and a tendency towards attention deficit/hyperactivity, rated by mothers and fathers. Teachers reported thought problems. Academic performance did not differ from controls.

The results were essentially unchanged after exclusion of adolescents with low IQ_{est}, except that SGA adolescents no longer had increased attention score compared with controls. The results persisted after adjusting for psychosocial factors. There were no gender differences in the VLBW group (adolescents with low IQ_{est} excluded) whereas boys had more attention and externalizing problems than girls in the SGA and the control group.

Mothers and fathers were the most reliable informants, even though the sensitivity was not optimal compared with in-depth interview, and their agreement was only moderate to good as to which children had scores in the clinical range. A combination of mother- and father-reports, and using a cut-off at the borderline clinical range, increased the sensitivity and may be preferable in a clinical setting. ASEBA and SDQ revealed essentially the same results. ASEBA provided a more differentiated picture, while SDQ showed its suitability for a brief screening. Nevertheless, in-depth psychiatric interview is necessary for a reliable diagnosis.

Paper III

Low birth weight adolescents: Quality of life and parent-child relations

The VLBW and SGA adolescents did not report more physical, emotional or behavioural problems than the controls, nor did they differ from the controls with regard to self-esteem or family functioning. However, the parents reported more behavioural problems and lower psychosocial health for VLBW adolescents than for controls. Worries about their health, abilities and well-being made a greater emotional impact on the parents, limiting the time they had for personal needs, and represented a greater burden upon family activities. When adolescents with low IQ_{est} were excluded, the parents still reported lower psychosocial health for VLBW adolescents, causing greater emotional and time impact on the parents.

In the SGA group, parents reported a tendency towards more behavioural problems compared with controls.

There were no group differences in perceived relational warmth reported by the adolescents, their mothers and fathers. The VLBW adolescents reported their parents to be protective, also after exclusion of adolescents with cerebral palsy, epilepsy, psychiatric disorders and low IQ_{est}. Emotional impact on the parents was strongly associated with having a VLBW child, the presence of a psychiatric disorder and cerebral palsy. Still, low birth weight parents did not have more mental health problems than control parents.

Paper IV

Cerebral MRI findings in VLBW and SGA children at 15 years of age

We found an increased risk of MRI abnormalities in the VLBW group compared with the control group. Four of five VLBW adolescents had ventricular dilatation, about one half had signs of white matter loss and thinning of the corpus callosum, and one third had signs of periventricular gliosis. There was no grey matter pathology. Nearly half of the VLBW adolescents had more than two types of abnormalities. The combination of findings such as reduced periventricular white matter, ventricular dilatation especially of the occipital horns of the lateral ventricles, thinning of the corpus callosum, and gliosis may all indicate perinatal PVL.

In both the SGA and the control group, one in five had ventricular dilatation, suggesting that this finding is rather common. The clinical implications warrant further study. Few had other abnormalities in the SGA and the control group.

Paper V

Low birth weight adolescents: Psychiatric symptoms and cerebral MRI abnormalities

We found that ADHD symptoms, assessed by the ADHD-Rating Scale IV (mother-report), were associated with white matter reduction and thinning of the corpus callosum in VLBW adolescents. Socioeconomic status and gender had little effect on the ADHD score in this group. Our results support the hypothesis of a specific form of ADHD in VLBW children, possibly caused by perinatal events influencing white matter connectivity and brain development. The four VLBW adolescents with symptoms of Asperger's disorder all had white matter reduction and ventricular dilatation, but associations were not statistically significant. Neither did we find associations between other psychiatric symptoms and abnormal MRI findings.

In the SGA and the control group, few had white matter reduction, thinning of the corpus callosum, and gliosis, which limited further analyses. Dilated ventricles were not associated with psychiatric symptoms or scores in these groups. In the SGA group, socioeconomic status was strongly associated with the ADHD score, suggesting that environmental factors may influence behavioural outcome in these children.

8 Discussion

The study hypotheses can be addressed as follows:
VLBW adolescents had increased prevalence of psychiatric symptoms and disorders compared with controls, and higher symptom scores on mother- father- and teacher-rated (not self-rated) questionnaires. The psychiatric problems were especially within the domains of attention deficit, anxiety and relational difficulties. Self-reported QoL did not differ from controls, but proxy reports by parents suggested lower scores on several QoL measures in the VLBW group. The VLBW adolescents reported their parents to be protective, but the warmth in the parent-child relationship was not affected by birth weight. Parents of VLBW adolescents experienced higher emotional burden, but not more mental health problems than parents of controls. The frequency of MRI abnormalities was higher in the VLBW than in the control group, and ADHD symptoms were associated with MRI abnormalities in the VLBW group.

Term SGA adolescents did not have increased prevalence of psychiatric symptoms or disorders assessed by interview, but an increased risk of subnormal functioning compared with controls. Parent- and teacher-rated (not self-rated) questionnaires displayed more behavioural problems, lowered social competence and a tendency towards attention deficit/hyperactivity. QoL, parent-child relations, emotional burden and parents' mental health did not differ from controls. The SGA group did not have more MRI abnormalities than the control group, and no associations were found between psychiatric symptoms and MRI abnormalities in the SGA group.

In the following discussion, we have included a few results that are not reported in the papers. These are indicated as follows: (results not reported in the papers).

8.1 Strengths and limitations

The strength of this study is the comprehensiveness of information collected from different sources, and the relatively large number of adolescents who underwent MRI scan. In the psychiatric assessment, we used both questionnaires and a semi-structured interview, and information was collected from the perspective of the adolescents themselves, their mothers and fathers, as well as their teachers. Perceived quality of life was reported by the adolescents, with proxy reports by their parents. The parent-child relations were mutually rated by parents and adolescents, and the parents' mental health

status was surveyed for both mothers and fathers. We made use of a broad assessment of health status, including assessment of cognitive abilities, and a medical examination.

Limitations are primarily the sample size and the possible effects of chance, bias and confounding. These concepts will be addressed in the following, with a closing discussion on causality of psychiatric problems.

Sample size

We wanted to include adolescents born in 1986-88 who had been selected for follow-up after birth, as the majority of them had been assessed at one and six years of age. The number of participants in each group was expected to be approximately 60. Based on previous research reports, power-calculations indicated that the number of VLBW adolescents versus controls would be sufficient to show expected differences. For SGA adolescents, the research was inconclusive as to whether they have increased risk of psychiatric problems. To demonstrate small differences between the SGA and the control group would require large numbers. Hence, we knew that the sample size of SGA adolescents might be marginal to show group differences, which turned out to be true. This is one of the main limitations of the study. Also, when testing for associations between psychiatric symptoms and MRI-pathology, we encountered the problem of limited sample size even in the VLBW group.

Chance

The psychiatric outcome was significantly worse for the VLBW group. The results were on the whole consistent across all instruments, and were mainly unchanged after exclusion of adolescents with low IQ_{est}. This indicates an association which is unlikely to be due to chance. Differences between the SGA group and controls were weaker and less consistent between parents and teachers. As these differences were smaller, lack of statistical significance may be due to the limited sample size, and a real difference may have been missed.

Bias

Of the adolescents available for the study, 73 % (199/271) participated (paper I-III). Birth weight and gestational age did not differ between those who consented to

participate and those who did not. It is therefore unlikely that our main results are caused by selection bias. In paper IV, 81% (175) of the 215 with psychiatric assessment underwent MRI scan. There were no differences in psychiatric parameters between participants with psychiatric assessment who consented to MRI scan and those who did not consent to MRI scan in any of the groups, making selection bias less probable.

The VLBW parents knew that their child belonged to a risk group, hence, information bias can not be ruled out. However, the examiners were blinded, and interviews were performed separately with adolescents and parents. This information was supplemented with teachers' reports on ASEBA, SDQ and ADHD-Rating Scale, making it less likely that the main results are caused by information bias.

The VLBW children were classified according to a birth weight ≤ 1500 g, and some of them may have been growth retarded *in utero*. However, they were all born preterm, and we have chosen to treat them as a group in this study. The 10^{th} percentile definition of SGA is crude, and may include a certain proportion of genetically small normal infants, whereas some growth retarded infants may have been classified as controls. Thus, the non-significant differences found between SGA and controls may be underestimates of the real differences.

Confounding

In multivariate analysis, the increased risk of psychiatric symptoms persisted after adjusting for psychosocial factors. Thus, it is unlikely that our main results on psychiatric symptoms are due to confounding. Analysis of the association between VLBW and the parents' emotional impact, suggested that gender and socioeconomic status could have a confounding effect. However, after adjusting for these factors, being the parent of a VLBW adolescent was still associated with increased emotional impact. In the VLBW group, neither gender nor socioeconomic status gave confounding effect on the ADHD-Rating Scale total score in a linear regression model, whereas in the SGA group, the model indicated socioeconomic status as a source of confounding.

Causality

We found a strong association between VLBW and psychiatric problems which could not be explained by gender, low IQ_{est} or psychosocial factors. The strength of association confirms a genuine effect of VLBW, and points to a possible biological

cause-effect relationship. This hypothesis is further supported by the finding of a significant association between ADHD symptoms, assessed by the ADHD-Rating Scale, and cerebral MRI abnormalities such as white matter reduction and thinning of the corpus callosum. We did not find a structural correlate for anxiety disorders or light autistic traits using qualitatively assessed classical MRI.

The association between SGA and psychiatric symptoms was weaker, and with the present sample size, we may have missed real associations. In this group, ADHD symptoms were not associated with cerebral MRI abnormalities, but with socioeconomic status.

One additional criterion for assessing causality is an appropriate time-sequence. Since our outcome variables are measured long after birth, we consider the time-sequence to be appropriate. Another additional criterion is dose-response relationship; that is a gradient of risk associated with degree of exposure.[69] Six of 12 with birth weight ≤ 1000 g and eight of 44 with birth weight > 1000 g had a psychiatric diagnosis. This difference was borderline significant ($p = 0.05$), and suggests a tendency towards increased risk with lower birth weight. Ten of 12 with birth weight ≤ 1000 g and 19 of 44 with birth weight > 1000 g had white matter reduction. This difference was statistically significant ($p = 0.02$), with OR = 6.3 (95 % CI: 1.2 – 32.3) as an estimate of the increased risk of having white matter reduction for those with birth weight ≤ 1000 g compared with those with birth weight > 1000 g (results not reported in the papers).

In sum, we have found a valid statistical association between VLBW and psychiatric problems, which is unlikely to be due to chance, bias or confounding. The association is strong, a hypothesis of biological vulnerability is credible and a dose-response-relationship is possible. The increased risk of cerebral MRI abnormalities with lower birth weight strengthens the hypothesis of biological vulnerability. However, this study can not explain the biological mechanisms involved in development of psychiatric symptoms after a preterm birth.

For term SGA adolescents, we found only a weak association between SGA and psychiatric symptoms. Lack of statistical power leaves the question of causality unresolved. However, our negative results must be interpreted with caution, and further research is needed to explore the psychiatric outcome of term SGA adolescents.

8.2 Psychiatric symptoms and disorders

8.2.1 Attention-deficit/hyperactivity disorder

The existence of attention deficit problems in VLBW children is well documented, even though reports on prevalence varies between 5 % and 32 %.[18,21,23,46,108,110,132,134,141] In our study, 7 % fulfilled the diagnostic criteria of ADHD, but 25 % had attention deficit symptoms ≥ 75 % of diagnostic criteria.

The question has been raised whether the attention problems of VLBW children fit with the existing ADHD concept, or represent a more specific "pure" form with mainly attention deficit, often without hyperactivity, and with a dominating neurological aetiology.[157] In the general population, the inattentive and combined inattentive/hyperactivity subtypes are equally prevalent among school-aged children. Hyperactivity tends to predict rule-breaking behaviour, and one of four children with ADHD is reported to have a co-morbid conduct disorder.[121] In our VLBW group, we found mainly attention deficit, without hyperactivity, and a low frequency of conduct symptoms. We were unable to confirm the male predominance reported in epidemiological studies.[121] However, this gender difference is less evident in the inattentive type than in the hyperactivity type.[137]

In regression analyses, VLBW had a significant influence on ADHD symptoms, so had brain pathology in the form of white matter reduction and thinning of the corpus callosum, both which are signs of white matter loss. Gender and socioeconomic status had little effect, as opposed to the control group. Hence, both our clinical and MRI findings support the hypothesis of a specific form of ADHD in VLBW children, mainly due to neurodevelopmental impairment of brain maturation.[21,139,157] A possible mechanism for this is perinatal ischemia and related events leading to PVL and subsequent loss of white matter tissue. This may in turn affect association and commissural fibres involved in networks dealing with attention and executive functions. Repeated incidents of asphyxia/ischemia may particularly damage the vulnerable striatum, which has a central role in ADHD.[87] Our MRI-findings, as well as the associations found between MRI abnormalities and ADHD symptoms, fit with the established hypotheses on the possible neuropathologic mechanisms of prematurity, and the subsequent risk of ADHD symptoms.[88,150]

The concept of Deficits in attention, motor control, and perception (DAMP) has been defined as the combination of ADHD and Developmental coordination disorder, constituting a subgroup of ADHD.[55] Children with DAMP are reported to have more academic problems and autistic type behavioural patterns than ADHD children without developmental coordination disorder.[55] Our findings of more ADHD symptoms, special educational needs and light autistic traits in the VLBW group, and the fact that these adolescents also had motor problems,[49] may fit with the characteristics of DAMP. Further analyses combining the results of the motor, neurocognitive and psychiatric assessments are needed in order to explore co-existence of problems within these domains.

The SGA adolescents did not have more ADHD symptoms than controls, when symptoms were assessed by interview or the ADHD-Rating Scale IV. However, the parents reported more attention deficit symptoms on ASEBA which became non-significant when adolescents with low IQ_{est} were excluded. Furthermore, the mothers reported more rule-breaking and externalizing problems, especially in boys. This result was not supported by teachers. Still, SGA adolescents may possibly have light ADHD symptoms with a tendency towards behavioural disturbance. According to a review of the literature by Wolke, there is some suggestion that behavioural problems are more frequent in SGA than in VLBW children.[157] We found no associations between ADHD symptoms and MRI abnormalities in the SGA group, while socioeconomic status influenced the ADHD score. This supports the opinion that environmental factors are more important for behavioural outcome than potential effects of growth failure in term SGA children and adolescents.[64]

8.2.2 Anxiety

Assessed by interview, the VLBW adolescents had higher prevalence of anxiety symptoms and disorders than controls. The anxiety disorders were separation anxiety disorder, generalized anxiety disorder, social phobia and specific phobia. Exclusion of individuals with low IQ_{est} reduced the prevalence of anxiety symptoms ($p = 0.09$) and disorders ($p = 0.07$), but the prevalence did not differ significantly between those with normal and low IQ_{est} (small numbers, result not reported in the papers). The parents reported higher scores on the ASEBA anxious/depressed scale, and more emotional symptoms on SDQ compared with controls. Furthermore, fathers and teachers reported

more withdrawal. Although earlier findings on anxiety and depression have been inconclusive,[30] some have reported a prevalence of 8 – 10 % (VLBW and birth weight < 2500 g, 6 – 12 years) for one or more specific anxiety diagnoses.[21,46,154] Our finding of anxiety disorders in 14 % of the VLBW adolescents support these studies.

There was no significant difference between SGA adolescents and controls with regard to anxiety symptoms and disorders on either interview or questionnaires, but teachers reported more withdrawal and thought problems for the SGA adolescents.

Why did the VLBW adolescents have anxiety problems? There are several possible explanatory hypotheses. Firstly, could these symptoms be due to biological factors? We did not find associations between qualitatively assessed MRI-pathology and anxiety symptoms, but more advanced techniques are most certainly required in order to examine the biology of emotions. It seems relevant to ask if anxiety symptoms could be generated by neonatal stress encountering immature regulatory systems, forming abnormal emotional and physiological patterns. Together with several cortical and subcortical structures, the limbic system of the developing brain is the emotion-processing circuit which handles anxiety. Its multiple interrelated areas involve the amygdala and hippocampus, activated in perception, generalization and memory storage of threat related cues.[120] Hypotheses are put forward that high level of distress combined with low self-regulatory ability, may increase anxiety sensitivity.[100] Stress has been shown to damage the hippocampus, leading to impaired learning and memory.[91] Also, the thalamus plays a role in perception of anxiety, initiating the neuroendocrine response to stress via the hypothalamic-pituitary-adrenal axis, with cortisol as the major stress hormone. A prospective study of preschoolers suggested that exposure to early maternal stress, especially maternal depression, may sensitize children's pituitary-adrenal responses, leading to increased cortisol levels during later stress exposure.[48] Others have found that elevations in children's cortisol levels may accompany internalizing problems, extreme behavioural inhibition, social wariness and withdrawal,[10,122] which have been linked to an increased risk of anxiety disorders.[19] It has been proposed that high levels of cortisol in shy children may induce changes in the amygdala, exacerbating their fearfulness.[122]

The neurobiology of anxiety is even more complex, and involves multiple neurotransmitter and neuroendocrine systems. It is also likely that genetics play a role.[70] To account for these complex mechanisms is beyond the scope of this thesis.

The main findings in our VLBW sample were high prevalence of both anxiety symptoms and ADHD symptoms. This leads to the second hypothesis: Is there a link between these two symptom domains? When assessed by K-SADS, only two of 12 with anxiety symptoms also had ADHD symptoms, and only two of 14 with ADHD symptoms also had anxiety symptoms. Furthermore, there were no significant differences in the ADHD-Rating Scale total score, ASEBA attention score or SDQ hyperactivity scale (all raters) between those with and without anxiety symptoms (results not reported in the papers). However, anxiety disorders and ADHD are known to share a high degree of co-morbidity.[120] Lack of statistically significant differences in our sample may be due to small numbers, or may in fact indicate less co-morbidity between these disorders in VLBW adolescents. According to Sallee and March, ADHD and anxiety disorders involve some of the same neurocognitive systems (arousal, activation, attention and vigilance), but with different responses.[120] They share inattentiveness and distractibility, but in ADHD, noradrenergic mediated attention is thought to be underactivated, while it is overactivated in anxiousness. Hence, cognitive neuroscience suggests that these disorders may share common underlying processes that result in co-morbidity at the symptom level, while showing distinctive patterns at the neurocognitive level.[120]

A third speculation may be that difficulties in the early attachment process, secondary to either child or parental factors,[36,84] may give rise to increased anxiety responses. According to attachment theory, infants of different attachment types are thought to develop different cognitions of interpersonal relationships, and dissimilar ways of regulating affect. The cognitions are thought to be organized as "Internal working models", defined as mental representations of the self, intimate others and the world, that guide interpersonal behaviour.[89] Attachment types are secure or insecure, with the latter subdivided into avoidant, ambivalent, and disorganized. Insecure infants lack confidence in their caregiver's availability, and present an overly cautious behaviour pattern characteristic of anxious individuals. The cognitive distortions of the world as unsafe and others as untrustworthy are more frequent among anxious individuals than among others.[151] Hence, insecure attachment appears to be a risk factor in the development of anxiety disorders. In our study, we did not assess attachment types as such. But using the Parental Bonding Instrument, we did not find signs of long-term relational problems, as the relational warmth was unaffected by low birth weight.

On the other hand, the VLBW adolescents reported their parents to be protective. However, the protectiveness from parents was not associated with anxiety symptoms or disorders (results not reported in the papers). Consequently, our study can not confirm a link between anxiety symptoms and abnormal parent-child relations in low birth weight adolescents.

A fourth speculation is that effects of the "vulnerable child syndrome" may be present. This concept was launched to illustrate the influence of the parents' expectations.[63] If the parents anticipate vulnerability in the child, their interventions may have an unintended effect, promoting vulnerability.[44] Increased parental perception of child vulnerability was related to social anxiety in a study of children with chronic illnesses,[8] and a significant association between parental perception of increased child vulnerability and internalizing problems was found in a study of high risk VLBW children at three to seven years.[37]

Finally, negative psychosocial experiences later in childhood may possibly give rise to anxiety in low birth weight children. One third of the VLBW adolescents received special educational services at school, and the VLBW group also had increased prevalence of neurocognitive (Kulseng et al. submitted) and motor difficulties.[49] Neurological abnormalities may lead to secondary emotional and/or behavioural disturbances by a multitude of possible mechanisms.[59]

In sum, the presence of anxiety symptoms in the VLBW group may involve various hypotheses, and this study can not give satisfactory answers to the questions raised. Further clarifications of the origin of anxiety in VLBW children are required. Our contribution is to ask some specific questions. And the hypotheses presented are not incompatible, as these mechanisms may well interplay. The development of the brain is extremely experience-sensitive.[120] Therefore, biology and experience work together, and can not be studied independent of each other.

8.2.3 Social skills

VLBW adolescents had higher scores on social problems and lower scores on social skills than controls on CBCL and TRF. They also demonstrated higher scores than controls on the Autism Spectrum Screening Questionnaire (ASSQ). Even when excluding the four adolescents with symptoms of Aspergers' disorder, as well as adolescents with low estimated IQ, the ASSQ score was higher in the VLBW than in the

control group ($p < 0.01$, result not reported in the papers). These light autistic traits should not mislead us to conclude that there is increased prevalence of autistic spectrum disorders, as our data can not support such a conclusion. But still, on asking the questions in the ASSQ, relational problems emerge which may help us understand the social problems often reported for VLBW adolescents. We hypothesise that these children may struggle with encoding and interpreting subtle cues of social relations. These problems may involve both cognitive mechanisms and emotional components.

We found a significant correlation between the ADHD total score (mother- and father-report) and the ASSQ score (Spearman's rho = 0.72, $p \leq 0.001$, nearly unchanged after exclusion of adolescents with low IQ_{est}) (results not reported in the papers). Those with ADHD symptoms had higher ASSQ sum scores than those without ADHD symptoms ($p = 0.003$). Using kappa-statistics, the agreement was moderate ($\kappa = 0.54$) as to which adolescents had ADHD total score and ASSQ score above the 90th percentile (results not reported in the papers). Co-existing ADHD and autistic spectrum traits are described by Gillberg,[56] and this co-morbidity applies especially for children with DAMP; the combination of ADHD and Developmental coordination disorder.[55] A possible common aetiology for specific relational problems and attention deficit in VLBW children should be further explored.

In our VLBW sample, those with anxiety symptoms had higher ASSQ sum scores than those without anxiety symptoms ($p = 0.02$, result not reported in the papers). There was also a significant correlation between the anxious/depressed score on ASEBA (mother-report) and the ASSQ score (Spearman's rho = 0.53, $p \leq 0.001$, unchanged after exclusion of adolescents with low IQ_{est}). These results suggest a possible link between relational problems and anxiety symptoms as well.

The correlations between social problems and symptoms of ADHD, as well as social problems and anxiety, render it necessary to discuss a new concept suggested to define a possible subgroup of Pervasive developmental disorders (PDDs), namely Multiple complex developmental disorder (MCDD). This construct is not yet included in the official diagnostic systems, but recommended primarily for the purpose of research. MCDD is characterized by three main dimensions: Impaired regulation of affective state and anxieties, social impairments and disinterest, and impaired cognitive processing, i.e. thought disturbance.[26] This construct, however, seems to involve a higher degree of impairment than was found in the VLBW sample. Researchers

speculate that children with MCDD may be at increased risk to develop schizophrenia in adulthood.[26] In a study of children with PDD, Sturm et al. found that MCDD constituted only a tiny fraction of all PDD cases.[136] To our knowledge, the studies on MCDD have not explored whether low birth weight might be a risk factor. And the possible link between the proposed set of symptoms and underlying neurobiological correlates are unclear.[136]

The four VLBW adolescents with symptoms of Asperger's disorder all had white matter reduction and ventricular dilatation. Imaging studies pinpoint a network that links medial prefrontal and temporal cortices as the neural substrate of intuitive mentalizing, and this network shows reduced activation and poor connectivity in Asperger's disorder.[54] A circuit involving the amygdala, orbital frontal cortex, anterior cingulate and temporal cortex may be important for social behaviour.[1,14,35] A general reduction in white matter might possibly affect the advanced network of social cognition, but our data are not sufficient to support this speculation.

In the SGA group, none had symptoms of Asperger's disorder, and the group did not have significantly increased ASSQ score compared with controls ($p = 0.08$). Hence, to be born SGA does not seem to involve an increased risk of developing the specific relational problems that we found in the VLBW group.

8.2.4 Other psychiatric disorders

Increased prevalence of depression has been reported in one study using questionnaires in adolescents with birth weight ≤ 1000 g.[119] However, we did not find more depressive symptoms or disorders by interview in the VLBW and SGA group than in the control group. Both ASEBA and SDQ cover anxiety and depression in one combined scale, making it difficult to differentiate between these two concepts.

Though the mothers reported more conduct problems for VLBW adolescents compared with controls, we did not find increased prevalence of conduct symptoms or disorders assessed by interview. Furthermore, we found low frequency of risk-taking behaviour such as use of alcohol or drugs. It has been claimed that the combination of ADHD and anxiety disorder reduces the risk of co-morbid conduct disorder.[120] Putting together the symptoms of anxiety and attention deficit with lack of hyperactivity and conduct problems, a picture emerges of adolescents who are careful and do not engange in sensation seeking behaviour. Our findings are consistent with results from a follow-

up study of VLBW adults at 20 years of age, reporting high frequency of internalizing symptoms, but low frequency of antisocial behaviour, alcohol and drug abuse.[66,67]

Teachers reported thought problems in the VLBW group, especially obsessions and strange behaviour. A few studies have described similar findings.[71,155,158] It is unclear what these symptoms imply, and whether they could be precursors of more serious psychiatric disorders. They may possibly correlate with both cognitive dysfunction and the specific relational problems. We also speculate that the thought problem scale on ASEBA blends real thought problems with anxiety symptoms.

Assessed by interview, none had manic or bipolar, psychotic or eating disorders. A few had other psychiatric disorders such as adjustment disorder, elimination disorder, posttraumatic stress disorder, stuttering and tic disorder. However, these were not more frequent in the VLBW or the SGA group than in the control group.

8.2.5 Usefulness of screening questionnaires

The two general screening questionnaires; ASEBA and SDQ, were rated by the adolescents themselves, their mothers, fathers, and teachers. Comparison with in-depth psychiatric interview made possible analyses of sensitivity and specificity. Self-reports did not reveal group differences even though the VLBW group had more psychiatric symptoms and disorders, assessed by interview. Hence, sensitivity was low and specificity high, showing the insufficiency of self-reported questionnaires in psychiatric assessment at this age. Mothers and fathers were fairly reliable informants, even though their agreement as to which children had clinical range scores was only moderate to good. The combination of mother- and father-reports increased the sensitivity on ASEBA, illustrating the advantages of including reports from both parents.

ASEBA gave a more differentiated picture than SDQ, which on the other hand may be preferable for screening as it is very short, and has greater emphasis on strengths. Since both questionnaires can be useful, selection should be based on the purpose and setting. However, their limitations must be kept in mind. They do not provide diagnostic assessment as symptom scores are not equivalent to DSM-IV or ICD-10 diagnostic criteria. In fact, sensitivity was low compared with diagnoses, but increased at the expense of lowered specificity when using a lower cut-off than the 90th percentile, which is commonly used as clinical range cut-off. In a clinical setting, we recommend a cut-off at the 84th percentile (borderline clinical range) in low birth weight

populations, in order to uncover as many as possible of those with psychiatric problems, well aware that some false positive subjects will be included. Further psychiatric assessment is then needed. However, in research, an optimal combination of sensitivity and specificity is essential, and Receiver Operating Characteristic curve may guide the choice of an adequate cut-off.

8.3 Quality of life and parent-child relations

We did not find group differences in self-perceived QoL measures. This was not very surprising, as others have reported likewise.[20,25,31,40,143] Yet, VLBW adolescents may have low self-esteem,[110] and a minority of ELBW adolescents may experience reduced health-related QoL.[117] In a study of term SGA as young adults, they were as likely to be employed, married and satisfied with life as were controls, even though they had lower academic education and professional attainment.[135]

Furthermore, others have previously reported discrepancies between subjectively perceived and proxy rated QoL.[40] Proxy responses by parents correlate poorly with the perceptions of their children, and children are more optimistic than adults regarding QoL.[45,75] Still, as we try to explore the adolescents' genuinely perceived QoL, the adolescents should be our primary source, even though their perception changes with age.[45] How others perceive their well-being is supplementary information.

Researchers have been concerned about possible long-term difficulties in parent-child bonding for VLBW children. Difficulties may arise partly due to child factors, as the infants are less responsive, partly due to maternal factors related to high family stress and preoccupation about the infant's safety.[24,33,36,51,84] Furthermore, in the general population, environmental stressors associated with low socioeconomic status may interrupt early attachment and subsequently lead to reduced relational qualities.[53] In our study, we did not find significant group differences in socioeconomic status. Moreover, being born VLBW or SGA did not influence the warmth in the parent-adolescent relationship at 14 years of age, indicating no long-term effect of potential difficulties in early attachment.

The VLBW adolescents reported their parents to be more protective than did the control adolescents, also after exclusion of individuals with disorders and disabilities. At least two explanations are possible: The parents may be prone to develop a habit of

overprotection, which is understandable after the birth of an initially fragile child. On the other hand, the parents may appropriately consider the need of protection to be above average, as we found that even healthy VLBW adolescents could have problems. Parental perception of child vulnerability has been thought to bring about overprotection.[142] A study of high risk VLBW children showed that parents who perceived their child as vulnerable, had more difficulties with separation from the child, but showed no other patterns of overprotection.[37]

Parents of VLBW adolescents experienced increased emotional impact, which was strongly related to the health status of the adolescents. Child psychiatric disorders are known to cause substantial levels of parental burden,[7] and we found that the presence of a psychiatric disorder had the strongest effect, followed by cerebral palsy. Despite the increased emotional burden, the mothers and fathers in our study did not have more mental health problems than controls. Also, when the parents' mental health was included in regression analyses, these factors could not explain the increased risk of psychiatric symptoms in the VLBW group.

8.4 Comments on selected subgroups

8.4.1 Gender

Epidemiological studies have shown gender characteristics in the prevalence of some psychiatric symptoms and disorders. Generally, there is a male preponderance in almost all early onset disorders that involve some form of neurodevelopmental impairment; hyperactivity, language disorders and autism.[114] The ratio of boys : girls for ADHD is roughly 3 : 1.[121] Asperger's disorder is about four times more common in boys than in girls.[61] For anxiety disorders, girls are generally overrepresented.[80] The same applies to depression in adolescence,[60] and eating disorders.[114] Boys are reported to have more conduct problems than girls during childhood, whereas girls tend to develop depressive and anxiety disorders during adolescence.[61]

In our study, we observed this traditional gender pattern for ADHD symptoms and externalizing behaviour in the control group. For other psychiatric symptoms, the numbers were probably too small to identify gender differences among controls. In the VLBW group, there were no gender differences in any symptom domains on psychiatric interview or questionnaires, except that girls had higher emotional symptom score than

boys on SDQ (mother- and father-reports, $p < 0.05$). However, this difference did not persist after exclusion of adolescents with low IQ_{est}. The increased prevalence of ADHD symptoms and higher mean scores of both attention deficit and light autistic traits were evenly distributed between genders. MRI-findings did not show gender differences in the VLBW group, even when adolescents with low IQ_{est} were excluded (results not reported in the papers). Hence, it seems that VLBW reduces the male bias for neurodevelopmental vulnerability found in the general population. Other researchers have reported parallel findings in VLBW and ELBW populations.[21,110,139] Lack of gender differences in vulnerability for psychiatric problems has also been reported in child populations with brain disorders in general.[59]

In the SGA group, girls had more emotional/internalizing symptoms than boys, while boys had more attention and externalizing problems. This was similar to the gender profile in the control group, and to findings in epidemiological studies.

8.4.2 Birth weight ≤ 1000 g and twins

In the cohort (paper I-III), 12 had birth weight ≤ 1000 g. Six of them had a psychiatric diagnosis. Of these six, three had low IQ_{est}, two had cerebral palsy, three had thinning of the corpus callosum, and five (one missing) had white matter reduction and ventricular dilatation (results not reported in the papers). Hence, the group of children with extremely low birth weight had high frequency of co-morbid disorders and MRI pathology. This falls in line with other studies. In VLBW children at 7-8 years, Horwood et al. found evidence of a gradient of risk with birth weight, as ELBW children had higher rates of difficulties than the other VLBW children.[74]

Ten participants were twins, of whom six were in twin pairs. Their mean birth weight was 1257 g (SD: 130) and none had birth weight ≤ 1000 g (results not reported in the papers). Six of them had psychiatric symptoms ≥ 75 % of diagnostic criteria, but only one had a psychiatric diagnosis. Four had low IQ_{est}, one had cerebral palsy, five had thinning of the corpus callosum and white matter reduction, and nine had ventricular dilatation. The small numbers limit statistical inference. Except for low IQ_{est}, these frequencies correspond to the results for the whole VLBW sample.

Twins have been objects for genetic studies, but can also be studied from another point of view; the special situation of being a twin, and its consequences on development and mental health. Perinatal mortality and morbidity are higher in twins

than in singletons, and accordingly cumulative incidences of various handicaps are higher in twins.[94] Another study found that parents reported a non-significant trend of boy twins towards having more behavioural/emotional disorders than boy singletons, but according to teachers, the twins were rated as less disturbed than singletons.[95] However, growth retarded ELBW twins are reported to have more motor, mental, visual and behavioural problems than their co-twin without growth retardation.[96] Hence, the psychiatric outcome of twins is likely to be influenced by the degree of growth retardation. Our number of twin participants is not sufficient to contribute to this research.

8.4.3 Cognitive abilities and psychiatric symptoms

During a broad neuropsychological assessment, estimated IQ was calculated. The neuropsychological results are not a part of this thesis. Still, cognitive abilities are relevant parameters when psychiatric results are discussed. Mental retardation increases the risk for psychiatric illness; on average 30 % of mentally retarded children have a psychiatric disorder, higher rates are found with a greater degree of retardation.[149] In addition to experiencing the same range of psychiatric problems as in the general population, the frequencies of autism, psychoses, behavioural disorders and ADHD are increased.[149] Increased prevalence of anxiety disorders (22 %) was found in a sample of children with borderline to moderate intellectual disability.[38]

Given this knowledge, we first analysed the data for the whole study population, and then after excluding adolescents with low IQ_{est} (IQ_{est} below 2 SD of the mean value in the control group). We found that the results were mainly unchanged, except for reduced frequency of anxiety symptoms and disorders. Still, even after exclusion of adolescents with low IQ_{est}, the VLBW group had significantly lower mean IQ_{est} than controls ($p < 0.01$, result not reported in the papers). Furthermore, IQ_{est} influenced the risk for psychiatric symptoms in the VLBW group compared with the control group even when adolescents with low IQ_{est} were excluded (logistic regression analysis; unadjusted OR: 3.7, 95 % CI: 1.5 – 8.8, adjusted for IQ_{est}: 2.3, 95 % CI: 0.9 – 5.9, results not reported in the papers). Thus, IQ was associated with VLBW as well as with psychiatric symptoms. Is IQ then a confounder which should be controlled for? A confounding factor is associated with the exposure (VLBW), and independent of that exposure, is a risk factor for the outcome (psychiatric symptoms).[69] But lowered IQ_{est} in

the VLBW population is likely to be dependent of the exposure, and as such, is not a confounder. A more probable biological mechanism is a causal pathway between VLBW, affected IQ and psychiatric symptoms. Hence, if the purpose is to assess psychiatric problems irrespective of mediators, IQ should not be controlled for.

Furthermore, it is relevant to discuss whether low IQ_{est} should lead to exclusion of individuals in a population based follow-up study. Researchers have handled this question differently.[18] The strength of a population based study is to establish true prevalence rates for disorders in a natural cohort, which is crucial in the research on low birth weight.[115] However, the role of IQ certainly needs to be discussed. Cognitive abilities are likely to be affected by genetic and environmental influences, as well as by preterm birth. Low IQ is an important outcome measure in follow-up of low birth weight, as well as an additional risk factor for psychiatric illness. Therefore, in order to give a comprehensive view in this study, results are mainly reported for the total sample, supplemented with results when adolescents with low IQ_{est} are excluded.

8.5 Brain and mind: Nature and nurture

The brain is the organ of the mind. Nature is dependent on nurture, and the outcome of nurture is dependent on nature.[43] Furthermore, along with their parents' genes, all children inherit their parents, their peers, and the community they live in. This social niche is an "envelope of life chances" (Eisenberg).[43] Nature, nurture and the social niche jointly mould brain structure. In early life, there is a great proliferation of neurons, providing a substrate for environmentally induced structural changes: activity selects synapses that will persist, while inactivity results in regression and apoptosis.[43] In addition, researchers have uncovered a previously unrecognized potential for producing new neurons.[47] As structure follows function, responsive interaction between infants and their caretakers is crucial to biological as well as to psychosocial development.[43] Genes and biology set the stage and boundaries for the possible, environment shapes the action.[44]

How does brain immaturity at birth influence the interaction between structure and function? Our understanding has to bring together biological, psychosocial and developmental factors in an integrated model. Development is at one and the same time a social, a psychological, and a biological process.[44] The immature brain of a very

preterm infant differs from the brain of a full term infant. Processes of cerebral organizing proceed, and are forced to be carried out under different environmental conditions, including a risk of suboptimal nutrition. Furthermore, the brain may be exposed to damaging incidents like infection, ischemia or haemorrhage, which may alter the function of parts of the brain.[150] Hence, the stage is set slightly differently for VLBW children compared with term children.

Brain disorders (structural, cerebral palsy, epilepsy) are associated with increased risk of most psychiatric problems, yet, neurological factors do influence the type of psychiatric disorder: Hyperactivity and Pervasive developmental disorders are markedly more frequent in children with brain disorders.[59] Our results fit with this well documented knowledge, as we found increased prevalence of attention deficit and increased score for light autistic traits (ASSQ). The associations between ADHD symptoms (ADHD-Rating Scale score) and white matter reduction support the view of a dominant neurological basis. Still, we must not fall into the trap of excluding the effect of other influences. We aknowledge the effects of psychosocial factors, possibly as contributors in forming brain structure, partly by learning. In the development of a child's unique personality, genes and brain are modified by inter-personal experiences in low birth weight children as in others. The warmth in the parent-child relations can be used as one measure of such inter-personal experiences. We found that this quality of care was not affected by birth weight.

The results are interpreted within the theoretical framework for this study, acknowledging the reciprocal action of bio-psycho-social factors. In a different framework, other aspects might be emphasized. However, in addition to finding the model useful, we have demonstrated strong support for the hypothesis of an increased biological risk for VLBW children.

8.6 Resilience

In opposition to the traditional "problem seeking" in child and adolescent psychiatry, focus has been directed towards coping and resources. Resilience refers to the ability to show adequate social and cognitive competence despite the presence of risk factors.[53] Research on resilience factors is still modest, especially in biologically high risk children. Three main dimensions characterize stress-resistant children:[53]

1. Dispositional attributes (temperament, cognitive abilities, self-beliefs etc.)
2. Family characteristics (warmth, closeness, cohesion etc.)
3. Availability and use of external support systems by family members

Our study is not a study of resilience; however, the theme should be addressed in future research. The results on quality of life and parent-child relations may contribute to this line of thinking, putting emphasis on protective factors, such as family relations and functioning. The warmth in the parent-child relationship might be protective against further development of psychiatric symptoms in the VLBW group.

8.7 The limitations of psychiatric concepts

The professional luggage of a child psychiatrist contains the theoretical framework, acquired knowledge and experience gained during years of working with youngsters and their families. A child psychiatrist is trained to perform diagnostic work, putting names and numbers on the patient's problems. This assessment is the essential starting point for any treatment. With most patients, we find the diagnostic principles useful, but now and then we meet children and adolescents who do not quite fit the map of psychiatric concepts. In meeting low birth weight adolescents, I often found these concepts less useful. The problem was not to decide on diagnosis or no diagnosis, but I started to recognise common traits for which I had no label. The widespread attention deficit problems revealed special characteristics. Still, the concept of ADHD, inattentive type, was helpful. But my reflections grew when VLBW adolescents turned out to have higher scores than controls on the Autism Spectrum Screening Questionnaire, indicating functional disadvantages in social relations. No psychiatric diagnosis can be used to cover these traits; however, they seem to be specific traits, which are more frequently found in VLBW than in control adolescents. A parallel comprehension is expressed by Skuse in a review lecture; stating that as we are beginning to understand the neural processes underlying psychiatric disorders, we may discover that these substrates do not neatly adhere to our ICD-10 or DSM-IV categorisation.[128]

8.8 Ethical aspects

Some ethical aspects need to be addressed. Firstly, should this study be done? Research is essential in order to gain knowledge that can reduce the risk of aversive incidents,

prevent development of disease, treat disease and relieve sequelae. This is particularly important when medical progress makes it possible to rescue infants at the edge of viability.

On the other hand, eventual side effects have to be considered. This study required extensive assessment of young people in the midst of their puberty, revealing personal, partly intimate information. The requirement to give personal information also applied for their parents. The participants' contribution was considerable with regard to both time and effort. However, the examinations were not invasive or painful.

We were concerned that the parents would find the questionnaires too extensive, and that we might loose some participants due to this. We planned to use mothers as the main informant representing the parents. However, the Regional Committee for Medical Research Ethics advised us to treat mothers and fathers equally. Hence, we asked both parents to score the questionnaires separately, which gave a unique set of data.

Written information was given to the parents as well as to the adolescents, who gave informed consent prior to attendance. The researchers endeavoured to create a comfortable setting for the participants during the examinations. They could withdraw from the study at any time.

At the end of the consultation, the participants (adolescents and parents) received feedback on the psychiatric evaluation. Those in need of psychiatric services were referred to the local child and adolescent psychiatric clinic. After publication of the first results, a seminar was held for the participants. We then presented all main group results from the study. Those who wanted an individual consultation after this seminar were given an appointment.

Taking all considerations into account, it is our opinion that the study was well within ethical boundaries.

9 Summary

VLBW adolescents

We found that the VLBW adolescents had specific emotional and cognitive traits. Some of them fit with psychiatric concepts and others do not. They had an increased risk of developing psychiatric symptoms and disorders compared with controls, especially attention deficit, anxiety and relational problems affecting their social skills and overall functioning. Academic achievement was reduced. The attention problems were widespread, but only a minority fulfilled the diagnostic criteria of Attention-deficit/hyperactivity disorder. Increased prevalence of anxiety symptoms and disorders may be due to a number of factors, comprising both biological/neuroendocrine and psychosocial mechanisms. The peer problems and deficits in social skills may indicate specific difficulties in relating and adjusting to others, with deficits in comprehending the subtle cues of social relations. The implication of thought problems reported by teachers is unclear. Adolescents with birth weight ≤ 1000 g showed a tendency towards more psychiatric disorders than those with birth weight between 1000 and 1500 g. The lack of gender differences demonstrates that prematurity exceeds the usual effect of gender regarding vulnerability for developing psychiatric symptoms.

We found that the VLBW adolescents perceived self-esteem and quality of life as others did at the age of 14. However, parents reported functional disadvantages and reduced quality of life measures for their adolescents. The parents worried more for their children's functioning and well-being, especially if the child had a psychiatric disorder or cerebral palsy. Still, being born VLBW did not influence the warmth in the parent-child relationship, nor did the parents have more mental health problems.

As the association between VLBW and psychiatric problems could not be explained by SES or the parents' mental health, a biological cause-effect relationship seems plausible. The frequency of cerebral MRI abnormalities was higher in the VLBW group than in the control group. Furthermore, ADHD symptoms were associated with white matter reduction and thinning of the corpus callosum, while other psychiatric symptoms were not associated with MRI abnormalities. These results support the hypothesis of a specific ("pure") type of ADHD with a dominant neurological aetiology, while interacting psychosocial experiences play a minor part. Our study indicates that

being born VLBW involves a biological vulnerability with increased risk of psychiatric symptoms.

SGA adolescents

Although every fifth SGA adolescent had psychiatric symptoms, assessed by interview, the prevalence of symptoms and disorders did not differ significantly from controls. Yet, screening questionnaires displayed more behavioural problems, lowered social competence and a tendency towards attention deficit/hyperactivity. Teachers reported withdrawal and thought problems, while academic performance did not differ from controls. Boys had more attention and externalizing problems than girls.

Generally, on psychiatric measures, the term SGA group seemed to fall in-between the VLBW and the control group, resembling the control group more than the VLBW group.

The SGA adolescents and their parents reported self-esteem and quality of life as in the control group. Being born SGA at term did not influence the warmth in the parent-child relationship, and the parents did not have more mental health problems than others. The frequency of cerebral MRI abnormalities in the SGA group did not differ from the control group, and no associations were found between psychiatric symptoms and MRI abnormalities.

10 Conclusions

The VLBW adolescents had increased prevalence of psychiatric symptoms and disorders, and reduced social and academic skills. Term SGA adolescents had discrete behavioural and attention deficit symptoms, but not increased prevalence of psychiatric disorders. The adolescents perceived their quality of life as others, whereas the parents reported functional disadvantages and reduced quality of life measures for their VLBW adolescents. The VLBW parents experienced increased emotional impact, but not more mental health problems. The warmth in the parent-child relationship was unaffected by birth weight. The VLBW, but not the SGA group, had a higher frequency of cerebral MRI abnormalities than the control group. ADHD symptoms were associated with white matter reduction and thinning of the corpus callosum in the VLBW group, while no associations were found between psychiatric symptoms and MRI abnormalities in the SGA group.

11 Clinical implications

Our results should draw attention to the fact that VLBW children may need long-term health services. The results give grounds for follow-up programs for VLBW children through childhood and adolescence, focusing on mental health, learning difficulties and other developmental disabilities. The children may have special educational needs that should be met throughout their schooling career.

Screening questionnaires can be used in order to identify children at risk of developing psychiatric disorders. Although structural MRI is not essential for diagnostic assessment, a finding of white matter reduction may be compatible with ADHD symptoms. Once the diagnosis of ADHD has been given, adequate treatment including medication and special educational services should be initiated.

As low birth weight adolescents may have a broad spectrum of problems, they need an integrated approach addressing both mental and physical health.

12 Directions for future research

In my effort to answer the aims of the thesis, new research questions emerged as my knowledge expanded. Many questions remain unanswered. The following topics need to be explored in low birth weight populations:

- What are the important risk factors that being born with low birth weight entails?
- Is it possible to expand our knowledge on associations between more specific brain abnormalities and psychiatric disorders in low birth weight adolescents?
- Are the present results applicable for new generations of low birth weight children?
- Are psychiatric problems long-lasting?
- Are there specific temperamental and resilience characteristics in low birth weight populations?
- Do intervention programs work?

The first two topics will be explored in further analyses of available data in this study. Associations between brain structure and psychiatric disorders will be examined using advanced technology of MRI-based volumetric measurements and diffusion tensor imaging.

The other questions can tentatively be answered by repeated follow-up studies, long-term follow-up into adult age, exploration of temperament and resilience factors, and randomized clinical trials with intervention programs. The latter could for example be a specific follow-up program, attention training, or early intervention focusing on attachment, parent-child relations and the emotional burden for parents.

The research on low birth weight is faced with great challenges; the rapid progress of medical technology and treatment requires consecutive surveillance of those exposed, and evidence based feedback to those putting new medical achievements into practice.

13 Closing remark

I wish to return to the quotation of Albert Einstein in the introduction: "*Not everything that can be measured counts and not everything that counts can be measured"*.
I sincerely hope that the measurements presented are relevant for those concerned. At the same time, I am convinced that we have touched only parts of what counts for low birth weight adolescents and their families. Life is much more than researchers can ever reveal. In focusing on details and numbers, my real learning was to discover the greatness of the human mind.

14 References

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15 Papers I - V

ORIGINAL ARTICLE

Psychiatric symptoms and disorders in adolescents with low birth weight

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Arch Dis Child Fetal Neonatal Ed 2004;**89**:F445–F450. doi: 10.1136/adc.2003.038943

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Accepted 6 November 2003

Objective: To evaluate the prevalence of psychiatric symptoms and disorders associated with low birth weight.

Design/study groups: A population based follow up study of 56 very low birthweight (VLBW: birth weight $\leqslant$ 1500 g), 60 term small for gestational age (SGA: birth weight $<$ 10th centile), and 83 term control (birth weight $\geqslant$ 10th centile) children at 14 years of age.

Outcome measures: Schedule for affective disorders and schizophrenia for school aged children, attention deficit/hyperactivity disorder (ADHD) rating scale IV, autism spectrum screening questionnaire, and children's global assessment scale.

Results: VLBW adolescents had a higher prevalence of psychiatric symptoms (46%) than controls (13%) (odds ratio (OR) 5.7, 95% confidence interval (CI) 2.5 to 13.0) and more psychiatric disorders (25%) than controls (7%) (OR 4.3, 95%CI 1.5 to 12.0), especially anxiety disorders. Although 25% of the VLBW adolescents had attention problems, ADHD was diagnosed in only 7%. Four VLBW adolescents had symptoms of Asperger's disorder, and the VLBW group had a higher sum score than controls on the autism spectrum screening questionnaire. Although more SGA adolescents had psychiatric symptoms than controls (23% *v* 13%), the difference was not statistically significant. Results remained essentially the same when adolescents with low estimated intelligence quotient were excluded, and persisted after possible psychosocial confounders had been controlled for.

Conclusion: VLBW, but not SGA adolescents, have a high risk of developing psychiatric symptoms and disorders by the age of 14, especially attention deficit, anxiety symptoms, and relational problems.

Follow up studies of very low birthweight (VLBW) children have documented increased prevalence of neurodevelopmental disabilities and cognitive deficits.[1–3] There has been a growing awareness of psychiatric problems.[4–7] The most consistent finding is an increased risk of attention deficit/hyperactivity disorder (ADHD), especially the inattentive type.[3 6 8 9] Anxiety disorders, depression, and thought problems may also occur.[6 7]

For children born small for gestational age (SGA) at term, the outcome is less clear, especially when it comes to social and emotional development.[6 10–14] VLBW and term SGA infants differ in biological basis and vulnerability, hence the long term outcome may vary. Most studies are performed in childhood using questionnaires.[3] Although there are some follow up reports in adolescence, our knowledge on psychiatric disorders in this age group is limited, and few have used psychiatric interview as a diagnostic tool.[4 5 7 15–20] By using in depth psychiatric assessment, we wanted to evaluate whether the prevalence of psychiatric symptoms and disorders is higher in VLBW and SGA adolescents than in adolescents with normal birth weight, and describe the characteristics of psychiatric symptoms and disorders in these groups.

MATERIAL AND METHODS

Study design

This study is a population based follow up at 14 years of age of two groups of adolescents with low birth weight (VLBW and term SGA) compared with a control group of normal birth weight. The VLBW children were admitted to the neonatal intensive care unit at the University Hospital in Trondheim (the referral hospital) in 1986–1988. Children born in 1988 were assessed thoroughly at 1 and 6 years of age.[21–23] The SGA and control children were born to mothers living in the Trondheim region. They were enrolled before week 20 of pregnancy in a multicentre study between January 1986 and March 1988.[24 25] A 10% random sample of women (with one or two previous pregnancies) was selected for follow up during pregnancy. At birth, all the children born to mothers in the random sample and all the SGA children were included for follow up.[26] The present study was carried out between November 2000 and October 2002, and included a psychiatric assessment, an evaluation of cognitive and motor abilities, and a neuropaediatric examination.

Study population

VLBW adolescents

VLBW was defined as a birth weight $\leqslant$ 1500 g. Ninety nine children were admitted to the neonatal intensive care unit in 1986–1988. Of these, 23 died, one child with trisomy 21 was excluded, and six had moved. Of the remaining 69, 13 did not consent to participate at follow up. Thus 56 (81%) were examined (30 boys, 26 girls). Twelve had a birth weight $\leqslant$ 1000 g. Ten participants were twins, of whom six were in twin pairs.

SGA adolescents

Of 1200 eligible women, 104 (9%) gave birth to an SGA child, defined by a birth weight $<$ 10th centile of all infants in the multicentre study, adjusted for gestational age, sex, and parity.[25] At follow up, 12 had moved. Of the remaining 92, 32

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASSQ, autism spectrum screening questionnaire; CGAS, children's global assessment scale; DSM-IV, *Diagnostic and statistical manual of mental disorders*, fourth edition; IQ_{est}, estimate of intelligence quotient; SGA, small for gestational age; VLBW, very low birthweight

What is already known on this topic

- VLBW children have increased risk of emotional and behavioural problems, especially attention problems
- Psychiatric outcome for term SGA children is less clear

What this study adds

- Prevalence of psychiatric symptoms and disorders in VLBW and term SGA adolescents, based on in depth psychiatric assessment
- Description of psychiatric symptoms and disorders in these groups, highlighting:
  - Attention deficit symptoms were common in VLBW adolescents, however, only a minority had ADHD
  - Deficits in social skills and autistic spectrum symptoms occurred in the VLBW group
  - Psychiatric problems affected the overall functioning of both VLBW and SGA adolescents

did not consent, leaving 60 (65%) for assessment (28 boys, 32 girls).

Control adolescents

The control group comprised 120 children with a birth weight ⩾ 10th centile for gestational age, born at term to mothers in the 10% random sample. At follow up, 10 had moved. Of the remaining 110, 27 did not consent, leaving 83 (76%) who participated (35 boys, 48 girls).

Non-participants

There were no differences in mothers' age at childbirth, duration of pregnancy, or the infants' birth weight, body length, and head circumference between those who participated and those who did not consent in any of the groups.

Methods

Psychiatric assessment

Psychiatric symptoms and disorders were diagnosed using the semistructured interview Schedule for affective disorders and schizophrenia for school aged children (KSADS).[27 28] This interview is performed separately with parent and adolescent. It consists of a screening part and supplementary diagnostic interviews. Conclusions are drawn according to the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV).[29] The interviewer differentiates between diagnosis, symptoms ⩾ 75% level of diagnostic criteria, or neither.

Of the 199 adolescents, the first author assessed 171, and another child psychiatrist carried out 28 interviews. The first 27 interviews with adolescents were videotaped and scored to test interrater reliability. The intraclass correlation coefficient was 0.91 for all symptoms, 0.86 for anxiety symptoms, and 0.86 for ADHD symptoms. A third senior child psychiatrist, blinded to the first evaluation, performed a second diagnostic assessment based on the written interviews. Subsequently, diagnostic consensus was obtained. The child psychiatrists were blinded to birth weight status.

The interviewer scored the adolescents' overall functioning on the children's global assessment scale (CGAS).[30] This scale ranges from 1 to 100, divided into 10 main categories. A score above 80 denotes good functioning.

The psychiatric interview was supplemented with the autism spectrum screening questionnaire (ASSQ),[31] as part of the parents' interview, and the teachers' report on ADHD rating scale IV.[32 33] Parents stated their own mental health on symptom checklist-90-R (SCL-90-R), and we used the global severity index as a single summary measure of psychological distress.[34]

Evaluation of cognitive abilities

An estimate of intelligence quotient (IQ_{est}) was calculated using four of 10 subscales of Wechsler intelligence scales (WISC-III)[35]: vocabulary, arithmetic, block design and picture arrangement.[36] We defined ''low IQ_{est}'' as below 2 SDs of the control group mean value. Data were analysed both including and excluding children with low IQ_{est}.

Socioeconomic status

Socioeconomic status was calculated according to Hollingshead's two factor index of social position, based on a combination of parents' education and occupation.[37]

Ethics

The regional committee for medical research ethics approved the study protocol. Written informed consent was obtained from adolescents and parents.

Statistical analysis

SPSS 11.5.1 was used for data analysis. Three group comparisons were made using one way analysis of variance for variables with a normal distribution and Kruskal-Wallis for ordinal data. If a difference was found between groups ($p < 0.05$), two group comparisons were made using Scheffe's post hoc test for normally distributed variables and the Mann-Whitney U test for variables with a non-normal distribution.[38] Differences in proportions between groups were analysed by the χ^2 test. Odds ratios (OR) with 95% confidence interval (95%CI) were calculated as an estimate of the relative risk that a child with low birth weight had psychiatric symptoms and disorders, compared with the control group. To control for possible confounders, we used binary logistic regression[38] to calculate adjusted OR, first in a bivariate analysis, followed by a multivariate analysis (backward stepwise) for covariates altering the unadjusted OR > 10%.

RESULTS

Group characteristics

Table 1 shows family and child characteristics. There were no significant differences between groups with regard to mothers' or fathers' education, socioeconomic status, monthly income, or maternal or paternal mental health. Likewise, there were no sex differences between the groups. Of the 56 VLBW adolescents, seven (13%) were living in single parent families, compared with five (8%) in the SGA and 15 (18%) in the control group (ns).

Ten (18%) VLBW adolescents had low IQ_{est} compared with four (7%) SGA and three (4%) controls. Cerebral palsy was diagnosed in six (11%) VLBW (four diplegia, one hemiplegia, one quadriplegia), and one SGA adolescent (diplegia). Four of the VLBW and the one SGA with cerebral palsy had low IQ_{est}. Two VLBW and one control adolescent had epilepsy. There were no major visual or hearing impairments.

Psychiatric assessment by semistructured interview (KSADS)

Of the 56 VLBW adolescents, 26 (46%) had emotional or behavioural problems ⩾ 75% of diagnostic criteria, compared with 11 of 83 (13%) controls (OR 5.7, 95%CI 2.5 to 13.0) (table 2). The most common symptoms among VLBW adolescents were attention deficit (OR 6.6, 95%CI 2.0 to 21.3 *v* controls) and anxiety (OR 3.5, 95%CI 1.2 to 10.0 *v*

Table 1 Family and child characteristics in two groups of low birthweight adolescents compared with a control group at 14 years of age

	VLBW (n = 56)	SGA (n = 60)	Control (n = 83)
Family characteristics			
Maternal			
Age (years)	42.3 (5.0)	42.1 (3.6)*	44.0 (4.5)
Education (years)	13.5 (3.4)	12.9 (3.1)	14.2 (2.9)
Mental health†	0.26 (0.22)	0.27 (0.26)	0.28 (0.23)
Paternal			
Age (years)	45.7 (5.9)	44.4 (3.6)	46.0 (4.8)
Education (years)	13.1 (3.7)	13.4 (2.8)	14.1 (3.1)
Mental health‡	0.31 (0.42)	0.17 (0.17)	0.18 (0.17)
Socioeconomic status	3.3 (1.3)	3.4 (1.3)	3.8 (1.1)
Monthly income (1000 NOK)	31.8 (10.9)	30.9 (9.9)	29.5 (9.9)
Child characteristics			
Birth weight (g)	1174 (233)§	2921 (211)§	3691 (459)
Gestational age (weeks)	28.8 (2.7)§	39.5 (1.1)	39.6 (1.2)
Assessment age (years)	14.1 (0.3)	14.2 (0.3)	14.2 (0.3)

Values are mean (SD).
*$p < 0.05$ *v* controls. Three group comparisons performed with analysis of variance and Scheffe's post hoc test for parametric data, and Kruskal-Wallis and Mann-Whitney U test for non-parametric data.
†Mothers' mean global severity index on symptom checklist-90-R[34] was missing for six VLBW, one SGA, and nine control adolescents.
‡Fathers' mean global severity index on symptom checklist-90-R[34] was missing for 10 VLBW, six SGA, and 15 control adolescents.
§These were the selection criteria, and differed by definition versus controls ($p \leqslant 0.001$).
VLBW, Very low birth weight; SGA, small for gestational age.

controls). Four VLBW adolescents had symptoms of Asperger's disorder, compared with none in the control group ($p < 0.05$).

Psychiatric disorders were diagnosed in 14 (25%) VLBW adolescents compared with six (7%) controls (OR 4.3, 95%CI 1.5 to 12.0) (table 2). Anxiety disorders were most prevalent (OR 4.4, 95%CI 1.1 to 17.6 *v* controls), whereas four (7%) had ADHD compared with one control (ns). One VLBW adolescent had Asperger's disorder. Six of 12 (50%) with birth weight $\leqslant$ 1000 g and eight of 44 (18%) with birth weight $>$ 1000 g had a psychiatric diagnosis ($p = 0.054$).

Nine of the 10 VLBW adolescents with low IQ_{est} had psychiatric symptoms, and four had a diagnosis (ADHD, Asperger's disorder, anxiety disorders). Of the two VLBW adolescents with cerebral palsy without low IQ_{est}, one had ADHD.

Although 14 (23%) SGA adolescents had psychiatric symptoms, and six (10%) had a psychiatric disorder, this did not differ significantly from controls (table 2).

There were no sex differences in the VLBW and SGA group, whereas in the control group more boys than girls had ADHD symptoms ($p < 0.05$).

Few had experienced drinking $\geqslant$ 3 units of alcohol (two VLBW adolescents, three SGA, five controls) (ns). One adolescent in each group admitted experimenting with other substances (cannabis, amphetamine).

ADHD rating scale IV

VLBW adolescents had higher mean attention score and total score than controls, without significant difference in hyperactivity score (table 3). Although the SGA group had higher total score than controls, the difference was not significant. Boys had a higher total score than girls in the control ($p < 0.01$) and SGA groups ($p < 0.05$), but not in the VLBW group ($p = 0.30$) (data not shown).

Autism spectrum screening questionnaire (ASSQ)

The VLBW group had higher mean sum score than controls (table 3), whereas the SGA group showed a trend towards a higher sum score compared with controls ($p = 0.08$). There were no sex differences. VLBW adolescents had high scores on the items: ''Lives somewhat in a world of his/her own with restricted idiosyncratic intellectual interests'', ''Has a literal understanding of ambiguous and metaphorical language'', ''Uses language freely but fails to make adjustment to fit social contexts or the needs of different listeners'', ''Lacks empathy'', ''Wishes to be sociable but fails to make relationships with peers''.

Children's global assessment scale (CGAS)

VLBW adolescents had lower mean CGAS score than controls (table 3). Scores below 80 were found in 37 of 56 (66%) VLBW, 17 of 83 (21%) control (OR 7.6, 95%CI 3.5 to 16.3), and 24 of 60 (40%) SGA (OR 2.6, 95%CI 1.2 to 5.4 *v* controls) adolescents. There were no sex differences in any of the groups.

Excluding adolescents with low IQ_{est}

When adolescents with low IQ_{est} were excluded, the results were essentially unchanged, except that the VLBW group had a reduced prevalence of anxiety symptoms ($p = 0.09$) and disorders ($p = 0.07$) compared with controls.

Multivariate analyses

With the outcome variable symptoms of any psychiatric disorder ($\geqslant$ 75% of diagnostic criteria), logistic regression analysis was run to evaluate the confounding effect of psychosocial factors (table 4). Paternal education and maternal and paternal mental health were the only factors that influenced the increased risk of psychiatric symptoms in the VLBW group more than 10%. When these variables were included in multivariate analysis, the increased risk associated with VLBW was 5.8 (95%CI 1.9 to 17.4), with maternal mental health as the only variable causing a significant change. Analogously, after multivariate analysis, the risk associated with SGA was 2.9 (95%CI 1.0 to 8.2), with only paternal mental health causing a significant change.

DISCUSSION

In this study we found that nearly every other VLBW adolescent had psychiatric symptoms. One in four had a psychiatric diagnosis, anxiety disorders being the most prevalent. Attention deficit problems were acknowledged in every fourth VLBW adolescent, but only a minority fulfilled the diagnostic criteria. Moreover, relational problems and deficits in social skills were common among VLBW adolescents, and some had autistic spectrum symptoms. Although every fifth SGA adolescent had psychiatric symptoms, they did not differ significantly from controls.

The strength of this study is the thoroughness of the psychiatric assessment, using both questionnaires and a semistructured interview, and different sources of information. Even though the VLBW adolescents had widespread emotional or behavioural symptoms, many did not reach the diagnostic level of a psychiatric disorder. However, the CGAS results indicate that the psychiatric problems were affecting the overall functioning in both the VLBW and the SGA group, causing strain for the adolescents and their families.

The psychiatric outcome was significantly worse for the VLBW group, with consistent results across all instruments. This association is unlikely to be due to chance. The lack of statistical significance for the SGA group may be due to the limited sample size.

Of the eligible children, 73% (199/271) took part in the study. There were no differences in key variables between participants and those who did not consent to participate. It is therefore unlikely that our main results are caused by selection bias.

Table 2 Psychiatric symptoms and diagnoses according to DSM-IV, based on in depth psychiatric interview, in two groups of low birthweight adolescents compared with a control group at 14 years of age

	VLBW (n = 56)	SGA (n = 60)	Control (n = 83)
Symptoms ⩾ 75% of diagnostic criteria			
Symptoms any psychiatric disorder	26 (46)***	14 (23)	11 (13)
Of these			
Symptoms anxiety disorders	12 (21)*	7 (12)	6 (7)
Symptoms depressive disorder	3 (5)	3 (5)	0
Symptoms ADHD	14 (25)***	4 (7)	4 (5)
Symptoms conduct disorder	1 (2)	3 (5)	3 (4)
Symptoms Asperger's disorder	4 (7)*	0	0
Other symptom categories	5 (9)	3 (5)	3 (4)
⩾2 symptom categories	9 (16)	4 (7)	5 (6)
Diagnostic level			
Any psychiatric disorder	14 (25)**	6 (10)	6 (7)
Of these			
Anxiety disorders†	8 (14)*	4 (7)	3 (4)
Depressive disorder	2 (4)	0	0
ADHD	4 (7)	2 (3)	1 (1)
Conduct disorder	0	2 (3)	1 (1)
Asperger's disorder	1 (2)	0	0
Other disorders‡	4 (7)	1 (2)	2 (2)
⩾2 diagnoses§	5 (9)*	2 (3)	1 (1)

Values are number (%).
*p < 0.05, **p < 0.01, ***p ⩽ 0.001 *v* controls. χ^2 test was used to analyse differences in proportions between groups, with Fisher's exact test when cell number less than five.
†Anxiety disorders: separation anxiety disorder, generalised anxiety disorder, social phobia, or specific phobia.
‡Other disorders: adjustment disorder, elimination disorder, post-traumatic stress disorder, stuttering, tic disorder. None had manic or bipolar, psychotic, or eating disorder.
§Comorbid diagnoses: ADHD, adjustment disorder, anxiety disorder, Asperger's disorder, conduct disorder, depressive disorder, elimination disorder, post-traumatic stress disorder, stuttering.
DSM-IV, *Diagnostic and statistical manual of mental disorder*; fourth edition[29]; VLBW, very low birth weight; SGA, small for gestational age; ADHD, attention deficit/hyperactivity disorder.

The parents of VLBW children knew that their child belonged to a risk group. However, the examiners were blinded, and assessment was based on separate interviews with adolescent and parent, including clinical judgment and teachers' report on ADHD rating scale, making it less likely that the results are caused by information bias.

The VLBW children were classified according to a birth weight ⩽ 1500 g, and some of them may have been growth retarded in utero. However, they were all born preterm, and we have chosen to treat them as a group in this study. The 10th centile definition of SGA is crude, and may include a certain proportion of normal small infants, whereas some growth retarded infants may have been classified as controls. Thus, the non-significant differences found between SGA and controls may be underestimates of the real differences.

The results were mainly unchanged when we excluded the adolescents with low IQ_{est}. Moreover, the increased risk of psychiatric symptoms among VLBW adolescents persisted after possible psychosocial confounders had been controlled for.

Table 3 Results on questionnaires: ADHD rating scale IV, autism spectrum screening questionnaire, and children's global assessment scale in two groups of low birthweight adolescents compared with a control group at 14 years of age

	VLBW (n = 56)	SGA (n = 60)	Control (n = 83)
ADHD rating scale IV (teachers' report)†			
Attention score	7.1 (6.0)***	5.1 (6.4)	3.8 (5.9)
Hyperactivity score	2.7 (4.4)	3.0 (5.3)	2.1 (4.4)
Total score	9.8 (9.0)***	8.1 (10.9)	5.9 (10.0)
ASSQ sum score	5.5 (5.9)***	3.0 (4.7)	2.0 (2.7)
CGAS score	72.8 (16.5)***	82.3 (10.8)	85.3 (8.2)

Values are mean (SD).
***p < 0.001 *v* controls. Three group comparisons performed with analysis of variance and Scheffe's post hoc test for parametric data, and Kruskal-Wallis and Mann-Whitney U test for non-parametric data.
†Teachers' report was missing for 11 VLBW, eight SGA, and 11 control adolescents.
ADHD rating scale IV, Attention deficit hyperactivity disorder rating scale IV[32 33]; ASSQ, autism spectrum screening questionnaire[31]; CGAS, children's global assessment scale[30]; VLBW, very low birth weight; SGA, small for gestational age.

Table 4 Odds ratio (OR) with 95% confidence intervals (CI) as an estimate of the relative risk of psychiatric symptoms in two groups of low birthweight adolescents compared with a control group at 14 years of age, adjusted for psychosocial factors: psychiatric symptoms ⩾75% of diagnostic criteria any disorder

	VLBW *v* control (n = 139)		SGA *v* control (n = 143)	
	OR	95%CI	OR	95%CI
Unadjusted OR	5.7	2.5 to 13.0	2.0	0.8 to 4.8
Adjusted for:				
Maternal				
Age	5.6	2.4 to 12.9	1.8	0.7 to 4.4
Education	5.5	2.4 to 12.5	1.8	0.7 to 4.4
Mental health†	7.1	2.7 to 18.8	2.1	0.8 to 5.4
Paternal				
Age	5.6	2.4 to 12.8	2.1	0.9 to 5.1
Education	5.0	2.2 to 11.8	1.9	0.8 to 4.6
Mental health‡	4.7	1.8 to 12.4	3.1	1.1 to 8.6
Socioeconomic status§	6.2	2.6 to 14.4	1.8	0.7 to 4.4
Monthly income	6.0	2.5 to 14.2	1.9	0.8 to 4.8
Single parent	5.6	2.5 to 12.9	2.0	0.8 to 4.8

Bivariate logistic regression analysis displaying adjusted OR for possible confounding factors.
†Global severity index on symptom checklist-90-R[34] was missing for six VLBW, one SGA, and nine control adolescents.
‡Global severity index on symptom checklist-90-R[34] was missing for 10 VLBW, six SGA, and 15 control adolescents.
§Hollingshead's two factor index of social position.[37]
VLBW, very low birth weight; SGA, small for gestational age.

Our results on psychiatric symptoms are consistent with other studies on VLBW adolescents at ages 10–14 years.[4 5 15 18 39] Prevalence reports on psychiatric disorders vary from 24% to 32%, which is well in keeping with our results.[5 15 39]

The prevalence of anxiety disorders corresponds to reports of 8–10% in VLBW and LBW (birth weight $<$ 2500 g, ages 6–12).[5 19 40] We did not find an increased prevalence of depression, which has been reported in one study of adolescents with birth weight $\leqslant$ 1000 g.[20]

Our finding that 25% of VLBW adolescents had considerable attention deficit symptoms is in keeping with other studies.[3] Reports on the prevalence of ADHD vary between 5% and 32%,[5 15 18 19 39 41–43] presumably because of differences in study design, inclusion criteria, assessment age, and methods. We found that only 7% had ADHD according to DSM-IV criteria. This supports the minority of researchers who claim a low prevalence of ADHD in adolescence.[15 18 41] The male predominance described in children with ADHD[44] was not found in the VLBW group, nor did they have conduct disorders. This is consistent with several reports in which the authors argue that VLBW children have a specific (''pure'') form of ADHD with a dominating neurological cause.[5 6 45]

We found autistic spectrum symptoms in the VLBW group. Studies on autism include pregnancy complications and intrauterine growth retardation as risk events, but the main conclusion is that there is a strong genetic component in the cause of autism.[46–48] Few follow up studies of VLBW children have reported on autistic spectrum symptoms,[19 49] although there are reports on deficits in social skills.[18 19 50] Sykes *et al*[50] suggested that VLBW children have problems adjusting to the social environment, because of a failure in self regulatory functions. This hypothesis is further elaborated by Davis and Burns.[51] Hille *et al*[52] argued that the attention deficit may cause difficulties in social relations through poor processing of cognitive stimuli. We speculate that the core point may be specific problems in relating to other people, with deficits in comprehending the subtle clues of social relations, comprising both emotional and cognitive components.

In this study, we found an association between VLBW and psychiatric problems that could not be explained by socioeconomic status or the parents' mental health. A biological cause-effect relation seems plausible, as these children are born with immature brains and a high risk of damaging incidents in the neonatal period.[5 6 8 16 40 43 45 52 53] To be born SGA at term seems to involve less biological risk of psychiatric problems.[13] We also recognise that psychosocial experiences may interact with the biological vulnerability, as reported in other studies.[4 13 54] Regardless of the cause, our results should draw attention to the fact that VLBW children may need long term health services.

In conclusion, we found that VLBW, but not SGA adolescents, have a high risk of developing psychiatric symptoms and disorders by the age of 14, especially attention deficit, anxiety, and relational problems affecting their social skills.

ACKNOWLEDGEMENTS

We thank the teenagers themselves, their parents and teachers for their cooperation and interest in the study. We also thank the child and adolescent psychiatrists Mari Jordet Bruheim and Sigrun Opsal Vilsvik for performing interviews and diagnostic reassessment work, physiotherapist Kari Anne I Evensen for assistance with the manuscript, and paediatrician Jon Skranes for valuable research advice.

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Department of Child and Adolescent Psychiatry, Norwegian University of Science and Technology supported this study.

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ELSEVIER

Low-Birth-Weight Adolescents: Psychiatric Symptoms and Cerebral MRI Abnormalities

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To explore associations between psychiatric symptoms and cerebral magnetic resonance imaging abnormalities in low-birth-weight adolescents, 55 very low-birth-weight (≤1500 gm), 54 term small for gestational age (birth weight <10th centile) and 66 term control adolescents (birth weight ≥10th centile) were assessed at 14-15 years of age. Outcome measures were Schedule for Affective Disorders and Schizophrenia for School-Age Children, Attention-Deficit/Hyperactivity Disorder Rating Scale IV, Autism Spectrum Screening Questionnaire, and qualitatively assessed cerebral magnetic resonance images. The very low-birth-weight group manifested increased prevalence of psychiatric symptoms and disorders compared with controls ($P < 0.001$), especially symptoms of attention-deficit/hyperactivity disorder, and high frequency of ventricular dilatation, white matter reduction, thinning of corpus callosum, and gliosis ($P < 0.01$ vs controls). The Attention-Deficit/Hyperactivity Disorder Rating Scale score was significantly associated with white matter reduction and thinning of corpus callosum in this group. The term small for gestational age group had increased prevalence of psychiatric symptoms compared with control subjects, but not more frequent abnormalities on cerebral magnetic resonance imaging. In conclusion, attention-deficit/hyperactivity disorder symptoms were significantly associated with white matter reduction and thinning of corpus callosum in very low-birth-weight adolescents. No associations were found for other psychiatric symptoms and brain abnormalities in any of the groups.

Indredavik MS, Skranes JS, Vik T, Heyerdahl S, Romundstad P, Myhr GE, Brubakk A-M. Low-Birth-Weight Adolescents: Psychiatric Symptoms and Cerebral MRI Abnormalities. Pediatr Neurol 2005;33: 259-266.

Introduction

To be born preterm with very low-birth-weight involves increased risk of psychiatric symptoms and disorders in adolescence, especially symptoms of attention-deficit/hyperactivity/disorder, anxiety disorders, and reduced social skills [1-3]. To be born small for gestational age at term may involve a slightly increased risk of emotional, behavioral and attention problems [4]. Preterm very low-birth-weight and term small for gestational age infants differ in biological basis and vulnerability. This may imply different developmental trajectories and mental health outcome. In addition, psychosocial experiences may interact with the biological vulnerability and contribute to their psychological well-being [5,6].

In very low-birth-weight children, qualitative magnetic resonance imaging studies have demonstrated periventricular lesions, dilated lateral ventricles, and thinning of corpus callosum, which may be correlates to perinatal periventricular leukomalacia [7-9]. In magnetic resonance imaging studies using quantification techniques, reduced brain volume, both regionally and in total, have been described [10,11]. Cerebral magnetic resonance imaging abnormalities may persist into adolescence and adulthood [9,11-13].

Up to now, we are not aware of any studies reporting cerebral magnetic resonance imaging findings in term small

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Received February 15, 2005; accepted May 2, 2005.

doi:10.1016/j.pediatrneurol.2005.05.002 • 0887-8994/05/$—see front matter

for gestational age adolescents, beyond studies on the pituitary gland in short stature small for gestational age children [14].

The aim of the present study was to explore associations between psychiatric symptoms and qualitatively assessed cerebral magnetic resonance imaging abnormalities in two groups of low-birth-weight adolescents, compared with a control group.

Material and Methods

Study Design

This investigation is a follow-up study at 14-15 years of age of very low-birth-weight and small for gestational age adolescents, compared with a control group of normal birth weight. The very low-birth-weight children had been admitted to the neonatal intensive care unit at the University Hospital in Trondheim in 1986-1988. They were either born at this hospital or transferred from a local hospital after birth. Those admitted in 1988 were assessed thoroughly at 1 and 6 years of age [7]. The small for gestational age and control children were born to mothers living in the Trondheim region. They were enrolled before week 20 of pregnancy in a multicenter study between January 1986 and March 1988 [15]. A 10% random sample of women was selected for follow-up during pregnancy. At birth, all children of mothers in the random sample and all small for gestational age children were included for follow-up. The present study included a psychiatric assessment, an evaluation of cognitive abilities, a neuropediatric examination, and cerebral magnetic resonance imaging.

Study Population

This study includes 175 adolescents who completed both psychiatric and magnetic resonance examination (77 males and 98 females).

Very low-birth-weight adolescents. Very low-birth-weight was defined by a birth weight ≤1500 gm. In 1986-1988, 121 children were admitted to the University Hospital in Trondheim. Of these, 33 died, one child with trisomy 21 was excluded, and six had moved. Of the remaining 81, 65 (80%) participated in psychiatric assessment, of whom 55 (68% of 81) completed the magnetic resonance imaging scan (28 males and 27 females). Twelve of the participants had birth weight ≤1000 gm; 12 were twins, of whom 8 were in twin-pairs.

Small for gestational age adolescents. Of 1200 eligible women, 109 (9%) gave birth to a small for gestational age child at term, defined by a birth weight <10th centile of all infants in the multicenter study, adjusted for gestation, sex, and parity [15]. At follow-up, 12 had moved. Of the remaining 97, 65 (67%) participated in psychiatric assessment, of whom 54 (56% of 97) completed the magnetic resonance imaging scan (22 males, 32 females).

Control adolescents. The control group comprised 122 children with a birth weight ≥10th centile for gestation, born to mothers in the 10% random sample. At follow-up, 10 had moved. Of the remaining 112, 85 (76%) participated in psychiatric assessment, of whom 66 (59% of 112) completed the magnetic resonance imaging scan (27 males and 39 females).

Methods

Clinical Assessment

Psychiatric symptoms and disorders were diagnosed using the semi-structured interview: Schedule for Affective Disorders and Schizophrenia for School-Age Children [16], performed separately with parent and adolescent. Conclusions were drawn according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [17]. The child psychiatrist, who was unaware of birth weight status, differentiated between diagnoses, symptoms reaching the 75% level of diagnostic criteria, or no clinically significant problems. The assessment was supplemented with Autism Spectrum Screening Questionnaire [18], scored during interview, and mother-report on Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-Rating Scale IV) [19].

An estimate of the adolescents' intelligence quotient was calculated using four subscales of the Wechsler Intelligence Scales, Third Edition [20]: Vocabulary, Arithmetic, Block Design, and Picture Arrangement. We defined "low estimated intelligence quotient" below 2 S.D. of the mean value in the control group. A medical examination was performed to assess the prevalence of cerebral palsy and other neuropediatric disabilities. Parents completed Symptom Checklist-90-Revised, and the Global Severity Index was used as a summary measure of psychological distress [21]. Socioeconomic status was calculated according to Hollingshead's Two Factor Index of Social Position, based on a combination of parents' education and occupation [22].

Cerebral Magnetic Resonance Imaging

Cerebral magnetic resonance imaging was performed on a 1.5-Tesla Siemens Symphony. Every examination included sagittal T_1-weighted spin echo images, axial proton density weighted and T_2-weighted spin echo images, and axial inversion-recovery T_1-weighted images. Two experienced radiologists qualitatively assessed the images independently and thereafter in consensus. They had no knowledge of the neonatal histories, earlier magnetic resonance imaging results as well as results of the psychiatric assessment. Size of ventricles, periventricular white matter reduction, corpus callosum thinning, white matter gliosis, and gray matter abnormalities were classified as normal, mild, moderate, or severe. This grading was subsequently dichotomized between normal and abnormal (mild/moderate/severe). Criteria for ventricular dilatation included localized and diffuse dilatation of the lateral ventricles, as well as angulation of the occipital horns. White matter thickness was qualitatively judged, and gliosis was reported as focal or diffuse. Criteria for thinning of corpus callosum included focal posterior and diffuse thinning compared with normal mature corpus callosum of the age group, described by Barkovich and Truwit [23]. The magnetic resonance imaging assessment is reported in a previous paper [24].

Ethics

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

Statistical Analysis

SPSS for Windows version 11.5 (SPSS Inc, Chicago, IL) was used for data analysis. Three-group comparisons were made using one-way analysis of variance for variables with a normal distribution, and Kruskal-Wallis test for ordinal data. If these tests indicated differences between groups (defined by an alpha level < 0.05), two-group comparisons were made using Scheffé's post hoc test for normally distributed variables, and Mann-Whitney U test for variables with a non-normal distribution. Differences in proportions between groups were analyzed by the chi-square test. Prevalence ratios with exact 95% confidence intervals were calculated to estimate the prevalence of psychiatric symptoms in very low-birth-weight adolescents with magnetic resonance imaging abnormalities relative to those without magnetic resonance imaging abnormalities using the Epitab procedure in STATA version 8 (Stata Statistical Software: Release 8.0, 2003; Stata Corp., College Station, TX). Linear regression was performed to analyze the influence of cerebral magnetic resonance imaging findings on the ADHD-Rating Scale total score. This score, assessed on an ordinal scale, was not completely normally distributed. Therefore, regression was performed

Table 1. Family and child characteristics in two groups of low-birth-weight adolescents compared with a control group

	VLBW Mean (S.D.) n = 55	SGA Mean (S.D.) n = 54	Control Mean (S.D.) n = 66
Family characteristics			
Maternal - age (yr)	42.6 (5.0)	42.4 (3.6)	44.2 (4.6)
Education (yr)	13.2 (3.3)	13.0 (3.2)	13.9 (2.9)
Mental health‖	0.26 (0.22)	0.29 (0.28)	0.28 (0.24)
Paternal - age (yr)	46.0 (6.0)	44.8 (3.5)	46.2 (4.9)
Education (yr)	12.8 (3.4)*	13.4 (2.6)	14.2 (3.3)
Mental health‡	0.34 (0.43)	0.17 (0.17)	0.18 (0.18)
Socioeconomic status	3.2 (1.3)	3.5 (1.3)	3.7 (1.1)
Monthly income (1000 NOK)	30.2 (8.8)	31.0 (10.9)	30.3 (9.8)
Child characteristics			
Birth weight (gm)	1189 (244)§	2852 (302)§	3676 (499)
Gestation (wk)	29.0 (2.7)§	39.2 (1.5)	39.5 (1.4)
Psychological assessment age (yr)	14.2 (0.3)	14.2 (0.3)	14.2 (0.3)
MRI assessment age (yr)	15.0 (0.6)†	15.4 (0.6)	15.4 (0.4)

* $P = 0.05$ vs controls.
† $P \leq 0.01$ vs controls.
‡ Fathers' mean Global Severity Index on Symptom Checklist-90-Revised [21] was missing for 8 VLBW, 9 SGA, and 10 control adolescents.
§ These were the selection criteria, and differed by definition vs controls ($P \leq 0.001$). Analysis of variance with Scheffé's post hoc test for parametric data, Kruskal-Wallis and Mann-Whitney *U* test for nonparametric data.
‖ Mothers' mean Global Severity Index on Symptom Checklist-90-Revised [21] was missing for 6 VLBW, 5 SGA, and 8 control adolescents.

Abbreviations:
NOK = Norwegian Kroner
SGA = Small for gestational age
VLBW = Very low-birth-weight

both with raw and logarithm-transformed data. As the results were mainly unchanged, the raw data are presented.

Results

Group Characteristics

Family and child characteristics are summarized in Table 1. There were no group differences in mothers' or fathers' age, mental health, socioeconomic status, or income. The proportion of males and females in each group did not differ significantly. Magnetic resonance imaging scans were performed on average 1.1 (S.D.: 0.5) years later than the psychiatric assessment, and at a slightly younger age for the very low-birth-weight adolescents than for control adolescents ($P < 0.01$). Eleven (20%) very low-birth-weight adolescents had low estimated intelligence quotient compared with 3 (6%) small for gestational age and 3 (5%) controls. Five of 11 very low-birth-weight and 2 of 3 small for gestational age adolescents with low estimated intelligence quotient had a psychiatric disorder. Cerebral palsy was diagnosed in 6 (11%) very low-birth-weight (5 diplegic, 1 hemiplegic) and 1 small for gestational age adolescent (diplegic). Four of six very low-birth-weight and the one small for gestational age adolescent with cerebral palsy manifested a psychiatric disorder, and all adolescents with cerebral palsy exhibited magnetic resonance imaging abnormalities. One very low-birth-weight adolescent had epilepsy. There were no major visual or hearing impairments.

Psychiatric Assessment

Psychiatric disorders were diagnosed in 15 (27%) of 55 very low-birth-weight adolescents, compared with 4 (6%) control adolescents ($P < 0.001$) (Table 2). Seven (13%) had an anxiety disorder ($P < 0.05$ vs control subjects), whereas 4 (7%) had attention-deficit/hyperactivity disorder ($P < 0.05$ vs control subjects). Psychiatric symptoms reaching the 75% level of diagnostic criteria were evident in 27 (49%) very low-birth-weight adolescents compared with 7 (11%) control adolescents ($P < 0.001$). Twelve (22%) very low-birth-weight adolescents manifested attention-deficit/hyperactivity disorder symptoms ($P < 0.001$ vs control subjects), 10 (18%) had anxiety symptoms ($P < 0.05$ vs control subjects), and 4 (7%) manifested symptoms of Asperger's disorder ($P < 0.05$ vs controls). In the small for gestational age group, 4 (7%) had a psychiatric disorder (not significant), and 13 (24%) manifested psychiatric symptoms ($P < 0.05$ vs controls). Other disorders or symptoms were not more frequent in the very low-birth-weight group or the small for gestational age group compared with the control group (data not shown).

Table 2. Psychiatric outcome variables in two groups of low-birth-weight adolescents compared with a control group

	VLBW n (%) 55 (100)	SGA n (%) 54 (100)	Control n (%) 66 (100)
K-SADS interview			
Diagnostic level			
Any psychiatric disorder	15 (27)‡	4 (7)	4 (6)
Anxiety disorders	7 (13)†	2 (4)	2 (3)
ADHD	4 (7)†	2 (4)	0
Asperger's disorder	1 (2)	0	0
Symptoms ≥ 75% of diagnostic criteria			
Symptoms any psychiatric disorder	27 (49)‡	13 (24)†	7 (11)
Symptoms anxiety disorders	10 (18)†	5 (9)	4 (6)
Symptoms ADHD	12 (22)‡	4 (7)	2 (3)
Symptoms Asperger's disorder	4 (7)†	0	0
Scales	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
ASSQ sum score	5.9 (5.9)‡	3.1 (4.8)	2.1 (2.3)
ADHD-Rating Scale (mother-report)			
Attention deficit score	6.0 (5.3)‡	4.3 (5.2)	2.8 (3.2)
Hyperactivity score	2.9 (3.6)*	2.8 (3.9)	1.5 (1.8)
Total score	8.9 (8.1)‡	7.1 (8.8)	6.6 (7.5)

* $P = 0.05$ vs controls.
† $P < 0.05$ vs controls.
‡ $P \leq 0.001$ vs controls.
Chi-square test (Fisher Exact test when cell number < five).
Kruskal-Wallis and Mann-Whitney *U* test (ordinal data).

Abbreviations:
ADHD-Rating Scale IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV [19]
ASSQ = Autism Spectrum Screening Questionnaire [18]
K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children
SGA = Small for gestational age
VLBW = Very low-birth-weight

Very low-birth-weight adolescents had higher mean sum score than control adolescents on the Autism Spectrum Screening Questionnaire (Table 2). On ADHD-Rating Scale IV (mother-report), the very low-birth-weight group had higher mean attention deficit and total score than the control group, whereas the hyperactivity score was borderline significant ($P = 0.05$ vs control subjects) (Table 2). The small for gestational age group did not differ from control adolescents on these variables.

The group of 12 very low-birth-weight adolescents with birth weight <1000 gm differed from those >1000 gm in the frequency of attention-deficit/hyperactivity disorder (3 of 12 vs 1 of 43, $P < 0.05$). When adolescents with low estimated intelligence quotient were excluded, the very low-birth-weight group still manifested more psychiatric symptoms and disorders compared with the control group ($P \leq 0.001$ and $P < 0.05$ respectively, data not shown).

Magnetic Resonance Imaging Results

The magnetic resonance imaging results are reported in detail in a previous paper [24]. Of the 55 very low-birth-weight adolescents, 26 (47%) manifested thinning of corpus callosum, 29 (53%) white matter reduction, 45 (82%) dilated ventricles, and 16 (29%) gliosis. There were no gray matter abnormalities.

In the term small for gestational age group, 1 had thinning of corpus callosum, 3 white matter reduction, 10 (19%) dilated ventricles, and 2 gliosis. Of the control adolescents, 4 had thinning of corpus callosum, 1 white matter reduction, 14 (21%) dilated ventricles, and 5 gliosis.

The magnetic resonance imaging abnormalities were significantly more frequent in the very low-birth-weight group compared with the control group ($P < 0.01$), and the differences remained after exclusion of adolescents with low estimated intelligence quotient (data not shown). The group of 12 very low-birth-weight adolescents with birth weight <1000 gm differed from those >1000 gm in the frequency of white matter reduction (10 of 12 vs 19 of 55, $P < 0.05$).

Psychiatric Problems and Cerebral Magnetic Resonance Imaging

Associations between cerebral magnetic resonance imaging abnormalities (thinning of corpus callosum, white matter reduction, and ventricular dilatation) and specific symptom scores and disorders are presented for the very low-birth-weight group in Tables 3 and 4. No associations were evident for gliosis (data not shown). The prevalence of interview-assessed attention-deficit/hyperactivity disorder symptoms was somewhat higher in those with white

Table 3. Prevalence ratios with 95% confidence intervals of psychiatric disorders or symptoms among VLBW adolescents according to MRI abnormalities

	Thinning of Corpus Callosum n = 26			Reduced White Matter n = 29			Dilated Ventricles n = 45		
	n*	PR	(95% CI)	n*	PR	(95% CI)	n*	PR	(95% CI)
Diagnoses									
Any psychiatric disorder (n = 15)	8	1.3	(0.5-3.0)	10	1.8	(0.7-4.6)	12	0.9	(0.3-2.6)
Anxiety disorders (n = 7)	4	1.5	(0.4-6.0)	4	1.2	(0.3-4.9)	5	0.6	(0.1-2.5)
ADHD (n = 4)	2	1.1	(0.2-7.4)	4	—	—	4	—	—
Symptoms ≥75% of diagnostic level									
Any symptom group (n = 27)	15	1.4	(0.8-2.4)	16	1.3	(0.7-2.3)	23	1.3	(0.6-2.9)
Anxiety symptoms (n = 10)	6	1.7	(0.5-5.3)	5	0.9	(0.3-2.8)	8	0.9	(0.2-3.6)
ADHD symptoms (n = 12)	7	1.6	(0.6-4.3)	9	2.7	(0.8-8.2)†	12	—	—

* Number of those with psychiatric symptoms or disorders.
† $P = 0.08$ vs no white matter reduction, chi-square test (Fisher Exact test). Psychiatric symptoms and disorders assessed by semistructured interview: Schedule for Affective Disorders and Schizophrenia for School-Age Children [16].

Abbreviations:
ADHD = Attention-deficit hyperactivity disorder
CI = Confidence interval
MRI = Magnetic resonance imaging
PR = Prevalence ratio
VLBW = Very low-birth-weight

matter reduction compared with those without reduction (prevalence ratio = 2.7, 95% confidence interval: 0.8-8.2), and all four with diagnosed attention-deficit/hyperactivity disorder had white matter reduction and dilated ventricles (Table 3). Furthermore, attention-deficit/hyperactivity disorder symptoms assessed by the ADHD-Rating Scale were significantly associated with white matter reduction and thinning of corpus callosum ($P < 0.05$) (Table 4). This correlation was mainly due to a strong association between these magnetic resonance imaging abnormalities and attention deficit score, whereas the association with hyperactivity score was not statistically significant. Four very low-birth-weight adolescents with symptoms of Asperger's disorder all had white matter reduction and ventricular dilatation, but associations were not statistically significant. Neither did we find associations between anxiety symptoms or the autistic spectrum sum score and magnetic resonance imaging findings.

In the small for gestational age group and the control group, few had thinning of corpus callosum and white matter reduction, which limited further analyses. Dilated ventricles were not associated with psychiatric symptoms or scores in these groups.

Multivariate Analyses

Linear regression was first performed with the birth weight groups only. Both being very low-birth-weight and small for gestational age was significantly associated with the ADHD-Rating Scale total score ($P = 0.001$ and $P < 0.05$ respectively, data not shown). Further analyses were carried out separately within each birth weight group. In

Table 4. Cerebral MRI findings and results on screening questionnaires in a sample of 55 VLBW adolescents

	Thinning of Corpus Callosum		Reduced White Matter		Dilated Ventricles	
	Yes n = 26 Mean (S.D.)	No n = 29 Mean (S.D.)	Yes n = 29 Mean (S.D.)	No n = 26 Mean (S.D.)	Yes n = 45 Mean (S.D.)	No n = 10 Mean (S.D.)
ASSQ sum score	6.2 (6.7)	5.6 (5.1)	6.4 (6.7)	5.2 (4.9)	6.1 (6.3)	4.9 (3.8)
ADHD-Rating Scale†						
Attention deficit	7.5 (5.5)*	4.4 (4.7)	7.5 (5.7)*	4.1 (4.2)	6.4 (5.6)	4.4 (3.8)
Hyperactivity	3.9 (4.4)	1.8 (2.0)	3.6 (4.4)	2.0 (2.0)	3.2 (3.8)	1.4 (1.5)
Total score	11.4 (9.1)*	6.3 (6.0)	11.1 (9.2)*	6.1 (5.4)	9.6 (8.7)	5.8 (3.7)

* $P < 0.05$ vs no pathology.
† Mother report.
Mann-Whitney *U* test (ordinal data).

Abbreviations:
ADHD-Rating Scale IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV [19]
ASSQ = Autism Spectrum Screening Questionnaire [18]
MRI = Magnetic resonance imaging
VLBW = Very low-birth-weight

Table 5. ADHD-Rating Scale total score* as dependent variable in linear regression, adjusted for sex, socioeconomic status, and MRI findings in a group of 51 VLBW adolescents

Analysis Block	Adj. R^2	Independent Variables	Regression coeff. (B)	Regression (95% CI of B)	Standardized coeff. (β)	*P*
Model 1: Sex and socioeconomic status						
	0.01	Sex (male/female)	−2.53	(−7.06 to 1.99)	−0.16	0.266
		Socioeconomic status (increasing)	0.95	(0.76 to 2.67)	0.16	0.270
Model 2: Adding MRI variables separately (adjusted for sex and socioeconomic status)						
	0.07	Thinning of corpus callosum	4.50	(0.03 to 8.98)	0.28	0.049
	0.10	White matter reduction	5.10	(0.75 to 9.46)	0.32	0.023
	0.02	Dilated ventricles	3.26	(−2.46 to 8.98)	0.16	0.257

Linear regression.
* Mother-report.

Abbreviations:
ADHD-Rating Scale IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV [19].
CI = Confidence interval
MRI = Magnetic resonance imaging
VLBW = Very low-birth-weight

the very low-birth-weight group, no association was found between sex or socioeconomic status and the attention-deficit/hyperactivity disorder score (model 1, Table 5). Thinning of corpus callosum and white matter reduction were associated with the attention-deficit/hyperactivity disorder score, after adjustment for sex and socioeconomic status (model 2, Table 5).

In the small for gestational age group, increasing socioeconomic status was significantly associated with a reduced attention-deficit/hyperactivity disorder score ($P = 0.001$), whereas sex and magnetic resonance imaging abnormalities, i.e. dilated ventricles, did not influence the results (data not shown). In the control group, both sex and socioeconomic status had borderline significant effects ($P \leq 0.06$), whereas magnetic resonance imaging abnormalities (dilated ventricles) did not influence the score (data not shown).

Discussion

In this study, the mother-reported ADHD-Rating Scale total score was associated with white matter reduction and thinning of corpus callosum in very low-birth-weight adolescents. Significant associations were not found between other psychiatric symptoms and abnormal magnetic resonance imaging findings. Socioeconomic status and sex had little effect on the attention-deficit/hyperactivity disorder score in the very low-birth-weight group. In the small for gestational age group, psychiatric symptoms were not associated with magnetic resonance imaging abnormalities, whereas socioeconomic status strongly influenced the attention-deficit/hyperactivity disorder score.

Strengths and Limitations of the Study

The strength of this study is the thoroughness of the psychiatric assessment, using both questionnaires and a semistructured interview, and the large number of participants who underwent magnetic resonance imaging scans. The psychiatric and the magnetic resonance imaging assessments were performed by experienced specialists who had no knowledge of group adherence. Although magnetic resonance imaging scans were performed at a slightly younger age for the very low-birth-weight adolescents than for control adolescents, this age difference can not explain the increased frequency of abnormal magnetic resonance imaging findings in the very low-birth-weight group. The age difference between the psychiatric and the magnetic resonance imaging assessment should not affect the results, because associations were demonstrated for attention-deficit/hyperactivity disorder symptoms, which are unlikely to be short-dated.

All three study groups are fairly large. Still, numbers within each group having both psychiatric symptoms and magnetic resonance imaging findings are limited. Especially in the small for gestational age group and the control group, numbers are too small for statistical inference.

The association between white matter reduction and the mother-reported ADHD-Rating Scale score was, however, present and unlikely to be the result of chance. There were no differences in psychiatric parameters between participants who consented to magnetic resonance imaging scan and those who did not consent to magnetic resonance imaging scan in any of the groups. Hence, it is unlikely that the associations found between the attention-deficit/hyperactivity disorder score and magnetic resonance imaging findings are caused by selection bias. In the use of questionnaires, information bias cannot be excluded as the parents are aware of the increased risk of health problems for their children. However, we have previously reported that the mothers' ratings on questionnaires were reliable in this study, compared with in-depth psychiatric interview [4]. We

adjusted for sex and socioeconomic status in regression analysis to rule out possible confounding effects.

We chose not to exclude adolescents with low estimated intelligence quotient or cerebral palsy from the main analyses as we consider these conditions to be intermediate links in the causal chain between very low-birth-weight and psychiatric outcome, and not confounders that should be controlled for. Exclusion of adolescents with functional disadvantages would imply selection of a rather healthy subsample as the study group.

We are aware that the magnetic resonance imaging abnormalities described are gross and nonspecific findings. Still, the qualitative magnetic resonance imaging assessment reflects methods available in a clinical setting, and the results indicate that even with this rough method, associations may be found between attention deficit symptoms and white matter reduction in very low-birth-weight adolescents.

Associations Between Psychiatric Symptoms and Magnetic Resonance Imaging Findings

In attention-deficit/hyperactivity disorder in general, neuroimaging studies have suggested structural abnormalities in those regions of the brain that are involved in executive functions; the frontal lobe–basal ganglia networks [25]. Structural magnetic resonance imaging studies with quantification techniques have demonstrated a moderate size reduction in the frontal lobes, parts of the corpus callosum, and in the cerebellum [26,27]. Using advanced quantitative techniques, Sowell et al. have reported cortical abnormalities in prefrontal, temporal, and parietal regions, which may subserve attention and behavioral inhibition [28]. Decreased brain volumes are observed in both white and gray matter, with most marked decrease in white matter [26]. As we evaluated the magnetic resonance imaging scans qualitatively, our results are not quite comparable. Yet, the association between white matter reduction and the attention-deficit/hyperactivity disorder score in the very low-birth-weight group may correspond to the reported reduced brain volumes in white matter regions.

In very low-birth-weight children, there are relatively few reports on the relationship between magnetic resonance imaging findings and behavioral symptoms. In a study of high-risk preterm children at ages 5 to 7, symptoms of attention-deficit/hyperactivity disorder were related to periventricular lesions, mainly periventricular leukomalacia [8]. In very low-birth-weight adolescents, behavior was found to be significantly associated with ventricular dilatation, thinning of corpus callosum, and abnormal white matter signal [9]. These two studies may be consistent with our results. Another study of very low-birth-weight adolescents demonstrated thinning of corpus callosum without significant association to attention-deficit/hyperactivity disorder, diagnosed by interview [12]. This finding may in fact also be consistent with the results of the present study, as neither were we able to find statistical significant association between interview-assessed attention-deficit/hyperactivity disorder symptoms and magnetic resonance imaging abnormalities. Hence, these apparently conflicting results may be due to the different assessment methods, as symptom scores on questionnaires are not equivalent to DSM-IV diagnostic criteria used in interview. Furthermore, interview-based diagnostic assessment uses threshold cutoffs, whereas questionnaires provide continuous parameters.

In a recent tensor imaging study, white matter disturbance in the internal capsules bilaterally and the posterior corpus callosum was associated with attention deficit, scored on a neuropsychological assessment scale [29]. Despite different magnetic resonance imaging techniques, this study lends support to our results.

The multivariate analyses in the present study suggest that attention-deficit/hyperactivity disorder symptoms, mainly inattention, are associated with very low-birth-weight and brain abnormalities. A possible mechanism for the loss of white matter tissue and thinning of corpus callosum is perinatal events leading to periventricular leukomalacia; this may in turn affect association and commissural fibers involved in networks dealing with attention. Our results may support the hypothesis of a specific form of attention-deficit/hyperactivity disorder in very low-birth-weight children, with inattentive type symptoms, which may be mainly due to neurodevelopmental impairment in brain maturation [2].

To our knowledge, the present study is the first to compare cerebral magnetic resonance imaging findings and psychiatric symptoms in term small for gestational age adolescents. Dilated ventricles, which were found in 19%, were not associated with attention-deficit/hyperactivity disorder symptoms. However, socioeconomic status was strongly associated with these symptoms, suggesting that environmental factors may influence behavioral outcome in children with intrauterine growth retardation, as reported by Hack [6].

All four very low-birth-weight adolescents with symptoms of Asperger's disorder had white matter reduction and ventricular dilatation. In the research on autism, hypotheses are put forward that social behavior is linked to a specialized circuit centered on the amygdala, involving orbital frontal cortex, anterior cingulate, and temporal cortex [30]. A diffusion tensor imaging study of autistic adolescents reported disruption of white matter tracts between regions implicated in social cognition; in and adjacent to the anterior cingulate, corpus callosum, and prefrontal areas [31]. Hence, the high ordered function of social intelligence may involve extended networks comprising cortex, subcortical structures, and white matter circuits. We can speculate that a general reduction in white matter tissue may affect this advanced network, but our data are not sufficient to clarify the question.

Conclusion

In this study using qualitative magnetic resonance imaging results, attention-deficit/hyperactivity disorder symptoms, assessed by ADHD-Rating Scale IV, were found to be associated with white matter reduction and thinning of corpus callosum in very low-birth-weight adolescents. Other psychiatric symptoms were not associated with magnetic resonance imaging abnormalities. These results support the hypothesis of a specific form of attention-deficit/hyperactivity disorder in very low-birth-weight children, possibly caused by perinatal events influencing white matter connectivity and brain development. In the small for gestational age and the control group, psychiatric symptoms were not associated with magnetic resonance imaging abnormalities.

We want to thank the teenagers themselves and their parents for their cooperation and interest in the study. The study was funded by Department of Child and Adolescent Psychiatry, Norwegian University of Science and Technology, and Research Funds at St. Olavs Hospital, Trondheim University Hospital. Part of the study group was recruited from a multicenter study sponsored by the U.S. National Institute of Child Health and Human Development, NIH (NICHD contract No. 1-HD-4-2803 and No. 1-HD-1-3127).

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