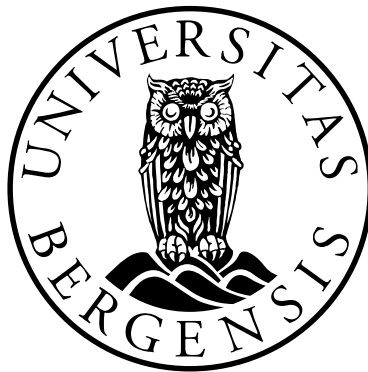


Imaging of the brain and of the lungs in young adults born prematurely and / or with a low birth weight.

Radiological findings and associations with clinical features.

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1. ABBREVIATIONS

- BP Bronchopulmonary
- BPD Bronchopulmonary Dysplasia
- BHR Bronchial Hyper Responsiveness
- BW Birth weight
- CC Corpus Callosum
- CF Cystic Fibrosis
- CLD Chronic Lung Disease
- CLDI Chronic Lung Disease in Infancy
- COPD Chronic Obstructive Pulmonary Disease
- CP Cerebral Palsy
- CPAP Continuous Positive Airways Pressure
- CRP C-Reactive Protein
- CSF Cerebrospinal Fluid
- CT Computer Tomography
- CUS Cerebral Ultrasonography
- DESHI Diffuse Excessive High Signal Intensity
- DQ Developmental Quotient
- DTI Diffusion Tensor Imaging
- DWI Diffusion Weighted Imaging
- ELBW Extremely Low Birth Weight
- FA Fractional Anisotropy
- FEF₂₅₋₇₅ Forced expiratory flow at between 25 and 75% of FVC expired
- FEF₅₀ Forced expiratory flow at 50% of FVC expired
- FEV₁ Forced expiratory volume in first second
- fMRI Functional Magnetic Resonance Imaging
- FRC Functional Residual Capacity
- FVC Forced Vital Capacity
- GA Gestational Age, no of weeks since first day in last menstrual period
- GM Germinal Matrix
- GMH Germinal Matrix Haemorrhage
- HRCT High Resolution Computer Tomography
- HU Hounsfield Unit
- IUGR Intrauterine Growth Restriction
- IVH Intraventricular Haemorrhage
- IQ Intelligence Quotient
- LBW Low Birth Weight
- LFT Lung Function Test
- LMP Last Menstrual period
- MD Mean Diffusivity
- MRI Magnetic Resonance Imaging
- NBW Normal Birth Weight
- nCPAP Nasal Continuous Positive Airway Pressure
- NEC Necrotising Enterocolitis
- PDA Persistent Ductus Arteriosus
- PEF Peak Expiratory Flow

- PLIC Posterior Limb of Internal Capsule
- PMA Post Menstrual age i.e. number of weeks since last menstrual period
- PROM Premature rupture of membranes
- PV Periventricular
- PVL Periventricular Leukomalacia
- RDS Respiratory Distress Syndrome
- ROP Retinopathy of Prematurity
- RV Residual Volume
- SD Standard Deviation
- SGA Small-for-Gestational age
- TBV Total Brain Volume
- TLC Total Lung Capacity
- US Ultrasonography
- VLBW Very Low Birth Weight
- VPT Very Preterm
- WBV Whole Brain Volume
- WHO World Health Organization
- WM White Matter

2. ABSTRACT

Background and Purpose: Premature birth is defined as a birth occurring earlier than 37 gestational weeks, and typically occurs in 6% of all pregnancies in Europe (1). All premature babies are at risk for health problems but the earlier a baby is born, the greater the risk for serious complications (2). Two of the main organs greatly affected by premature birth are the lungs and the brain and the overall aim of this study was to address imaging techniques commonly used in the follow-up of these organs in prematurely born or babies with low birth weight, by

- establishing a scoring system for pulmonary findings as assessed by High Resolution Computer Tomography (HRCT)
- reporting the prevalence of pulmonary HRCT findings and investigate the associations of these HRCT findings with neonatal factors and lung function tests in children and young adults born with a birth weight below ≤ 1000 g or a gestational age below ≤ 28 weeks
- establishing Magnetic Resonance Imaging (MRI) based reference intervals for different brain structures and by
- reporting the prevalence of cerebral MRI findings, with a special focus on the Corpus Callosum (CC), in young adults born with a birth weight below 2000g.

Materials and Methods: All study subjects were born within a defined area of Western Norway (Hordaland and Sogn og Fjordane counties) during the period 1982 to 1992, and had their medical care at Haukeland University Hospital, which is the only provider of neonatal intensive care within this area. The present work is based on three cohorts.

The lung study involved two different cohorts; one including a total of 46 adolescents born between 1982 and 1985, and a second cohort including 35 children born during 1991-1992. During these two periods, all those born with a gestational age (GA) ≤ 28 weeks or a birth weight ≤ 1000 g were included in prospective, longitudinal studies, of which a total of 74 were examined with HRCT during 2001-2002. The mean age at HRCT examination was 18 and 10 years, respectively. The lung function tests were performed within two weeks of the HRCT, and included assessment of airway dimensions, airway reactivity and lung volumes. For the purpose of the present study, we collected neonatal characteristics and whether or not there was a diagnosis of Bronchopulmonary Dysplasia (BPD) from previous reports.

The brain study involved 174 subjects born with a BW < 2000g, between 1986 and 1988, of which 113 agreed to have a MRI examination (65.3% of the eligible cases) during 2006-2007. 91% of the cases were also born prematurely and 61% had a birth weight below 1500g. A control group born during the same period, and recruited at age 5 years, was also included in the present long-term follow-up during 2006-2007. All study (n=113) and control (n=100) subjects had a 3 Tesla MRI examination performed. The images were assessed both subjectively and objectively, with the observers masked for grouping and additional information. Data on socioeconomic status (SES) were obtained from questionnaires at a follow-up at 11 years of age, and cognitive abilities were assessed at five and 11 years using age appropriate Wechsler scales. At 19 years cognitive abilities were assessed using the Wechsler Abbreviated Scale of Ability (WASI) 25. Prorated IQ was estimated from the two subtests; word comprehension test and matrixes.

Results: Lung: 87% of the premature survivors had abnormal findings at HRCT, with linear and triangular opacities being the more common. Only one case with emphysema was detected. The inter- and intra observer agreement was moderate to good for “total score”, as well as for “linear opacities”, “triangular opacities”, “mosaic perfusion” and “air trapping”, with weighted Kappa values ranging between 0.4 and 0.7. When using the old classification of for BPD, i.e. oxygen dependency and radiological findings at day 28 of life, no significant association between BPD and long-term HRCT findings was found. However, when using the new classification, i.e. oxygen dependency at postmenstrual age 36 weeks, a significant association was demonstrated between the total HRCT score and moderate/severe BPD. A history of prolonged requirements for oxygen treatment predicted subsequent HRCT abnormalities, and days of supplemental oxygen appeared to be the single most important factor predicting structural lung abnormalities. All of the assessed lung function variables (FEV₁, FEF₅₀ and FEF₂₅₋₇₅ and the ratio RV/TLC) were significantly associated with linear / triangular opacities and with the total HRCT score.

Brain: Based on a subjective assessment of the 100 controls, two subjects were judged to have moderately and 36 to have mildly dilated lateral ventricles by observer one, while figures for observer two were one and 14, respectively. Overall, the two observers agreed on 15 having either mild or moderate dilatation (Kappa 0.43). Dilatation of the lateral ventricles and loss of bulk of white matter were seen in 40% of the Low birth weights vs.15% of the controls, while thinning of CC was seen in 20% of the Low birth weights and in 7% of the

controls. The MRI findings were not significantly related to any of the pre-, peri- or early postnatal factors available for statistical analysis. Sex specific reference intervals for adolescents born term were presented.

The Low birth weight survivors had a smaller total Corpus Callosum area than the controls, but this group difference disappeared when correcting for forebrain volume. When analysing the sub-divisions of the CC, we found a significant group difference regarding the posterior 3rd (splenium).

Conclusions: The prevalence of pulmonary changes in premature survivors, as assessed by HRCT, is high, but the findings are subtle. Number of days with supplementary oxygen in the neonatal period is the most important factor for predicting these abnormal findings. The structural lung abnormalities are associated with airflow- and lung volume measurements. The accuracy of the proposed scoring system was acceptable. The refined and simplified scoring system allowed for assessment of a maximum score.

Subjective assessment overestimates ventricular size compared with measurements and the use of reference intervals. Thus, a high total of 15% of healthy adolescents was judged to have dilated lateral ventricles as assessed by an experienced neuroradiologist, underscoring the need for our new, MRI based reference intervals. Separate reference intervals for healthy 19 years olds have been presented. Based on subjective assessment, dilatation of the lateral ventricles, loss of bulk of white matter and thinning of Corpus Callosum were more commonly seen among Low birth weights than among controls, however, the findings must be interpreted in the light of the aforementioned.

Adolescents born with a BW < 2000g have a smaller posterior Corpus Callosum than their peers born term.

Pulmonary HRCT and brain MRI demonstrated several findings consistent with prematurity / and or a low birth weight, and some of the findings were associated with neonatal factors and clinical findings. Our results do not justify the use of routine HRCT or brain MRI's during follow-up of these individuals.

3. LIST OF PAPERS

LUNG:

- 1) **HIGH-RESOLUTION CT OF THE CHEST IN CHILDREN AND YOUNG ADULTS WHO WERE BORN PREMATURELY: FINDINGS IN A POPULATION-BASED STUDY.** Aukland SM, Halvorsen T, Fosse KR, Daltveit AK, Rosendahl K. AJR Am J Roentgenol. 2006 Oct;187(4):1012-8.
- 2) **NEONATAL BRONCHOPULMONARY DYSPLASIA PREDICTS ABNORMAL PULMONARY HRCT IN LONG-TERM SURVIVORS OF EXTREME PRETERM BIRTH.** Aukland SM, Rosendahl K, Owens CM, Fosse KR, Eide GE, Halvorsen T. Thorax. 2009 May; 64(5):405-10. Epub 2009 Jan 21

BRAIN:

- 1) **ASSESSING VENTRICULAR SIZE: IS SUBJECTIVE EVALUATION ACCURATE ENOUGH? NEW MRI-BASED NORMATIVE STANDARDS FOR 19-YEAR-OLDS.** Aukland SM, Odberg MD, Gunny R, Chong WK, Eide GE, Rosendahl K. Neuroradiology. 2008 Dec; 50(12): 1005-11. Epub 2008 Jul 12.
- 2) **CEREBRAL MRI AND COGNITION IN NON-HANDICAPPED, LOW BIRTH WEIGHT ADULTS.** Odberg MD, Aukland SM, Rosendahl K, Elgen IB. Pediatr Neurol. 2010 Oct; 43(4): 258-62.
- 3) **SELECTIVELY REDUCED POSTERIOR CORPUS CALLOSUM SIZE IN A POPULATION-BASED SAMPLE OF YOUNG ADULTS BORN WITH LOW BIRTH WEIGHT.** Aukland SM, Westerhauen R, Plessen KJ, Odberg MD, Elgen I, Peterson BS, Ersland L, Rosendahl K. Accepted. AJNR. American Journal of Neuroradiology

4. BACKGROUND INFORMATION

A. GENERAL

Premature birth is defined as a birth occurring earlier than 37 gestational weeks, and typically occurs in 6% of all pregnancies in Europe (1). Approximately 70% of premature babies are born between 34 and 36 weeks, while 20% are born between 28 and 33 weeks and about 6% at less than 28 weeks (3). All premature babies are at risk for health problems, but the earlier a baby is born, the greater the risk for serious complications (2), and as such, dating is important. As antenatal dating, both based on the last menstrual period (LMP) and ultrasound is flawed with methodological difficulties, birth weight is commonly used instead. Low birth weight is related to premature birth or intrauterine growth restriction (IUGR), or both. WHO defines Low Birth Weight (LBW) as birth weight below 2500g, Very Low Birth Weight (VLBW) below 1500g and Extremely Low Birth Weight (ELBW) below 1000g.

During 1992, 20 millions were born with a birth weight below 2500g, constituting approximately 16% of all live-births (4) worldwide, of which 90% in low income countries.

In Norway, the occurrence of premature delivery has been fairly constant for the last 30 years with a reported prevalence of 60 per 1000 live birth in 2009 (5). ELBW is reported in 0.7 per 1000 live birth, VLBW in 1.2 per 1000 live birth and LBW in 5.3 per 1000 live births (5).

Similar figures were found in a population based study from Vestfold county, southern Norway, with prevalences of 0.7 per 1000 live births and 4.5 per 1000 live births for VLBW and LBW, respectively (6). The overall the perinatal death rate of all newborns in Norway during 2009 was as 4.4 per 1000 live births (5).

Although the reported survival rates of babies born prematurely varies, there has been a recent increase for those born with a gestational age (GA) of at least 23 weeks (7). The Neonatal Research Network (8) report a survival to discharge-rate of 84 % for VLBW infants born in 1995-96, but according to a recent published epidemiological study from Norway, the 5-year survival rate of the very preterm is still as low as 20% for children born at 23 to 27 weeks of gestation compared to 99% for term born children (7).

Due to organ immaturity, premature babies are at risk for complications during the newborn period, such as apnoea, respiratory distress syndrome (RDS), cerebral haemorrhage / injury, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, jaundice, anaemia and sepsis / infections (2). For those born at GA 23 weeks, chronic lung disease (CLD) appears in 57-86% and severe disability in 34% as compared to 16-71% and 12-35% for those born at GA 25 weeks. Similar, the list of complications after VLBW is also quite extensive. Necrotising enterocolitis (NEC) develops in 6% (9) and approximately 50% will be in need of surgery. Symptomatic Persistent Ductus Arteriosus (PDA) is found in 25% and approximately ¼ of these are in need of surgery (9). Nearly one in five had at least one episode of septicaemia (9). Retinopathy of Prematurity (ROP) is only seen in very preterms (GA below 33 weeks), with reported incidence of nearly 30% in VLBWs (10). Rickets has been reported in as many as one in three in exclusively breastfed VLBW infants (11). Supplemental vitamin D and calcium after birth is expected to reduce this figure significantly, but in a recent study of ELBW infants (12), the frequency remained high despite current nutritional support.

LBW survivors have been studied to a lesser degree, but in a recent paper a large proportion of the morbidity associated with preterm birth is disproportionately due to the late preterm infant (13). This is the fastest-growing sector of all preterm births and this group, also has an increased risk of complications, such as thermal instability, hypoglycaemia, feeding difficulties, respiratory distress, hyperbilirubinemia, and sepsis (13). Regarding the outcome in these groups, a large population based study (major handicapped excluded) of adolescents surviving BW below 2000g, have shown neurocognitive impairments (14;15). In addition growth disturbance with reduced height have been shown in the same cohort at age 19 years (16).

Two of the main organs greatly affected by premature birth are the lungs and the brain, wherefore imaging of these organ systems have been addressed in this thesis.

B. LUNG DISEASE AFTER PREMATURE BIRTH

1. EPIDEMIOLOGY

Pulmonary disease following premature birth and neonatal respiratory distress syndrome was initially described in the 1960's (17;18) and the term Bronchopulmonary disease (BPD) was introduced by Northway in 1967 (19). BPD most often occurs in infants with VLBW and a GA less than 30 weeks (20;21). In a study from the US, approximately 20% of VLBWs developed BPD (8;21).

However, the reported incidence varies significantly, from 3 to 43% (8;22;23), according to methods of ascertainment, classifications used for BPD, composition of the cohorts under investigation and differences in treatment policies (24). Bancalari observed BPD in two thirds of babies born with a birth weight between 500g and 750g, as opposed to only 1% of those born with birth weight between 1251-1500g (22). Paralleling an improvement in neonatal care, a lower prevalence of BPD was expected, but due to a higher survival rate of the smaller premature infants, these figures are hard to interpret. Taken together, the literature supports the fact that improved respiratory treatment regimens lead to lower rates of BPD (24). Whether or not development of chronic lung disease also affects the neurodevelopmental outcome was addressed in a study by Anderson and co-workers (25). They conclude that BPD represents an additional risk factor for neurodevelopmental impairment and that BPD seems to be related to a global cognitive impairment, rather than to a specific impairment. Several investigators (26-28) have expressed concern of survivors of preterm birth / BPD developing chronic obstructive pulmonary disease (COPD) in adult life, but longer follow-up studies are needed to clarify to give an estimation of the severity of this problem (21).

2. PATHOGENESIS

In premature birth, the immature lungs are exposed to ex-utero environment before the pruning of the distal airways and the formation of the alveoli is complete. The small airways are pruning during 24-28 weeks gestational age, followed by sacculation, or formation of alveoli, from 28 to 32 weeks. At this stage some alveoli are present, but they are not uniformly distributed until gestational week 36 (29-31). A proper gas exchanging does not

taking place until the formation of the alveoli has been completed (30;31). Premature birth implies a scenario of immature, nearly non-gas-exchanging lungs and a simultaneously impairment or arrest in the alveolar formation and development of the distal lung vasculature (32). Whether or not an arrest in alveolar formation in itself affects the lung development in newborns is unclear (33). What is clear, however, is that a dysfunctional gas exchange often necessitates mechanical ventilation and supplement of oxygen, which in turn affect further development of the alveoli (32). The use of mechanical ventilation is thought to be of higher importance for an alveolar arrest / impairment than the prematurity itself (32;33).

In addition, the lack of surfactant may lead to increased tension within the primary alveoli and alveolar collapse, causing a hyaline membrane disease / respiratory distress syndrome. This condition may in itself require mechanical ventilation. Although the administration of exogenous surfactant may reverse the respiratory distress (34) it does not seem to improve the alveoli formation (29;32;35). All in all, the introduction of exogenous surfactant and prenatal steroids has not changed the histopathological pattern markedly (32).

The development of BPD is thought to be multifactorial, with the classical triad of “prematurity”, “oxygen” and “mechanical ventilation” playing important roles, either in an additive or parallel manner. Oxygen itself is probably able to arrest the septation of the lungs (36;37) and to induce chronic lung damage. But mechanical ventilation without high oxygen tension can also lead to lung injury, similar to BPD (38;39). In addition; pulmonary oedema as a result of persistent ductus arteriosus (PDA) is shown to predispose to the development of BPD (40-42). Recently, inflammation has assumed a greater etiological importance in BPD development (43-45). Other factors as decreased granulocyte-response in the preterm lung (46) are also discussed as contributors to the disease development.

In a study of extremely premature infants, the role of these perinatal factors on the BPD incidence were evaluated (22) and the most striking finding was probably the importance of PDA as a risk factor (particularly if combined with sepsis). In addition the study proved an association between lower birth weight / lower GA and BPD development. The impact of these “new” co-factors in comparison to the classical factors as oxygen toxicity and mechanical ventilation is unclear.

3. BPD-ISSUES

The development of chronic lung disease in these premature infants was described already in 1967, with Northway introducing the term Bronchopulmonary dysplasia (BPD) (19). This condition was not only seen in the smallest prematures, but also in larger premature infants with RDS and / or treated with prolonged high-pressure mechanical ventilation with high oxygen concentration. The classification of BPD has been changed during the last 40 years. Initially the term BPD was used to describe a chronic pulmonary disease associated with the use of intermittent positive-pressure respirators and high oxygen concentration for more than 140 hours (19). National Institutes of Health (NIH) proposal of BPD criteria in 1979 included a continued oxygen dependency during the first 28 days plus compatible clinical and radiographic changes (47). The criteria of BPD, given by The Bureau of Maternal and Child Health and Resources Development in 1989 (48) include 4 elements; 1) positive Pressure ventilation during the first two weeks of life for a minimum of three days, 2) clinical signs of respiratory compromise persisting longer than 28 days of age, 3) requirements for supplemental oxygen longer than 28 days to maintain a PaO₂ above 50 mmHg and 4) chest radiograph with findings characteristic of BPD.

These criteria were appropriate for the classical form of BPD, but not for the “newer” form of BPD (49). A major drawback of these criteria is the use of *oxygen dependency* at one-time-point i.e. at 28 days of life, regardless of GA or con-current disease at this time point. In the NIH consensus 2000 (50), Jobe and Bancalari re-defined the criteria of BPD, adding another time point of assessment; 36 weeks post-menstrual age (PMA). The criteria of radiographic changes were removed and the BPD was divided into a mild, moderate or severe form depending on the full-filled criteria.

Instead of using the term BPD, several authors now prefer to report on chronic lung disease (CLD) of prematurity. Chronic Lung Disease of Infancy (CLDI) include any pulmonary disease resulting from a respiratory disorder in the neonatal period (21;51) and CLD of prematurity / BPD accounts for the majority of CLDI cases. But CLDI may develop in newborns who were not in need of prolonged oxygen treatment in the neonatal period (21) and all these terms are (unfortunately) used interchangeably to describe chronic lung disease after treatment for RDS in preterm infants (52).

4. RADIOLOGY

a. Chest radiograph

At present, two main radiological modalities are used to investigate lung damage after premature birth, namely radiography and CT. The chest radiograph remains the most important tool for the neonatologist in handling respiratory distress and its acute complications. It is also the modality of choice for later evaluation of BPD development. The pioneer study on BPD by Northway and colleagues in 1967 included 32 infants, all with severe respiratory distress syndrome and requirement of 24 hours (or more) of mechanical ventilation with high oxygen concentration (19). The radiological findings were related to the stage of the disease and consisted mainly of rounded radiolucent areas and thinner strands of densities (Figure 1a). In a follow-up 23 years later, the radiographic score was higher in the BPD group than in the control group, but the radiological findings were relatively subtle (53), including hyperlucent areas, blebs, peribronchial cuffing and pleural thickening. They did not find any correlation between the radiographic findings and the respiratory symptoms or between the x-ray findings and the pulmonary function (53).

Griscom et al (54) compared radiographic findings in BPD survivors (age 8-9 years) to survivors of hyaline membrane disease without BPD and to ex-prematures without respiratory problems in the neonatal period. In addition to a subtle reduction of the antero-posterior diameter of the chest, thin linear densities were the only consistent finding in the BPD group.

Both the increased awareness of the potential adverse effects of continuous high-pressure oxygen treatment and the introduction of exogenous surfactant, have changed the clinical features (22;49), the prognosis (22;49) and the radiological appearance of the BPD survivors (55). The high-grade stages of BPD are now rare and the radiographic changes have usually disappeared after two years of age (55) and if persistent, the findings are subtle (Figure 1b).

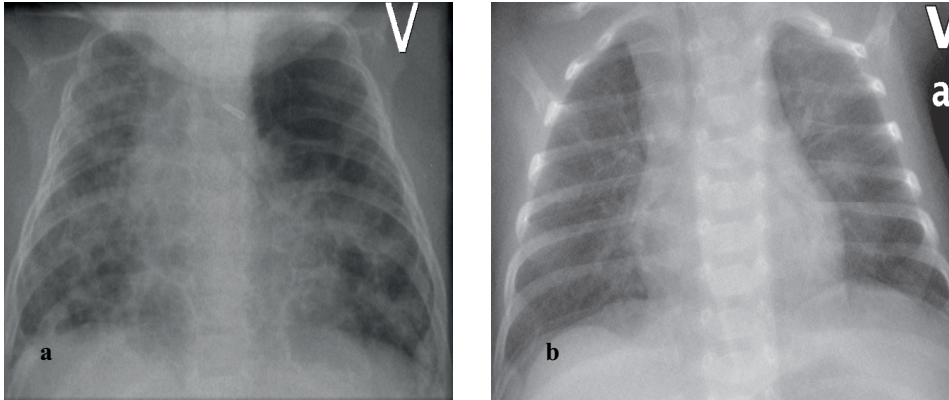


Figure 1a/b. Illustration of a) “Classic BPD” chest radiograph; rounded radiolucent areas and coarse strands of densities, in a girl, 3 months of age with GA 25 weeks and Birth Weight 840g and b) “New BPD” chest radiograph; with mild peribronchial cuffing in seven weeks old girl with GA 31 weeks and Birth Weight 1200g.

b. High Resolution Computer Tomography (HRCT)

Parallel to the improved treatment regimens of premature babies and the consequent reduction of chest radiograph findings, the computer tomography techniques evolved, allowing for the detection of minor structural pulmonary changes. This encouraged several investigators to examine BPD survivors with HRCT (56-58) (Table 1). Oppenheim and co-workers’ study from 1994 is probably the first to describe the HRCT findings in BPD survivors (57). They investigated 23 young children with a mean age 4 years, with continuous pulmonary signs and symptoms and showed abnormalities in all cases. Well-defined linear opacities and triangular, sub pleural opacities were seen in nearly all cases and in 87%, areas with hypo-attenuation and vascular distortion were detected. The lack of bronchiectasies was another important finding of this study.

A Japanese research group examined 22 infants with CT (59), created a scoring system and correlated these scores to a clinical score. At HRCT, hyperaeration was the most frequent finding and it was the only reproducible finding (i.e. with an acceptable agreement) and the only finding that correlated to the clinical score. The study of older children (mean age 10y) with a history of BPD, by Aquino and co-workers in 1999 (56), confirms a high rate of the CT findings (abnormal CT in 24 out of 26) and with areas of decreased attenuation, reticular

opacities and architectural distortion being the most important findings. In addition 92% had air trapping on expiratory scans and the CT findings correlated well with pulmonary function abnormalities. Howling et al examined 5 adult BPD survivors (58) and confirmed the high occurrence of multifocal areas of reduced lung attenuation and perfusion. As a supplemental finding, they described a reduction of the ratio between bronchus and artery diameter, suggestive of a reduced bronchial diameter.

A retrospective review of 41 BPD-survivors (age 10-20 months) born with VLBW (60) revealed abnormal CT findings in all cases. The triad of hyperlucent areas, linear opacities and triangular opacities was the most common finding and the pattern is similar to the findings in premature born in the pre-surfactant era (56-58). Nineteen young adults born with a birth weight < 1500g and with a need of supplemental oxygen at GA 36 weeks were examined with CT and all had abnormal findings (61). Opposite to previous studies, they reported a high prevalence of emphysema (84%), defined as “areas of very low attenuation containing no perceptible parenchymal anatomy” (56). They also found a correlation between the extent of emphysema and the FEV₁ z score. In a recent study, 26 children born with VLBW and a history of BPD were examined with HRCT at age 6 to 8 years (62). Abnormal findings were found in 73% of the cases, with emphysema and linear opacities being the two most frequent findings.

Table 1. Studies on HRCT findings in ex-prematures, published between 1994 and 2009.

First author and publication year	Ref. no	Inclusion criteria	N	Mean age at examination	Main findings
Oppenheim 1994	(57)	BPD Current symptoms	23	4y (2 m-13y)	- CT better than x-ray. - Multifocal areas of hyperaeration, linear and triangular opacities. - No bronchiectasies.
Aquino 1999	(56)	BPD	26	10y (5-18y)	- Decreased density, architectural distortion, air trapping. - CT findings correlate with lung function. - CT findings correlate with days of supplemental oxygen
Howling 2000	(58)	BPD	5 10 ctr	25y (20-26y)	- Pathological findings in 100% - Reduced lung attenuation, bronchial wall thickening and decreased bronchus-to-pulmonary artery ratios
Mahut 2007	(60)	BPD + VLBW	41	16 months (10-20mo)	- Abnormal findings in 100 % - Hyperlucent areas, lin.opacities, triang. opacities and bullae. - Most common CT findings correlate with lung function tests - CT findings correlate to oxygen exposure
Wong 2008	(61)	BPD (moderate /severe) + VLBW	19	19y (17-33y)	- Abnormal findings in 100 % - Emphysema in 84% - Severity of radiological emphysema was inversely related to FEV ₁ - No neonatal data predicted the CT findings
Broström 2009	(62)	VLBW +/- BPD	26	6-8y	- Abnormal findings in 73% - Emphysema found in 38% - Linear opacities found in 38% - 58% of those with abnormal scans had a FEV ₁ < 80% pred.

Several HRCT scoring systems exist for the evaluation of cystic fibrosis (CF) (63-66). De Jong and co-workers evaluated these systems (67) and conclude that the reproducibility is acceptable and that the scores obtained correlate to the results of the lung function tests (LFT). Ochiai and colleagues (68) proposed a new scoring system of CT findings in the assessment of BPD in the neonatal period, with a classification into one of 3 categories; hyperexpansion, emphysema or fibrous / interstitial abnormalities. This scoring system was based on a chest x-ray system. This scoring system was based on 42 preterm infants, applied in the newborn period and at time of discharge. To our knowledge, no validated scoring system for older children or adults born prematurely exists.

c. Pathological-radiological correlation

In the classic BPD, histological examination of the lungs shows emphysema, atelectasis and fibrosis (19), changes which are easily detected on a chest radiographs (19). In addition hypertrophy of smooth muscles in the bronchial and the arterial walls can be seen. Together, these changes caused airway obstruction, pulmonary hypertension and cor pulmonale. In milder forms of BPD, as described by Griscom et al in 1989, chest radiographs show linear densities only, however, the autopsy correlate is sparse (54). In a study of 28 autopsies (at age 3-40 months), patchy alveolar septal fibrosis was the main finding, but also areas with hyper expansion and atelectasis were found (69). Griscom and colleagues suggest that the linear densities identified on chest radiographs, represented fissures / grooves produced by traction from fibrosis near the pleural surface (54). In the new form of BPD with survival into childhood and young adulthood, no autopsies are available for correlation studies. In these ex-premature adolescents and young adults, the chest radiograph is often completely normal or near normal (54). But the introduction of HRCT has elucidated several “minor” findings in these subjects with linear opacities, triangular opacities and hypoattenuated areas being the three most frequent (56-58).

5. LONG TERM SEQUELAE

Several studies have shown that survivors of BPD suffer long-term pulmonary sequelae. A controlled survey from 1990, including 26 BPD surviving adolescents / young adults, showed that 68% of the cases had airway obstruction, 52% had airway hyper reactivity, and 23% had severe pulmonary dysfunction or current symptoms of respiratory problems (53). Doyle and co-workers, in a similar study of 180 14 years old born with VLBW, showed that those with a history of BPD had lower values for airflow variables, but that the overall group had clinical lung function comparable to the term controls (70). In a recent population based study including 46 extremely premature born young adults (birth weight below 1000g or GA below 28 weeks) lung function tests at age 18 years showed a decreased FEV₁ and increased bronchial hyper responsiveness (BHR) (26). Several factors have been proven to accelerate the normal ageing process of the lung; cigarette smoking, childhood pneumonias (26;71) and bronchial hyper reactivity (26). In the population described by Halvorsen, the preterms had experienced more pneumonia in childhood, had more BHR, used more asthma medication and had the same smoking habits as the age-matched controls. Thus, they had a higher risk of accelerated lung ageing. Doyle and co-workers showed that cigarette smoking had a greater negative influence on the respiratory function in young adults of extremely low birth weight (ELBW), than in the term born controls (72). In the review article “Airway Function Measurements and Long-term Follow-Up of Survivors of Preterm Birth With and Without Chronic Lung Disease” by Narang, Baraldi, Silverman and Bush (52) in 2006, they summarise the “documented” effect on the airway function at long term. They conclude that the ex-preterms have more respiratory symptoms and that airway hyper responsiveness is common in ex-prematures. The lung function test studies have shown reduced lung function in this group but the studies suggest an improvement over time. In addition, BPD seems to be a risk factor for limited respiratory reserves during exercise (52). Chronic obstructive pulmonary disease (COPD) may start early in childhood (26) and although there is no follow up study of BPD survivors into middle age, yet, some authors raise the question of premature birth and BPD inducing COPD in adulthood (28;73).

C. BRAIN AFFECTION AFTER PREMATURE BIRTH / LOW BIRTH WEIGHT

1. EPIDEMIOLOGY

The severity and prevalence of neurologic damage associated with premature birth or low birth weight, depends on the outcome measure under investigation; MRI findings, neuromotoric status or neuro-cognitive status. Sequelae after premature include major handicaps, such as cerebral palsy (CP), mental retardation, deafness and visual loss (74), and minor handicaps, such as learning problems, impaired attention and behavioural problems (15;75;76). Further, the incidence of psychiatric disease is also higher among Low birth weight children, among those born at term (77).

Several studies have investigated the rate of CP after premature birth. In an UK population-based register study, rates of 57 per 1000 for those with birth weight below 1000g, vs. 40 per 1000 for those with BWs between 1000-1500g were reported, as compared to an overall, population based CP rate of 1.7 per 1000 live births (78).

The use of MRI findings as a surrogate for outcome have been used in several studies, however, many of these epidemiological studies are flawed by selection bias such as inclusion of those with CP or other major handicaps only. In a systematic review of MRI findings in children with CP (79), 86% of the MR examinations were reported as abnormal. Ex-prematures without CP is reported to have increased risk of behavioural problems or cognitive impairments (15;77) and certain MRI findings seem to be associated with these symptoms/signs (80). According to the literature, ex-prematures with neuropsychological impairment or psychiatric symptoms are unlikely to have a completely normal MRI scan (80;81), while the association between MRI pathology and minor cognitive impairment is unclear (81). In an unselected study by Dyet et al 119 infants born at 23 to 30 weeks, underwent serial MRIs (82). At the initial examination, soon after birth, 44% had a normal MRI, decreasing to 8% when imaged at term-equivalent age. The major finding at term-MRI was Diffuse Excessive High Signal Intensity (DESHI). The research group found no association between initial MR findings and outcome at 18 months, but a significant association between findings at term-MRI and outcome at 18 months.

The prevalence of MRI findings in ex-premature in later life is influenced by a variety of factors; inclusion criteria (for instance including those with a major handicap), type of MRI examinations (qualitative vs. quantitative), interpretation of findings as normal or abnormal (for instance prominent ventricles). Skranes and co-workers report abnormal MRI in 84%, when examining 55 15-year-olds with VLBW (83). Opposed to this, Nagy report abnormal MRI in only 15 out of 74 (20%) VLBW adolescents (mean age 14.9y) (84). This discrepancy may in part be explained by the simple fact that Skranes' group categorized ventricular dilatation as an abnormal finding, but Nagy and colleagues did not.

2. TYPES OF INJURY AND PATHOGENESIS

There is no official - or agreed classification of types of brain injury in newborns. It is common to classify according to radiological findings (CUS and MRI), for instance the Papile classification of cerebral haemorrhages (85). Sometimes the classification is based purely on radiological findings alone such as DESHI, on pathological correlates such as haemorrhagic infarction or on etiological factors such as punctate ischemic lesions or on a mixture of these factors.

The germinal matrix in prematures consists of neurone-glia cell precursors, which derive their blood supply from tiny, temporary vessels. These vessels are especially fragile and differ from the permanent vessels in their microstructure (86). The fragility of the vessel wall combined with disturbance of cerebral blood flow (86) and lack of autoregulation of cerebral blood flow (87), may account for the rupture of these vessels in germinal matrix. The haemorrhage may extend into the ventricles and the situation is then regarded as a Grade II Haemorrhage, according to the classification by Papile (85). In cases where the intraventricular haemorrhage leads to ventricular dilatation, it is termed a Grade III Haemorrhage (85). The exact mechanism of ventricular dilatation is not known, but it seems reasonable that blood products / clot formation obstruct the aqueduct or interferes with the normal CSF absorption in arachnoid villi or brain tissue. However the exact mechanism of the communicating hydrocephalus is debated (88). Indications for surgical intervention of a subsequent hydrocephalus are still controversial, as are the preferred techniques (89;90). In some cases a mild dilatation is temporary and no intervention is judged necessary, however, the radiological findings must be carefully interpreted within the clinical context.

A germinal matrix haemorrhage may compromise the small venules draining the brain parenchyma in the hemisphere, leading to venous congestion and sub sequentially to venous infarction with secondary haemorrhage (91). This venous infarction was previously called Grade IV Haemorrhage (85). Such infarcts may evolve without any visible intraventricular haemorrhage.

It is undebatable that white matter is affected by premature birth and periventricular leukomalacia (PVL) is probably the most serious event. As the name indicates, the lesions are situated in white matter (“leuko”) around the lateral ventricles (“periventricular”) and the brain tissue is softened (“malacia”). The softening is due to necrosis and cysts may appear on imaging. But also a non-cystic PVL may develop and even if the prevalence of cystic PVL is decreasing, it is not obvious that the burden of WM disease as a whole is decreasing. In addition, autopsy studies have shown that white matter damage that is non-detectable on MRI (92) is frequent and consists of microscopic necrotic foci and gliosis. The PVL is shown to be associated with neurone loss in white matter (sub-plate neurones and late-migrating neurones), axonal damage, dysfunctional myelination, but without loss of oligodendrocytes (93). Selective vulnerability of the oligodendrocyte precursors is central in the pathogenesis of PVL (87;94). These cells seem to be strongly affected by various stimuli, most important hypoxic-ischemic events and / or infection / inflammation. The immature vasculature (with risk of vessel rupture) in combination with lack of autoregulation of perfusion may create hypoxia to the tissue. The hypoxia then leads to glia activation with inflammatory reactions that may account for the development of PVL. During recent years, several studies have indicated that infection (choriamnionitis) may be the trigger of such an inflammatory cascade and that the future, primary goal is to protect the premature brain by preventing the inflammatory damage (87).

Another, recently detected white matter “disease” is the Diffuse Excessive High Signal Intensities (DESHI) found in white matter of preterms at term-equivalent MRI scans. It is still unclear what DESHI actually represents; whether it is vasogenic oedema, reduced axonal diameter, damage to the oligodendrocytes or just a maturational delay (82;95).

Occasionally, non-specific small focal lesions are found within the white matter in preterms. Based on signal intensity properties on MRI, these are thought to be haemorrhagic-ischemic of origin (95). The cortex may also be affected in pre-terms (96) and may be associated with

PVL (97). It is unclear whether late preterm infants are more vulnerable to grey matter injury than the term infants (98). Morphometric studies have shown reduced cortical thickness in some areas, but it is not clear whether this represents a separate entity or whether it is secondary to WM damage (96). In autopsy studies (93) neurone loss is found both in the white matter and in cortical grey matter, but also in central grey matter (basal ganglia / thalamus) and a quantitative volumetric MRI study of preterms with PVL, confirms abnormalities in the thalamus (99). A high rate of cerebellar haemorrhage is found on autopsy in VLBW infants but does not seem to be a parallel event to the supratentorial haemorrhages (100). The pathogenesis of these haemorrhages is uncertain.

3. RADIOLOGY

a. Ultrasonography (US)

Ultrasonography is still the initial method for imaging the preterm brain. It is easy accessible and without any radiation hazard (or other proven side-effects). It may be performed at the neonatal intensive care unit, with the premature lying in the incubator. With modern ultrasonography equipment and a relatively large anterior fontanel, the overview of the neonatal brain is excellent in most cases. Even if the examination is operator-dependent, both the sensitivity and the specificity in detecting Germinal Matrix Haemorrhage- Intraventricular Haemorrhage (GMH-IVH) are high (101). Already in 1983, Papile et al (102) proved a direct relationship between grade of haemorrhage and major handicap in early childhood. The sensitivity for US in detecting PVL, is however poorer than for MRI (103). The characteristic periventricular flaring may be hard to differentiate from normal appearing periventricular white matter with normal high echogenicity. In cases with cystic PVL, small cysts typically appear in approximately 2 weeks (104) and will then easily be detected by US. But this is not the case in non-cystic PVL, which limits the role of US in the prognostic work-up (105). After 1 year of age (closure of the anterior fontanel) cerebral US can no longer be used in the follow-up of ex-prematures.

b. Computertomograhv (CT)

CT is also sensitive in detecting intracranial haemorrhage, but the relatively high radiation dose and the need of transportation to the CT unit have nearly precluded this examination of premature brain injury. In addition, discrimination between white and grey matter is poor yielding a low sensitivity in detecting WM disease (106). Thus CT does not play a role in follow-up in ex-premature children (106).

c. Magnetic Resonance Imaging (MRI)

Introduction of MRI has revolutionised brain imaging, mainly because of the improvement in resolution and thereby the ability to visualise anatomical details. Even as important is the unique discrimination between grey and white matter. Several brain MRI studies of ex-prematures / low birth weight survivors, have been performed during the last 10-15 years. The heterogeneity among these studies is quite large; both in regards to *type of MRI examination* and to *study population*. The initial studies were primarily *qualitative studies*, in which the results were based on subjective evaluation of the MRI findings, without any measurements performed (Table 2).

Table 2. Qualitative studies on cerebral MRI in children and adolescents born premature or with a low birth weight.

First author and year of publication	Ref. no	Group	Age	No	Main findings
Cooke RW 1999	(107)	VLBW	15-17y	87 (8)	42.5% of VLBW had abnormal scans. No association between MRI and school performance.
Inder TE 2003	(108)	VLBW	Term	100 (10)	WM abnormalities↑ Predictors of WM damage: low GA, maternal fever, sepsis
Indredavik MS 2005	(80)	VLBW SGA	15y	55/54 (66)	MRI correlated to psychiatric disease: ADHD associated to WM reduction and CC thinning
Isaacs EB 2004	(109)	<30w	15y	65 (0?)	Normal MRI in 50%. No association between MR abnormalities and IQ
Miller SP 2005	(110)	<34w	Preterm -term	89	59% normal outcome. Abnormal outcome associated to WM lesions, ventriculomegali, IVH
Nagy Z 2009	(84)	VLBW	12-16y	74 (69)	Abnormalities in 21 out of 143. 20 of these mild.
Skranes JS 1992, 1993	(111; 112)	VLBW	1y	27 / 31	74% abnormal myelin, 26% focal WM pathology, 37% cortical atrophy, 44% irregular lateral ventricles
Skranes JS 1997	(113)	VLBW	6y	20	Gliosis (in WM) predict impairment in motor function.
Skranes JS 2005	(83)	VLBW SGA	15y	55/54 (66)	VLBW: Ventricular dilatation in 82%, WM reduction in 53%, CC thinning in 47%, gliosis in 29%.
Stewart AL 1999	(114)	<33w	14y	72 (21)	Abnormal scans in 40 out of 72 preterms, in 1 out of 21 controls. WM, CC, ventricular pathology common
Woodward LJ 2004	(115)	VLBW	Term	66	Linear association between MRI pathology and neurological tests.

Later, quantitative studies (Table 3), studies using Diffusion Tensor Imaging (DTI) (Table 4) and Functional imaging (fMRI) of ex-preterm young adults (mean age 20y) have been published (Table 5).

Table 3. Quantitative studies on cerebral MRI in children and adolescents born premature or with a low birth weight.

First author and year of publication	Ref. no	Group	Age	No (controls)	Main findings
Abernethy LJ 2002	(116)	VLBW	15-16y	87 (8)	Nucl. caudatus & hippocampal volume ↓
Allin M 2004	(117)	VLBW	23y	32 (18)	TBV/ WM / GM vol. → Lat.vent. vol. ↑ (41%). GM: WM ratio ↑
Caldu X 2006	(118)	<33w	13y	25 (25)	CC size correlates with GA, IQ and memory performance.
Dyet LE 2006	(82)	<30w	Birth-term	119 (0)	Outcome correlated to WM abnormalities. and ventricular dilatation
Fearon P 2004	(119)	VLBW	23y	33 (18)	Ventricular vol. ↑. Posterior CC vol.↓, TBV / GM / Hippocampus volume →
Inder TE 2005	(120)	VLBW	Term	100 (10)	Cortical GM vol. ↓. Deep nucleus GM vol. ↓. CSF vol.↑
Isaacs EB 2004	(109)	<30w	15y	65 (0?)	Association between IQ and specific regions
Kesler SR 2004	(121)	VLBW	7-11y	73 (33)	Occipital horn↑.Frontal / parietal GM ↑. Maternal education predicts cog. function
Martinussen M 2005	(122)	VLBW SGA	15y	50/49 (58)	Reg. cortical thick. in pariet.-temp.-occ↓, frontal↑.Cort.GM vol.: TBV ratio ↓
Narberhaus A 2008	(123)	<33w	14y	52 (52)	Posterior CC ↓ CC size correlate to prefrontal functions
Nosarti C 2002	(124)	VLBW	15y	72 (47)	WBV vol.↓, Cortical GM vol.↓, Hippocampal vol.↓, Lateral ventricles ↑
Nosarti C 2004	(125)	VLBW	15y	72 (51)	Total CC vol. ↓. Very preterm boys: Ass. between CC size and verbal score
Nosarti C 2005	(126)	VLBW	15y	72 (51)	Volume of left nucleus caudatus neg. correlated to the hyperactivity score
Peterson BS 2000	(96)	VLBW	8y	25 (39)	Regional cortical volumes ↓ associated with IQ scores.
Rademaker KJ 2004	(127)	<32w	7-8y	221 (0)	Total CC area↓ CC area correlated to motor function
Reiss AL 2004	(128)	VLBW	8y	65 (31)	GM and WM ↓ in pre terms. Preterm boys WM ↓
Woodward LJ 2005	(129)	VLBW-<32w	Term	92 (103)	Ass.between qual. and quant. MRI findings and “working memory” at 2y

Table 4. DTI studies in children and adolescents born premature or with a low birth weight.

First author and year of publication	Ref. no	Group	Age	No (Controls)	Main findings
Kontis D 2009	(130)	<33w	19y	63 (45)	Altered microstructure in genu of CC in female preterms. Associated to performance IQ
Nagy Z 2009	(131)	VLBW	12-18y	74 (69)	FA ↓ in posterior CC, fornix and external capsule
Skranes J 2007	(132)	VLBW	15y	34 (47)	FA ↓ in CC, internal and external capsule and superior-, middle superior-, inferior fasciculus
Vangberg TR 2006	(133)	VLBW SGA	15y	34/42 (47)	VLBW: FA values in CC↓, internal capsule↓, superior fasciculus↓. SGA: no differences

Table 5. fMRI studies in children and adolescents born premature or with a low birth weight.

First author and year of publication	Ref. No	Group	Age	No (controls)	Main findings
Lawrence EJ 2010	(134)	<33w	20y	22 (22)	Functional neuronal differences mediated by structural variation in specific regions and GA
Peterson BS 2002	(135)	VLBW	8y	26 (8)	Preterms engage different pathways.
Rushe TM 2004	(136)	<33w	14y	6	“Frontal response” ↑ and “Occipital response” ↓

Taken together, the studies vary substantially in terms of *age at MRI scanning*. Based on this criterion, the studies may be divided into four groups; scanning at term-equivalent, in childhood, in adolescence and in adulthood.

MRI studies of prematures performed at term-equivalent age show that their brains appear different from those of term born babies, suggesting that the brain develops differently ex-utero and in-utero (95). MRI studies performed later in childhood / adolescence / adulthood are probably more capable of deciding degree of permanent injury and the possible relationship between MRI findings and clinical outcome. In terms of *subject inclusion* the studies vary to some degree; the majority have examined groups consisting of survivors of VLBW, while other researchers use GA below 33 weeks as inclusion criterion. The studies also differ in whether individuals with major handicaps are included or not.

The main findings are relatively consistent among the studies and a summary of these findings are given below:

Ventricular dilatation has been found in several qualitative studies and seems to be present already early in life, at term-equivalent age (110) and age 1 years (111). Quantitative studies have confirmed this, both at term (120), in childhood (121), in adolescence (124) and in early adulthood (117;119).

White matter is affected in individuals born preterm and /or with low birth weight. *Loss of bulk of white matter* is probably a parallel finding to the *ventricular dilatation* and is reported both in qualitative studies (83) and quantitative studies (121). In contrast, no group difference in segmented WM volume was found in a study of 32 young adults (23y) with VLBW and 18 term-born controls (117). *Focal white matter lesions* are also found in numerous qualitative studies, at term (82), at 1 year (111), at 6 years (113) and in adolescence (83).

Grey matter affection is difficult to detect using subjective evaluation only, but quantitative studies have shown that GM is affected in these individuals. Inder et al (120) found a reduction in both cortical GM volume and deep nuclear GM volume in VLBWs at term, whereas others have found regional GM volume differences (96;121;122) with increased GM volume in some regions and reduced volume in others. Interestingly, studies in young adults (117;119) have not proven any reduction of GM matter volume in VLBW individuals. Parallel to this; a reduced volume of *Hippocampus* is shown in quantitative studies in childhood (96) and in adolescence (124), but not in early adulthood (119). A reduction of *Whole / Total brain volume (TBV)* is found in several quantitative studies (96;124) and is often introduced as a covariate to investigate whether specific brain structures are disproportionately reduced in size. The only adult-study (119) did not show any reduction in TBV in the VLBW group.

Corpus Callosum, as a major central white matter structure, is often highlighted in the literature of imaging ex-prematures and low birth weight survivors. Diffuse thinning of Corpus Callosum is found in qualitative studies (83;114) and several quantitative studies have reported a reduced total CC area in VLBW individuals (96;125) and in very preterm born individuals (118;127). Results from studies looking at sub-regions of CC, indicate that this area reduction is driven mainly by a size reduction of the posterior part of CC (119;123). In a

recent Diffusion Tensor Imaging studies, alterations in microstructure of CC are reported. Vangberg et al (133) and Skranes (132) both report reduced Fractional Anisotropy (FA) in CC (and in internal / external capsule), whereas Nagy et al (131) found a reduced FA in the posterior part of CC in VLBW adolescents. Kontis and co-workers did not, however, confirm these findings, when looking at 66 very preterm born young adults (19y) (130). They did not find any effect of group for FA values and only group difference in Mean Diffusivity (MD) in the genu, for the females. The most important studies of CC are listed in Table 6.

Table 6. MRI studies addressing the Corpus Callosum in children and adolescents born premature or with a low birth weight.

First author and year of publication	Ref. No	Group	Age	No (controls)	Main findings
Allin M 2007	(137)	< 33 w	15y 19y	72 (34)	CC grows dramatically in VPT adolescents. Growth is associated to neuropsychological outcome
Caldu X 2006	(118)	< 33 w	13y	25 (25)	CC size correlates with GA, IQ and memory performance
Fearon P 2004	(119)	VLBW	23 y	33 (18)	Posterior CC volume ↓
Nagy Z 2009	(131)	VLBW	15y	74 (69)	FA ↓ in posterior CC, fornix and external capsules
Narberhaus A 2007	(123)	< 33 w	14y	52 (52)	VPT: CC size ↓, posterior part most. Positive association between CC and prefrontal functions.
Nosarti C 2004	(125)	< 33 w	14-15y	72 (51)	Total CC volume ↓ 7.5%. Association between CC size and verbal score in VPT boys.
Rademaker KJ 2004	(127)	VLBW	7-8y	204 (21)	Total CC area ↓. CC area correlated to motor function

The MRI findings seem to vary by *time of examination*, i.e. whether the scan has been performed in the preterm period, at term-equivalent age, in childhood, in adolescence or in adulthood.

The number of MRI studies of preterms performed in **the preterm period** is still sparse, but some have been performed at **term-equivalent age**. Inder and colleagues focused on white matter damage in a large MRI study (at term equivalent age) in VLBW infants and revealed

that low GA, maternal fever and sepsis were predictors for WM damage (108). In addition they found that GM injury was closely related to WM injury (108) and that there was a reduction in both cortical-and deep grey matter (120). Yoo et al have shown that DTI and fibre tractography is possible to perform in preterm neonates (138), but the value of these MRI examination at this age, is unclear.

More important than the MRI findings alone are the possible associations between MRI findings at term and neurological outcome. Results from such studies are now appearing in the literature. Woodward et al examined 92 very preterms and found associations between qualitative and quantitative MRI findings at term and object working memory at 2 years of age (129).

Several researchers have studied the MRI findings in **childhood**. As discussed earlier, the studies differ in inclusion criteria and in type of MRI study (qualitative vs. quantitative).

Dyet et al (82) performed serial MRIs from birth to 18-36 months of age in very preterm (<30w) infants and found an association between WM abnormalities / ventricular dilatation and neurodevelopmental status at 18-36 months of age (corrected age). Quantitative MRI studies in mid-childhood years have shown significant group differences between VLBW and controls in regional cortical volumes (96;121). Most studies in this field are cross-sectional by nature, except for the studies by Skranes and co-workers in Trondheim. Their research group published already in 1992, a paper on MRI findings at age one year in a cohort of 27 VLBW (111), followed by a new MRI study at age 6y (113).

Several researchers have studied MRI in **adolescents** born with VLBW. Abernethy et al (116) looked for associations between MRI findings and IQ / attention deficit in 87 VLBW survivors at age 15-16 years but did not prove any significant association, when using a subjective assessment of the MRIs. However, when using volumetric assessments, significant associations were found. Nosarti and colleagues also studied 15-years- old VLBW survivors (no 72) and found a significantly smaller whole brain volume and cortical grey matter volume in the VLBW, compared to the controls (124). In addition the VLBWs had a 42% increase in the size of the lateral ventricles. The Trondheim group has also performed an extensive MRI study on adolescents born with VLBW. First, in a qualitative MRI study, in comparing the VLBW with a SGA group and a control group (83) looking for associations between subjectively assessed MRI findings and psychiatric symptoms (80). Next in measuring

cortical thickness using an automatized morphometric method (122) and finally in performing Diffusion Tensor Imaging (132;133).

There are relatively few MRI studies on **adults** born premature and / or with LBW. The group at Institute of Psychiatry, King's College London published two papers in 2004, on brain volumetrics in 23 years old born with VLBW (117;119) and report an increase in volume of the ventricular system, but no group difference in whole brain volume.

After the development of advanced MRI techniques, many “prematurity” researchers have shifted their focus away from anatomical-volumetric changes and towards microstructure and functional imaging. Looking at the free motion of the water molecule (water diffusion) is a measure of the tissue integrity and in the **Diffusion Tensor Imaging** (DTI) technique, the sum and direction of the diffusion is analysed in separate tissue ellipsoids. The Trondheim group (133) applied this technique on their cohort consisting of 34 VLBW, 42 SGA and 47 control adolescents. The main finding in this study was a reduced Fractional Anisotropy (FA) in several WM areas in the VLBW individuals and the authors speculate if reduced myelination is the cause of this. In the Stockholm Neonatal Project, Nagy and co-workers examined 74 VLBW adolescents and 69 controls and reported lower FA values in the posterior part of Corpus Callosum (CC) (131). Kontis and co-workers also applied the DTI technique on CC in a cohort of 19 years olds (no 63) born very preterm (<33 weeks) (130) and demonstrated alterations in WM structure (higher Mean Diffusivity) in the genu of CC in the very preterm-born females.

Already in 2002 Peterson and colleagues (135) performed **fMRI** in a group of preterm children (age 8y). In a passive language comprehensions task the ex-preterms engaged different pathways than the age-matched controls. In a fMRI study of ex-preterm young adults (mean age 20y) alterations in brain activation were demonstrated and the ex-preterms had both areas of reduced activation (as compared to the controls) and increased activation (134). Interestingly, the increased activation in the left parahippocampal gyrus was associated with increased grey matter volume in the same area.

The association between radiological findings and clinical parameters have been investigated in both cross-sectional studies, prospective studies, retrospective studies and in (a few) longitudinal studies. Overall, these studies may be divided into two separate groups:

- 1) Studies investigating the association between MRI findings and clinical outcome.
- 2) Clinical-radiological correlation; i.e. studies investigating the relation between MRI findings and clinical / neuropsychological feature at a certain time point.

d. Association between MRI findings and clinical outcome

Several studies have been conducted in order to establish the predictive / prognostic value of early MRI findings (at term equivalent age). An extensive review article published in 2008 by Hart AR and colleagues (139) summarises the current evidence on MRIs predictive role regarding neurodevelopment.

White matter: Several studies have shown an association between cystic periventricular (PV) damage and cerebral palsy / motor delay at 2 years of age (110), but also between cystic PV damage and poor cognitive outcome (129;140). The outcome after diffuse PV white matter damage is even more uncertain. Several studies have failed to demonstrate any association between these MRI changes and developmental outcome (103;110;141) and for the DESHI finding; the prognostic value is even more controversial (139). DWI / DTI allows for a quantification of WM damage and one study has shown an association between mean ADC values in centrum semiovale at term-equivalent age and DQ at age 2 years (142).

Abnormal or absent signal in the Posterior Limb of Internal Capsule (PLIC) predicts poor motor outcome, in a small study (143). The relationship between Corpus Callosum size at term-equivalent age and later developmental outcome has not been investigated in prospective studies. Regarding WM volume, Peterson et al found that WM volume in specific regions were related to cognitive and motor development at 18-20 months corrected age (144).

Lateral ventricles. Several studies have explored the possible prognostic value of ventricular size at term, but even if large ventricles do identify those at risk, it is an inaccurate marker and does not preclude normal outcome (139).

Grey matter: Several researchers have explored the relationship between cortical thickness and cognition, but few studies look at the predictive value of cortical thickness at term. Peterson et al (144) did show a correlation between GM volumes in specific areas and motor outcome at age 18-20 months.

Cerebellum. Shah et al (145) did not find any correlation between cerebellar volume at term and outcome at 2 years of age.

e. Clinical – radiological correlation

Several studies have been conducted to explore the relationship between MRI findings and clinical parameters, but the studies vary substantially both in regard to study population (preterm, VLBW etc.) and to chosen outcome parameter (motor function, IQ, school performance, behaviour, and neuropsychology). So even if major trends are demonstrated, it is impossible to draw robust due to inconsistencies in study design.

There seems to be a relation between MRI findings (subjectively assessed) and motor function (Movement ABC) / Visuo-motor function (VMI-IV) in VLBW adolescents (81), but this effect may be driven by the participants with major handicaps (CP). When this group was excluded, the association was much weaker. Stewart et al studied very preterm adolescents (14-15y) and did not find any relation between MRI abnormalities and neurological outcome (114). In contrary, Rademaker et al found a strong correlation between CC size / area and motor function at school age, but this large study of preterm children (no 204) included children with cerebral palsy (no 15) (127).

Numerous studies have investigated the relationship between MRI findings and cognitive function. No relation between MRI findings and school performance was observed in 87 VLBW children (age 12-13y) (107) while another study showed a clear relation between MRI findings and behavioural score (Rutter behavioural score) (114). As a parallel, Indredavik et al found that ADHD-related symptoms were associated with WM reduction and thinning of CC (80).

Quantitative MRI studies have shown associations between MRI measurements and cognitive function has been shown: regional cortex volumes and IQ (96), Corpus Callosum area and prefrontal functions (123), GM-WM distribution and neurodevelopment (sum of scores) (146). In a DTI study of very preterm born young adults, Kontis and co-workers found altered microstructure in the genu of CC and that this alteration was related to lower performance IQ (130). In addition, measurement of caudate volumes in 72 adolescents (very preterm) suggests that behavioural problems are associated to volume reduction of the left caudate nucleus (126).

Based on their systematic review, Hart and colleagues (139), conclude that

1) MRI identifies structural changes better than US, 2) The histological proof of subtle MR findings reflect pathology lacks, 3) MRI should be performed around term-equivalent age 4) Whether MRI will ever be able to predict neurodevelopmental outcome accurately is uncertain and 5) MRI of all preterm neonates for prognostic reason cannot be justified.

5. AIMS OF THE STUDY

The overall aim was to address imaging techniques commonly used in the follow-up of lung and brain disease of prematurely born, or born with low birth weight, by

- establishing a scoring system for pulmonary findings as assessed by HRCT
- reporting the prevalence of pulmonary HRCT findings and investigate the associations of these HRCT findings with neonatal factors and lung function tests in children and young adults born with a birth weight below 1000g or a gestational age below 28 weeks
- establishing MRI based reference intervals for different brain structures, and by
- reporting the prevalence of cerebral MRI-findings, with a special focus on the Corpus Callosum, in young adults born with a birth weight below 2000g

6. STUDY DESIGN AND SUBJECTS

The present work is two-part, addressing 1) lung involvement in prematurely born babies and 2) brain involvement in babies born with a birth weight below 2000g, 91% of whom were also born prematurely.

All study subjects were born within a defined area of Western Norway, Hordaland County and Sogn og Fjordane County (Figure 2), during the period 1982 to 1992, having their medical care at Haukeland University Hospital. Haukeland University Hospital is the only provider of neonatal intensive care within this area. The annual birth rate within the catchment area of the study was 5433 (1982) and 6162 (1992). The senior medical staff at the

Neonatal Intensive Unit was essentially similar in the three inclusion periods (lung study 1982- 1985 & 1991-1992, brain study 1986-1988). During this decade (1982-1992) the management of premature infants developed in several aspects with the introduction of exogenous surfactant as one of the more significant improvements. In addition antenatal corticosteroids were gradually introduced and other factors as better assisted ventilation, better surveillance of blood gases and oxygen therapy, focus on nutrition, more aggressive treatment of persistent ductus arteriosus, all contributed to an increased neonatal survival and decreased neonatal morbidity.

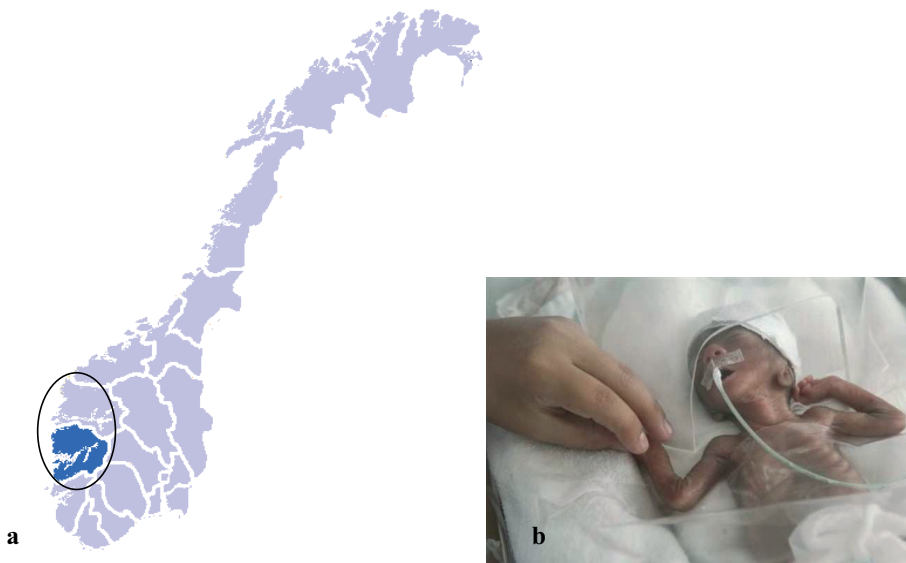


Figure 2. Map of Norway, showing the catchment area of the study (encircled area); Hordaland County (dark blue colour) and Sogn og Fjordane County (purple colour), b) a 2 week old girl born at 24 weeks gestational age.

A. LUNG STUDY (PAPERS 1-2)

1. STUDY POPULATION

The lung study involved two different cohorts; one including a total of 84 subjects born between 1982 and 1985, and a second cohort including 46 subjects born during 1991-1992 (Figure 3). During these two periods, all those born with a $GA \leq 28$ weeks or a birth weight \leq

1000g (n=130) were included in prospective, observational studies. A total of 33 and 11 from each of the groups had died, leaving 86 subjects for the present study. All eligible, 51 adolescents from the first and 35 children from the second cohort were invited to participate in a long-term follow-up during 2001-2002 (Figure 3). Of these, 5 from the first cohort were not able / refused to take part in the clinical follow-up, leaving 81 for the clinical follow-up. 5 from the first group and 2 from the second group were not able / refused to perform a HRCT examination. Thus, a total number of 74 subjects (57% of the original cohorts and 86% of those still alive in 2001-2002), 41 from the first and 33 from the second cohort, were included in the present HRCT study (Figure 3). Two of the examinations were not available in a soft copy for the study on HRCT findings (Paper 1), but was later found on hard copy and then scanned in the PACS system and included in the association study (Paper 2).

Exogenous surfactant (Exosurf®) was available to the second birth-cohort only and was administered to 15 (47%) of the subjects. Routines for administration of postnatal corticosteroids were similar for the two periods.

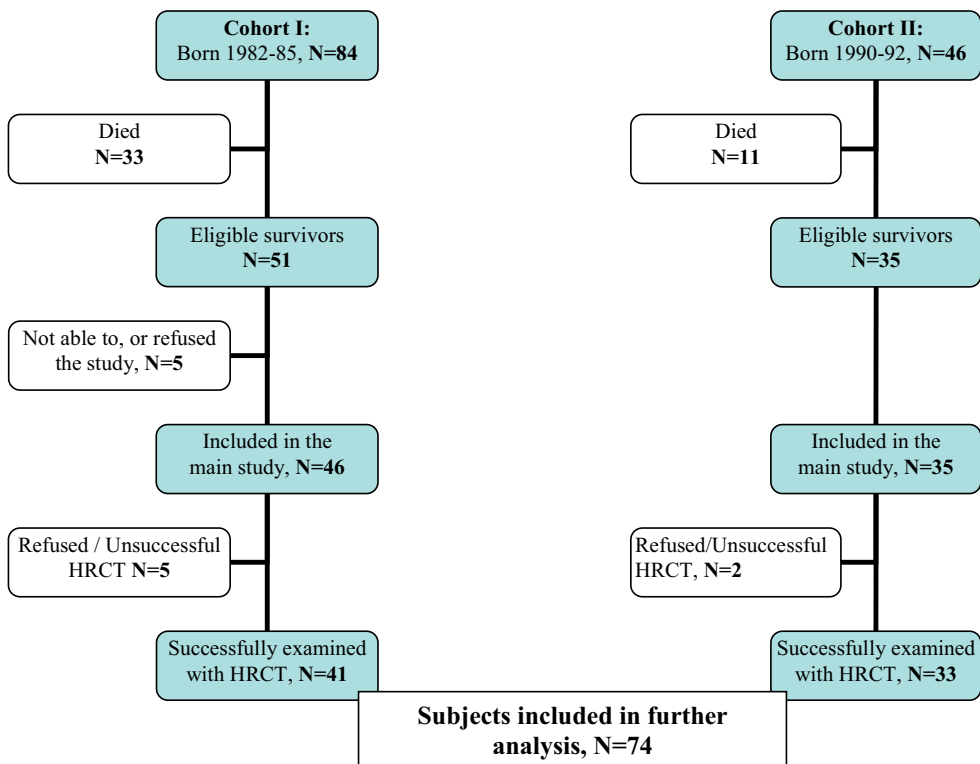


Figure 3. Flow chart of the complete cohorts.

Neonatal characteristics by the presence of non-, mild or moderate BPD for the total study population of 74 subjects, as well as for the two cohorts separately, have been reported before (26) and are given in Tables 7, 8 and 9. For the total study group, mean GA was 27.0 weeks (SD 1.5) and the mean birth weight was 973 (SD 206). Bronchopulmonary dysplasia (BPD) was diagnosed in 56 subjects using the criteria by Northway et al (need of supplemental oxygen at day 28) (55). Using the refined classification suggested by Jobe et al (50), 43/74 (58%) had non or mild and 21/74 (28%) had moderate to severe BPD (Table 7).

Table 7. Neonatal characteristics by BPD of the total study population (n = 74).

Bronchopulmonary dysplasia (BPD) as defined according to the NEW classification by Jobe et al (50).				
	Non (n = 18)	Mild (n = 35)	Moderate or severe (n = 21)	p-value
Number of females (% of group)	12 (63%)	20 (53%)	9 (38%)	0.123 *
Gestational age in weeks (SD)	28.1 (1.2)	26.7 (1.4)	26.3 (1.5)	< 0.001 †
Birth weight in grams, mean (SD)	1121.4 (160.6)	968.0 (201.3)	852.4 (169.7)	< 0.001 †
Days with ventilator treatment, median (range)	0.9 (0 - 4.8)	8.9 (0 - 40.0)	20.5 (1.7 - 54.5)	< 0.001 †
Days with oxygen therapy, median (range)	10 (1 - 26)	45 (28 - 71)	103 (55 - 257)	< 0.001 †

*P-values assess trends within the preterm population across increasing severity of neonatal BPD. * χ^2 -test for trend. † Linear regression.*

Table 8. Neonatal characteristics by BPD of the cohort born during 1982-1985 (n = 41).

Bronchopulmonary dysplasia (BPD) as defined according to Jobe et al (50).			
	Non or mild (N =31)	Moderate or severe (N =10)	p-value
Number of females (% of group)	15 (48%)	4 (40%)	p>0.05*
Gestational age in weeks (SD)	27.2 (1.3)	27.0 (1.3)	p>0.05†
Birth weight in grams, mean (SD)	1054 (198)	868 (125)	p= 0.002†

*P-values assess trends within the preterm population across increasing severity of neonatal BPD. * χ^2 -test for trend. † Linear regression.*

Table 9. Neonatal characteristics by BPD of the cohort born during 1991-1992 (n = 33).

Bronchopulmonary dysplasia (BPD) as defined according to Jobe et al (50).			
	Non or mild (N =22)	Moderate and severe (N =11)	p-value
Number of females (% of group)	17 (77%)	5 (45%)	p>0.05*
Gestational age in weeks (SD)	27.2 (1.7)	25.7 (1.5)	p= 0.017†
Birth weight in grams, mean (SD)	971 (198)	838 (207)	p>0.05†

*P-values assess trends within the preterm population across increasing severity of neonatal BPD. * χ^2 -test for trend. † Linear regression.*

2. HIGH RESOLUTION CT EQUIPMENT / PROTOCOL

The CT examinations were done without any sedation. All examinations were performed on a single-detector CT (HiSpeed Advantage, GE Healthcare). The CT protocol was as follows: slice thickness 1.25mm, 120kV, 50-100mA, lung algorithm and 512 x 512 matrix. Inspiratory scans were performed in all cases, with a scan interval of 10mm, while expiratory scans were performed in the majority of the cases (95%), at 20mm intervals.

3. HIGH RESOLUTION CT EVALUATION / SCORING SYSTEM

The CT examinations were analysed using a PACS workstation with a standardized window / level setting (Window Width 1540 HU, Window Level – 400 HU), but with a possibility of adjustment. We used a novel scoring system for the semi-objective assessment of pulmonary change seen on HRCT in children born prematurely (56;57;60). The initial prototype defined markers of chronic change such as linear / triangular opacities, bronchiectasies, emphysema and bullae, as well as non-specific consolidation and collapse. According to Bhalla's scoring system developed for cystic fibrosis (63), each of 20 lung segments were scored, giving a maximum score of 152 when including the 13 variables having a maximum score. The variable "numbers of bullae" had no such maximum score and therefore was excluded from the total score. The findings were marked on a separate radiographic template (Figure 4), and registered in a score sheet (Table 10).

All the HRCTs were assessed by two blinded, independent observers marked for additional data, reader 1 and reader 2, both paediatric radiologists with extensive experience. Reader one re-read the images on a second occasion after 6 months.

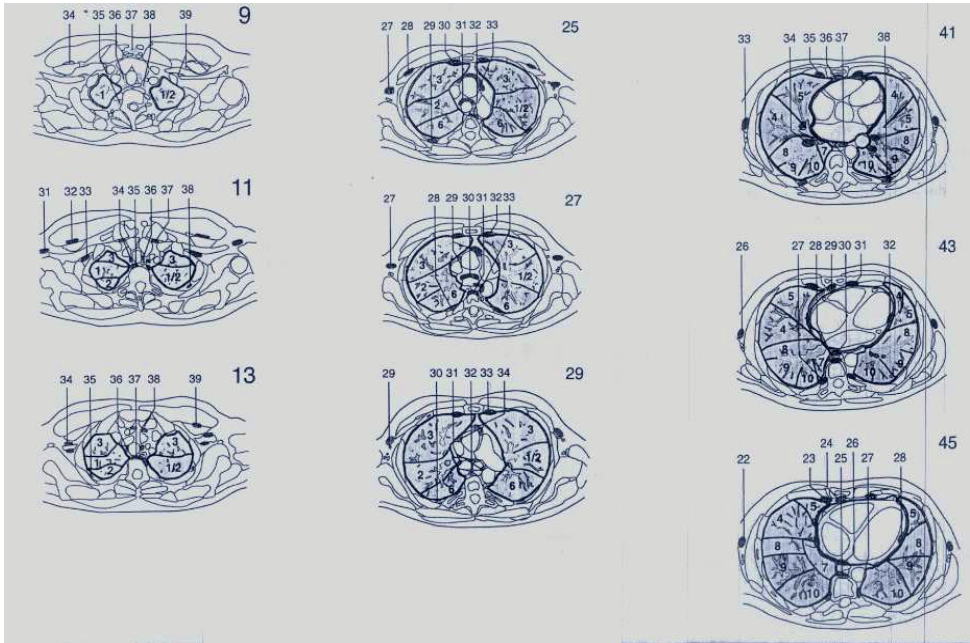


Figure 4. Part of the radiographic template used, showing the segmental borders within the upper parts of the lungs.

Table 10. The initial score sheet used for the assessment of pulmonary change in adolescents and young adults born with GA \leq 28 weeks or a birth weight \leq 1000g (Paper 1).

1	Well defined linear opacities, radiating from the periphery toward the hilum	0=absent, 1=one segment...max.20
2	Triangular sub pleural opacities, defined as small triangles with a pleural base and an internal apex	0=absent, 1=one segment...max. 20
3	Bronchus/bronchiole: artery diameter ratio	0=absent, 1=one segment...max. 20
4	Severity of mosaic perfusion in inspiration	0=absent, 1=one segment...max. 20
5	Severity of air trapping in expiration	0=absent, 1=one segment...max. 20
6	Severity of bronchiectasies	0=absent, 1=mild (luminal diameter slightly greater than diameter of adjacent blood vessel), 2=moderate (lumen 2-3 times the diameter of the vessel), 3=severe (lumen >3 times diameter of vessel)
7	Extent of bronchiectasies (No. BP segments)	0=absent, 1=one segment... max.20
8	Severity of peribronchial thickening	0=absent, 1=present, all degrees
9	Extent of mucus plugging (No. BP segments)	0=absent, 1=one segment... max.20
10	Generations of bronchial divisions involved (bronchiectasies/plugging)	0=absent, 1=up to 4 th gen., 2=up to 5 th gen., 3=up to 6 th gen. and distal
11	Bullae	0=absent, 1=one bullae, etc. Number of bullae R: ...(No) L... (No)
12	Severity of emphysema (No. BP segments)	0=absent, 1=one segment... max.20
13	Collapse/consolidation	0=absent, 1=sub segmental, 2=segmental, lobar
14	Thickening of interlobar septi	0 =absent, 1= unilateral, 2= bilateral

Based on the initial experiences (Paper 1) we refined and simplified the scoring system, excluding 4 of the 14 markers, namely *extent of bronchiectasies*, *extent of mucus plugging*, *generations of bronchial divisions involved* and *thickening of interlobar septi* (Table 11). Linear opacities and triangular, sub pleural opacities were regarded as one parameter. Next, using the original radiographic templates with the marked pathology, reader one created new

scores based on pulmonary lobes rather than on segments, thus reducing the theoretical score. Scores for all six lobes (regarding lingula as a separate lobe) were created according to the presence (1) or absence (0) of the finding under investigation.

Table 11. A refined score sheet used for the assessment of pulmonary change in adolescents and young adults born with GA \leq 28 weeks or a birth weight \leq 1000g (Paper 2), yielding a minimum score of 0 and a maximum score of 50.

1	Linear or triangular, sub pleural opacities	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
2	Decreased Pulmonary Attenuation Hypoattenuation (“mosaic perfusion”) in inspiration	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
3	Decreased Pulmonary Attenuation Hypoattenuation (“air trapping”) in expiration	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
4	Bronchus/bronchiole: artery diameter ratio	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
5	Bronchiectasies	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
6	Peribronchial thickening	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
7	Bullae	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
8	Emphysema	Scoring per lobe 0 = absent, 1 = present Maximum score = 6
9	Collapse / consolidation	0=absent 1=sub-segmental 2= segmental

4. LUNG FUNCTION TESTS

All pulmonary lung function tests were performed within two weeks of the CT scan. Three aspects of lung function were tested; airway dimensions, airway reactivity and lung volumes. Airway dimension was evaluated using spirometry (Vmax22 spirometer). Forced expiratory volume in the first second (FEV_1), forced expiratory flow at 50% (FEF_{50}) and at 25-75% (FEF_{25-75}) of forced vital capacity (FVC), total lung capacity (TLC), residual lung volume (RV) and the ratio RV/TLC were recorded, and the values were expressed as percentages of predicted. Lung volumes were measured using body plethysmography (Autobox 6200) and the following lung volumes were recorded FRC (functional residual capacity), TLC (total lung volume), RV (residual volume) and RV/TLC ratio (Figure 5). The main results from the lung function tests have been reported elsewhere (26;73).

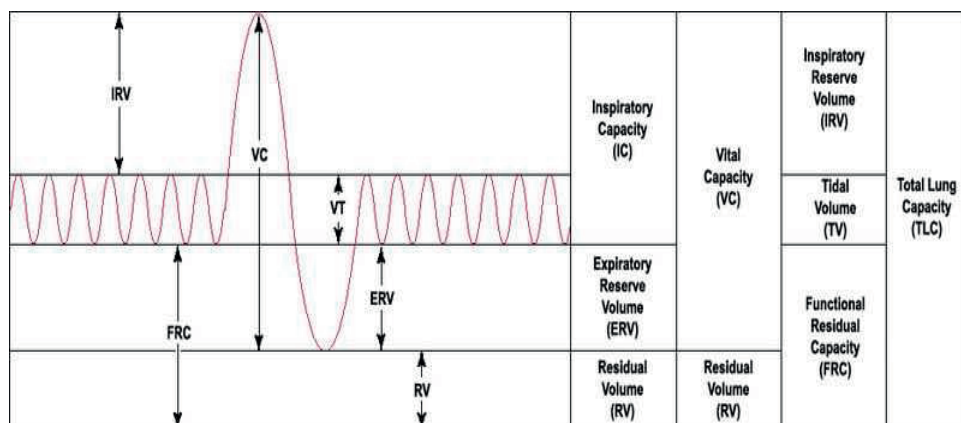


Figure 5. Schematic presentation of lung function parameters.

In our study of association between HRCT findings (paper 2) and lung function tests we included three airway dimension variables (FEV_1 , FEF_{50} and FEF_{25-75}) and two lung volume variables (TLC and RV/TLC). Lung function data for the study population are given in table 12.

Table 12. Lung function data by degree of BPD in the study population of 74 children / adolescents.

	Non or mild BPD N = 53	Moderate or severe BPD n = 21	p-values
FEV₁	89.8 (86.0, 93.6)	80.9 (76.2, 85.7)	0.004
FEF₅₀	83.4 (77.8, 88.9)	68.1 (56.4, 79.8)	0.021
TLC	102.1 (98.1, 106.2)	102.4 (97.0, 107.8)	0.935
RV/TLC	21.2 (19.6, 22.8)	25.3 (22.0, 28.5)	0.026

Except for the ratio RV/TLC, figures are group mean values (95% confidence interval) expressed as percentages of predicted. The criteria for classification of BPD are given in the text. The p-values refer to differences between the two subgroups of BPD.

C. BRAIN STUDY (PAPERS 3-5)

1. STUDY POPULATION AND CLINICAL DATA

This is a population based, controlled observational study including young adults born with a low birth weight (BW < 2000g). The initial study group included 174 eligible subjects without major handicaps and BW < 2000g, all born in the county of Hordaland, Norway, between April 1st 1986 and August 8th 1988 (Figure 6). A total of 134 participated in a clinical follow-up during 2006-2007, of whom 113 agreed to have a MRI examination (65.3% of the eligible cases) (Figure 6). The initial control group were recruited into the clinical study at age 5 years and consisted of 163 healthy children born during the same period as the Low birth weight cases (1986-88), with a GA of more than 37 weeks, a birth weight above 3000g and with no need of neonatal intensive care. Methods of recruitment / selection of the controls have been thoroughly described in previous reports (147). Adolescents who had suffered head injury, undergone brain surgery or had been diagnosed with any other significant disease, including cerebral palsy, were excluded from the present MRI-follow-up in 2006-2007.

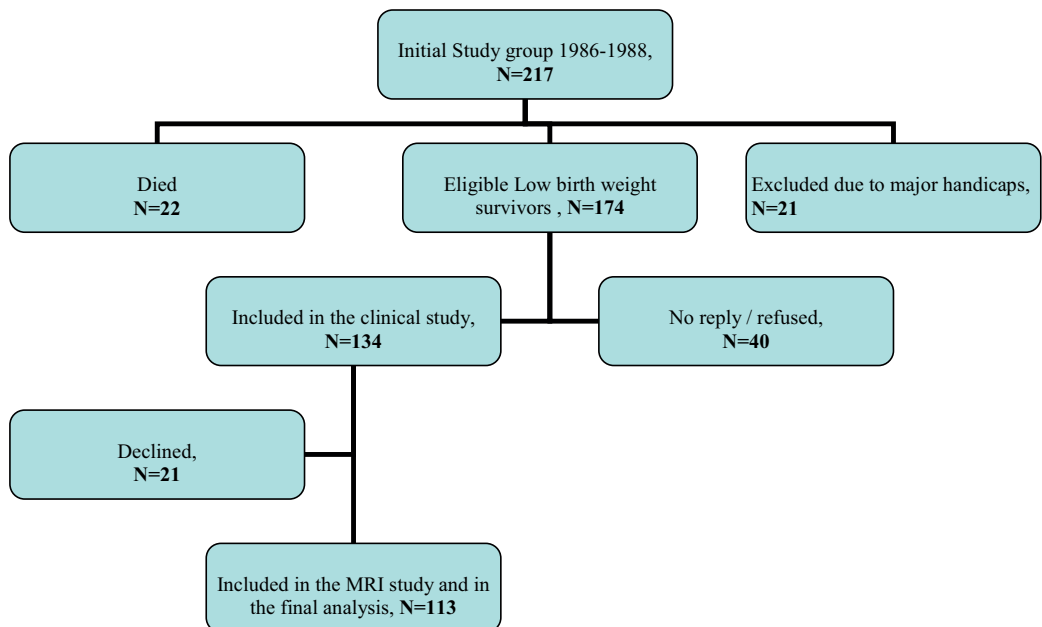


Figure 6. Flow chart of the complete study group (low birth weight).

At follow-up during 2006-2007, the 100 of the initial 163 healthy controls (54 females, 46 females) agreed to participate. Their mean age was 18 years and 9 months (SD 7.5 months, range 17 years 8 months to 20 years 3 months).

Clinical data assessed during the previous follow-ups at 5 and 11 years of age, used within in the present study: Among the 113 cases (49 males, 64 females), 69 (61.1%) had a birth weight between 1500-2000g and 44 (38.9%) had a birth weight below 1500g (Table 13) (16). Prenatal, perinatal and neonatal data on this cohort have been presented previously (16;77;147;148). Birth weight ratio (BW ratio) and head circumference ratio were computed as the ratio between the actual and the respective measures at the 50th percentile for GA (Table 13).

Table 13. Prenatal, perinatal and neonatal data for the total study group of 113 adolescents (49 males and 64 females) born with a low birth weight, by weight group.

	Total low birth weight (N = 113)	< 1500 g (N = 44)	1500-1999 g (N = 69)
Prenatal factors:	N (%)	N	N
Pre – eclampsia	34 (30%)	19	15
Placental abruption	9 (8%)	1	8
Maternal smoking in pregnancy	50 (44%)	19	31
Intrauterine stress ^a	20 (18%)	11	9
Chorionamnionitis ^b	12 (11%)	6	6
Prenatal continuous variables:	Mean (SD)	Mean (SD)	Mean (SD)
Birth weight ratio ^c	0.83 (0.18)	0.81 (0.18)	0.84 (0.18)
Birth head circumference ratio ^c	0.98 (0.06)	0.98 (0.06)	0.98 (0.06)
Birth and neonatal factors:	N (%)	N	N
Apgar score at 5 minutes < 7	11 (10%)	8	3
< 30% breast milk in neonatal ward	33 (29%)	15	18
Gender male/female	49/64	20/24	29/40
Birth/ neonatal continuous variables:	Mean (SD)	Mean (SD)	Mean (SD)
Days of assisted ventilation or oxygen ^d	5 (13)	11 (18)	1 (5)

Data on socioeconomic status (SES) were obtained from questionnaires at a follow-up at 11 years of age, and cognitive abilities were assessed at five and 11 years using age appropriate Wechsler scales (149). At 19 years cognitive abilities were assessed using the Wechsler Abbreviated Scale of Ability (WASI) 25. Prorated IQ was estimated from the two subtests; word comprehension test and matrixes (149). Demographic data for both the Low Birth Weight and the Normal Birth Weight group at age 11 is given in Table 14. Notice that a significant difference between the two groups is detected in maternal education (lower in Low birth weight families) and for factors evaluating maternal-and family distress (higher in the Low birth weight families).

Table 14. Socioeconomic data for the families of the low and normal birth weight groups, collected at the follow-up at 11 years of age^a.

	Low birth weight (N=96) Mean (SD)	Normal birth weight (N= 80) Mean (SD)	p-value
Paternal education (in years)	12.4 (3.5)	13.3 (3.5)	0.08
Average income	43.2 (3,2)	47.4 (5.4)	0.6
Maternal education (in years)	12.4 (3.0)	13.5 (2,4)	<0.01
Maternal age (in years)	31.7 (4.8)	32.7 (4.9)	0.2
Maternal psychological distress^{b,d}	0.18 (1,11)	-0.14 (0.80)	0.03
Maternal Raven Score^{b,e}	0.56 (0.49)	0.56 (0.50)	1.0
Parent Domain stress^{b,f}	0.21 (0.96)	-0.04 (0.94)	0.1
Total Parental Stress^{c,f}	0.24 (1.05)	-0.13 (0.94)	0.03
Family life event^{c,f}	1.2 (1.2)	1.3 (1.4)	0.7

^a Data obtained at 11 years of age: data were missing for 13 of the low birth weight and 20 of the normal birth weight subjects participating at age 19 years.

^b Factor scores z-transformed to a mean of 0 and a standard deviation of 1 were used.

^c Child Rearing Practices Report, CRPR.

^d Symptom Check List Revised, SCL-90R.

^e Raven Progressive Matrices Test. The age corrected score, z-transformed to a mean of 0 and a standard deviation of 1 is used.

^f Parental Stress Index, Norwegian translation. Parental Domain score reflect area in general parenting. Total Parental stress includes area of the child behaviour.

2. MRI EQUIPMENT / MRI PROTOCOL

All MRI scans were performed at the Department of Radiology, Haukeland University Hospital, Bergen, Norway during the period January 2006 to June 2007. We used a GE Signa Excite HD 3.0 Tesla (3T) scanner and all examinations were performed by two experienced MRI radiographers under the supervision of an experienced paediatric radiologist (SMA) with special interest in neuroimaging. The MRI protocol included a sagittal T1 weighted volumetric sequence (Spoiled Gradient Echo (SPGR), TR 5.9, TE 1.3, slice-thickness 1.0 mm, scan time 8:56 minutes) and an axial T2 weighted sequence (Fast Spin Echo (FSE), TR 4740.0, TE 102.0, slice-thickness 2.5 mm, scan time 4:03 minutes). The T2 weighted sequence was angulated parallel to a line intersecting the anterior and the posterior commissures (AC-PC line).

3. IMAGE ANALYSIS – GRADING SYSTEM OF MORPHOLOGY

Subjective assessment: First, two experienced paediatric neuroradiologists assessed the T1- and T2 weighted images subjectively, and scored the following structures as being normal = 1, or having a mild = 2, moderate = 3 or severe = 4, degree of pathology: *size of the lateral ventricles and of the subarachnoidal spaces, volume of white matter, size of Corpus Callosum, vermis, cerebellar hemispheres and the anterior commissure, grey matter abnormalities and focal white matter abnormalities* (Table 15) (Figure 7). The classification into normal or mild-moderate-severe pathology had been used by both observers for years, and no further standardisation was performed prior to the present assessment since we wanted to examine the existing inter-observer agreement. To avoid ascertainment bias related to the assumed normality of the control group, MRI scans from the study group (n=113) as well as from the control group (n=100) were read during the same sessions, the observers being masked for grouping and clinical information.

Table 15. MRI score sheet used for the subjective assessment of cerebral change in 213 young adults, 113 from the study group and 100 controls. Minimum score = 9, maximum score = 45.

1	Dilatation of the lateral ventricles	Non = 1, Mild = 2, Moderate = 3, Severe = 4
2	Loss of bulk of White Matter	Non = 1, Mild = 2, Moderate = 3, Severe = 4
3	Focal White Matter abnormalities	Non = 1, Mild = 2, Moderate = 3, Severe = 4
4	Grey Matter abnormalities	Non = 1, Mild = 2, Moderate = 3, Severe = 4
5	Diffuse thinning of the Corpus Callosum	Non = 1, Mild = 2, Moderate = 3, Severe = 4
6	Focal thinning of Corpus Callosum	Non = 1, Mild = 2, Moderate = 3, Severe = 4
7	Decreased size of the Cerebellar hemispheres	Non = 1, Mild = 2, Moderate = 3, Severe = 4
8	Decreased size of the Cerebellar Vermis	Non = 1, Mild = 2, Moderate = 3, Severe = 4
9	Increased depth of the Subarachnoidal Space	Non = 1, Mild = 2, Moderate = 3, Severe = 4
10	Reduced size of the Anterior Commissure	Non = 1, Mild = 2, Moderate = 3, Severe = 4

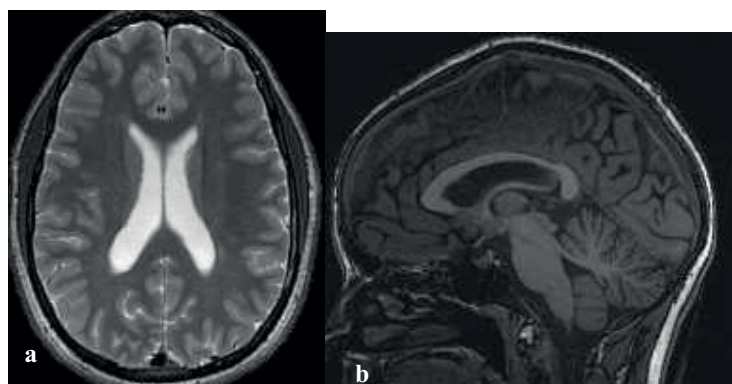


Figure 7. Cerebral MRI of an eighteen-year-old male a) axial T2 weighted image (left) and b) sagittal T1 weighted image (right); example of images used for the subjective evaluation.

Objective assessment: Next, one experienced paediatric radiologist (SMA) measured the following structures on the axial T2 weighted images a) at the level foramen of Monroe: width and depth of the frontal horns, the frontal subarachnoid space and frontal interhemispheric distance. The frontal subarachnoid space was measured 5mm from the

midline b) at the level of the third ventricle: the diameter of the 3rd ventricle, the width of the occipital horns and depth of the largest occipital horn. The head circumference was estimated from the occipito-frontal and bi-parietal skull diameters (measured at the level of foramen of Monroe), under the assumption that the skull has an elliptical shape. An illustration of four of these measurements is given in Figure 8. Both the subjective evaluation and the measurements were performed using an imaging software program (Nordic ICE©).

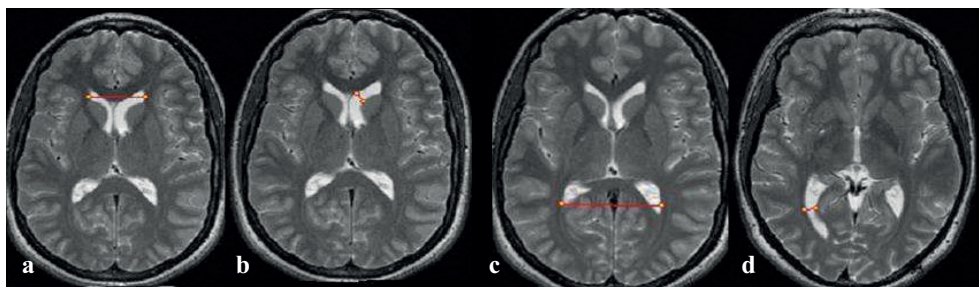


Figure 8. Axial T2 weighted images of a nineteen year old female a) measurement of frontal horn diameter b) left frontal horn depth c) occipital horn width and d) right occipital horn depth.

4. MEASUREMENTS OF THE CORPUS CALLOSUM

Initially, the forebrain brain volume (FBV; cerebral volume excluding brain stem and cerebellum) was determined using in a semiautomatic procedure implemented in Matlab (Math Works, Natick, MA, USA). The sagittal images were re-aligned and the optimal mid-sagittal slice was resliced following the longitudinal fissure with a visible arachnoidea and non-visible white matter. This re-alignment was performed in SPM5® / Matlab R2009a ®.

After re-alignment, the images were exported to MRIcron® and the number of voxels in the cross sectional area of Corpus Callosum was counted. The total area in square mm were estimated based on the voxel size and then the Corpus Callosum was sub-divided following the operational definition proposed by Witelson (150). The total callosal area was subdivided in three thirds relative to the genu-splenial line (connecting the anterior and posterior most points of the Corpus Callosum), resulting in the three sub regions: genu (anterior third), truncus (middle third), and the posterior third (Figure 9).

Callosal and forebrain size (FBV) estimates poses a different dimensionality (area vs. volume) and using FBV to adjust the Corpus Callosum area would result in an “overcorrection” for brain (151). Thus, we transformed the FBV into an “area-measure” (aFBV) using the following equation $aFBV = FBV^{0.667}$.

Callosal measures were then adjusted for forebrain size using two different approaches: (1) calculating relative Corpus Callosum size measures (relCC) by dividing the measures of each callosal sub region with the aFBV value for each subject; (2) calculating residualised Corpus Callosum measures (resCC) by using a linear regression to estimate the callosal sub region size that would be predicted from each individual’s forebrain size, and then subtracting the predicted from the measured size to obtain the resCC value.

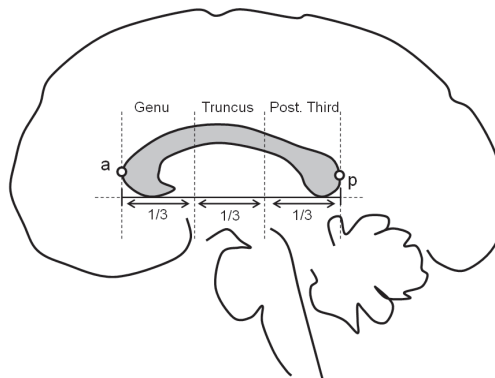


Figure 9. Schematic drawing of Corpus Callosum with sub regions; genu (anterior third), truncus (middle third) and posterior third.

C. ETHICS

The Regional Committee for Medical Research Ethics approved both the lung and the brain studies. Informed written consent was obtained from all participants and also from the parents if the participant was still underage. For the MRI study, all participants had a MRI risk assessment prior to inclusion. In cases of unexpected findings among both the cases and the controls, this was promptly and appropriately taken care of by one of the principal investigators.

D. STATISTICAL ANALYSIS

Paper #1. T-test for independent samples (non-parametric test; Mann-Whitney) was used in testing differences in the occurrence of pathological findings between females and males and between the two age groups. Agreement within and between observers (total HRCT-score and sub-scores) was examined by using Bland-Altman plots and weighted kappa (κ) statistics as appropriate. Kappa values were interpreted according to Altman (152) ($\kappa < 0.20$ = poor , $\kappa 0.21-0.4$ = fair , $\kappa 0.41-0.60$ = moderate , $\kappa 0.61-0.80$ = good , $\kappa 0.81-1.00$ = very good.). A non-parametric test (Mann Whitney) was used to evaluate differences in score between patients with and without BPD.

Paper #2. Lung function data were normally distributed and group comparisons were performed using Student's t-test. For the non-normally distributed HRCT scores, we used non-parametric u- test (Mann-Whitney U-test). Results were reported as means or median values (or both), as appropriate. Single linear regression analyses were used to examine relationships between HRCT scores (response variable) and accessible neonatal variables. Under assumption of an existing co-linearity between neonatal variables, we performed a backward stepwise multiple linear regression analysis for the response variable *total HRCT score*. Those neonatal variables that were significantly related to *total HRCT score* in the initial single regression model, were included in the backward stepwise multiple linear regression analysis. Analyses of interaction effects were used to examine whether the influence from the examined neonatal variables differed between the two birth cohorts. Relationships between HRCT scores (response variables) and lung function data (FEV_1 , FEF_{50} , FEF_{25-75} and RV/TLC) were examined using simple linear regression models. Results are reported as determination coefficients (R square) and regression coefficients (β). R square estimates how much (in percentage) of the variance in the outcome variable (e.g. total HRCT score) that is explained by the chosen model (one or several explanatory variable(s) (e.g. FEV_1)). The β value illustrates the numeric change in an outcome variable, when one explanatory variable changes one unit and other variables are kept unchanged.

Paper #3. T-test for independent samples was used to compare the size of the right and the left ventricles. Differences in ventricular size according to sex were examined using a Student's t-test. Associations of the objective measurements with the subjectively classification (no, mild,

moderate or severe dilatation) were investigated using a non-parametric test for two independent samples (Mann-Whitney U-test), whilst associations of the frontal horn size with the head circumference, were tested using a linear regression model. Interobserver agreement was tested using Kappa statistics. In the comparison of ventricular size between those born at term and those born with a BW < 2000g, adjustment for head size was performed by creating a ratio between *Total Frontal horn width* and *Head Circumference* and between *Occipital horn depth of the largest* and *Head Circumference*.

Paper #4. The mean differences between the Low birth weight and control groups were tested with Student's t-test or non-parametric u- test (Mann-Whitney), as appropriate. A hierarchical, stepwise, multiple, linear regression analyses was performed with total MRI score as dependant variable and pre- peri- and early post-natal factors as independent variables.

Paper #5. The concept of 95% agreement (Bland / Altman) was used in the evaluation of interobserver agreement (153). Mean (M) and standard deviation (SD) were used for descriptive statistics. Pearson's correlation coefficient (r) was used to quantify the relationship between brain size as expressed by brain volume in mm³ and brain volume as expressed by area in mm². The initial group comparisons regarding brain volume and size of Corpus Callosum were tested using t-test for independent samples. The statistical analysis of group differences in callosal size was performed calculating three separate three-way analysis of variance (ANOVA) using non-corrected CC size, relative CC size and residual CC size, respectively, as dependent measures. All ANOVAs included two between subject factors, namely "group" (Low birth weight vs. control) and "sex" as well as a repeated-measure factor "callosal sub region". Significant interaction effects were followed up with paired t-tests or t-tests for independent samples. The effect size for all main and interaction effects was given as a proportion of explained variance (η^2). Effect sizes for comparisons between pairs of sub regions were given as Cohen's d.

All statistical analyses were performed using SPSS for Windows, version 15.0 or Statistica 8.0 (Statsoft Tulsa, OK, USA). All statistical tests were performed at a 5 % significance level.

7. RESULTS AND SUMMARY OF PAPERS

A. LUNG:

a. Paper # 1. HIGH-RESOLUTION CT OF THE CHEST IN CHILDREN AND YOUNG ADULTS WHO WERE BORN PREMATURELY: FINDINGS IN A POPULATION-BASED STUDY.

We set out to develop a scoring system for assessment of pulmonary injury of prematurity, to check the reproducibility of this system and to examine pulmonary change in a population of prematurely born children / adolescents. We included 74 subjects born at a GA of ≤ 28 weeks or with a birth weight ≤ 1000 g, during 1982-1985 (n=41) or during 1991-1992 (n=33). All had a HRCT performed during 2001-2002, including three expiratory images. Two of the examinations were not available in a soft copy for the study on HRCT findings (Paper 1), but was later found on hard copy and then scanned in the PACS system and included in the association study (Paper 2). Thus, 72 subjects were included in paper 1.

Following a thorough standardization of the suggested scoring system, the examinations were read independently by two paediatric radiologists who were masked for additional findings. One of the observers performed a second assessment at an interval of six months. We used a segment-based scoring system according to Bhalla et al (63), and scored the following findings as being present or absent for each of the 20 segments: linear opacities, triangular opacities, septal thickening, bronchus to bronchial artery ratio, mosaic perfusion in inspiration, air trapping in expiration, bronchiectasies (including degree and extension), peribronchial thickening, mucus plugging, emphysema, bullae and consolidation/collapse. This yielded a minimum score of 0 and a maximum score of 152, when excluding the score for bullae (which had no upper limit).

63 out of the 72 (88%) subjects had at least one abnormal finding on HRCT-examination, of which linear and triangular opacities were the most common; seen in 52 (72%) and 42 (42%) of the subjects, respectively (Figure 10). Mosaic perfusion was seen in 10 subjects and air trapping in 19 (Figure 11).

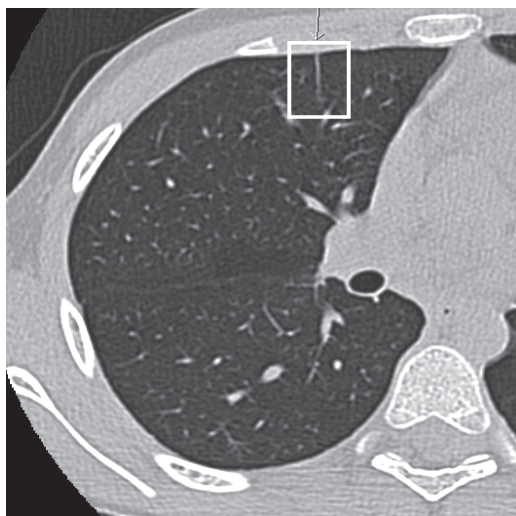


Figure 10. Inspiratory HRCT image of the right lung in a 19 years old male born at a gestational age of 27 weeks, illustrating a typical linear opacity in the right middle lobe, radiating from the periphery toward the hilum.



Figure 11. Inspiratory HRCT image of the right lung in an 18 years old female, showing an area of mosaic perfusion, hypo-attenuation and small-calibre vessels.

Less than 10% ($n = 7$) had bronchiectasies and only one had emphysema. Mean total score was 5.7 for the younger cohort (mean age 10y) and 7.9 for the older cohort (mean age 18.0y) ($p = 0.019$). No differences were seen according to sex or between males and females.

56 of the 72 subjects had a medical history of BPD as defined by Northway et al (55) and this group had a higher mean and median score for the total CT score and for the four most

common findings (linear opacities, triangular opacities, mosaic perfusion, air trapping), but the group differences were not statistically significant.

The intraobserver agreement was *very good* for the total score (wKappa value = 0.88), *good* for air trapping (wKappa= 0.71) and *moderate* for linear opacities (wKappa= 0.45), triangular opacities (wKappa= 0.45) and mosaic perfusion (wKappa= 0.45). Similar, the interobserver agreement was *very good* for the total score (wKappa= 0.87), *good* for air trapping (wKappa= 0.61) and *moderate* for linear opacities (wKappa= 0.39), triangular opacities (wKappa= 0.43) and mosaic perfusion (wKappa= 0.47) (152).

Conclusion: We have shown that several HRCT-markers of lung injury of prematurity can be assessed in a reproducible fashion using a semi quantitative scoring system. Approximately nine in ten children / adolescents born prematurely or with a birth weight \leq 1000g had pulmonary change, of which most were subtle linear and triangular opacities.

b. Paper # 2. NEONATAL BRONCHOPULMONARY DYSPLASIA PREDICTS ABNORMAL PULMONARY HRCT IN LONG-TERM SURVIVORS OF EXTREME PRETERM BIRTH.

In this study we opted at examining possible associations between pulmonary changes as assessed by HRCT and the results of lung function tests in the two aforementioned cohorts of children / adolescents. Based on our previous findings, we refined and simplified the HRCT scoring system for pulmonary injury of prematurity, excluding 4 of the 14 markers, namely extent of bronchiectasies, extent of mucus plugging, generations of bronchial divisions involved and thickening of interlobar septi. “Linear opacities” and “triangular, sub pleural opacities” were regarded as one parameter. Next, using the original radiographic templates with the marked pathology, reader one created new scores based on pulmonary lobes rather than on segments, thus reducing the theoretical score. Scores for all six lobes (regarding lingula as a separate lobe) were created according to the presence (1) or absence (0) of the finding under investigation. This scoring system had a minimum score of 0 and a maximum score of 50.

The lung function tests included FEV₁, FEF₅₀ and FEF₂₅₋₇₅ and the ratio RV/TLC, and were performed within two weeks of the HRCT examination.

Lung parenchymal abnormalities were demonstrated in 64 out of 74 (87%) subjects. Subtle linear and triangular opacities were found in 82% of the subjects, and contributed 64% to the total mean score of 3.6 (SD 3.0) points of a maximum score of 50.

There were statistically significant associations between the neonatal factors “gestational age”, “birth weight”, “artificially closed ductus arteriosus (PDA)”, “postnatal treatment with corticosteroids”, “number of days with ventilator treatment” and “number of days with oxygen treatment”, and the total HRCT score. No such associations were found for “antenatal treatment with corticosteroids”, “treatment with exogenous surfactant”, “intrauterine cigarette exposure” or “evidence of maternal infection”.

The neonatal variables that were statistically significantly associated with total HRCT score were included in a linear regression analysis and the final model contained only two variables significant at the 5% level, namely “number of days with oxygen treatment” and “number of days with ventilator treatment”. This model explained 33% of the variability in total HRCT score. Omitting the variable “number of days with ventilator treatment” from the model, the “number of days with oxygen treatment” still explained 31% of the variability in the total HRCT score, thus appearing to be the single most important explanatory variable, after adjusting for other co-linear neonatal variables.

All of the assessed lung function variables were significantly associated with “linear/triangular opacities” and with “total HRCT score” (Table 16).

Conclusion: The refined HRCT scoring system used allowed for a tailored assessment of pulmonary change of prematurity. Although pathology was seen in nearly 90% of the subjects, a low total HRCT score reflects the subtle nature of these findings. The HRCT changes were associated with lung function abnormalities. A history of prolonged requirements for oxygen treatment during the neonatal period was the most important factor for prediction of structural lung abnormalities in later life.

Table 16. Linear regression model, illustrating the association between lung function data and HRCT findings in 74 adolescents born with a BW of ≤ 28 weeks or with a birth weight ≤ 1000 g.

	<u>Linear / triangular opacities</u>			<u>Total HRCT score</u>		
	β	R^2	p	β	R^2	p
FEV₁	-0.028	0.055	0.044	-0.090	0.169	< 0.001
FEF 25-50	-0.027	0.128	0.002	-0.427	0.183	< 0.001
FEF₅₀	-0.030	0.173	< 0.001	-0.063	0.236	< 0.001
RV / TLC^a	0.072	0.075	0.021	0.149	0.101	< 0.001

^a Four of the 74 preterms performing a HRCT were not able to enter the pletysmograph. For the RV/TLC variable, data on 70 preterms were included in the regression analysis.

The lung function test was used as a predictor variable and the HRCT finding as response variable. In addition to p-values, the determination coefficients, R^2 (percentage of the variability of an outcome variable) and the β values (numeric change in an outcome variable, when one predictor variable changes one unit while the others are kept fixed) are given.

B. BRAIN:

a. Paper # 3. ASSESSING VENTRICULAR SIZE: IS SUBJECTIVE EVALUATION ACCURATE ENOUGH? NEW MRI-BASED NORMATIVE STANDARDS FOR 19-YEAR-OLDS.

In this paper we aimed to examine the agreement for subjective assessment of brain morphology and to establish reference intervals for commonly used cerebral measurements. We included 100 healthy adolescents constituting the control group in an observational study addressing the development of children born with low birth weight (BW < 2000g) at Haukeland University Hospital during the period 1986-1988 (“The Hordaland project, Low birth weight, young adults: Mental and Somatic health”). All were born healthy with a birth weight more than 3000g, and had a 3T MRI examination performed during the period between January 2006 and June 2007. Mean age at scanning was 18 years, 9 months (SD 7.5 months).

The MR protocol included a sagittal T1 weighted volumetric sequence and an axial T2 weighted sequence. Based on both sequences the size of the lateral ventricles was subjectively

judged as being normal, mildly, moderately or severely dilated by two paediatric neuroradiologists, independently. To avoid ascertainment bias related to the assumed normality of the control group, identical MRI scans of 113 ex-premature 17-19-years olds (constituting the test group) were evaluated simultaneously, the two observers being masked for grouping and any clinical information.

In a second session, the biparietal and occipito-frontal diameters, width and depth of the frontal horns, the depth of the frontal subarachnoid spaces and the distance between the hemispheres (frontal interhemispheric distance) were measured.

A total of 38 of the 100 healthy subjects were judged to have either moderately (n= 2) or mildly (n= 36) dilated lateral ventricles by at least one of the two observers. There was a moderate agreement between the two observers for assessment of ventricular size (Kappa value = 0.43).

The mean head circumference was 31mm higher for males than for females (Table 17). Similar, mean ventricular size, except for the depth of the right frontal horn and third ventricle width, was larger for males; however, the observed differences were partly accounted for by the larger head circumference. A table with sex specific normative standards for different cerebral measurements, given as mean and ranges, and additional 2.5, 10, 50, 90 and 97.5 percentiles, was created (Table 17, 18 and 19).

Conclusion: Sex specific reference intervals for various cerebral measurements were established. Subjective assessment of ventricular size is fairly accurate, with a moderate agreement between observers, and tends to over diagnose dilatation of the lateral ventricles.

Table 17. MRI based reference intervals for various cerebral measurements in healthy 17-19 years olds, by sex.

MRI measurements	Males (n=46) Mean in mm (SD)	Females (n=54) Mean in mm (SD)	p-value*	Adjusted p-value **
Head circumference	558.3 (16.7)	526.8 (14.7)	<0.001	----- --
Bi-parietal diameter	152.7 (6.0)	143.1 (4.7)	<0.001	----- --
Occipito-frontal diameter	199.5 (6.6)	189.0 (6.5)	<0.001	----- --
Frontal horn width (total)	35.0 (2.4)	32.6 (2.4)	<0.001	0.026
Frontal horn width-right	17.3 (1.7)	15.9 (1.4)	<0.001	0.080
Frontal horn width-left	17.4 (1.4)	16.3 (1.2)	<0.001	0.084
Frontal horn depth-right	3.2 (1.7)	2.7 (1.2)	0.073	0.119
Frontal horn depth-left	3.8 (2.0)	3.0 (1.5)	0.026	0.043
Third ventricle width	3.5 (0.9)	3.1 (0.9)	0.057	0.129
Occipital horn width (total)	63.4 (3.7)	58.5 (4.2)	<0.001	0.140
Occipital horn depth of the largest	6.7 (2.6)	5.3 (2.4)	0.006	0.018
Frontal subdural space	1.8 (0.8)	1.9 (0.5)	0.685	0.030
Frontal interhemispheric distance	0.3 (0.7)	0.3 (0.6)	0.802	0.405

* Student's T- test

** Adjusted for head circumference

Table 18. MRI-based reference intervals for various cerebral measurements based on 54 healthy 17-19 years old females.

MRI measurements	Mean in mm, (SD ^a)	Range in mm	Percentiles				
			2.5	10	50	90	97.5
Head circumference ^b	526.8 (14.7)	493-564	495.6	507.5	525.5	545.5	562.1
Bi-parietal diameter	143.1 (4.7)	135-155	135.0	136.0	143.0	150.0	154.3
Occipito-frontal diameter	189.0 (6.5)	174-201	174.8	179.6	189.0	197.5	201.0
Frontal horn width (total)	32.6 (2.4)	28.1-39.4	28.5	30.0	31.9	35.7	39.4
Frontal horn width-right	15.9 (1.4)	13.1-19.7	13.1	14.1	15.9	17.8	19.7
Frontal horn width-left	16.3 (1.2)	14.1-19.7	14.1	15.0	15.9	17.8	19.3
Frontal horn depth-right	2.7 (1.2)	0.9-6.0	0.9	1.3	2.7	4.2	6.0
Frontal horn depth-left	3.0 (1.5)	0.9-7.6	1.1	1.3	2.7	5.1	7.6
Third ventricle width	3.1 (0.9)	1.9-5.6	1.9	1.9	2.8	4.3	5.6
Occipital horn width	58.5 (4.2)	50.6-69.4	51.0	54.4	58.1	65.6	69.4
Occ. horn depth of the largest	5.3 (2.4)	1.9-12.2	2.0	2.8	4.8	8.5	12.2
Frontal subdural space	1.9 (0.5)	0.9-3.9	0.9	0.9	2.1	2.1	2.1
Frontal interhem. distance	0.3 (0.6)	0.0-1.9	0	0	0	1.9	1.9

^a Standard deviation

^b Estimate based on bi-parietal and occipito-frontal diameters

Table 19. MRI-based reference intervals for various cerebral measurements based on 46 healthy 17-19 years old males.

MRI measurements	Mean in mm, (SD ^a)	Range in mm	Percentiles				
			2.5	10	50	90	97.5
Head circumference ^b	558.3 (16.7)	522-600	522.9	535.0	559.0	577.5	598.6
Bi-parietal diameter	152.7 (6.0)	139-166	139.2	144.0	153.0	159.3	166.0
Occipito-frontal diameter	199.5 (6.6)	184-214	184.7	191.7	199.0	208.6	213.8
Frontal horn width (total)	35.0 (2.4)	29.1-40.3	29.4	31.6	34.7	38.4	40.3
Frontal horn width-right	17.3 (1.7)	14.1-21.6	14.1	15.0	16.9	19.7	21.4
Frontal horn width-left	17.4 (1.4)	15.0-20.6	15.0	15.0	17.4	19.1	20.4
Frontal horn depth-right	3.2 (1.7)	0.9-7.3	1.0	1.3	2.7	6.0	7.2
Frontal horn depth-left	3.8 (2.0)	0.9-8.6	1.0	1.3	3.4	6.8	8.5
Third ventricle width	3.5 (0.9)	1.9-6.6	1.9	2.5	3.7	4.7	6.4
Occipital horn width (total)	63.4 (3.7)	54.4-70.3	54.7	58.1	63.8	68.4	70.3
Occ. horn depth of the largest	6.7 (2.6)	1.9-12.2	2.1	3.5	6.6	10.3	12.2
Frontal subdural space	1.8 (0.8)	0-5.7	0.2	0.9	2.0	2.3	5.2
Frontal interhem. distance	0.3 (0.7)	0-2.8	0	0	0	1.2	2.7

^a Standard deviation

^b Estimate based on bi-parietal and occipito-frontal diameters

For adolescents born with a BW < 2000g, the mean head circumference was 27 mm higher for males than for females ($p < 0.001$) (Table 20) (data not published). No significant differences were seen in ventricular size according to sex (Table 20).

Table 20. MRI-based reference intervals for various cerebral measurements based on 113 17-19 years olds born with a BW < 2000g, 49 males and 64 females (data not published).

MRI measurements	Males (n=49) Mean in mm (SD)	Females (n=64) Mean in mm (SD)	p-value*
Head circumference	547.1 (14.6)	519.5 (14.1)	$p < 0.001$
Bi-parietal diameter	130.8 (5.8)	123.7 (4.9)	$p = 0.031$
Occipito-frontal diameter	196.9 (5.6)	187.4 (7.0)	$p < 0.001$
Frontal horn width (total)	34.8 (3.4)	32.1 (2.9)	$p = 0.206$
Frontal horn width-right	16.6 (2.0)	15.7 (1.8)	$p = 0.774$
Frontal horn width-left	17.1 (1.8)	15.9 (1.6)	$p = 0.303$
Frontal horn depth-right	2.8 (2.0)	3.3 (1.9)	$p = 0.793$
Frontal horn depth-left	3.3 (2.2)	4.0 (2.1)	$p = 0.826$
Third ventricle width	3.9 (1.1)	3.8 (2.1)	$p = 0.213$
Occipital horn width (total)	62.5 (4.3)	57.6 (4.0)	$p = 0.105$
Occipital horn depth of the largest	8.0 (3.8)	7.5 (4.0)	$p = 0.546$
Frontal subdural space	2.0 (0.5)	2.2 (0.9)	$p = 0.760$
Frontal interhemispheric distance	0.4 (0.8)	0.3 (0.8)	$p = 0.293$

* Student's T- test

Mean head circumference in males born low birth weight was 547.1 mm (SD 14.6mm) vs. 558.3 mm (SD 16.7 mm) in those born at term ($p < 0.001$), while the mean biparietal diameter was 130.8 mm (SD 5.8 mm) vs. 152.7 mm (SD 6.0 mm) ($p < 0.001$) (Table 21). The rest of the measurements did not differ significantly except for occipito-frontal diameter (Table 21).

After adjustment for head circumference had been preformed, there were still no significant group differences regarding the frontal horns, but the occipital horns were proportionately larger among the low birth weight males ($p = 0.031$).

Similar, for females the most significant difference was found for biparietal diameter (Table 21). Females born with a low BW had larger lateral ventricles than those born at term, with a mean left frontal horn depth of 4.0 mm (SD 2.1 mm) vs. 3.0 mm (SD 1.5 mm) ($p = 0.021$) and a depth of the occipital horn of 7.5 mm (SD 4.0 mm) vs. 5.3 mm (SD 2.4 mm) ($p = 0.001$) (Table 21).

Table 21. Comparison between cerebral MRI measurements in our Low birth weight group vs. Control group (data not published).

MRI measurements	Low birth weight. Males (N=49) Mean in mm (SD)	Control Males (N=46) Mean in mm (SD)	p-value*	Low birth weight. Females (n=64) Mean in mm (SD)	Control Females (N=54) Mean in mm (SD)	p-value*
Head circumference	547.1 (14.6)	558.3 (16.7)	p < 0.001	519.5 (14.1)	526.8 (14.7)	p = 0.006
Bi-parietal diameter	130.8 (5.8)	152.7 (6.0)	p = 0.001	123.7 (4.9)	143.1 (4.7)	p < 0.001
Occipito-frontal diameter	196.9 (5.6)	199.5 (6.6)	p < 0.001	187.4 (7.0)	189.0 (6.5)	p = 0.181
Frontal horn width (total)	34.8 (3.4)	35.0 (2.4)	p = 0.618	32.1 (2.9)	32.6 (2.4)	p = 0.343
Frontal horn width-right	16.6 (2.0)	17.3 (1.7)	p = 0.055	15.7 (1.8)	15.9 (1.4)	p = 0.482
Frontal horn width-left	17.1 (1.8)	17.4 (1.4)	p = 0.315	15.9 (1.6)	16.3 (1.2)	p = 0.172
Frontal horn depth-right	2.8 (2.0)	3.2 (1.7)	p = 0.390	3.3 (1.9)	2.7 (1.2)	p = 0.075
Frontal horn depth-left	3.3 (2.2)	3.8 (2.0)	p = 0.285	4.0 (2.1)	3.0 (1.5)	p = 0.021
Third ventricle width	3.9 (1.1)	3.5 (0.9)	p = 0.055	3.8 (2.1)	3.1 (0.9)	p = 0.307
Occipital horn width (total)	62.5 (4.3)	63.4 (3.7)	p = 0.279	57.6 (4.0)	58.5 (4.2)	p = 0.184
Occipital horn depth of the largest	8.0 (3.8)	6.7 (2.6)	p = 0.051	7.5 (4.0)	5.3 (2.4)	p = 0.001
Frontal subdural space	2.0 (0.5)	1.8 (0.8)	p = 0.283	2.2 (0.9)	1.9 (0.5)	p = 0.031
Frontal interhem. distance	0.4 (0.8)	0.3 (0.7)	p = 0.124	0.3 (0.8)	0.3 (0.6)	p = 0.987

* Student's T- test

b. Paper # 4. CEREBRAL MRI AND COGNITION IN NON-HANDICAPPED, LOW BIRTH WEIGHT ADULTS.

In this study we aimed to 1) describe cerebral MRI findings in a cohort of 113 young adults born with a birth weight below 2000g, 2) compare these findings to the MRI findings in the control group (n=100) and 3) examine possible associations between the MRI findings and pre-, peri- and early postnatal factors.

The study is based on the same study cohort / controls and MRI examinations as described under paper 3, thus subjects and the MRI technique / analysis have not been repeated here.

The clinical assessment revealed a group difference in height (5.9 cm lower in the low birth group and systolic blood pressure (4mmHg higher in the low birth group). The current health and body mass index were similar in the two groups (16). At 19 years of age the mean prorated IQ score was 6 points lower for the low birth weights than for the controls (95 IQ points, (SD 13) vs. 101 IQ points (SD 14) IQ points, $p=0.001$).

Dilatation of the ventricles and loss of bulk of white matter were seen in 45 (40%) of the Low birth weight group and 15 (15%) of the controls (Figure 12). Similar, thinning of the Corpus Callosum was more common in the low birth weight group, than among the control subjects (31% vs. 7%) (Figure 12) (Table 22). We did not find any significant associations between factors related to the peri- and early postnatal period and MRI findings.

Conclusion: Based on a subjective assessment, both thinning of the Corpus Callosum and mild dilatation of the lateral ventricles were common findings in low birth weight survivors. Similar findings were, however, quite common among normal controls. The MRI findings were not associated with any of the pre-, peri- and early postnatal factors tested for.

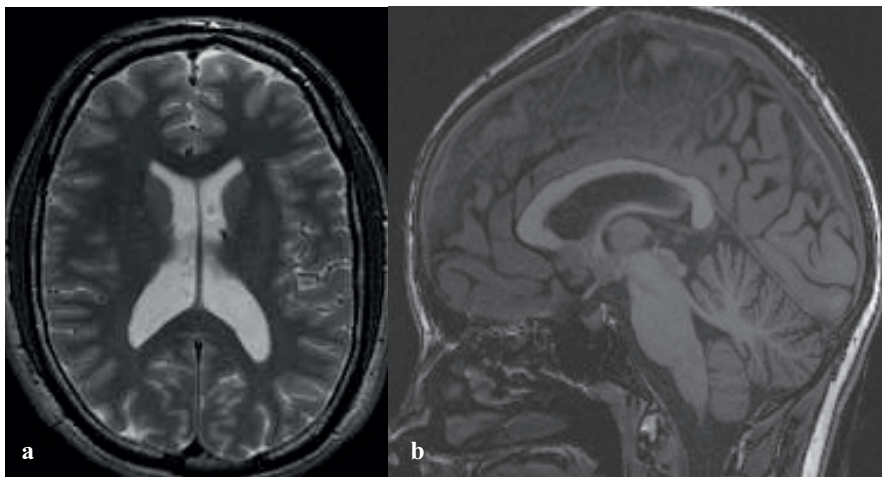


Figure 12 a) Axial, T2w image of a 20 years old female born with a BW of 1320g, showing mildly dilated lateral ventricles and b) sagittal, T1w image of a 18 years old male showing mild thinning of the Corpus Callosum.

Table 22. MRI findings at 19 years of age for the low birth weight and normal birth weight groups.

MRI Outcome	Low birth weight N = 113 (%)	Normal birth weight N = 100 (%)	Odds ratio	95% CI	p-value
Dilatation of lateral ventricles	45 (40%)	15 (15%)	3.8	1.9 – 7.3	< 0.001
Loss of bulk of white matter	45 (40%)	15 (15%)	3.8	1.9 – 7.3	< 0.001
Diffuse thinning of Corpus Callosum	35 (20%)	7 (7%)	6.0	2.5 – 14.2	< 0.001
Gliosis / focal white matter abnormalities	14 (31%)	4 (4%)	3.4	1.1 – 10.7	0.028
Any of the above abnormalities	49 (43%)	16 (16%)	4.0	2.1 – 7.7	< 0.001

c. Paper # 5. SELECTIVELY REDUCED POSTERIOR CORPUS CALLOSUM SIZE IN A POPULATION-BASED SAMPLE OF YOUNG ADULTS BORN WITH LOW BIRTH WEIGHT.

In this paper we aimed at 1) measuring the size of the Corpus Callosum in a cohort of ex-premature 19 years olds and a group of age-matched controls, 2) exploring different methods of correcting for total forebrain volume and 3) examining group differences in size, including sub divisions of Corpus Callosum.

All together 113 low birth weight survivors (BW < 2000g) (without major handicaps) and 100 controls underwent a cerebral 3Tesla MRI examination as described previously. The area of the Corpus Callosum was measured on a realigned midline image using a voxel based technique (SPM5) and subdivided into three parts (genu, truncus and dorsal third). In correcting for total forebrain volume different methods were explored; first constructing a ratio between the CC area measurement (mm²) and forebrain volume (mm³) - and an “arealised” forebrain volume expressed in mm^{0.667} and second, by using a regression model considering “arealised “ brain volume as the independent variable and CC measurements as dependant variables.

The size of the CC was significantly related to the total brain volume ($r = 0.32$, $p < 0.001$).

We found that the size of the Corpus Callosum was smaller for the Low birth weight group than for normal controls, with a mean CC-area of 553.4 mm^2 (SD 98.3) for the Low birth weight group vs. 584.1 mm^2 (SD 82.7) for the controls ($p = 0.014$), but this difference disappeared after adjusting for forebrain volume. However, when analysing the three separate sub regions of Corpus Callosum, we found that the posterior third was significantly smaller in the Low Birth group compared to the controls (Figure 13).

Conclusion: The Low birth weight survivors in this study do have a smaller total Corpus Callosum area than the age matched controls, however, the difference disappeared by correcting for forebrain volume, suggesting that this CC size reduction is part of an overall forebrain size reduction. The size reduction of the posterior third of the CC was, however, consistent, warranting further investigation.

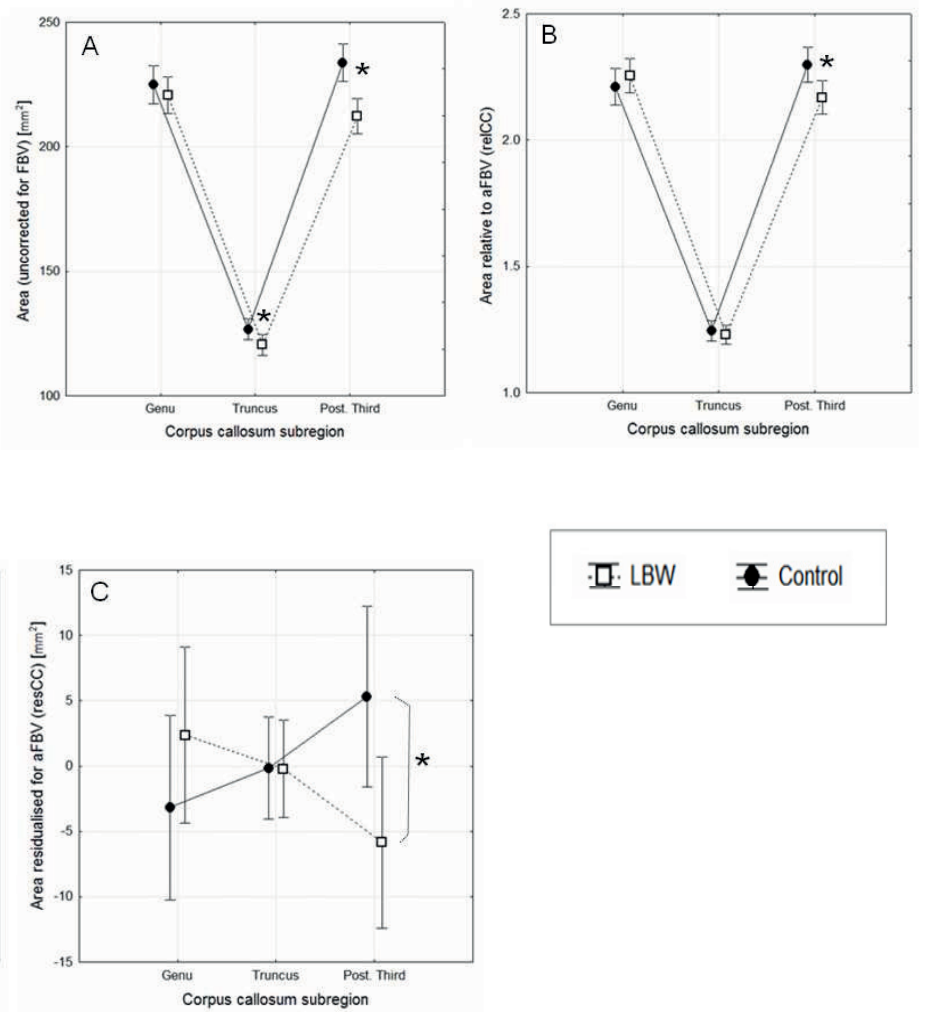


Figure 13. Depicts the group means (error bars: 95% confidence interval) of sub regional Corpus Callosum size:

- A) Uncorrected for forebrain volume
- B) Residualised for brain size (ResCC) and
- C) Relative to brain size (RelCC).

The asterisk (*) denotes a significant post-hoc comparison between the low birth weight and control group.

8. DISCUSSION

The survival rate after premature birth or low birth weight has increased considerably during the last decades and the number of long term survivors increases. Both the brain and the lungs are vulnerable to prematurity / low birth weight and much research has been undertaken trying to establish early markers of later disease and disability. Imaging has become a commonly used technique in the follow-up of ex-premature children and adolescents, however, standardised methods of ascertainment, definitions and classification of pathology as well as normal references are lacking. In this thesis I aimed to shed some light on a few of these issues.

The comparison of our results to those of others was not straightforward, as the design of the published studies varies significantly. In the following I shall address some of the difficulties met.

A. LUNG STUDY

1. STUDY DESIGN

Our study was part of an on-going observational study of ex-premature babies born within the catchment area of Haukeland University Hospital during 1982-1992. We used prospectively collected data from previous follow-ups as well as clinical and HRCT data collected for the purpose of the present study. For ethical reasons, a control group was not considered appropriate.

Two populations born prematurely, ≤ 28 weeks gestation or with a birth weight ≤ 1000 g were examined with HRCT during 2001-2002; one including 41 adolescents born during 1982-1985 and one including 33 children born during 1990-1992. The initial cohorts of eligible individuals comprised 46 and 35 newborns, respectively, without any differences according to sex ($p = 0.182$), GA ($p = 0.071$), BW ($p = 0.056$) or the occurrence / severity of BPD in the newborn period ($p = 0.545$).

At follow up in 2001-2002, their mean ages were 18 and 10 years, respectively, with nearly 50% lost to follow-up among the older vs. only 28% in the younger group, but losses to follow-up were mainly caused by subjects having died in the newborn period. Only a few of the survivors refused to participate or were unavailable, without any systematic dropout in either group. Both cohorts were therefore considered population based. Assuming that those having died were the most severely affected, these dropouts would lead to an underestimation of findings, more so for the older group. Opposite, for the seven attendees who did not have HRCT performed, 5 from the older and 2 from the younger age group, we hypothesize that 6 of them were in good health and therefore did not show up for the HRCT (one was medically unable to perform the examination). The fact that these 7 did not differ (as a group) from the 74 attendees with regards to lung function tests (FEV_1 % 81% vs. 87% $p = 0.281$) supports this. Thus, these dropouts should not have lead to an overestimation of our findings.

We performed HRCT scores for both age groups separately, as well as for the whole group. The youngest cohort had a lower total HRCT score (5.7 vs.7.9; $p = 0.019$), less “triangular opacities” (1.1 vs.2.3; $p = 0.018$) and less “air trapping” (0.8 vs.1.8; $p = 0.027$) than the children aged 17-19 years, but no significant group differences were found for the other parameters. Even if there were statistically significant group differences, we considered these to be minor and thus pooled the data for some of the analysis.

CT equipment and protocol

The HRCT scans were performed on a General Electric Hi Speed Advantage CT, obtaining 1.25-mm sections at 10 mm intervals in inspiration and at 20 mm intervals in expiration. Others would typically use 1 mm sections; however, the difference will probably not influence the results. All images were analysed subjectively using a pre-set window-level, in accordance with others; Aquino et al, Howling et al, Oppenheim et al (56-58).

CT evaluation and scoring system

Most authors advocate a subjective assessment of the lung parenchyma (56-58), although some have suggested additional measurements to assess reduced lung attenuation (HU below - 950) (61) or a decreased bronchus / artery ratio (58) as markers of air trapping or reduced bronchial dimensions in the lung. However, none of these markers have been validated in larger series. Except for a study by Kubota and colleagues devising a scoring system for BPD based on 3 mm CT sections, no scoring system for the assessment of chronic lung disease of

prematurity existed (59). We therefore set out to define a novel system, based on a validated system for the assessment of pulmonary change in another chronic lung disease, namely cystic fibrosis (63). According to this system, each of 20 lung segments was scored for the presence of both chronic but also active / inflammatory changes (67;154). Based on findings reported in previous studies on BPD survivors (56;57), additional markers such as triangular and linear opacifications were added, yielding a minimum score of 0 and a maximum score of 152 (based on 13 of the 14 variables).

The accuracy of the applied scoring system was acceptable for all the different markers under investigation, with weighted Kappa values ranging from 0.4 to 0.6 between readers and from 0.5 to 0.7 for the same reader. The fair agreement between readers for some of the disease markers such as linear opacities and triangular opacities underscores the need for thorough standardisation prior to assessment. None of the abovementioned studies had addressed the accuracy, or repeatability of the scores, which were based on primary consensus (56;58;61) or consensus in cases of disagreement only (57). When categorizing into normal vs. abnormal findings, inter-rater agreement varied from 75% to 93% for our four most frequent findings. This compares well with the results of Oppenheim and colleagues, who reported on a significant disagreement in 5 out of 23 (22%) subjects (57).

Our original scoring system using un-weighted raw scores from the scales was limited by its lack of a maximum score and its inability to differentiate between significant and insignificant pathology as well as the degree of extension. We therefore refined the scoring system, first by excluding two of the three variables defining bronchiectasies and collapsing linear and triangular opacities, thus improving the balance between various findings. Next by excluding findings not seen in any of the subjects, namely mucus plugging and thickened interlobar septae, and third by scoring bulla as being present or not (yes-no) rather than counting the numbers. This left us with nine variables, most of which were markers of chronic lung change. Fourth, we reduced the number of areas to be scored, from 20 segments to 6 lobes (Paper 2), yielding a minimum score of 0 and a maximum score of 50. The conversion from the “old” to the “new” system was based on the anatomical maps / templates performed by observer 2 (second reading). Thus, the lung changes were not re-scored, but merely collapsed from segmental to lobar findings, resulting in lower, but better balanced scores with a defined upper value. Additional repeatability studies were thus not judged relevant, however, there is

no reason to believe that the kappa values would have been poorer than that reported for the original and more complex scoring system.

Summary: Our study is, to our knowledge, the largest population based HRCT study of extreme-preterm children / adolescents and is unique in that it includes both BPD and non-BPD survivors. Despite some limitations, the scoring system devised had an acceptable accuracy and appeared to be useful in a research setting.

2. OUR RESULTS AS COMPARED TO THOSE OF OTHERS.

THE IMPORTANCE OF THE CLASSIFICATION USED FOR BPD.

As mentioned earlier, comparing our results to those of others is not straightforward, particularly due to the varying inclusion criteria used but also due to a change in the classification of BPD which was introduced by Jobe in 2001 (50). According to this, mild BPD is defined as “need of supplemental oxygen at day 28”, and moderate to severe as “need of supplemental oxygen at 36 post-menstrual weeks”, as opposed to the old classification; oxygen dependency at day 28 combined with radiographic changes (19). (The background and history of this discussion is given in the Background Information, Lung study / section 4B3).

Wong and colleagues examined a group of ex-BPDs at age 19 years (range 17-33 y), using the new classification of BPD, all with a moderate or severe BPD (61). The mean GA of this cohort was 27 weeks (range 24-30 weeks). In contrast, others have used the old classification, including Aquino and colleagues who examined a group of ex-BPDs with a mean GA of 28 weeks, ranging from 22 to 36 weeks, and a mean BW of 900g, ranging from 482-2350g (56). The use of different criteria for BPD obviously influences the composition of the cohort under investigation as to BW and GA.

Oppenheimer and colleagues in their study of 23 ex-premature children (mean age 4y) using the old BPD classification, and added a second criteria, namely those with signs of chronic pulmonary dysfunction at time of inclusion (57).

In comparison, we included all ex-prematures born during two different time periods, giving a population-based dataset. Influenced by the on-going discussion on BPD, we used the old

classification in paper 1 (78% BPD), showing no association between BPD status and HRCT findings, and the new classification in paper 2, focusing on the individuals with moderate-severe BPD (28%) showing the opposite.

Given the abovementioned differences in study design, our finding of fewer parenchymal abnormalities (86%) is in accordance with prior studies, in which only BPD survivors were included; for instance Aquino and colleagues (abnormalities in 92%) (56). Others have reported on pulmonary changes in all of their cases (57;58;61). None of the studies with which we compare have estimated a total HRCT score allowing for direct comparisons.

Assuming that small opacities and mosaic perfusion are less serious findings than emphysema and / or architectural distortion, the overall impression is that our study identified milder pathology and less (presumably) serious abnormalities in comparison to the others (56;61).

Linear opacities in the periphery, radiating towards the hilum, were seen in 72% and small, sub pleural *triangular opacities* were seen in 58% of the cases in our study. This is a lower prevalence than Oppenheim et al (57) described, 96% and 100% respectively. Aquino et al report triangular opacities in 92% (56). In our experience it is often difficult to separate linear opacities from small vessels and triangular opacities may be confused with the normal “attachment” of the interlobar septum to the inner surface of the thoracic wall. This diagnostic inaccuracy may lead to over-estimation of these findings. Next; are linear opacities and triangular opacities part of the same disease entity and are they always co-existing? Oppenheim et al (57) report that linear opacities face a deep triangular sub-pleural opacity in 96% of the cases, indicating their co-existence. If this is true, a separate score for these two entities (as we performed) may overestimate the grade of pathology. The pathological correlate to these radiological findings is not known, but Griscom et al (54) speculate that the triangular opacities represent pleural grooves and that the linear opacities may represent strands of atelectasis (54;57). But caution should be made, firstly, since there are no studies indicating the prevalence of these minor abnormalities in non-ex-prematures (i.e. are these “normal” findings) and secondly, the reproducibility of these findings is not very impressive (wKappa 0.39 for linear opacities and 0.43 for triangular opacities).

Areas of **reduced lung attenuation** on HRCT were seen in 14% of the cases on inspiratory scans compared to 26% on expiratory scans. This finding is rather non-specific, and would be

consistent with a primary injury to the airspace as well as a primary injury to the vasculature. In chronic lung disease of prematurity the mechanism is thought to be that of a primary airspace injury, but again, imaging is not able to differentiate between these two mechanisms, which may well be co-existing (32).

To differentiate between reduced lung attenuation in in- and expiration, we chose to use the terms mosaic perfusion and air trapping, respectively. In the literature these two terms are often used interchangeably, causing some confusion since the term mosaic perfusion originally was introduced to describe “regions of varied attenuation, interpreted as secondary to regional differences in perfusion” (155). In retrospect we would prefer more descriptive terms, such as reduced lung attenuation in inspiration / expiration in line with that used by Howling and Aquino (56;58). Others have used the term hyperaeration (57) or hyperlucency (60). The possible combination of airway and vascular disease may also contribute to the differences seen in in-and expiration, suggesting that the mechanism for lung disease in prematurity is more complex than was originally thought (32).

The reported prevalence of reduced lung attenuation varies between 48% (57) and 100% (58). Aquino et al (56) used a semi-quantitative technique to grade the air trapping on expiratory scans and defined air trapping as “areas of persistent radiolucency within the lung parenchyma during expiration”. Wong et al (61) report only air trapping and no hypoattenuation, but it is not clear whether this “air trapping” only was seen on expiratory scans. Some include only inspiratory scans thereby avoiding the problem (57;58). Even if the definition and grading of these hypoattenuated areas are quite unclear and variable, we believe it is an important finding. It is perhaps the most consistent finding among the different studies and clearly represents some morphological (and functional) disturbance in the lungs. Regardless of whether this represents lung areas with decreased ventilation and / or entrapment of air, the gas exchange within this unit is reduced and subsequently affects the lung function. These HRCT findings may indicate pathology in the small airways / terminal bronchioles with an alteration in elastic and fibrous interstitial network. This may reduce the elastic recoil and increase the small airway resistance (156;157) and decrease expiratory flow rates. This corresponds well to our lung function test results, as discussed later. This pathological framework differs from the “old” BPD in which the surfactant-dependant development of alveoli was seriously affected with subsequent intense inflammation and loss of normal architecture (emphysema and fibrosis) (21).

Emphysema is commonly defined as “areas of very low attenuation containing no perceptible parenchymal anatomy” (56). Only one of our subjects had emphysema, a finding that corresponds well with those of others (56-58). In contrast, Wong and colleagues reported 16 out of 19 (84%) adult BPD survivors to have emphysema (61). However, selection bias may have influenced the results in this study, as only 19 (14%) subjects from original cohort consisting of 133 subjects, performed the HRCT examination. There are several other possible explanations for their high prevalence of emphysema. First; only survivors of moderate-severe BPD of which none had been treated with surfactant in the neonatal period, were included. Second, the authors based the diagnosis of emphysema on quantification of lung-density using Hounsfield Units. The fact that they did not describe any cases of reduced attenuation with preserved architecture, however, suggests that their findings may have represented areas of hypoattenuation rather than emphysema. Another possibility would be that emphysema develops over time, as the mean age of his study group was significantly higher than ours, i.e. median age of 19 years, ranging from 17 to 33 years.

Based on our findings and the available literature, emphysema does not appear to be a common HRCT finding in ex-prematures. Similar, *bullae* also seem to be an infrequent finding. We report bullae in 4% in comparison to none in other studies (56;57), whereas Wong et al probably define the bullae as small areas of emphysema (61).

Bronchiectasies is a central feature in central airway diseases, such as cystic fibrosis (63), but seems to be an infrequent and non-consistent finding in survivors of premature birth / BPD. We found bronchiectasies in 10% of the cases in comparison to 8% (56), 5% (61) and 0% (57). The evaluation of bronchus diameter (in relation to adjacent artery) was done subjectively in our study (and in Aquino’s) (56) and the interrater and intraobserver agreement for this finding was poor. In order to evaluate the bronchiectasies, quantitative studies must be conducted (with scanning in a controlled phase of inspiration). But for the time being, there is no robust evidence to suggest that bronchiectasies represents an important part of the BPD sequelae scenario.

The term “*bronchus-to-pulmonary artery diameter ratio*” was introduced by Howling and co-workers in 2000 (58). They measured external diameters of the neighbouring bronchus-artery in five young adult BPD survivors, and reported a reduced ratio as compared to

controls, indicating a reduced bronchial diameter. We were not able to replicate their finding using a subjective assessment, and nor were Wong and colleagues (61). Squamous metaplasia, peribronchial fibrosis and prominent hypertrophy of peribronchial smooth muscle have been described in BPD (69) and this might explain a reduced bronchus diameter, but a parallel reduction in vessel diameter should be expected (down-regulation of perfusion in a poor ventilated area) thus balancing out this finding.

Some authors describe **architectural distortion** (56;61) as a separate finding along with the opacities and hypoattenuation. Architectural distortion is reported in 69% (56) and 42% (61) of the cases, but the entity is not clearly defined in these studies. Aquino suggests that it represents scarring and if that is the case, it may represent an irreversible damage of the lung. We did not observe any cases of architectural distortion in our cohort, which either means that our cases were less affected, or that we did not recognise such findings.

We introduced *thickening of interlobar septa* as a separate finding and report this in approximately 10% of the cases. The reproducibility of this finding was low (prevalence 10% vs. 22%) and the literature lacks studies that describe this separate, specific finding. However, thickening of the *interlobular* septa is a common feature of many diffuse lung diseases (158).

Summary: Our main findings at HRCT (opacities, hypoattenuated areas, air trapping) are consistent with previous literature. We believe that emphysema and bronchiectasies are infrequent findings in these populations and that the overall pathology detected at HRCT is relatively minor.

3. ASSOCIATION BETWEEN BPD STATUS AND HRCT FINDINGS

As discussed previously, the classification of BPD did influence the results of the statistical analyses in our association study. In our first study (paper 1), 56 out of the 72 ex-prematures had a history of BPD, according to the “old” classification of BPD. The overall trend was that the BPD group had a higher mean HRCT score, but the group difference did not reach statistical significance ($p = 0.11$, Mann Whitney U test). This could be explained by low numbers, or more likely, by the non-specificity of the clinical diagnosis of BPD. Clearly, these results may imply that there is no association between lung disease in the newborn period and radiological findings later in life, but this view is not supported by other

researchers (56-58;61), who all conclude that there is a significant association between BPD and findings at HRCT. Our study is, to my knowledge, the only in which non-BPD survivors are included, thus allowing for comparison of HRCT findings in BPD survivors vs. in non-BPD survivors.

In the second part of our study, we refined and simplified the scoring system, thus re-grouping the participants according to the “new” BPD classification (50). Subjects with moderate / severe BPD had significantly higher total HRCT score than the subjects without a history of BPD or only a mild BPD. The group difference was also significant for the opacities and the hypoattenuated areas. Thus, an increased severity of BPD predicts a significant increase in structural abnormalities at HRCT later in life and this correspond to the clinical work-up of these cohorts; Halvorsen et al showed that the BPD classification (BPD severity) significantly predicted FEV₁ (26). As the BPD diagnosis is based on the need of supplemental oxygen at a certain time point, the number of days of supplemental oxygen is not surprisingly associated with findings at HRCT (see later discussion).

Summary: When using the new classification of BPD, we found a significant association between moderate / severe BPD and HRCT findings. This corresponds to previous clinical and radiological studies addressing BPD survivors.

4. ASSOCIATION BETWEEN NEONATAL FACTORS AND HRCT FINDINGS

Our findings regarding association between neonatal factors and HRCT findings correspond (partially) to other studies. Aquino et al (56) created z-scores for the different HRCT findings and different lung parameters and tested the correlation. They found a correlation between decreased density and architectural distortion and signs of obstruction i.e. FRC ↑, RV/TLC ↑, FEV₁ ↓. But they did not find any significant correlation between reticular opacities and lung function parameters. In the study by Mahut et al (60) the linear / triangular opacities were inversely correlated to the FRC measurements. This, in turn, corresponds to the findings in a clinical study of lung function at term (159), in which infants with severe BPD had lower FRC. As the study by Mahut deals with infants (age 10-20 months) the lung parameters assessed were different from ours, with no RV/TLC ratio available. Forced expiration was

measured as the maximum expiratory flow at functional residual capacity (VmaxFRC), reflecting airway dimension and no correlation between opacities and VmaxFRC was found. Wong et al (61) found a significant correlation between severity of emphysema (on HRCT) and the lung function parameters. An increase in emphysema severity predicted lower FEV₁, lower FEF₂₅₋₇₅ and higher RV.

All in all, although the results are somewhat inconsistent, there seems to be some evidence to support an existing association between HRCT findings and lung function tests. As discussed previously, the opacities found on HRCT may reflect altered elastic and fibrous networks in the lungs, leading to altered elastic recoil and increased small airway resistance. These changes may reduce the expiratory flow rates (FEF₅₀ and FEF₂₅₋₇₅) with “early” collapse of the small airways and secondary air trapping with increased Residual Volume (RV). In this model, the hypoattenuated areas may represent the air trapping.

Summary: We found a statistical significant association between HRCT findings and lung function parameters, both for the airway dimension and lung volume parameters. The literature is inconsistent in this field, but our results fit well into the pathological framework of altered elastic and fibrous networks in the lungs in the BPD survivors.

B. BRAIN STUDY

1. STUDY DESIGN as compared to others

The present study is part of a large, on-going observational project on children / adolescents born with a GA < 2000g within the catchment area of Haukeland University Hospital. We used prospectively collected data from previous follow-ups at 5 and 11 years of age, as well as clinical and radiological data collected for the purpose of the present study. The control group was recruited for the 5 years follow-up, and was also included in the 11 years follow-up.

The study originally included 217 cases born during the period April 1st 1986 - August 8th 1988. At the time of the present follow-up, 22 had died, another 21 were excluded due to

major handicaps, leaving 174 eligible adolescents for the present study. 134 of the 174 eligible survivors (77%) participated in the long-term clinical follow-up during 2006-2007 and of which 113 agreed to participate in the MRI study. There were no differences between those attending the MR study and the non-attendees with respect to mean BW, GA and area of residency. We therefore consider the study cohort to be population based.

Again, the published studies on ex-prematures vary substantially as to inclusion criteria, ascertainment and definition of pathologies and age at follow-up. It is worthwhile noticing that our study is one of only three population based studies worldwide, the second being a study by Skranes (83) and colleagues in Trondheim and the third a study by Nagy and colleagues in Stockholm (84). The Trondheim study included two separate groups and a control group; VLBW (no 55), small-for-gestational age (SGA; no 54) and controls (no 66) as compared to ours (Low birth weight and Controls) (83). Mean age at time of the MRI examination was 15 years as compared to 19 years in our study, and cases with major handicaps were not excluded. The Stockholm study (84) included 74 VLBW individuals and 69 age-matched controls, aged 15 years (range: 12-17y). This study differs from our study in the choice of population (VLBW vs. Birth weight <2000g), time of scanning (15y vs. 19y) and a lower attendance rate, 42% (76 out of 182) vs. 65% (113 out of 173) in our study.

Other comparable studies are not population based and also differs from our study in major inclusion criteria. A research group at Kings College London published already in 1999 (114) a MRI study including 72 adolescents (age 14-15y) born before week 33, and 21 age-matched term-born controls. They have later published several papers on brain morphometry, based on the same cohorts (124;125;146). Further, they have (117;119) undertaken a MRI study including 33 individuals from a VLBW cohort, using siblings as unmatched controls. None of the participants had major neurologic handicap. As these studies have used GA as inclusion criteria and not birth weight, valid comparisons are hard to make. A quantitative MRI study of long-term outcome of survivors of preterm birth (born before week 33) was published already in 2000 (96). This is also a case-control study, including a consecutive sample of 25 eight-year-olds, thus much younger than, and more “preterm” than our participants.

Summary: Previous studies have included survivors of VLBW (below 1500g) or GA below 33 weeks, but our study is, to our knowledge, the largest population based, controlled study, including all born with BW below 2000g. Our high attendance-rate and high number of

participants are other strengths. In comparable studies, MRI examination was performed in childhood or in adolescence, whereas in our study we examined young adults having more “mature” brains.

2. REFERENCE INTERVALS FOR ADOLESCENTS BORN TERM, AND SUBJECTIVE VS. OBJECTIVE ASSESSMENT

In clinical practice, head MRI’s are commonly assessed subjectively without any measurements being performed. The evaluation is influenced by a set of factors, including training and experience of the radiologist, prevalence and type of pathology in that particular practice and also on the availability of normal references for that particular population. Based on the control group of 100 young adults born healthy and with a BW < 3000g, we showed that subjective assessment is inaccurate but more important, that even very experienced paediatric neuroradiologists may overestimate ventricular size in a high proportion of cases. This new knowledge should definitely form our future practice in reporting brain scans.

In the subjective assessment of ventricular size, we found only a moderate inter-observer agreement, with a kappa value of 0.43. This is in concordance with a study of children with hydrocephalus (160), in which the authors report a poorer inter-observer reproducibility for subjective assessment (Interclass correlation (ICC) = 0.77) than for objective measurement (ICC = 0.95). Asymmetry of the lateral ventricles has been reported in an earlier study (161) and our results confirm this, the left lateral ventricle being the larger.

The high proportion of ventricles judged to be mildly or moderately dilated in a cohort of normal 19 years olds was surprising, and underscores the need for reference intervals. A high total of one in three and one in 7, respectively, were defined to have dilated ventricles by two experienced paediatric neuroradiologists. To avoid the assumption of normality, the examinations were mixed with our 113 cases, with the two observers masked for grouping.

Our new MRI based reference intervals for different cerebral measurements show wide normal variations, consistent with previous findings both in children up to 8 months of age (162) and in adults (163). This variation was prominent for different parts of the ventricles, particularly for the occipital horns. This fact emphasize the need of objective assessment in

judging the ventricular system, as the occipital horn tend to be more dilated than the frontal / temporal horns in ex-premature children (121).

To our knowledge, our study represents the first set of reference intervals for commonly used cerebral measurements.

The smaller head circumference seen in those born with a BW < 2000g than for those born at term was expected, particularly the smaller bi-parietal diameter. It is, however, noticeable that no differences in the ventricular size between the two groups were found for males before adjustments had been done for head size. After adjustment for head circumference had been performed, there were still no significant group differences regarding the frontal horns, but the occipital horns were proportionately larger among the low birth weight males ($p= 0.031$).

Opposite, females born with a BW < 2000g had larger occipital and frontal horns as well as subarachnoidal spaces than their peers born term. The differences increased after adjustments for head size had been performed.

3. MRI FINDINGS IN VLBW-LBW

Again, comparing studies is not straightforward, and before I do so, I want to remind the reader that the inclusion criteria used for the present study were a BW < 2000 g, and no major neurological deficits. Thus, ten of the subjects were actually term, i.e. with a GA of 37 weeks or more, but were small for gestational age (SGA).

Overall MR pathology

All in all, we demonstrated MR abnormalities, defined as “dilatation of lateral ventricles”, “loss of bulk of white matter”, “diffuse thinning of Corpus Callosum” and / or “gliosis / focal white matter abnormalities”, in 43% of the Low birth weight young adults. This figure compares well with a study by Cooke and colleagues (42.5%), examining 87 VLBW adolescents (107). In other studies of VLBW adolescents, the reported prevalence varies between 84% (83) and 23% (84). The wide variation is worrisome if it reflects true differences, however, methodological issues most likely play a major role. This assumption is supported by the fact that both the study by Skranes and our study showed a high proportion of pathological findings among the controls, suggesting an incorrectly set cut-off between

normality and pathology. The difference in prevalence between Nagy's and our study (23% vs. 43%), is however, more difficult to explain, but again, we speculate that differences in MR-reading and threshold setting play an important role. Again, the prevalence of MR abnormalities in the control group would support this (16% vs. 6%). An alternative explanation is that the Swedish group has a better MRI outcome than the Norwegian and UK groups and that this is influenced by the neonatal care practice at the institutions (84).

Prominent or dilated lateral ventricles are commonly reported in survivors of premature birth / low birth weight. We found mild or moderate dilatation in 40% of the Low birth weights and in 15% of the controls, when assessed subjectively. This compares well with previous qualitative studies, as both Cooke et al (107) and Skranes (83) et al report ventricular dilatation in VLBW adolescents in 28% and 82 %, respectively. Subjective assessment of the ventricular system is easily biased and this may explain some of the variation although there is a consistent trend towards enlarged lateral ventricles in these groups. The discrepancy between the reported percentages of ventricular dilatation may also be caused by differences in study population; for instance regarding mean birth weight (BW 1191g in the study by Skranes and colleagues (83) vs. 1574g in our study). The age at examination also varies between the different studies (15 y (83) vs. 19y in our study), but whether or not this variation may explain part of the discrepancy in reported ventricular dilatation, is unclear. Several quantitative studies, though, have reported a high prevalence of ventricular dilatation in ex-premature children. In a quantitative study of 72 adolescents (15y) born very preterm in the UK (124), the very preterm had a 42% increase in lateral ventricular size as compared to the controls (after controlling for brain volume and gender) and nearly identical figures were reported by Allin and al (117) and Fearon et al (119) when examining VLBW young adults (23y); a 41% and 46% increase in ventricular volume, respectively. In another quantitative study of ex-preterm children (mean age 9.2y) (121) the enlargement of the ventricular system among the preterms is confirmed, but the group difference seems to be confined to the ventricular body and the occipital horns. Thus, the prior literature is fairly consistent of dilatation / prominence of the lateral ventricles in survivors of very preterm birth / VLBW and our study adds that this also apply for those born with a birth weight less than 2000g.

The increased size of the lateral ventricles in these groups may be caused by CSF flow / absorption disturbance or expansion of CSF compartments due to reduction of white matter (WM). The former, regarded as hydrocephalus, may follow an IVH and develop in infancy

and may need subsequent intervention. An idiopathic hydrocephalus may also occur in older ex-prematures. But in most of these cases, the ventricular dilatation is due to a reduction of periventricular WM volume (ex-vacuo phenomena) and the ventricular dilatation and the loss of periventricular WM are strictly parallel findings (139). Both in our study and in the study by Skranes et al (83) the ventricular dilatation and loss of WM were scored separately, when creating a total MR score. Interestingly, Skranes report ventricular dilatation in 45 and loss of periventricular WM in 29 out of the 55 VLBWs, i.e. 16 cases with ventricular dilatation without loss of periventricular WM. Cooke et al avoid this problem, in reporting only ventricular dilatation and periventricular leukomalacia (with periventricular signal abnormalities) without any grading of the volume of periventricular WM.

Thinning of Corpus Callosum is frequently reported in cohorts of ex-prematures. We found diffuse thinning in 20% of the Low birth weight cases compared to none (84), 17% (107) and 47% (83) in previous qualitative studies. The wide variation between Skranes and our results (47 % vs. 20%) may indicate that the CC is more affected in the VLBW group than in the Low birth weight group, but may also be caused by inconsistent definition and evaluation of CC thinning. Skranes et al report diffuse thinning in 20% (83) and focal thinning in 27%, whereas we did not see any cases with focal thinning. Nagy et al report (84) no evidence of CC abnormalities in their study of 74 VLBW adolescents. The thinning of CC is easiest appreciated on a mid-sagittal T1 weighted image (as obtained by Skranes and by us), while Nagy et al performed axial acquisitions. Although the T1 weighted acquisition was a 3D dataset and re-sliced sagittal images were available, it is not clear if these images were used in the evaluation of CC.

Focal, periventricular white matter lesions were detected in 31% of the Low birth weight group in our study, in comparison to 32 % with periventricular leukomalacia (PVL) in the study by Cooke (107) and 29 % with periventricular gliosis in the study by Skranes et al (83). Even if the definitions of periventricular white matter disease differ somewhat in these qualitative studies, the consistency of focal WM disease in approximately 1/3 of the cases is noteworthy. We found these abnormalities in only 4% of the controls as compared to 8% in Skranes study (83), but these figures from the normal populations truly indicate that the MRI findings listed in this section are not pathognomonic of premature birth or low birth weight group.

Summary: We report MR abnormalities in 43% of the Low birth weight group young adults and this is in accordance to other studies (of VLBW survivors). The subjective assessment of ventricular dilatation is flawed with biases, but this finding seems to be as frequent in the Low birth weight group as in VLBW cohorts (approx. 40%). But ventricular dilatation is also reported with a high prevalence in the control group. A subjective evaluation of CC size is also difficult, but our study supports the literature reporting thinning of CC in ex-prematures / low birth weights.

4. ASSOCIATION BETWEEN NEONATAL FACTORS AND MRI FINDINGS

Several researchers have investigated the association between MRI findings and mental function (96;113) and between MRI findings and neuropsychological parameters (80), but few have, to our knowledge, searched for an association between neonatal factors and MRI outcome later in life.

We included multiple neonatal parameters in our statistical analyses; prenatal factors (*Pre-eclampsia, Placental abruption, Maternal smoking in pregnancy, Intrauterine distress, Choriamnionitis*), perinatal factors (*Birth weight, Birth head circumference ratio*) and postnatal factors (*Apgar score, Days of assisted ventilation or oxygen*). In the statistical work-up we found no association between these various parameters and the MRI findings in young adulthood. Again, it is difficult to find studies with which to compare our results. Inder et al (108) scanned 100 consecutive preterm born babies (range 23-32 weeks) at term and found that several neonatal factors, such as GA, maternal fever, newborn sepsis were highly predictive for white matter abnormality. The discrepancy between our study and the study by Inder et al is difficult to explain. It is unlikely that the WM abnormalities seen by Inder will disappear during childhood without leaving any focal WM abnormalities or loss of periventricular WM (and dilated ventricles). They included only the very preterms and there may be a statistically significant association between GA and MRI findings in their group of very preterm, but not in our cohort with more “mature” born subjects (GA between 24 and 40 weeks). Kesler et al (121) performed volumetric analyses of the brain in 73 preterm children (Birth Weight 600-1250g) and 33 term born controls at age 7-11 years. In this study; GA was only correlated to temporal grey matter volume and not to any other GM volumes, nor any WM measurements, whereas increased birth weight was associated with decreased parietal

GM, frontal GM and occipital horn volumes. Thus, the lack of association between neonatal factors and subjectively assessed, non-volumetric MR findings in our study may be in accordance to Kesler et al's "minor" associations. Similar, Peterson et al found an association between GA and regional brain volumes in very preterm 8 years olds (96). An association between Apgar score at 5 minutes and regional brain volumes was also found. This may indicate that volumetric analyses are necessary in order to detect any associations between neonatal factors and subsequent MRI findings.

Summary: We did not find any significant statistical associations between neonatal factors and the subjectively assessed MRI score at age 19 years, but several quantitative studies have shown an association between gestational age and brain volumes in specific areas.

5. CORPUS CALLOSUM IN VLBW-LBW

As discussed above, thinning of Corpus Callosum is a general impression in subjective evaluation of ex-premature / VLBW / LBW. We aimed to examine whether this finding was consistent using a case-control design and advanced morphometric analysis. Is this reduction in area only a part of an overall reduction of WM volume or CC is especially vulnerable to premature birth / low birth weight? Quantitative studies enable us to investigate this. Some studies have shown that the WM volume is generally reduced in ex-prematures and low birth weight survivors (84;139), including the CC white matter. Thus, to define the relative size of the CC necessitates an adjustment for brain size (151).

The method of adjustment varies somewhat but inserting whole brain volume as a covariate in variance-analyses has been used by several researchers (96;124). If there is no proven group difference in whole brain volume, one might leave out the adjustment (117), but it appears inappropriate to use WM volume as a covariate (123;125) if the aim is to “isolate” the CC vulnerability. In our study we corrected for forebrain volume by creating a “residualised” CC value and by creating a ratio between CC area and whole brain volume (“arealised”). To our knowledge similar approaches have not been used in similar studies and may partly explain the discrepancy in results between our studies and other studies of CC. We found that the Low birth weight group had significant smaller total CC area than the control group, but that this group difference disappeared after adjustments for forebrain volume had been performed. This in accordance to prior studies; Nosarti et al (125) did not find a significant group difference in total CC volume in their study of very preterm adolescents, nor did Narberhaus et al in a study of very preterm, in Spain (123). In contrast, Caldu et al (118) and Rademaker et al (127) both found significantly smaller total CC area in the very preterm group as compared to the control group. This inconsistency among studies is most likely caused by the variance in study population, for instance including children with cerebral palsy (127) and / or by a variance in study methodology (method of adjusting for total brain volume).

Qualitative studies have reported a thinning of CC and with a main affection of the posterior part (83;107). Quantitative studies of CC size in ex-preterms / VLBW have confirmed this finding. Despite the variance in study design and methodology, the majority report that the reduced CC area is driven by a smaller posterior part of CC in these groups. Whereas some authors report that several sub-regions (including posterior 1/3) are significantly reduced in

size (96;118;123;127), others report, as we do, an isolated effect of the posterior part of CC (119;125). The methods of dividing the CC into sections vary between studies, but this does not seem to affect the results significantly. Thus, there is an extensive support in the literature to claim that the posterior part of CC is especially affected in preterms and in VLBW survivors. Our study confirms that this also applies for all with birth weight below 2000g.

These quantitative studies do reveal group differences, but do not answer why the posterior part of CC is especially affected and we do not know whether this size reduction of the posterior part does have clinical implications. Neither do we have a clear understanding of the histopathological changes of the CC in these individuals. From an embryological point of view, the splenium is the last sub-region of CC to develop and mature (164) and Allin et al showed a growth spurt of CC between 14-15 years and 23 years in very preterms, and CC not reaching full maturity until young adulthood (137). So, theoretically, our finding of a smaller posterior CC in 19 years may only represent delayed growth and the possibility of no-significant group difference, if re-examined later in adulthood. Peterson et al (96) proved an inverse association between the size of the posterior CC and grey matter changes in the cortical projection area. But it is not clear whether the area reduction of the posterior 1/3 of CC is a primary or a secondary event, i.e. does the premature birth cause damage to WM tracts, consequently leading to damage of the cortical projection areas or vice versa; primary damage to cortex having secondary affect on CC.

The histopathological nature of the CC thinning is not fully investigated i.e. whether there is a thinning of the interhemispheric fibre bundles, a reduced number of fibres or a reduction of the thickness of the myelin sheets. An animal study inducing hypoxia in rats (165), indicate that a combination of these events takes place. DTI studies have been designed to investigate the tissue integrity in CC and Nagy et al (131) confirm microstructural findings in the posterior part of CC, with a decreased Fractional Anisotropy (FA). But in another DTI study by Kontis et al (130), no microstructural changes were found in the splenium. Thus, the present DTI studies do not fully explain what is really going on in the CC. In cases with reduced posterior 1/3, one might speculate if there exists an increased size in the other sub-regions of CC, as compensation. Our study suggests a non-significant trend of a possible compensation with enlarged genu of Corpus Callosum. This trend is not reported in the literature, to our knowledge.

And finally, does the reduced size of the posterior part of CC have any clinical implication or is it only a minor part of a big and complicated puzzle? In the study by Nosarti et al (125) of very preterm adolescents (14-15y), verbal IQ and verbal fluency score were positively associated with the mid-posterior surface area of CC (and the total mid-sagittal area), but in boys only. Whether this also is true for the Low birth weight group remains unclear. Neuropsychological data from our cohort (at age 5y) documented an impaired performance on visual tasks (76) in the Low birth weight group and it seems likely that this impairment is associated with change in interhemispheric connectivity in the posterior 1/3 of CC. Further analyses of the neuro- psychological data at 19 years in our cohort, enable us to search for further associations, for instance between the various sub-sectional CC areas and attention score. But, the size of CC is only important if it reflects a reduction in functional connectivity and / or an increased transfer time between the two hemispheres. So parallel to investigating the association studies between area and neuropsychological data, the DTI data ought to be analysed, in order to investigate if the changes in microstructure (measured with Mean Diffusivity or Fractional Anisotropy) are correlated to the macrostructure (area). These results may shed some new light on the pathophysiology, however, in order to validate the significance of these CC changes, prospective studies on the CC at term-equivalent age and later developmental outcome are needed.

Summary: We found a smaller total CC area in the Low birth weight group, but this group difference disappeared after adjusting for forebrain volume. But when analysing the sub-regions, a significant group difference of the posterior 3rd of CC was found and this is in accordance to several former studies, which indicate a specific vulnerability of the posterior part of CC. The clinical implication of this remains unclear and further investigation is needed.

9. MAIN CONCLUSIONS

Lung: 1. HRCT-markers of chronic lung disease of prematurity can be observed in a fairly reliable fashion, and used to make an objective scoring system. There was a moderate agreement between the two observers in all the evaluated parameters, whilst the intra-observer agreement was moderate to good. The accuracy of the proposed scoring system is acceptable for the single reader, although there is more variability between two different individuals.

This problem could be overcome if thorough standardization is performed. The refined and simplified scoring system allows for assessment of a maximum score.

2. In a population based cohort of children / young adults born with a GA of 28 weeks or less or with a BW below 1000g, nearly nine in ten have abnormal HRCT findings consistent with chronic lung disease of prematurity. Linear and triangular opacities are the most common, and typically, the findings are subtle.

3. There is a significant association between HRCT findings in children / young adults and moderate to severe BPD when using the “new” classification of BPD, whilst this association is absent when using the “old” classification. Days of prolonged oxygen treatment predicts subsequent HRCT findings, and this neonatal factor seems to be the single most important factor for prediction of structural lung abnormalities in later life.

4. There is a significant association between HRCT findings in children / young adults and lung function parameters.

Brain: 5. Subjective assessment of ventricular size is fairly accurate with a moderate degree of agreement between observers, but tends to overdiagnose dilatation of the lateral ventricles. New, sex-specific MRI based reference intervals for adolescents born at term with a BW > 3000g have been established. Adolescents born with low BW have smaller heads than those born at term, with a BW > 3000g. For males, unadjusted ventricular size does not differ according to birth weight, however after adjustments for head size, those born with low BW have larger occipital horns than those born at term with a BW >3000g. For girls, those born with a low BW have larger lateral ventricles and subarachnoidal spaces both before and after adjustments for head size, are performed.

6. In a population based cohort of young adults born with a BW < 2000g, thinning of Corpus Callosum and mild dilatation of the lateral ventricles are common findings as assessed subjectively, however, similar findings are frequently seen in young adults born at term. No significant associations between MRI findings and factors related to the peri- and early postnatal period were demonstrated.

7. Low birth weight survivors do have a smaller total Corpus Callosum area than those born at term with a BW > 3000g, however, the difference disappears by adjusting for forebrain volume, suggesting that this CC size reduction is part of an overall forebrain size reduction. The size reduction of the posterior third of the CC appears to be consistent.

None of the findings in the present studies would justify cerebral MRI as part of a routine follow-up of non-handicapped Low Birth Weights young adults, but awareness of findings typically seen in this group is necessary to provide correct MRI reports.

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