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BRONCHOPULMONARY DYSPLASIA FROM NEWBORN DISEASE TO LONG-TERM SEQUELAE

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To my beloved family

For sure, in quiet world sea of the thought,
there lie so many unknown isles,
and many stars are mirrored there maybe,
not yet discovered by the scientist.
If you can´t plough yourself the deep of waves,
so listen willingly to voices of the wise,
those wide-travelled, who with certain signs
are coming back from countries new.
But don´t believe what skippers tell you
of all tremendous things they saw,
about the riddle of the world, at last now solved by
them, of the philosopher´s stone that they have found

Esaias Tegnér
Epilogue at the Doctor Graduation in Lund, 1820

ABSTRACT

Bronchopulmonary Dysplasia (BPD) is a complication of premature birth that is associated with increased mortality and morbidity in infancy and impaired lung function and obstructive lung disease from childhood to adulthood. The pathogenesis of BPD is multifactorial, and may involve one or more of the following: a deficiency in surfactant production in the immature lung, chronic inflammatory processes before and after birth, oxidative stress, and trauma due to mechanical ventilation. Surfactant replacement therapy, which reduces acute lung injury in the preterm infant, could be one way to prevent later development of BPD. So far, surfactant therapy requires invasive intubation that may itself be traumatic. In this thesis, we evaluated an alternative, non-invasive way to deliver surfactant. This trial of surfactant inhalation via nasal CPAP in spontaneously breathing infants unfortunately did not prove beneficial.

Pre- and postnatal inflammatory processes may initiate and aggravate the course of BPD. Some of the underlying inflammatory processes e.g. activation of the neutrophil and macrophage systems, have been well described but other processes, such as the role of eosinophils and other inflammatory markers in the pathology of BPD, have not yet been well characterised. This thesis shows that levels of activated eosinophils in the circulation are elevated in infants with BPD, a sign of chronic, systemic inflammation. We also found that the degree of eosinophil activation was positively associated with the severity of BPD (as determined by the duration of supplementary O_2 treatment). Future studies may establish whether a causal relationship exists between states of eosinophil activation in preterm infants and BPD.

Moderate and severe BPD is associated with an increased risk for airway obstruction and low forced expiratory volume in childhood. As shown herein, respiratory mechanics is also altered in children with mild BPD. This finding is important because it emphasizes the need for careful clinical follow up of *all* BPD children, regardless of the severity of the disease, in order to minimize further deterioration in lung function. BPD not only affects lung function but general development as well; thoseffected may develop cognitive and motor performance deficits and exhibit behavioural difficulties.

This thesis also sheds new light on public health consequences of very preterm birth. We know little about the possible long-term consequences of premature birth for lung function in old age. In a unique birth cohort born in 1925-49 in Sweden, we found that moderate–to-very preterm birth is associated with obstructive lung disease in old age, the severity of which required frequent hospitalisation. The results from this historic cohort cannot be directly extrapolated to preterm infants born today. However, the much higher survival rate in the modern era of neonatal intensive care suggests that infants born preterm nowadays could be at even higher risk of developing obstructive airways disease in adult life than were previous generations. This finding emphasizes the importance of extending follow up programs into adult life.

Preterm birth is a global and serious health issue. A better understanding of its potential adverse impact in infancy and childhood may lead to better intervention and treatment strategies and improved long-term outcome.

LIST OF PUBLICATIONS

This thesis is based on the following papers, designated by Roman numerals (I-V).

I. Eva Berggren, Magnus Liljedahl, Birger Winbladh, Bengt Andreasson, Tore Curstedt, Bengt Robertson, Jens Schollin.
Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome.
Acta Paediatrica 2000 Apr;89(4):460-4.

II. Eva Berggren Broström, Miriam Katz-Salamon, Joachim Lundahl, Gunilla Halldén, Birger Winbladh.
Eosinophil activation in preterm infants with lung disease.
Acta Paediatrica 2007 Jan;96(1):23-8.

III. Eva Berggren Broström, Per Thunqvist, Gunilla Adenfelt, Elisabeth Borling, Miriam Katz-Salamon.
Obstructive lung disease in children with mild to severe BPD.
Respiratory Medicine, doi:10.1016/j.rmed.2009.10.008

IV. Eva Berggren Broström, Gunilla Adenfelt, Christina Lindqvist, Annika Örtenstrand, Aijaz Farooqi.
Motor performance, cognitive development and behavioral characteristics in children at school age with mild to severe BPD.
Manuscript

V. Eva Berggren Broström, Olof Akre, Miriam Katz-Salamon, David Jaraj, Magnus Kaijser.
Obstructive Pulmonary Disease in old age among individuals born preterm.
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
BPD	bronchopulmonary dysplasia
BW	birth weight
CBCL	children behavior checklist
CD9	cellular surface antigen
CLD	chronic lung disease
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DPPC	dipalmitoylphosphatidylcholine
DSM – 1V - R	diagnostic and statistical manual of mental disorders, fourth edition revised
ECP	eosinophil cation protein
FEF75-25	mid-expiratory flow at 75-25% of FVC
FEV1	forced expiratory volume at one second
FEV%	ratio FEV1/FVC
FVC	forced vital capacity
GA	gestational age
HRCT	high-resolution computed tomography
IOS	impulse oscillometry
IVH	intraventricular haemorrhage
IQ	intelligence quotient
MFI	mean fluorescence intensity
NICU	neonatal intensive care unit
NIDCAP	newborn individualized developmental care and assessment program
PBE	peripheral blood eosinophils
PDA	patent ductus arteriosus
PMA	postmenstrual age
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
Rrs	resistance
SHS	second-hand smoking
SGA	small for gestational age
VLBW	very low birth weight
Xrs	reactance
Zrs	respiratory impedance

1 INTRODUCTION

Bronchopulmonary dysplasia, BPD, is a complication of preterm birth.[1] Advances in neonatal intensive care strategies and technology have markedly improved survival rates of very low birth weight (VLBW) and changed the course of BPD. BPD is now considered the second most common pulmonary disease after asthma.

Prematurely born infants have lungs characterized by immature structure and surfactant deficiency, leading to respiratory symptoms with need for ventilator support and supplemental oxygen. The discovery of surfactant and advances that permitted its delivery to the lungs of those suffering from respiratory distress (IRDS) has revolutionized the treatment and survival of the preterm-born infant. Consequently, today more and more infants born very early in gestation are surviving. This has two important implications: (i) the number of infants who go on to develop BPD has increased; (ii) as the limits of viability have declined, the pathophysiology of BPD has also changed. Because it has been suggested that less invasive treatment decreases the incidence of BPD, the key to successful management of this increasingly common disorder in extremely preterm survivors may be to develop alternative, minimally-invasive preventative strategies.[2] This may reduce the severity of subsequent multi-system complications associated with BPD.

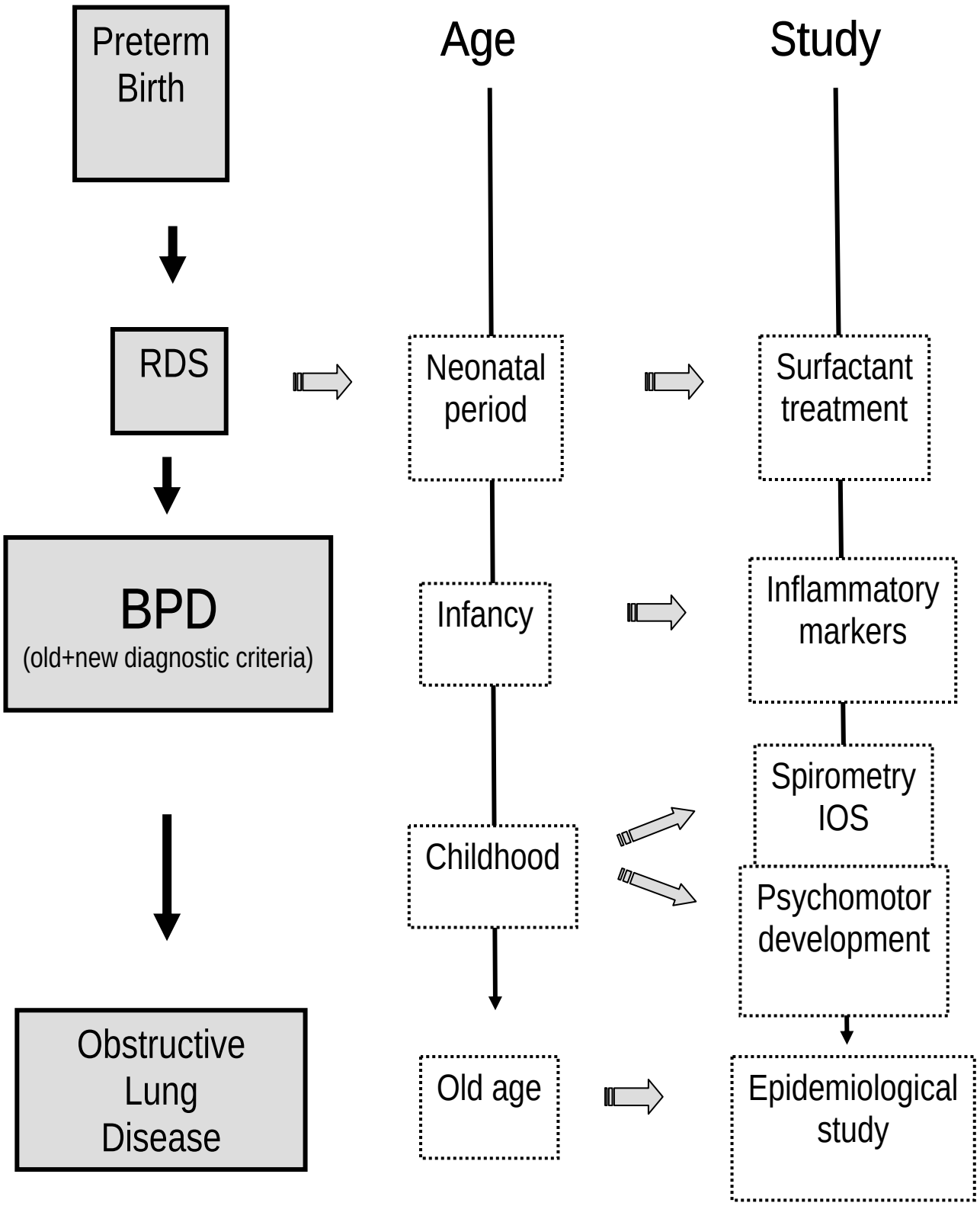
BPD is associated with effects on neurodevelopment and pulmonary function, and with an increased risk of reactive airways disease/asthma. Infants who develop BPD endure frequent respiratory-related hospitalizations in childhood, and are often dependent on continuous medication.[3]

One of the most serious concerns about BPD is its long-term impact on lung function, especially in old age. Normally, lung function peaks at about 40 years in a healthy population and then gradually declines. For lungs affected by BPD however, functional deterioration may commence much earlier than expected, resulting in severe obstructive lung disease developing at younger age.[4]

The aims of the studies described in this thesis were:

- To evaluate the efficacy of non-invasive surfactant delivery in the prevention of BPD.
- To determine whether eosinophil activation is part of the underlying inflammatory process associated with BPD.
- To analyze whether the severity of BPD predicts long-term outcome, including childhood lung function, psychomotor development, and adult health.

Flow chart describing age groups and study objectives



2 BACKGROUND

BPD - A NEWBORN DISEASE

2.1 PRETERM BIRTH

Preterm birth is defined as delivery before 37 weeks postmenstrual age (PMA), and very preterm birth as delivery before 32 weeks PMA. The number of preterm-born infants varies from country to country; in Sweden 6% of all pregnancies end preterm and approximately 1 % end in very preterm birth.[5]

The one-year-survival for all live born, extremely-preterm infants in Sweden has increased from 48% in 1990-92 to 70% in 2004-07. This has been accompanied by an increase in neonatal morbidity, except for severe IVH or PVL (the rates of which have remained unchanged).[6, 7]

2.2 LUNG DISEASE OF THE NEWBORN

2.2.1 IRDS

Infant respiratory distress syndrome (IRDS) develops immediately after birth because the immature lung of the preterm infant lacks surfactant. This deficiency results in low lung compliance and atelectasis. The resulting breathing difficulties are treated by instilling exogenous surfactant and providing supplemental oxygen and ventilatory support. Currently, the criteria used to define IRDS are: (i) presence of acute respiratory symptoms within 2 hours of birth; (ii) increasing oxygen requirements during the first 48 hours: (iii) characteristic chest x-ray showing retinogranular pattern and generally decreased air content of the lungs.[8]

These diagnostic criteria have recently been re-examined in the light of new evidence, some based on studies of chorionamnionitis.[9] Recently the response to treatment with surfactant was found to vary, depending on whether or not a fetal inflammatory response could be demonstrated. Lung inflammation already in fetal life may partly explain the progression of early (within days of birth) lung injury to BPD.[10] In another large cohort study at least three different patterns of IRDS were described during the first two postnatal weeks in those born extremely premature. One group – those with little / mild lung disease – recovered rapidly. A second group exhibited early and persistent pulmonary symptoms, whilst the third group exhibited pulmonary deterioration and an increasing need for supplemental oxygen and mechanical ventilation two weeks after birth.[11] These findings suggest that for infants born very preterm the severity of IRDS may range from mild to severe. IRDS of the very preterm infant is probably not, therefore, a single or uniform entity even though it is typically the diagnosis made when lung disease is present at or soon after birth.[9]

2.2.2 Bronchopulmonary dysplasia

The introduction of mechanical ventilation during the 1960s dramatically increased the survival of premature infants. However, as first described by Northway, increased survival was associated with severe respiratory and lung complications and considerable mortality.[12] Typical histological findings at autopsy - lung fibrosis and edema and emphysema – led to the disease being called bronchopulmonary dysplasia. Initially, BPD was considered to be a consequence of mechanical ventilation-associated barotrauma, and toxic oxidative stress due to high O_2. Today, the forms of BPD seen in infants born very early in gestation are somewhat different, and represent disorders of intrauterine inflammation and pathological extra uterine lung development characterized by alveolar simplification.[4]

Definition

The diagnostic criteria for BPD have varied considerably over time. The early definition of BPD of Northway was based on four criteria: (i) acute lung injury during the first week of postnatal life, (ii) clinical signs of chronic respiratory disease, (iii) the need for supplemental oxygen to maintain the PaO2 > 50 mmHg at PMA of 36 weeks, and (iv) chest radiograms showing persistent strands of density in both lungs.[12] In 1979 Bancalari and co-workers proposed three simple criteria to define BPD: (i) supplemental oxygen requirement at 28 days of postnatal life, (ii) abnormalities of the chest radiograph, and (iii) tachypnea in the presence of rales or retractions.[13]
Because these diagnostic criteria did not adequately predict long-term respiratory outcome, the definition was further refined to incorporate specific criteria for infants born before or after 32 gestational age weeks (National Institute of Child Health and Human Development). Now the diagnosis of BPD for infants born before 32 weeks is based on the need for supplementary oxygen at 28 days of age. Furthermore, the severity of BPD is graded at 36 weeks PMA as follows: 1) breathing air - mild BPD; 2) need for supplementary oxygen <30%- moderate BPD; 3) ≥ 30% supplementary oxygen and/or continuous positive airway pressure (CPAP) or ventilator - severe BPD. For infants born ≥32 weeks GA, grading is performed on postnatal day 56.[14]
The validity of these diagnostic criteria has been confirmed by several studies that have shown associations between the severity of BPD and adverse pulmonary and neuro-developmental outcomes and respiratory morbidity in early infancy. These criteria consequently provide an important means of evaluating outcomes in clinical trials comparing mortality and morbidity between different NICU´s.[15]

Incidence

As discussed above, the definition of BPD changed considerably during the last two decades. The incidence of BPD reported by different centres also varies considerably, because of variations in the oxygen saturation and ventilatory support targets, as well as the age at diagnosis (i.e. 28 days or gestational week 36). One study estimated that 30% of preterm infants born <1000 grams develop BPD.[16] For those <1,500 grams at birth, the incidence of BPD, defined as a need for supplemental oxygen or mechanical ventilation or continuous positive airway pressure (CPAP) at 36 weeks, varies from 19 - 36%.[17-20] Among 1-year survivors born in Sweden at 22 -26 weeks, the incidence of moderate BPD was 73 %.[7] The corresponding incidence of severe BPD was 25 %.[21]

Pathophysiology

The pathogenesis of BPD is multifactorial. Barotrauma and oxygen toxicity are considered to be the major causes, as originally described in 1967.[12] The *"old"*, or "classic" BPD, was characterized by inflammation leading to squamous metaplasia of the airway epithelium, obliterative bronciolitis, peribronchial fibrosis, airway smooth muscle hypertrophy, and hypertensive vascular lesions.[22] The lungs of infants with the *"new"* BPD show minimal alveolarisation, less airway epithelial and vascular disease, and milder forms of inflammation and fibrosis compared with the "old" BPD. Thus, as described by Baraldi and Filippone, "old" and "new" bronchopulmonary dysplasia are two different morphologic outcomes that reflect variable combinations of factors capable of injuring lungs at different stages of maturation. The introduction of antenatal corticosteroids and surfactant instillation has led to a reduction of the old and an increase of the new form of BPD. The latter is now regarded as a pulmonary developmental disorder.[4]

2.3 INTERVENTIONS

The most important and effective treatments to improve the outcome of immaturely-born infants are antenatal corticosteroids administered via the mother before birth, and surfactant replacement.

2.3.1 Antenatal corticosteroids

Antenatal administration of corticosteroids to women at risk of preterm labour before 34 weeks gestation is a well-established practice that accelerates fetal lung maturation. Steroids reduce neonatal mortality as well as the incidence of RDS and intraventricular haemorrhage in preterm-born infants.[23] Important questions, however, remain, e.g. which steroid product is best, when should treatment commence, and should it be repeated?[24]

2.3.2 Surfactant

History

In 1929 Kurt von Neergard was the first to perform experiments that suggested the presence of pulmonary surfactant was relevant for the newborn's first breath.[25] Nearly 25 years later, Richard Pattle[26] John Clements[27,28] and Chris Macklin[29] working independently at different centres on the effects of nerve gases on the lung, "rediscovered" surfactant and developed our understanding of its role in the lungs. In 1959, Mary Ellen Avery& Jerry Mead published convincing evidence that preterm infants dying of hyaline membrane disease lacked pulmonary surfactant. [30] Ten years later, not long after John F Kennedy's son died from IRDS, results from the first trials of nebulized synthetic surfactant to prevent RDS were published. Although these initial trials were unsuccessful, Göran Enhörning and Bengt Robertson subsequently demonstrated in the 1960´s that natural surfactant was effective in a rabbit model of RDS.[31-33] In 1980 Tetsuro Fujiwara reported treating 10 preterm infants with RDS with bolus doses of bovine surfactant,[34] initiating an era of randomized controlled trials (RCT). In a 2008 review, Henry Halliday concluded, "Surfactant was the first

drug developed solely for treatment of neonates. Its use has been a major advance in neonatology during the past 25 years."[35]

Substance

Surfactant production in humans begins in type II cells during the terminal sac stage of lung development. The lamellar structures of type II cells appear in the cytoplasm at about 20 weeks gestation. Their function is to store surfactant before it is released into the alveolar space. Term infants have an estimated alveolar storage pool of 100 mg/kg of surfactant, while preterm infants have approximately 4-5 mg/kg at birth. This alveolar surfactant can be broken down by macrophages and/or reabsorbed into the lamellar structures of type II cells. Pulmonary surfactant is composed of two main fractions: lipids and surfactant-specific proteins. Lipids account for approximately 90%, most of it phospholipids.[36]

Treatment

Treatment with exogenous surfactant improves gas exchange and survival of newborn babies with respiratory distress syndrome (RDS) [37, 38] In a Swedish cohort of 497 infants born before 27 gestational weeks in 2004-2007, 60 % of the infants were intubated at birth and surfactant was administered within 2 hours after birth to 61%.[7]

Surfactant is usually administered as a bolus in the central airways via an endotracheal tube. In many cases the tube can be removed soon afterwards, especially if the therapeutic response is favourable.[39-41] Postnatal treatment with nCPAP and surfactant decreases the severity of, and mortality from RDS and BPD, mainly by reducing the use of Mechanical Ventilation (MV) in the first postnatal days.[42] This "soft" approach – the use of CPAP instead of mechanical ventilation - was described more than twenty years ago by Avery et al. as a strategy to successfully decrease the incidence of BPD.[43] In a recent published study the incidence of moderate/severe BPD was 22% in Stockholm compared with 40% in Boston, possibly related to a lower rate of intubation and less mechanical ventilation in Stockholm.[44]

Concerns have been raised about whether variations in blood pressure and cerebral perfusion during and after surfactant treatment could possibly increase the risk of intra- and periventricular haemorrhage.[45-46] Many infants with RDS who initially respond to surfactant therapy develop BPD in the following weeks. With this in mind, attempts have been made to administer surfactant more gently i.e. by nebulization. The first clinical trials of nebulized surfactant for treatment of RDS using dipalmitoylphosphatidylcholine (DPPC) as single surfactant component, were inconclusive.[47] More encouraging results have been obtained with natural surfactants in various animal models of surfactant deficiency or depletion, although the amount of nebulized material required to achieve a therapeutic response was much larger than when administered in bolus form.[48-52] In a pilot study Winbladh et al described five babies with RDS who seemed to respond to treatment with nebulized surfactant.[50] In those cases, the surfactant was administered via a tight face mask from which the aerosol was inhaled.

More studies on non-invasive surfactant administration are urgently needed.[53] Intubation and mechanical ventilation to administer surfactant may lead to lung injury which in turn may lead to BPD.[54] In two small studies of surfactant delivery into the nasopharynx[55] or larynx via a mask[56] the incidence of RDS was reduced. However, larger randomized clinical trials are required to confirm these results.

2.4 INFLAMMATION AND IT'S ROLE IN DEVELOPMENT OF BPD

Two pathophysiologic processes seem to be decisive for BPD to develop: inflammation and pulmonary growth arrest. Exposing a premature infant to supplemental oxygen and mechanical ventilation at birth triggers inflammatory processes that induce lung injury.[57] This injury typically consists of epithelial and endothelial cell injury, protein leak, and an increase in pulmonary vascular permeability with an influx of platelets, neutrophils, and macrophages and proinflammatory cytokines. Production of the proinflammatory cytokines TNF-alfa, IL-1ß, and IL-8 is regulated in part, by the anti-inflammatory cytokine IL-10, which is reduced in infants who develop BPD. Fetal inflammation starts with chorioamnionitis, which is often caused by Ureaplasma infection.[58] The elevation in early inflammatory mediators seen in tracheal aspirates (and confirmed in animal studies), suggests that exposure of the premature lung to inflammation is an important early step in the development of BPD.[59] The initial lung injury may be aggravated by inappropriate resuscitation in the delivery room using high tidal volumes, or lung over distension during treatment for respiratory distress syndrome, or even by low-lung volume ventilation., leading to a further influx of inflammatory cells into the lung[59, 60] Complications such as patent ductus arteriosus, necrotizing enterocolitis, and other acute illnesses may reinitiate and prolong the inflammatory cascade. Leukocytes generally are found in tracheal lavages of infants who develop BPD.[61-64, 59] Studies suggest that these cells are involved in inflammatory lung injury.[65] Lymphocyte activation has also been demonstrated in infants with BPD.[66] Chronic, persistent lung inflammation contributes greatly to BPD by altering the lung's ability to repair. This in turn contributes to fibrosis, inhibiting secondary septation, alveolarization, and normal vascular development. Although corticosteroid therapy reduces inflammation and the duration of oxygen dependence, thus reducing the incidence of BPD, steroids have adverse effects on growth and development.[67-69] Clarifying the role of inflammation in the pathogenesis of BPD may help us eventually to develop alternative, non-steroidal anti-inflammation related treatment strategies .[57]

2.4.1 Eosinophil activation

Some aspects of BPD-associated inflammatory process are rather well studied, particularly the activation of the neutrophil and macrophage systems.[70] However, the role played by eosinophils in BPD is not yet clear[71,72], although it is well known that premature infants develop eosinophilia as newborns.[73,74]

In bronchial asthma – a disease with clinical similarities to BPD[75] - activated eosinophils degranulate in the airway, causing airway epithelial damage, inflammation and hypersensitivity.[76] Some of these effects have been attributed to the eosinophilic cationic protein (ECP), a highly cytotoxic granule protein.[77] Eosinophil activation involves changes in the intracellular expression of the EG2 epitope of this protein (ECP) as well as the monoclonal antibody EG2. Because there is a positive correlation between bronchial mucosal EG2-positive cell counts and serum ECP levels, the latter may serve as an index of local airway eosinophil activation in bronchial asthma.[78] The extent of eosinophil activation can also be gauged in part by CD9, a cellular surface antigen present on peripheral blood

eosinophils (PBE).[79] The biological function of CD9 is yet not clearly understood but it may be involved in the initial phase of cell activation.

BPD - LONG-TERM SEQUELAE

2.5 SCHOOL-AGE OUTCOME OF PREMATURITY AND BPD

Although the majority of infants born preterm do well in the short to medium term, they may be at increased risk of developing impairments later on in life e.g. as adults. In a 2007 review, Marilee Allen highlighted emerging evidence that preterm birth poses a major public health problem in the USA.[80] There has been a shift in focus away from early evidence of higher rates of cerebral palsy and intellectual disability in preterms, to more recent studies which describe subtle disabilities such as school and behaviour problems.[81] Neonatal illness, especially BPD, is considered by many to increase the risk of neurodevelopmental impairment in preterm-born infants.[82] Lung disease may be associated with language delay, visual-motor impairment, lower average intelligence, academic difficulties, attention and behaviour problems, memory deficits and executive dysfunction.[83]

2.5.1 Respiratory outcome

There is limited and somewhat conflicting data about the long-term respiratory outcome in adults who were born prematurely. In a BPD cohort from the late 1960's Northway et al found mild-to-moderately reduced lung function in early adulthood.[84,85]Doyle et al. recently reported a decline in pulmonary function from 8 to 18 years of age in a large cohort of BPD survivors,[86] a finding that has been confirmed by others.[87, 88] Some improvement in lung function was however noted between 7 and 10 years.[89-91]

Despite the fact that the severity of BPD has declined over the past decade, it remains a leading cause of long-term respiratory dysfunction.[92, 93] In the longer term, infants with BPD may be at increased risk of developing obstructive pulmonary disease in adulthood. Thus, systematic programs of lung function follow-up in clinical as well as research settings, are needed to determine the severity of long-term lung impairment and to evaluate the efficacy of medical treatments.

Airway obstruction

Several studies of children born preterm have shown more-or-less normal lung volumes in those who were healthy, but lower forced volumes in those with BPD. The reduction in forced vital capacity (FVC%) could be due to restriction of the lung and/or hyperinflation. FEV1 - the most commonly used marker of obstructive lung disease – declines slowly in progressive lung diseases such as COPD. Several follow-up studies on BPD at various ages have shown that FEV1 may lie within the normal range (>80% predicted) but be slightly lower than in healthy controls. [96, 87] Oscillometry is useful in identifying airway dysfunction e.g. bronchial obstruction, bronchial hyper-reactivity, and bronchodilator responsiveness.[97] It has the technical advantage of allowing measurements during spontaneous tidal breathing. Since it requires minimal cooperation, oscillometry is ideally suited for children younger than 5 years, who are often difficult to study by conventional spirometry. Furthermore, this method is also suitable for children with neurological manifestations that may

otherwise hamper the assessment of ventilatory function even in later stages of childhood.
The use of IOS has been described in the evaluation of children with asthma and cystic fibrosis,[98] but only infrequently in preterm-born infants and children with or without BPD. Whether oscillometry is suitable for detecting abnormalities in this patient group therefore is yet to be evaluated. Malmberg et al. studied children at school age and found high airway resistance, and high reactance in children with BPD, suggesting that oscillometry could differentiate children with and without BPD.[99]

Association to atopy and asthma

BPD is characterised by asthma-like symptoms, but whether atopy/asthma and prematurity/BPD are somehow associated is an open question. In a1980 article "Family History of Asthma in Infants with Bronchopulmonary Dysplasia", Nickerson and Taussig first reported that a family history of asthma may be associated with bronchopulmonary dysplasia (BPD) in neonates.[100] A family history of asthma has also been suggested to be predictive of more severe forms of BPD.[101] Furthermore, an interaction between family history of asthma and radiographic evidence of BPD has been described.[102] Studies have also shown that a family history of asthma is positively associated with spontaneous preterm labour, which means that parents with family history of asthma are more likely to give birth to a VLBW infant.[103, 104]

Because premature birth interrupts the development of the lungs and immune system, it could conceivably increase the likelihood of asthma developing later in life. Evidence is inconclusive on this matter at present: some studies show an increased asthma risk in children born VLBW[105, 106] whilst others do not.[107] A history of asthma by 12 years of age was twice as common amongst VLBW compared with term-born children, with neonatal oxygen supplementation the most important risk factor. Mechanical ventilation during the neonatal period was also associated with bronchial hyper responsiveness at age 12.[108]

A Swedish epidemiological twin cohort study of almost 11,000 children aged 9-12 years found the overall rate of asthma to 13.7%. This study revealed that those with a birth weight ≤1999 g had the highest rate of asthma. Asthma was also more than twice as frequent in children with GA ≤31 weeks compared with those born at term age.[109] In utero and perinatal influences may increase the risk of asthma: childhood asthma was more frequently reported by mothers with complications during pregnancy and labour, and by those whose infants weighed <2.5 kg at birth (adjusted odds ratio [ORadj] 2, 1.35, 1.57, respectively).[110]
In addition to these epidemiological studies, associations between lung dysfunction and birth weight have been confirmed in follow-up studies using a variety of methods, including spirometry (forced expiratory volume in 1 s and forced vital capacity), plethysmography (total lung capacity and functional residual capacity), and lung function and diffusing capacity measurements. [111]

Very low birth weight per se is not associated with an increased prevalence of atopy.[85, 112,113] In fact, prematurity reduces the long-term risk of atopy.[114] In a Swedish study by Mai et al. very low birth weight was not significantly related to allergic rhinoconjunctivitis, eczema or positive skin prick tests.[108] As suggested by Baraldi and Filippone[4] the term “asthma” should be used with caution because asthma and chronic lung disease are two separate clinical entities — some symptoms overlap,

but the causal mechanisms, risk factors, responses to treatment, and natural history are different.[113-116]

Structural changes

The structural description of BPD-affected lungs is largely based on autopsy specimens from those infants most severely affected. For infants with less severe BPD, little is known about the correlation between structural changes, lung mechanics and neonatal history. In recent years, follow-up studies with high resolution computed tomography (HRCT) have shown multiple abnormalities, including hyperlucent areas (88%), linear opacities (95%), triangular subpleural opacities (63%) and bullae (51%).[117-123] In the absence of bronchiectasis, linear opacities and triangular subpleural opacities probably indicate fibrosis, and hyperlucent areas may correspond to abnormal alveolar development and reduced distal vascularisation, both of which constitute the key findings in "new" BPD. Oxygen exposure was the factor most strongly associated with these HRCT abnormalities and reduced lung function, irrespective of gestational age at birth.[120,121] As suggested by Aukland, a prolonged need for supplemental oxygen may be both a marker of lung injury and a cause of further lung damage. Whatever role oxygen supplementation plays, prolonged requirements appear to be a strong prognostic indicator of subsequent functional and structural abnormalities in these infants.
Young adults aged 18–26 years born preterm and who had oxygen requirement at 36 weeks of PMA, also suffered from emphysema.[123] Because HRCT often reveals lung pathology in former BPD infants, it is likely / possible that damage to the lung parenchyma may slowly progress and eventually manifest as obstructive pulmonary diseases in adulthood/old age.

Understanding the basis of these and other pathological findings is essential for improving future medical management of this population.
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2.5.2 Developmental outcome

Neurological sequelae are more common in very low birth weight children with BPD than in those without chronic lung complications (40% compared with 6%, respectively).[124] The issue is whether this difference reflects lung disease *per se* or other complications, such as intraventricular haemorrhage (IVH) or periventricular leucomalacia (PVL). There is evidence that BPD is associated with an increased risk of brain white matter damage (WMD; odds ratio [OR] = 5.9).[125-128] It has been suggested that BPD results in more unstable oxygenation and hypoxemic and hyperoxemic episodes, which may in turn negatively influence developmental outcome.[129-132] Inflammatory processes in BPD could also impact the brain as well as the lung. It has been shown that BPD alone without the presence of IVH/PVL, has deleterious effect on early development.[133, 134]

Motor skills

Motor development is often impaired in very-low-birth weight (VLBW) infants. The prevalence of disability varies depending on the criteria used to define neurological outcome. With respect to cerebral palsy, 5% of children born VLBW are affected. Minor motor performance problems are evident in about 50% of VLBW

children.[135-138] BPD also influences specific motor functions such as hand and eye-coordination.[133] The latter may reflect a particular sensitivity to subcortical damage and/or the susceptibility of neural pathways involved in visual control of arm movements. Impaired control of voluntary, goal-directed movements of the arm and hand could be due to damage in corticospinal motor (centrum semiovale) and visual pathways (central occipital white matter).[139] The development of new techniques of brain imaging with cerebral magnetic resonance has the potential to extend our understanding of neuro functional disturbances leading to motor and mental impairment.[140]

Early detection of minor handicaps is particularly important because early intervention may improve the quality of life of affected children.[141]
Many school activities focus on teaching complex motor tasks and skills, i.e. drawing and painting, cutting with scissors, ball skills, shoelace tying, etc. Generally, motor skills are assessed with the Movement Assessment Battery for Children (Movement ABC). Sixty-four % of all children with non-optimal Movement ABC scores had school problems at 5 years. Decreased learning capacity and motor performance problems at this age may predict later learning problems in other (social, cognitive) domains, as reported by Marlow and co-workers.[142] It has been shown that BPD *per se* adversely impacts on motor performance at 3 years,[143] but also that motor deficits may be missed in standard developmental assessments of very preterm-born children at 5 years. The Movement ABC should therefore be added to the developmental assessment follow-up of all very preterm and low-birth weight children.[144] De Kleine et al. followed very pretem infants without severe handicap and found an incidence of clinically important motor disorders of 20.5% - four times the incidence within the normal population. They also reported borderline disturbances in 22.5% of infants - about twice the incidence in the normal population.[144] A general prevalence of motor impairment of 50-55% has been reported by others.[145-149]

School performance

Academic performance of children with BPD is poorer compared with preterm controls.[150] Gray et al have shown that language abilities and reading skills are most affected,[151] possibly because of the vulnerability of the brain to hypoxia. Animal studies suggest that the somatosensory cortex, including Broca's area, is particularly vulnerable to hypoxic injury.[152] Some of the problems described in school-age children with BPD may be related to hypoxic episodes that pass unnoticed e.g. during feeding.[153] Poorer academic performance by children with BPD may also reflect frequent absences from school due to hospitalization, as described by Chye et al.[154] These findings emphasize the need for greater care and support of school-age children with a history of BPD, as well as their parents.

Cognitive function

Cognitive function refers to the psychological processes involved in perception, thinking, planning and expression. It describes intelligence and knowledge, our ability to conceive and categorize our memory, consciousness and feelings. Choosing the appropriate test of cognitive function depends on the subject's age.
The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, Swedish adaptation) is often used to evaluate cognitive ability.[155] This test provides Verbal and Performance IQ scores as well as the Full Scale IQ.

Behavioural problems

Behavioural difficulties in children could lead to problems and stress that affect the entire family as well as the child. Some studies of preterm-born children suggest they have more behavioural problems (especially attention deficits) compared to term infants[156,157] whilst other studies report no such differences.[158, 159] However, to what extent pulmonary disease affects behaviour is unclear, although some authors have found small differences between preterms with and without BPD, limited to internalizing problems on the parental report.[160,161] Identifying behavioural and emotional problems at follow-up is important because prematurity may contribute to attention-deficit hyperactivity disorder (ADHD). Children with ADHD have more neonatal complications than unaffected siblings, and exhibit more behavioural (particularly attention and impulsiveness) problems.[162] The pathophysiological causes of developmental delay in infants with BPD are probably multifactorial, and may include chronic, intermittent hypoxia, growth deficiencies, and altered environmental stimulation.[163,164] There are very little data on possible associations between developmental impairment and the ***severity*** of BPD,[143,163] disregarding GA at birth.

The Child Behaviour Checklist for Ages 6 to 18 (CBCL/6-18) systematically describes overall function, and is a part of the Achenbach System of Empirically Based Assessment (ASEBA) ™, [165] It consists of an integrated set of forms for assessing competencies, adaptive functioning and problems.

Mental disorder

The scoring profiles of the CBCL have been derived from statistical analyses of patterns of co-occurring problems, and may have a screening function. The dominant system used for psychiatric diagnostics is the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[166] The DSM categories, in contrast to the CBCL profiles, are not based on standardized assessments of children. However, data from the CBCL questionnaire may be useful in arriving at a diagnosis based on the DSM scale. Studies have shown significant associations between ASEBA scale scores and the DSM diagnosis. In a longitudinal twin study, based on measures of parental-reported maturity factor and behavioural problems, it was suggested that immaturity is associated with ADHD and other behavioural problems in 8-9 years old children.[167]

2.6 LONG-TERM PULMONARY SEQUELAE

2.6.1 Obstructive pulmonary disease in old age

One of the main issues raised regarding the prematurely born infant is what happens later on in life. Survival rates of very young and very sick babies have improved dramatically in recent years. The limits of viability have been pushed-back further and further, and survival of babies weighing less than 500 gram is now common. The premature infant is at risk for lung impairment in adolescence and early adulthood, but very little is known about associations between prematurity and pulmonary sequelae in old age.[168] Recently concerns have been raised about early childhood influences on lung development in later life.[169] These include smoking in the environment both before and after birth, infection and pollution. A number of themes have emerged. Antenatal factors such as smoking, in particular, have long-term consequences both on airway anatomy[170] and the fetal immune system.[171] Gene–environment interactions are crucial and may adversely affect lung development.[172]

Recent work has focused on the genesis of COPD among people who have never smoked. Evidence suggests that COPD is largely attributable to asthma and that non-smokers with mild asthma could develop clinically significant COPD in old age. This finding is important because preterm children (especially those who develop BPD) have signs of airflow limitation as young adults. One study of mild-to-moderate asthma showed clinically significant progression of chronic obstructive pulmonary disease.[173] Of those who had never smoked but developed COPD, 88% were females and 61% had a history of asthma. Of the smokers with COPD, however, only 18% were females and 5% had a history of asthma. Others have also showed in epidemiological studies of non-smokers with obstructive lung disease, associations with female sex, older age, lower income and a history of asthma. The risk of developing COPD is estimated to be 12 times higher in an adult diagnosed with asthma compared with non-asthmatic adults.[174-177] One of few population-based studies of the effects of LBW on respiratory disease found that VLBW survivors were 83% more likely to experience hospitalization for respiratory illnesses as young adults compared with normal birth weight individuals. For moderately LBW survivors (i.e. birth weight 1,500–2,499 g), the odds were 34% higher.[178]

We need to clarify the long-term consequences of early life events, particularly the role that heroic iatrogenic interventions may play in the pathway to disease in adulthood. We then need to proceed from observational studies to clinical trials to improve health of this new generation of adults.[179]

3 AIMS

The aims of this thesis were to improve our understanding of BPD from early life into old age. My particular interest has been to investigate non-invasive ways to improve the pulmonary care of preterm infants. Two additional questions addressed in the course of this thesis were: (i) could similarities between symptoms exhibited in asthma and BPD be partly due to early activation of the eosinophil pathway during the neonatal period? (ii) could BPD lead to an increased risk of respiratory obstruction and pulmonary disease much later on, in old age? Because BPD is a multisystem disease, lung function must not be studied in isolation - the impact on psychomotor outcome must also be evaluated. The specific aims of this thesis were:

- To gather proof-of-principle that non-invasive administration of nebulized surfactant during nasal CPAP treatment of IRDS improves lung function and oxygenation, as a basis for further investigation on how to prevent BPD.

- To test the hypothesis that eosinophil activation in preterm neonates is associated with BPD development.

- To determine whether early signs of atopy are more common in children born preterm with BPD.

- To determine whether there are associations between preterm birth and BPD, and signs of obstructive pulmonary disease in school-age-children and in old adults.

- To evaluate how the severity of BPD is associated with later airway obstruction and psychomotor outcome.

4 METHODS

4.1 STUDY POPULATION

- All studies were based on cohorts of preterm infants born in Sweden.
- The BPD-definition differed between the studies: the need for supplemental oxygen at 36 weeks of PMA was used in papers I and II, and the need for extra oxygen for more than 28 days was used in papers III and IV.

4.2 PAPER I

Thirty-two infants diagnosed with RDS from six Swedish neonatal units were randomized to treatment with nebulized surfactant, or to a control group, which did not receive surfactant (16 infants in each group). All infants were treated with CPAP. Surfactant (480 mg) was aerosolized in 34 ml NaCl, and administrated during 3 hours. The controls received standard care with CPAP.

4.3 PAPER II

Fifteen infants with BPD born in the referral area of the Söder Hospital were enrolled in this study. We compared these infants with 29 control preterm infants (<33 weeks gestation) born at Söder Hospital. Within this control group, 13 infants developed RDS (the "RDS" group), while 16 had no or only respiratory problems (the "healthy" group). Venous blood samples were collected from all infants at age 4 weeks. In addition, for those with BPD, blood samples were taken 2 weeks after the initiation of steroid inhalation treatment and again at a corrected age of 40 weeks. The total amount of peripheral eosinophils and neutrophils, serum-ECP and the eosinophil activation markers EG2 and CD9 was assessed.

4.4 PAPER III-IV

The study group consisted of 60 VLBW children, 28 with RDS who did not develop BPD, and 32 with RDS and BPD.
Paper III: pulmonary parameters were investigated with a health questionnaire, spirometry, impulse oscillometry, CT-scan, blood test for atopy, and immunology.
Paper IV: psychomotor and neurodevelopment function was measured by testing IQ, child behaviour and motor performance.

4.5 PAPER V

The source population for this cohort study was all births from 1925 to 1949 at four major delivery units in Sweden. We manually examined the approximately 250,000 births records during this period. We identified an exposed cohort by selecting all newborn infants with a gestational duration < 35 weeks and/or a birth weight < 2,000 grams for girls and <2,100 grams for boys. As unexposed cohort members, we selected subjects who were neither born preterm nor low birth weight. We selected the first child of same sex and hospital of birth born after each exposed subject. At the

commencement of follow up, there were 6,425 subjects in the cohort; of these, 2,931 were born preterm (<37 weeks), and 986 were born at 32 weeks or less.
Follow-up of hospital care for Asthma and COPD commenced on January 1st, 1987 and continued until December 31, 2006. The diagnoses were determined from the Hospital Discharge Registers.

4.6 METHODS

Cell membrane fixation and permeabilisation

The peripheral blood leukocyte preparations were treated with a membrane permeabilisation technique. This procedure separates eosinophils from neutrophils, permitting analysis of intracellular ECP and surface CD9 expression by flow cytometry.

Analysis by flow cytometry

The various leukocyte preparations were analysed and counted in a Flow Cytometer. In the flow cytometer cells are distinguished by their different light scattering properties, size and complexity/granularity. In the present study, we identified three separated leukocyte clusters in pre-treated blood samples: lymphocytes, neutrophils + monocytes, and eosinophils.

Impulse oscillometry

IOS, was used to measure the input impedance of the respiratory system. The output pressure and flow signals were analyzed for resistance (Rrs) and reactance (Xrs), the two components of the respiratory impedance (Zrs). Reactance is characterized by negative values i.e. the more negative the value, the more pronounced is small airway dysfunction. The resonance frequency (fres Hz; the frequency at which Xrs is zero) was also calculated. The advantage of this method is that it measures lung function during normal tidal breathing. Furthermore, because only minimal cooperation from the patient is required, it is particularly suitable for evaluating children.

Dynamic spirometry

Dynamic spirometry to produce flow-volume curves was performed using a pneumotachograph (Vitalograph), directly after the IOS measurement. The method is well known and easy to use. The equipment is inexpensive. The disadvantage of this method is that the patient must co-operate, which makes it unsuitable for use with children.

Reversibility test

The patient inhaled 5 mg salbutamol via a nebulizer (Ailos, Sweden). Fifteen minutes after administration of the b2-agonist, IOS and spirometry was repeated.

Movement Assessment Battery for Children

The Movement Assessment Battery for Children (Movement ABC) identifies and assesses difficulties in child motor development. The assessment is arranged in three sections: manual dexterity, ball skills and balance. The test is suitable for ages 4-12 years.

WPPSI-R

Cognitive ability is assessed via the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R, Swedish adaptation).[156] The WPPSI–R provides Verbal and Performance IQ scores as well as the Full Scale IQ.
The purpose is to assess in brief the general intellectual function of children aged 3-7 years. An IQ of 85-115 is considered normal range, 71-84 as subnormal and <71 as impaired. Generally, in most samples of children, there is a positive correlation between the Verbal IQ and the Performance IQ.

CBCL

The CBCL/6-18 obtains reports from parents, other close relatives, and/or guardians regarding a child's competencies and behavioural/emotional problems. Parents provide information for 20 competence items covering their child's activities, social relations and school performance. The report includes 118 items describing specific behavioural and emotional problems, plus 2 open-ended items for reporting additional problems. A criticism levelled at this method is that it covers some sensitive issues.

4.7 STATISTICAL METHODS

The statistical methods used in this thesis are described separately, in each paper.

Differences between groups were tested using Kruskal-Wallis analysis of variance and displayed graphically as Box-and-Whisker plots. The correlation between measurements was analyzed using linear regression analysis.
Multiple regression analysis was used to analyze the influence of a variety of independent risk factors. A forward stepwise regression was carried out to find factors that significantly contributed to variance.

P-values of <0.05 were considered significant.

4.8 ETHICAL CONCERNS

All studies were approved by the regional ethics committee of the Karolinska Institute, Stockholm, and by the local ethics committees of each participating hospital. Parents were fully informed about the purpose and procedures of the studies, and written informed consent was obtained.

One concern is whether it is ethical to use these methods to identify anomalies that may have implications for the future of a child. This can cause anxiety for children and parents alike. Investigations that identify dysfunction may lead, on the other hand, to better treatment and preventative advice and care.

5 RESULTS

5.1 SUBJECT CHARACTERISTICS

Perinatal characteristics of children in papers I-IV are shown in Table 1.

	Paper I	Paper II	Paper III & IV
Number of subjects	32	44	60
Age at study entrance	2-36 h	At birth	75,5 months
Gestational duration, weeks	31	29	28
Gestational range, weeks	27-34	24-32	24-32
Birth weight, gram	1615	1331	1130
Birth weight, range	755-2855	624-2130	597-2094
Gender, male, n (%)	11 (34)	24 (54)	36 (60)
Mechanical ventilation, n (%)	11 (34)	9 (20)	40 (67)
CPAP, n (%)	32 (100)	28 (64)	57 (95)
Prenatal steroids	24 (75)	38 (86)	38 (63)

Table 1. Perinatal characteristics of children in Paper I – IV.

5.2 PAPER I

A randomized control study of inhalation with surfactant to preterm infants with RDS.

Thirty-two infants diagnosed with RDS from six Swedish neonatal units were randomized, either to treatment with nebulized surfactant via nasal CPAP, or to a control group treated only with CPAP.

Both groups included in the study were similar with regard to gestational age, birth weight, steroids given before birth, sex, Apgar scores, and a/A PO_2 on entering the study. There was a trend towards a lower a/A PO_2 (not significant; Figure 1), but no differences between the number of infants needing mechanical ventilation, or duration on ventilator or CPAP. Two children in the treated group developed bronchopulmonary dysplasia. No side effects of the surfactant therapy were noted.

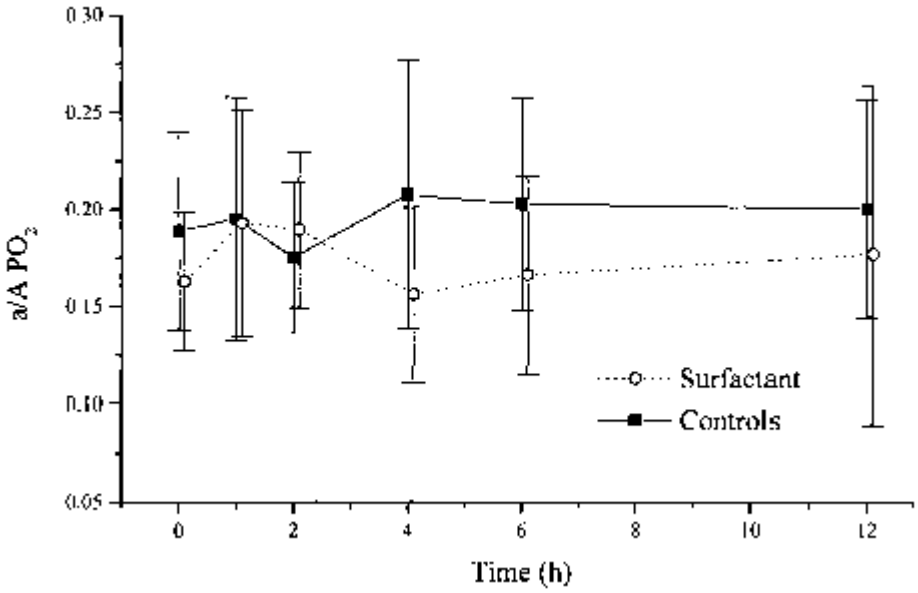


Figure 1. a/A PO2 in newborns with RDS treated with nebulized surfactant and in controls (mean±SD).

5.3 PAPER II

This was a prospective study (to term age) of eosinophil activation in preterm infants with RDS, BPD, or transient respiratory disease.

Fifteen infants with BPD were compared with 13 infants with RDS and 16 healthy preterm infants. Venous blood samples were collected from all infants at age 4 weeks. In addition, for the BPD group, blood samples were taken 2 weeks after the initiation of steroid inhalation treatment and again at a corrected age of 40 weeks. The total amounts of peripheral eosinophils and neutrophils, serum-ECP and the eosinophil activation markers EG2 and CD9 were assessed.

Eosinophil activation was present in BPD children, with high levels of eosinophils and ECP and low levels of CD9 (Table 2). These differences were not explained by variations in age or weight at birth. There was a significant positive correlation between ECP and EG2 for RDS and healthy infants, but not for infants with BPD. The BPD infants could be divided into two distinct subsets, one with relatively low EG2 values and normal ECP values, and the other with low EG2 values and abnormally high ECP values. Interestingly, the latter group all required supplemental oxygen for more than 50 days. For both groups of infants, a significant negative correlation was found between EG2 levels and the duration of the O_2 treatment.

	RDS	BPD	Healthy	p value	Difference
Eosinophils PBE/μL	797 (269–3056)	1414 (383–4353)	471 (184–2020)	0.03	BPD≠RDS=Healthy
ECP μg/L	12.8 (3.9–44)	34 (7.1–89)	9.8 (4.2–29)	0.002	BPD≠RDS=Healthy
EG2 MFI	27.4 (14.9–45.7)	22.9 (19.7–35.4)	29.9 (18.1–49)	0.09	ns
CD9 MFI	94 (66.5–118.2)	74.5 (64.3–99.6)	86.2 (31–125.8)	0.01	BPD≠RDS=Healthy
Neutrophils	11.8 (8.7–18.0)	13.6 (6.7–19.9)	9.8 (7.0–18.2)	0.12	ns

Data depict median (min–max). The eosinophil count and ECP levels were higher and CD9 levels lower in BPD infants compared with RDS infants and healthy preterms.
≠ depicts statistically significant difference.

Table 2. Immunological expressions of eosinophil activity at 4 weeks of postnatal age.

BPD infants commenced inhalation steroid therapy at age 4 - 6 weeks, and showed a significant decrease in the eosinophil count, the percentage of eosinophils, and the ECP levels after 2 weeks The EG2 levels increased, while CD9 levels and the neutrophil count remained unchanged (Figure 2a and b):

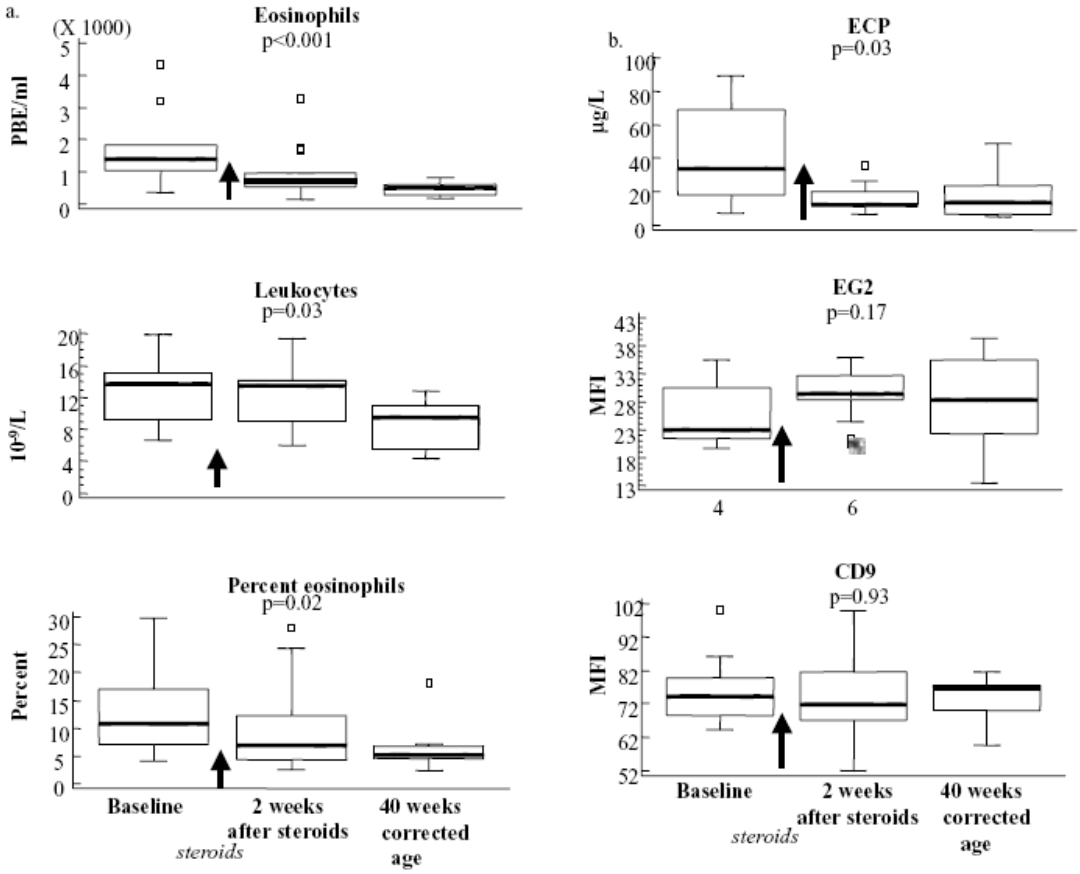


Figure 2 (a and b). Time course of changes in eosinophil activity markers in BPD infants. There was a significant decrease in eosinophils, percent eosinophils and ECP after the initiation of treatment with steroids. Arrows show initiation of treatment with steroids.

5.4 PAPER III-IV

This was a follow-up study at 6-8 years of age of children born prematurely with varying severity of respiratory disease. We evaluated pulmonary parameters and psychomotor development.

The study group consisted of 60 VLBW children, 28 with RDS who did not develop BPD, and 32 with RDS and BPD.
Paper III: pulmonary parameters were investigated via a health questionnaire, spirometry, impulse oscillometry, CT-scan, blood test for atopy, and immunology.
Paper IV: psychomotor function and neurodevelopment was evaluated by testing IQ, child behaviour and motor performance.

Paper III

Lung function
There were significant differences between preterm, non-BPD group and children with mild-moderate and severe BPD for all parameters tested by spirometry. Figure 3 shows the results for all four groups.

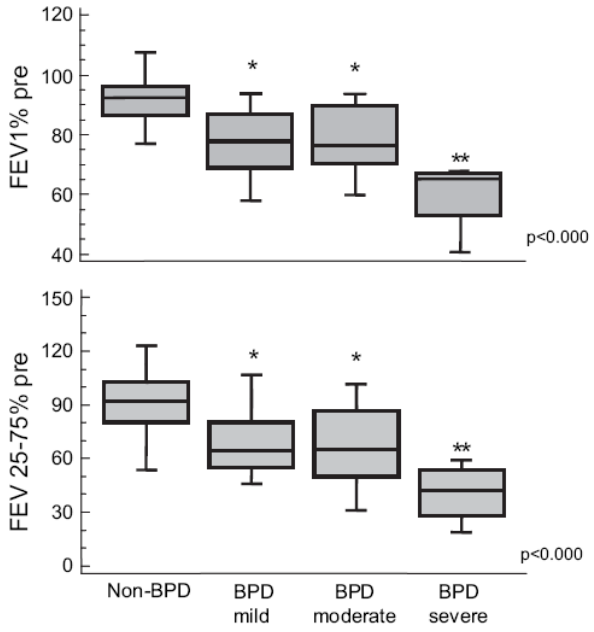


Figure 3. Spirometric measurements of FEV1% predicted and FEV25e75% predicted values in children at school age who suffered from different grades of neonatal lung disease. Notice the pronounced differences between the groups.

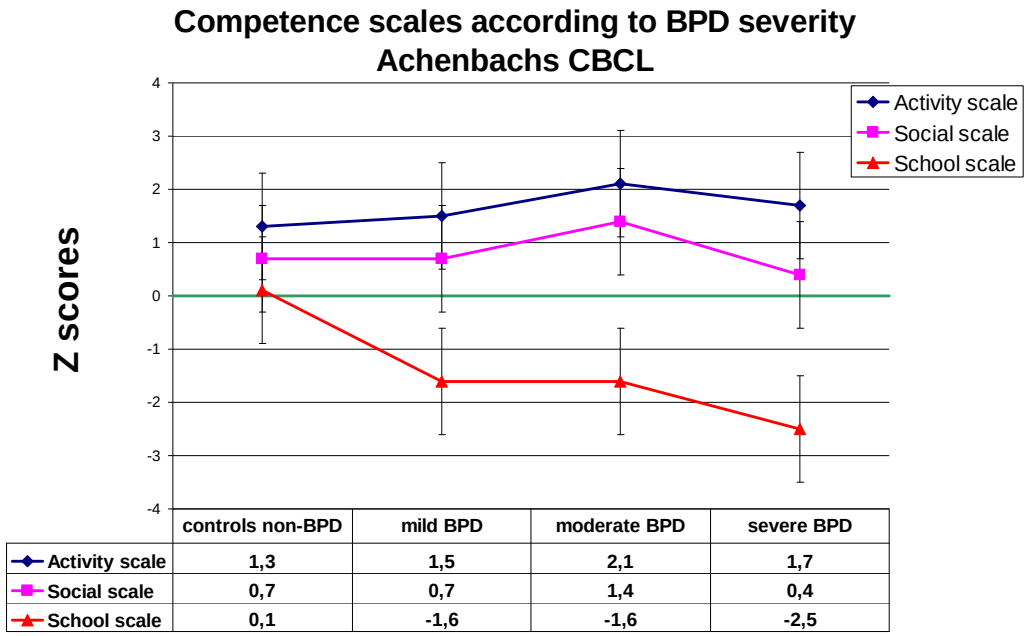
Significantly more children with BPD had an FEV1 below 80% predicted. Only 8/19 of these children described respiratory symptoms. In general, for children with severe BPD, there was evidence of deterioration in lung function in all parameters tested. Children exposed to second hand smoke had a significantly lower FEV1% pred, FEV1, FVC, and FVC % compared with non-exposed children. Respiratory reactance (Xrs5 and Xrs10) was also significantly higher in smoke-exposed children. There was a correlation between the results of spirometry and oscillometry. There was a correlation between low FEV1% pred and low levels of IgG, but no correlation between FEV1% pred and other immunological parameters.

HRCT
Of the 26 children assessed by CT scan, 19 children had abnormal scans and 11 of these had an FEV1 < 80% pred. Changes were also evident in children with mild BPD.

Paper IV:

Motor performance and IQ
Infants with BPD scored lower on tests of motor skill, due mostly to impairment of fine motor skills. The severe BPD group also exhibited more problems with balance. BPD was the strongest independent predictor of motor function, contributing 8.3-15.8% to total variability. Total IQ did not differ significantly between the non-BPD and BPD groups.

Competence
The grade of BPD was strongly associated with risk for increased school difficulties shown by the need for extra support in school, and by the CBCL school scale (Figure 4).



	controls non-BPD	mild BPD	moderate BPD	severe BPD
Activity scale	1,3	1,5	2,1	1,7
Social scale	0,7	0,7	1,4	0,4
School scale	0,1	-1,6	-1,6	-2,5

Figure 4. Competence scales in CBCL with activity, social and school scale.

Behaviour

According to parent CBCL reports, the mean *z* score for the whole study population was significantly higher than the population norms for anxious/depressed behaviour, 0.70 (*P* < .001); for social problems 1.35 (*P* < .001); for thought problems 3.1(P< .001), and for attention difficulties, 0.96(P = .001). There were significant differences between mean z scores for behavioural problems of the BPD and non-BPD groups, both in delinquent behaviour 0.7 vs. -0.3, (P =.02), and attention difficulties (P =.03) (Figure 5). Significant difference emerged between the groups with different grades of BPD and the non-BPD group regarding aggression and attention. Boys in the BPD-group showed more externalizing problems than girls.

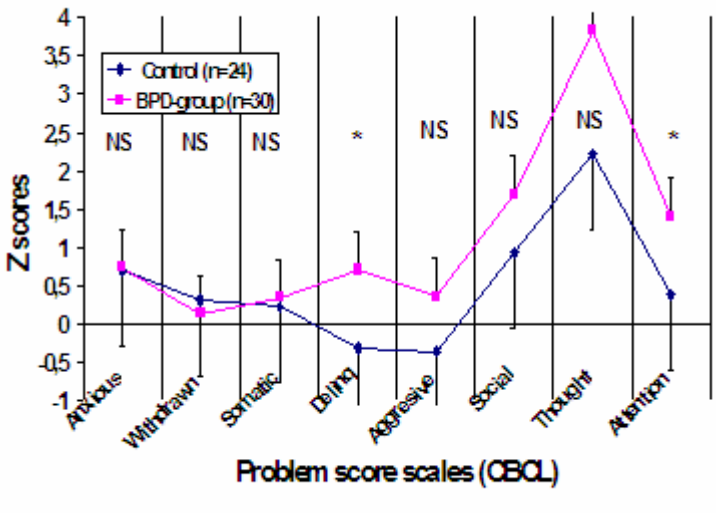


Figure 5. Children with BPD compared to preterm children without BPD (controls).

Diagnostic oriented syndromes

Analysis was performed on each of the six behavioural scales from the DSM-IV-R-oriented syndrome scales of the CBCL, and the three main CBCL scales of problem domains (internalising, externalising and total problem scales). The analyses revealed significant group differences on 2/ 6 DSM-IV-R-oriented syndrome scales of the CBCL (conduct and opposition-defiant behavioural problems; Table 3). This finding suggests the persistence of significant behavioural problems in these domains in BPD children after controlling for full scale IQ, gestational age, gender, and total motor scores assessed by movement ABC.

	BPD-group (n=30) **Mean (SD)**	**Preterm control (n=24)** **Mean (SD)**	**F ratio**	***P value***	**Effect size[a]**
Parent report (CBCL) Problem scores					
Total problem scores	26.5 (26.4)	18.6 (14.5)	.30	.59	.01
Internalizing scores	6.5 (6.8)	6.8 (5.7)	1.44	.24	.03
Externalizing scores	7.7 (9.6)	3.6 (3.8)	.01	.94	.00
DSM-oriented syndrome scales *(CBCL)*					
Affective problems	2.5 (3.3)	1.8 (1.9)	.97	.33	.02
Anxiety problems	1.8 (2.2)	1.2 (1.7)	.01	.91	.00
Somatic problems	.6 (.91)	.6 (1.1)	.01	.92	.00
ADHD problems	3.7 (4.3)	1.8 (2.6)	.05	.82	.00
Conduct problems	**4.9 (4.8)**	**.6 (1.2)**	**6.4**	**.015**	**.12**
Oppositional Defiant problems	**3.9 (2.5)**	**1.5 (1.7)**	**5.3**	**.026**	**.10**
Competence scale (CBCL), *z* score					
Activities scale	1.7 (1.1)	1.3 (1.3)	3.6	.06	.07
Social scale	.6 (1.5)	.7 (1.0)	.04	.85	.00
School scale	**-1.6 (2.2)**	**.08 (1.0)**	**8.1**	**.006**	**.15**

TABLE 3. Parental Reports on Behavioural Problems of Preterm children with BPD and Preterm controls without BPD at 6-8 Years of Age, and Adjusted Mean Scores for Competence Scales.

Poor motor skills were highly associated with BPD, the ADHD problem scale, the oppositional-defiant problem scale, and with poor school performance. Further interrelations are shown below (Figure 6).

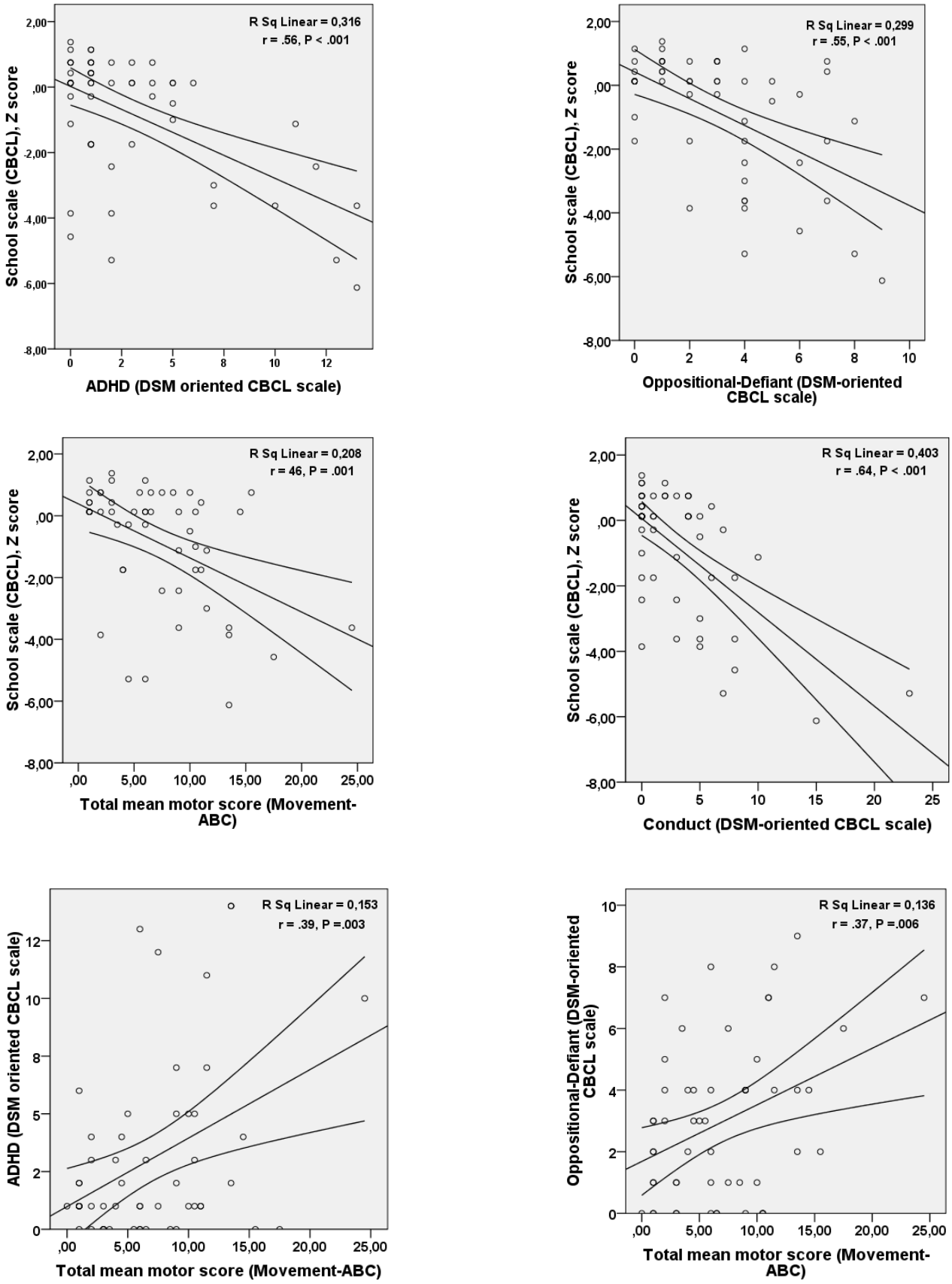


Figure 6. Interraltionship between Functions.

5.5 PAPER V

This study was a population-based survey of obstructive lung disease in old age amongst those born prematurely.

The source population for this cohort study was all births from 1925-1949 at four major delivery units in Sweden. At the commencement of follow up, there were 6425 subjects in the cohort, of whom 2931 were born preterm (<37 weeks), and 986 were born at a gestation of 32 weeks or less.
Follow-up of hospital care for Asthma and COPD started on January 1st, 1987 and continued until December 31, 2006. The diagnoses were determined from the Hospital Discharge Registers.

During follow up, 177 subjects were hospitalized with a principal diagnosis of an obstructive airways disease. Of these, 122 had COPD as the principal diagnosis and 45 had a principal diagnosis of asthma. Low birth weight was a risk factor for disease. A birth weight of 1500 - 1999 grams was associated with an almost twofold greater risk of any obstructive airways disease. When analyzing the underlying causes of low birth weight (i.e. preterm birth versus poor fetal growth), we found a negative association between gestational duration and risk of airways disease. For fetal growth, the association with risk was U-shaped rather than linear (Table 4).

	All			Men			Women		
	# cases	HR*	95% C.I.**	# cases	HR*	95% C.I.**	# cases	HR*	95% C.I.**
Birth weight									
<1500	6	2.34	(0.96-5.70)	1	0.81	(0.11-6.08)	5	4.57	(1.43-14.6)
1500–1999	30	1.86	(1.10-3.15)	12	1.57	(0.76-3.24)	18	2.79	(1.15-6.73)
2000–2499	23	0.97	(0.55-1.70)	12	0.80	(0.39-1.64)	11	1.45	(0.55-3.77)
2500–2999	27	1.40	(0.82-2.41)	16	1.22	(0.63-2.38)	11	1.89	(0.72-4.93)
3000–3499	26	1	reference	19	1	reference	7	1	reference
3500–3999	26	1.07	(0.62-1.84)	21	1.11	(0.60-2.07)	5	0.89	(0.28-2.81)
>=4000	12	1.13	(0.57-2.25)	11	1.32	(0.63-2.79)	1	0.39	(0.05-3.16)
P for trend:			0.046			0.87			0.0004
Gestational weeks									
<32	31	1.48	(0.96-2.27)	11	0.92	(0.48-1.77)	20	2.77	(1.39-5.54)
33–36	50	1.23	(0.85-1.78)	29	1.06	(0.67-1.68)	21	1.95	(1.00-3.83)
37–42	65	1	reference	50	1	reference	15	1	reference
>=43	4	0.79	(0.29-2.19)	2	0.59	(0.14-2.45)	2	1.44	(0.33-6.31)
P for trend:			0.047			0.84			0.0052
Fetal growth SD									
≤-2	20	1.91	(1.15-3.18)	8	1.27	(0.59-2.72)	12	2.98	(1.44-6.13)
> -2 to -1	24	1.42	(0.89-2.29)	14	1.26	(0.69-2.32)	10	1.76	(0.82-3.77)
> -1 to +1	60	1	reference	40	1	reference	20	1	reference
> +1 to +2	22	1.70	(1.04-2.77)	17	1.85	(1.05-3.28)	5	1.15	(0.43-3.12)
> +2	24	1.54	(0.96-2.48)	13	1.25	(0.67-2.35)	11	1.95	(0.91-4.15)
P for trend:			0.93			0.44			0.27
Total	150			92			58		

Table 4 . Risk of obstructive airways disease by sex, birth weight, gestational duration, and fetal growth.

Stratifying by sex revealed different risk patterns for women and men. There was no significant association between birth weight and risk for males, but a more than fourfold greater risk of obstructive airways disease for women born <1500 grams compared with women whose birth weight was 3000 - 3499 grams. Likewise, preterm birth was a strong risk factor for obstructive airways disease among women but not among men (Table 4).

When analyzing COPD and asthma separately, low birth weight was a risk factor for COPD as well as asthma. For asthma, there was a significant trend for increasing risk with decreasing birth weight. Different risk factor patterns were evident for gestational duration and fetal growth. For COPD, there was no consistent association between gestation and risk, whereas short gestation was a strong risk factor for asthma. Both low birth weight and short gestation were strong risk factors for asthma among women but not among men. A statistical test for interaction revealed no significant heterogeneity between males and females for birth weight or gestation.

We found no increase in risk for lung cancer among subjects born preterm or with poor fetal growth. On the contrary, there was a statistically significant positive association between lung cancer and birth weight as well as gestation.

6 DISCUSSION

Surfactant nebulization-no beneficial effect

Non-invasive administration of surfactant is one potentially important way of reducing and minimizing the mechanical trauma associated with treating the critically ill newborn. In the present study (*paper I*), we investigated whether surfactant can be administered as an aerosol delivered via the Infant Flow CPAP system, avoiding the need for intubation. We were unable to demonstrate any beneficial effects of this alternative mode of treatment, either immediately during the period of nebulization, or subsequently in outcome. Amongst babies randomized to receive surfactant aerosol, values for a/A PO_2 and arterial pH at entry were slightly lower than in the control group, a difference that persisted throughout the study period. Although the difference was small, it could nevertheless have masked a potentially subtle beneficial effect of this mode of surfactant administration. The apparent lack of effectiveness could also being partly due to loss of aerosolized material in the nasal CPAP device. The amount of surfactant reaching and retained in the lungs might therefore be too low to compensate for the underlying deficiency, or to counterbalance the surfactant inhibitors present in the airspaces. An alternative but perhaps less likely explanation is that nebulization interferes with the quality of the surfactant material administered. Although the number of subjects was small, the strength of the study was that we used a randomized control approach to evaluate this novel therapy, Similar, disappointing results were reported when different nebulization set-ups were compared in two other studies.[180, 181]

Successful treatment of RDS by aerosolized surfactant using a jet nebulizer and delivery of the aerosol via a nasopharyngeal tube has been reported.[182] The INSURE method, which involves a short period of intubation to administer surfactant followed by extubation to CPAP,[40] has minimized the time on mechanical ventilation but invasive intubation is still required.

The clinical importance of using minimally traumatic methods to administer surfactant was demonstrated by a recent multicenter study, which evaluated surfactant delivery via a thin endotracheal catheter. Subjects in this study were VLBW infants breathing spontaneously on CPAP (2010), and the results obtained were impressive.[183] Although the infants receiving the novel therapy were more immature than those receiving the standard treatment, the mortality rate, need for mechanical ventilation and oxygen at discharge, and number of infants with BPD were all significantly lower in the former. These findings emphasize the importance of improving on current techniques to administer aerosolized surfactant and ensure its spread to the distal airspaces during spontaneous breathing.

Activated eosinophils

The purpose of this study (*paper II*) was to compare eosinophil acitvity of healthy preterm born infants and those with RDS and BPD during the neonatal period. We demonstrated that the eosinophil count was elevated in infants with BPD compared with their counterparts who were healthy or with RDS. We also found evidence of eosinophil activation associated with BPD (increase in ECP levels and decrease in EG2 and CD9 levels). Eosinophil activation, as indicated by ECP levels at age 4 weeks, was positively correlated with the duration of supplemental oxygen therapy in infants with BPD. Furthermore, the eosinophil count fell promptly once steroid treatment was initiated, as occurs during steroid treatment of other eosinophil-driven

diseases. We did not, however, find any association between eosinophil counts and ECP levels, as reported by others.[72] A plausible explanation for this discrepancy is that the eosinophils in our BPD babies were more highly activated. Overall, our findings suggest that eosinophilia may play a role in the pathogenesis of BPD.

The only published study of eosinophil involvement in neonatal BPD showed, as we did, that infants with BPD had an elevated peripheral eosinophil count that correlated with the ECP level. There was, furthermore, a strong correlation between eosinophil levels in the periphery and intratracheal aspirates.The peripheral eosinophils therefore appear to be activated in sick premature infants, which may in turn correlate with the severity of BPD. [72]
At school age, children with BPD have asthma-like symptoms. It is not yet clear whether this is due to chronic inflammation and increased bronchial responsiveness and bronchial lability, as occurs in asthma. The ECP concentration in peripheral blood was significantly higher in schoolchildren born very preterm compared with controls. Since ECP is considered to be a sign of activation of eosinophils involved in airway inflammation, inflammation may be present even in school-age children born pre-term.[1884 185]
Furthermore, it has been suggested that eosinophil activation during the neonatal period is a response to bacterial antigens.[186] Antigen-mediated eosinophil activation could trigger a toxic inflammatory eosinophil response, contributing to the development of BPD.

Psychomotor and behavioural impairment

Our findings in *paper IV* reveal that BPD affects psychomotor development and behaviour. We showed that BPD was the strongest independent predictor of motor dysfunction, contributing 8.3-15.8 % of the overall variability (Table 5). Tasks requiring fine motor skills and balance were the most severely affected.

Logistic regression analysis of poor or borderline motor outcome according to the Movement ABC (n=60)

	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
BPD mild, moderate, severe	11.5* (2.3-56.6)	13.2* (2.4-74.4)	13.7* (2.4-77.5)	9.6* (1.3-72.7)	9.0* (1.5-53.2)	12.2* (1.9-76.6)	15.8* (2.6-97.2)	8.3* (1.4-49.8)
Smoke in home environment		5.6* (1.4-22.9)	4.6 (0.8-26.8)	5.4* (1.3-22.2)	6.4* (1.5-27.9)	5.2* (1.1-24.6)	6.7* (1.6-28.6)	5.1* (1.2-21.6)
Smoke during pregnancy			1.4 (0.2-8.8)					
Gestational age <28w				1.6 (0.3-8.1)				
Birthweight <1000g					3.4 (0.8-14.7)			
ROP stage 3 or 4						1.2 (0.2-6.9)		
IVH grade 1-2							3.5 (0.6-21.5)	
Sepsis								3.2 (0.7-13.5)

Variables entered in the equation: together with BPD mild moderate severe and Smoke in home environment was gestational age less than 28 weeks, birthweight less than 1000g, retinopathy of prematurity (ROP) stage 3 or 4, intraventricular haemorrhage grade 1-2 and sepsis in the neonatal period respectively.

Table 5.

Our findings agree with published data showing that the respiratory problems are associated with poor (low) performance scores on the Movement ABC.[187-191]
The fact that fine motor skills seem to be most affected is particularly interesting. Because performance in this assessment depends on eye-hand coordination, low scores may reflect sub-cortical damage, visual impairment, or damage to the visual neural pathways in the white matter.[192] Visual abnormalities not only affect perception, but also indirectly affect the development of motor control. We showed, in addition, that there was a significant association between impaired motor function, competence, and behavioural problems.

The extent to which premature birth contributes to behavioural and emotional problems at school age is still largely unknown. The risk of behavioural problems, such as attention deficit hyperactivity disorder, is reportedly 2·6–4·0 times greater in very preterm infants in early childhood.[193-196]

The total population in our study showed more signs of anxiety / depression, and more social, cognitive and attentional deficits than the normal Swedish population. Children with BPD also showed more signs of delinquent behaviour, attention difficulties and were more aggressive than non-BPD children. Boys with BPD exhibited more externalizing problems than did girls with BPD. The most commonly described behavioural deficit of the preterm-born child is a tendency to internalize, to become withdrawn and anxious, and to report frequent somatic complaints. An unusual (up to 11-fold higher) rate of depression has also been reported in these children.[134, 197-199]

The underlying cause remains unknown. It has been suggested that cognitive deficits, environmental factors and gender-associated difficulties may all contribute to poor self-esteem in BPD children.[200]

A more likely explanation is that pre- and post-neonatal events in combination with hypoxic and inflammatory processes adversely affect the development of the vulnerable, immature brain. This hypothesis receives support from MRI studies showing white-matter damage (WMD), a marker for risk of moderate and severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory impairment. Gray-matter abnormalities also occur but to a less extent. BPD is associated with an increased risk of WMD probably because of shared risk factors and causal pathways.[128] Technical advances in MRI techniques may soon allow us to identify early structural neurological lesions associated with subsequent neurodevelopment risk, ultimately improving the prognosis for individual children.[201-203]

The increased incidence of motor and developmental difficulties has also had a significant impact on school performance. We demonstrated that significantly more children in the BPD group had school difficulties compared with the non-BPD group (paper IV). Logistic regression analysis after adjusting with full scale IQ, gender, gestational age and motor skills, revealed that the grade of BPD was strongly and positively associated with an increased risk of school problems (Table 6).

Independent variable	0R	95% CI	P value
BPD (grade)b	6.9	1.6 – 30.4	0.01
Sex (male vs female)	5.6	0.78 – 39.5	0.09
Motor score (M-ABC)c	0.9	0.68 - 1.2	0.38
Full scale IQd	0.9	0.84 - 0.98	0.01
Gestational age (weeks)	1.6	0.76 – 3.3	0.23
Birth weight (g)	1.0	0.99 - 1.0	0.05

Table 6. Multivariate-Logistic Regression Analysis of Correlates of School difficulties. Children (N = 54).

Saigal and colleagues showed that 72% of adolescents of birth weight <750 g, 53% within the 750–1000 g range, and 13% with normal birth weight (controls) had school difficulties, and that these were more prevalent in boys.[204]

In contrast to other studies, our study population had a normal IQ, with no difference between those with and without BPD.
Lung disease is by some authors considered a risk factor for cerebral palsy and thought difficulties. Moreover, BPD increases the risk for language delay, visual-motor impairment, academic difficulties, memory deficits, executive dysfunction, attention and behavioural problems.[83]

The difficulties described above seem to persist into adolescence and early adulthood. Compared with parents of control adolescents, parents of preterm-born children report more cognitive difficulties in sons, whilst daughters show evidence of more anxiety/depression, withdrawal, and poor attention.[205, 206] The self-image of young adults born preterm was not, however, different from controls.[205]

It is consequently crucial to take into account respiratory outcome in the long-term follow-up of BPD infants to school age and beyond. Evidence increasingly points to a link between early lung function abnormalities and respiratory outcome later in life.[207, 208]

Pulmonary sequelae

In a follow-up study of school-age children (*paper IV*) we found evidence of impaired lung function in those with BPD. Forced vital capacity (FVC % predicted) was within the normal range for the ‘‘control’’ preterm born children, but was significantly reduced in those with mild to severe BPD. This finding is consistent with published data showing more-or-less normal lung volumes in healthy prematurely born children but slightly lower forced volumes in those with BPD. The reduction in FVC% could be due to restrictive lung disease or lung hyperinflation. FEV1 - the most commonly used marker of obstructive lung disease - deteriorates slowly in progressive diseases such as COPD. Several follow-up studies of BPD at various ages have shown that although FEV1 may lie within the normal range (>80% predicted), it tends to be slightly lower than in healthy controls.[95, 96] We found that the FEV1 was significantly reduced in children with BPD. More importantly, at age 6-8 years, half of the children with BPD had an FEV1 below the normal range, compared with only one-sixth of the non-BPD group. This finding is consistent with data from others showing that BPD is associated with mild-to-moderately reduced lung function in early adulthood.[86]

Although lung function impairments were most pronounced in severe BPD, preterm children with mild-to-moderate BPD also differed significantly from those without BPD. This is a new and unexpected finding in a school-age cohort. Although one study has shown that lung function at term-age reflects the severity of BPD,[209] most other follow-up studies either excluded children with mild BPD or combined them with preterm non-BPD children. Our data indicate that that this latter approach is incorrect. Children with mild BPD must not be neglected, and must receive the same careful follow-up that those with more severe BPD receive. Another important finding is that despite the fact that the majority of children with BPD had an FEV1 below 80%, less than half of these children reported respiratory symptoms.

Respiratory follow-up must therefore include an objective assessment of lung function.

Pulmonary function testing is an important component of the clinical follow-up of all children born preterm, but particularly for those with BPD. Thorough follow-up should include lung function tests, and a description of the severity of symptoms and response to medical treatment with bronchodilatators. One of the problems associated with lung function measurements of the very young is that most methods require sedation and experienced, well-trained staff. An alternative method which we evaluated - impulse oscillometry (IOS) – has two advantages: it can be used in infants as young as 2-3 years, and requires no sedation. The equipment is easy to use, and testing can be done during normal tidal breathing. Our results indicate that it provides clinically useful information. We found evidence of high resistance and high (i.e. more negative) reactance in children with BPD. We also showed that reactance at low frequencies is a highly sensitive marker of lung dysfunction in prematurely born children, and may in fact differentiate the severity of BPD. These findings are consistent with published data that indicate oscillometry is useful in differentiating children with and without BPD.[99]
In view of the close agreement between IOS and spirometry as reported by both our and Malmberg's studies, we conclude that IOS is a diagnostically useful alternative to spirometry for evaluating lung function in very young, "uncooperative" subjects. Because pulmonary function testing with spirometry and/or oscillometry is relatively inexpensive and simple to perform, it should be included in the follow-up of all children with BPD.[210]

The need for systematic, functional respiratory follow-up of former BPD children is urgent in view of the potential long-term sequelae. At present, very little is known about respiratory function in adulthood and old age of those born preterm. There is concern, however, that survivors of BPD may be more susceptible to developing chronic obstructive pulmonary disease (COPD).[88, 113]

In a population-based study (*paper V*), we found that low birth weight is, in fact, a risk factor for obstructive airways disease in old age. This increase in risk is associated both with preterm birth and with poor fetal growth. We also found preterm birth to be a strong risk factor for asthma amongst women but not men, suggesting different risk factor profiles for each sex.
Ours was a unique study with long-term perspective into old age. The study cohort was born in the 1920-1940´s. Consequently, it differs significantly from the preterm population today. In general, infants surviving in the 2000´s are born earlier, are much more immature, and are more seriously ill as neonates. The concern is that today's preterm infants will perform more poorly in old age than the population we have described in our epidemiological study. The increase in iatrogenic lung side effects resulting from advances in treatment may further influence long-term lung function. Technological developments today ensure the survival of more and more infants who, until recently, were not viable. The price we pay for rescuing these infants might be an increase in the risk of pulmonary dysfunction and obstructive lung disease in adulthood.
We showed that women are particularly at risk for developing obstructive lung disease in old age. One possible explanation why is that young, asthmatic girls have more severe obstruction than boys.[211] If this is not adequately treated early on it may ultimately accelerate the progression of obstructive lung disease later in life. Another possibility is that because lung capacity and inspiratory muscle strength are lower in women, they experience more dyspnoea and less effective treatment with short-acting

beta-agonists.[212]. A third possibility is that women are more susceptible to the side effects of environmental exposure to tobacco smoke ("passive smoking") than are men.[213]

The marked differences between sexes are illustrated by the fact pre-pubertal boys are more frequently diagnosed with asthma than are girls. After puberty, however, asthma is more commonly diagnosed in girls.[214, 215] It seems that this trend continues until menopause, when the difference between the sexes narrows but never completely vanishes.[216]

One reason why asthma appeared to be more common in women in our cohort could be that women have higher rate of hospital admission for obstructive lung disease. If the rate of hospital admission was lower for men with obstructive impairments, their asthma rate may have been understated.

It is important to recognise the limitations of a clinical diagnosis. COPD and asthma are often difficult to differentiate because of overlapping symptoms.[217] Despite a fundamentally different phenotype, COPD and asthma are both characterized by airflow obstruction. Recent studies also indicate there are strong epidemiologic and clinical links between asthma and COPD: adults with active asthma are up to 12 times more likely to develop COPD over time.[218]

Although our findings cannot necessarily be extrapolated to the very preterm-born population of today, they may nevertheless be relevant to many infants. Preterm birth is serious, global health issue today. Understanding its potential adverse impact on health may lead to better and earlier intervention and treatment strategies to improve long-term outcome.

7 CONCLUSIONS

Many perinatal complications are associated with inflammatory changes. These changes may in turn influence the long-term outcome of the preterm infant.

- Intubation and mechanical ventilation, both of which may be necessary for the survival of an infant with RDS, can trigger and aggravate the process of inflammation. Preventing or minimizing these inflammatory changes may be possible if surfactant can be delivered less aggressively via a combination of nebulizer and CPAP To date, however, this approach has proven unsatisfactory, since no improvements in either oxygenation or neonatal morbidity have been observed. The development of alternative, effective, minimally invasive methods to deliver surfactant therefore remains one urgent challenge facing neonatology today.

- Eosinophils are typically activated by exposure to foreign substances / antigens e.g. in food as well as bacteria. The eosinophils may play an important role in the pathogenesis of BPD-related inflammation. Moreover, the state of ***eosinophil activation*** appears to be closely linked to the severity of BPD.

- Inflammatory processes early in life appear have a significant impact on long-term ***pulmonary function***. At 6-8 years, children with BPD exhibit airway obstruction with significantly reduced respiratory airflow, and most show structural abnormalities on CT scan. We have shown that such changes may be present even in children with the mildest form of BPD. All children diagnosed with BPD – regardless of its severity – should therefore be included in routine follow-up programs.

- Children with BPD exhibit deficits in fine motor performance, and significantly more behavioural problems and school difficulties than preterm children without lung disease. Consequently, BPD may influence ***psychomotor development*** at school age.

- Being born premature may affect health in adulthood and old age. In a unique epidemiological study of adults born preterm in the early-mid 20th century, we showed that the risk of developing obstructive ***lung disease in old age*** was significantly elevated in this group generally, but especially amongst women. These findings are particularly relevant to the future of the "new generation" of BPD survivors of today. BPD-associated respiratory problems that arise during infancy and childhood and persist into adolescence and young adulthood may be early signs of increased vulnerability to COPD in old age.

The long-term effects of BPD on health and development indicate that BPD should no longer be considered simply as a paediatric disease. As a result, specialists in adult pulmonology must be aware of the potential hazards of BPD. Adult physicians should be on the alert for early warning signs of respiratory insufficiency in this population, since early diagnosis and treatment can slow the progression of potentially debilitating diseases such as COPD.

8 FUTURE PERSPECTIVES

Looking to the future, we face exciting challenges if we are to successfully reduce the number of infants who develop BPD. Our work suggests some ways in which clinical research could improve our understanding of BPD and lead to more effective strategies for preventing and treating this disease. Two potentially important future approaches to reduce the incidence of BPD will be the introduction of new techniques to successfully deliver surfactant with minimal trauma during early-stage RDS, and the introduction of non-steroidal anti-inflammatory drugs.

In addition to medical advances, nursing interventions such as introduction of Newborn Individualized Developmental Care and Assessment Program (NIDCAP), have already been shown to improve neurodevelopmental outcome in BPD.[219] We must also pay more attention to the psychological needs of the newborn, and provide support for the family of the preterm-born infant during their difficult time. One of the fundamental prerequisites for success is, of course, to allow parents the opportunity to remain with their hospitalized child around the clock. Preliminary evidence indicates that this could also help reduce the risk of BPD.[220] Unfortunately, at present, most parents are separated from their infant for periods of up to several hours each day, with care during these periods being provided by NICU staff.

We must also adopt a more proactive approach to intervention after an infant has been discharged home. BPD is a multisystem disorder and requires interdisciplinary follow-up. Ideally we should develop specialist BPD teams to provide integrated care. These teams should include neonatologists, neuro-pediatricians, physiotherapists, nutritionists, pulmonary doctors, psychologists, and specialist nurses. Centres with established expertise and competence must conduct post-discharge intervention studies, and formulate evidence-based guidelines to improve outcome for preterm graduates.

Because there are similarities as well as differences between BPD and asthma, future research needs to focus on defining the specific characteristics of BPD, such as the extent of inflammation, hyper-reactivity, changes in lung volume and exercise ability, and heterogenicity of symptoms. The treatment of BPD must be continuously re-evaluated. The standard treatments used for asthma may not be appropriate. A more indivdualized approach tailored to each child's circumstances may be required.

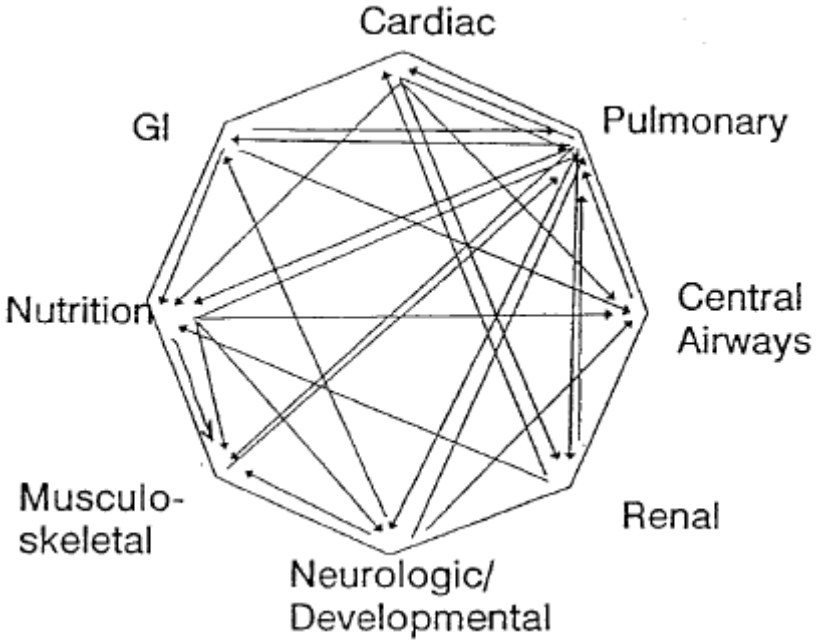
We must also develop and improve the long-term pulmonary follow-up of those with BPD.[221] As the new generation of preterm infants grows into adulthood, longitudinal lung function studies may reveal whether those with BPD will eventually develop COPD-like symptoms in old age. Adult physicians must be encouraged to become involved in the study of the new pulmonary diseases that emerge during the perinatal period.

Studies of asthma reveal that genetic variants play a role in determining lung function and susceptibility to COPD in high-risk groups. We must determine whether this is also true of BPD in children.[222]

With more - and younger - preterm-born infants surviving today, we must focus resources on improving their future quality of life, particularly their behavior, school performance, motor skills and mental health. We must also consider the likely long-term impact of associated cardiovascular and pulmonary impairments much later in life, in old age.
The medical treatment of the preterm-born infant has improved dramatically thanks to antenatal steroids, surfactant and various ventilation strategies. However, illness as well as the treatment provided itself often results in an unsatisfactory outcome and one major complication - BPD. Aggressive early mechanical ventilation and treatment with supplemental oxygen is responsible for much of the subsequent chronic pulmonary dysfunction.

Summery
Inflammation is only one pathway contributing to the pathogenesis of BPD. Because BPD is a multisystem disease, interactions between pathophysiological changes affecting multiple organ systems are involved. This must be taken into account when initially assessing and following-up preterm infants with BPD.[196]

Figure 7. Interactions between organ systems in infants with BPD. Each arrow represents an interaction that has been shown to be of significance in the pathophysiology of BPD.



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Helt visst I tankens stilla världshav än
där ligga många obekanta öar,
och mången stjärna speglas där kanske,
ej hittills upptäckt utav forskarens öga.
Kan du ej plöja själv de djupa vågor,
Så lyssna villigt till de vises röster,
de vittberestes, som med säkra tecken
tillbakavända från de nya landen.
Men tro ej allt vad skeppare förtälja
om oerhörda ting, som de erfarit,
om världens gåta äntligen löst av dem,
och om den vises sten, som de ha funnit.

Esaias Tegnér,
Epilog vid magisterpromotionen i Lund 1820