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OPTIMIZED GROWTH AND REDUCED MORBIDITY IN PRETERM INFANTS

– FOCUS ON NUTRITION AND SATURATION TARGETS

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Karolinska Institutet

Stockholm 2018

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Cover: Lisa Öhman, 2018
Published by Karolinska Institutet.
Printed by E-Print AB 2018

ISBN 978-91-7831-026-5

“You don’t make progress by standing on the sidelines, whimpering and complaining.

You make progress by implementing ideas.”

Shirley Chisholm

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– focus on nutrition and saturation targets

THESIS FOR DOCTORAL DEGREE (Ph.D.)

by due permission of Karolinska Institutet, will be publicly defended in English
in Aulan, Elevator C, 6th floor, Stockholm South General Hospital, Stockholm

Friday 18th of May 2018 at 9.30 am

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ABSTRACT

Preterm birth alters the conditions during an important period of growth and organ maturation. Extremely preterm infants have a high risk of developing morbidity. Retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) originate in a disturbed retinal and pulmonary development. Associations between nutrition and risk of ROP and BPD have been demonstrated in some previous studies. Practical guidelines published 2005 included recommendations of higher early macronutrient intakes after preterm birth, compared to previous guidelines. One well known risk factor for ROP is oxygen exposure. As a result of five coordinated randomized trials, European saturation target guidelines were revised 2013.

The objective of this thesis is to study neonatal practices potentially associated with the risk of developing ROP and BPD. In addition, this thesis examines the adherence to implemented new recommendations of nutritional intakes and saturation targets. The overall aim is to increase the quality of care, in order to improve outcome in the high-risk population of extremely preterm infants.

Paper I examined growth patterns in a large cohort of infants born in gestational age (GA) 23 0/7 to 30 6/7 weeks. Longitudinal data were used to investigate differences in growth patterns. The results demonstrated reduced postnatal weight gain in infants who developed ROP and BPD compared to infants without these diseases. The growth patterns differed depending on gestational age and postnatal age.

Paper II used detailed nutritional data from infants born between 2004 and 2011 at GA <27 weeks to study whether early energy and protein intakes were associated with initial growth and risk for ROP and BPD. The results showed that higher intakes of energy and protein were associated with improved weight development the first week of life. Increased energy intake during postnatal days 7 to 27 was associated with a reduced risk of ROP among infants with fewer than ten days of mechanical ventilation. Increased energy and protein intake during postnatal days 7 to 27 was associated with a reduced risk of BPD among infants born during 2008 to 2011.

Paper III showed that nutritional intakes have increased continuously during 2004 to 2011 in Stockholm. This coincided with implementation of a bundle of interventions aiming at improved nutrition. During 2004 to 2009 the majority infants had lower protein intakes the first postnatal days than the then prevailing guidelines recommended.

Paper IV studied peripheral oxygen saturation in infants born at GA 23 0/7 to 30 6/7 with two different saturation targets and alarm limits. Higher saturation target and tighter alarm limits were associated with an increased proportion of time within the target range and a reduced oxygen saturation variability. Mean oxygen saturation and the proportion of time with hyperoxia were increased with the higher target range.

In conclusion, this thesis highlights the importance of neonatal practices. Increased early nutritional intakes are associated with reduced initial growth restriction and morbidity. Poor postnatal weight gain is a marker for disease. Improved nutritional regimen and enhanced focus on postnatal growth may improve outcomes for extremely preterm infants. It is important to monitor adherence to guidelines as there is room for further improvement in quality of care.

LIST OF SCIENTIFIC PAPERS

I. **Cohort study of growth patterns by gestational age in preterm infants developing morbidity**
Klevebro S, Lundgren P, Hammar U, Smith L E, Bottai M, Domellöf M, Löfqvist C, Hallberg B, Hellström A
BMJ Open. 2016;6(11):e012872.

II. **Early energy and protein intakes and associations with growth, BPD and ROP in extremely preterm infants**
Klevebro S, Westin V, Stoltz Sjöström E, Norman M, Domellöf M, Edstedt Bonamy A-K, Hallberg B
Submitted Manuscript

III. **Improved nutrition for extremely preterm infants – A population based observational study**
Westin V, Klevebro S, Domellöf M, Vanpée M, Hallberg B, Stoltz Sjöström E
Clinical Nutrition ESPEN. 2018;23:245-251.

IV. **Altered oxygen saturation targets, alarm limits and peripheral oxygen saturation**
Klevebro S, Hammar U, Holmström G, Bottai M, Hellström A, Hallberg B
Submitted Manuscript

CONTENTS

LIST OF ABBREVIATIONS

BPD	bronchopulmonary dysplasia
BW	birth weight
BWSDS	birth weight standard deviation score
CI	confidence interval
DAG	directed acyclic graph
DM	donor milk
DOHaD	developmental origins of health and disease
ELBW	extremely low birth weight
ELGA	extremely low gestational age
FiO_2	fraction of inspired oxygen
GA	gestational age
IGF-I	insulin-like growth factor one
IUGR	intrauterine growth restriction
MOM	mothers own milk
MV	mechanical ventilation
NEC	necrotizing enterocolitis
OR	odds ratio
PaO_2	partial pressure of oxygen in arterial blood
PDMS	patient data monitoring system
PMA	post menstrual age
ROP	retinopathy of prematurity
RR	risk ratio
SGA	small for gestational age
SNQ	Swedish neonatal quality register
SpO_2	peripheral capillary oxygen saturation
SWEDROP	Swedish national register for retinopathy of prematurity
VLBW	very low birth weight
VLGA	very low gestational age
WSDS	weight standard deviation score

1 BACKGROUND

1.1 PREMATURITY

1.1.1 Incidence and Definitions

Preterm birth is a global health issue with an estimated 15 million infants affected each year.[1] Preterm birth is defined by the World Health Organization (WHO) as birth before 37 completed weeks of gestation. In 2012 report, WHO estimated the global rate of preterm birth to be 10% although there is a great variation between regions and countries. The lowest preterm birth rate was reported in the Northern European countries.[1] In 2016, the preterm birth rate in Sweden was 5.6%, and 0.9% of the infants were born before 32 0/7 weeks of gestational age (GA) according to the Swedish Neonatal Quality register (SNQ).[2, 3] A population-based study of infants born in Sweden between 2004 and 2007 (EXPRESS) reported that 2.3 of 1000 live-born infants were born before 27 0/7 weeks of GA.[4]

Common classifications of infants in neonatal research are by GA or birth weight (BW) (Table 1).

Table 1.
Classification of infants by gestational age and by birth weight.

Classification by GA[1]	Gestational duration	Birth weight	**Classification by BW**
VLGA	28 to <32 weeks	<1500 gram	**VLBW**
ELGA	<28 weeks	<1000 gram	**ELBW**

VLGA: very low gestational age; ELGA: extremely low gestational age; VLBW: very low birth weight; ELBW: extremely low birth weight

Preterm birth is either spontaneous or initiated due to maternal or fetal illness. Spontaneous preterm birth follows preterm labor or preterm pre-labor rupture of the membranes. The cause of spontaneous preterm birth is likely multi-factorial and in most cases the triggering mechanism is unknown, although both genetic and environmental risk factors may be at play.[5, 6] Intrauterine infection, urinary tract infection, and uteroplacental vascular disease are known risk factors of spontaneous preterm birth. Obstetric and fetal indications that may cause preterm delivery are placental hemorrhage, preeclampsia, and intrauterine growth restriction (IUGR). Maternal diseases that increase the risk of preterm delivery include diabetes, hypertension, and obesity.[5, 6]

1.1.2 Mortality

Mortality after preterm birth increases with decreasing GA and varies between countries and the availability of health resources. In 2016, Sweden's neonatal mortality was 17.8% for infants born before 28 0/7 weeks of GA and 2.8% for infants born between 28 0/7 weeks and 32 6/7 weeks of GA.[2] In EXPRESS, the one-year survival was 52% in gestational week 24, and 85% in gestational week 26.[4] Table 2 reports the rates of survival to discharge per

gestational week in Sweden. Compared to Sweden, other regions in Europe and North America have demonstrated slightly higher mortality rates.[4, 7-9] A recent study of infants born in Norway between 2013 and 2014 showed higher one-year survival in gestational weeks 25 and 26, and lower survival in gestational weeks 23 and 24 compared to Sweden during the period 2004-2007.[4, 10] Draper et al. demonstrated remaining differences in preterm mortality between 19 European regions after accounting for maternal and infant characteristics. The regional variations were greatest among the most immature infants.[11] The differences between centers and countries imply there is room for further improvements in care.

Table 2. Survival to discharge in Sweden

	Gestational Week							
	22	23	24	25	26	27	28	29
n/N (%)	34/82 (41)	150/262 (57)	239/343 (70)	380/454 (84)	450/509 (88)	539/582 (93)	624/672 (93)	650/674 (96)

Data from 2007–2015 (GA 22–25 weeks)[12] and 2007–2013 (GA 26–29 weeks)[13]

1.2 DEVELOPMENT OF NEONATAL CARE

1.2.1 Advances in neonatal care

Over the last several decades, obstetric and neonatal care have improved. Administration of antenatal corticosteroids to mothers with threatening preterm birth reduce neonatal mortality, risk of several neonatal morbidities, and early respiratory disease.[14] The use of surfactant, continuous positive airway pressure, and advanced ventilator settings with less barotraumatic ventilators further support pulmonary development.[15-17] Skin-to-skin care has been associated with reduced rates of infection and hypothermia as well as increased breastfeeding rates and improved growth.[18] Nutritional management in neonatal care has improved more recently.[19]

Sweden's neonatal mortality has decreased among preterm infants. (Figure 1). Platt et al. showed increased survival and a reduced proportion of cerebral paresis among VLBW infants between 1980 and 1996.[20] Increased survival of ELGA infants was also demonstrated between the years 1991 to 1993 and 2001 to 2003.[21] In that study, the proportion of infants with severe disability among the survivors increased. Comparing 1995 with 2006, the EPICure studies found improved survival for ELGA infants in England, but no reduction in morbidity.[9] The main research focus is now on improvement of long-term morbidity for the youngest most vulnerable infants.

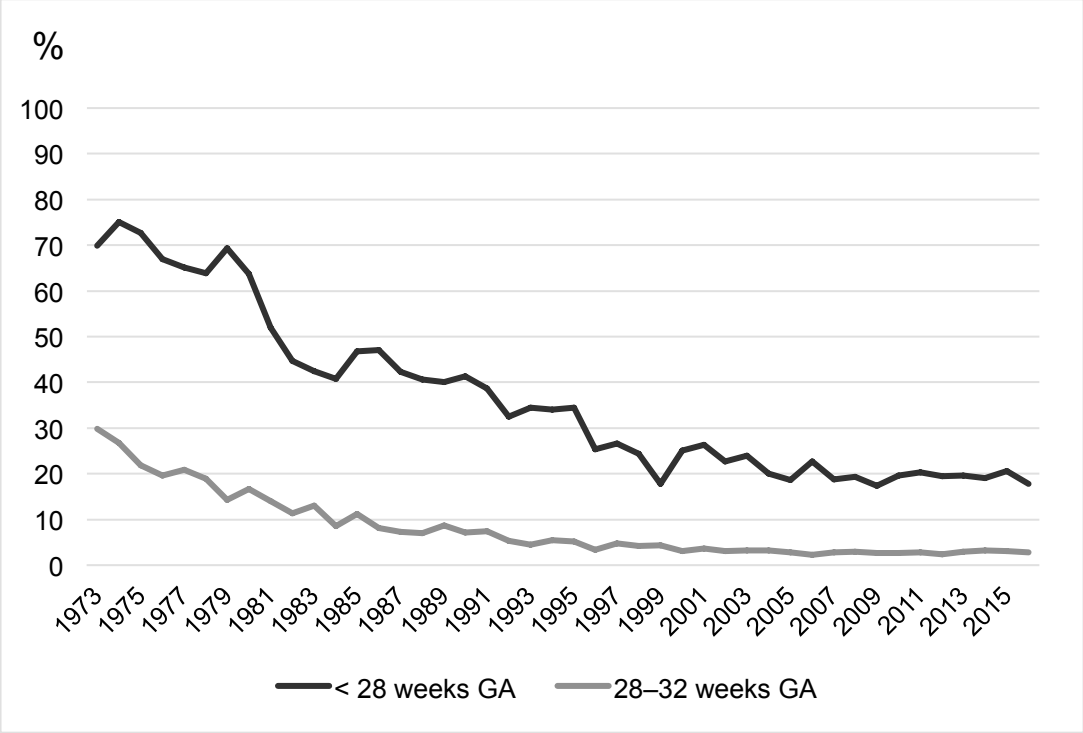

Figure 1. Neonatal mortality among preterm infants born before 28 0/7 weeks of GA and between 28 0/7 and 32 6/7 weeks of GA in Sweden between 1973 and 2016.[2]

1.2.2 Implementation of knowledge

Neonatal research aims to improve neonatal survival and quality of life for affected infants. Research can provide basis for recommendations and enables the practice of Evidence-Based Medicine, the use of best available knowledge from science in integration with clinical judgment in the care of individual patients.[22] Guidelines are developed to support the use evidence from research. Evidence-based guidelines should include statements regarding the quality of evidence and strength of recommendation using, for example, the GRADE system.[23] Zeitlin et al. showed that evidence-based care decreases mortality and severe morbidity in preterm infants.[24] Other studies have also demonstrated improved results after active implementation of evidence-based care.[25-27]

Several studies have examined obstacles to the implementation of new knowledge into clinical practice. The complexity of care and organizational as well as cultural barriers limit the possibilities to successfully implement evidence-based reccomendations.[28-30] Glasziou et al. described important limiting factors in an "evidence pipeline."[31] Knowledge regarding limitations can be used in a structured approach to introduce new practice. Johnson et al. performed a study to monitor and guide implementation of nutrition guidelines and demonstrated successful and sustained practice.[32] The study used Normalization Process Theory[33] to model four mechanisms related to health care professionals; these mechanisms resemble the initial limiting factors described by Glasziou et al. The first mechanism is to understand the need for change. The second mechanism addresses the understanding of what needs to be done. The third mechanism addresses the effort to change practices. The fourth mechanism is "reflexive monitoring," feedback aimed at demonstrating the benefit of new

practices. In addition, Johnson et al. found that improved nutritional products increased the possibility of change.[32] Glasziou et al. also identified the availability as an important factor for success.[31]

1.3 NUTRITION

Growth and development cannot take place without access to nutrients. In an optimal in utero setting, all macro- and micronutrients needed are provided through the umbilical cord. In the neonatal care setting, extremely and very preterm infants are initially nourished through the parenteral route, and enteral nutrition (EN) is introduced gradually. The potential for absorption and utilization of nutrients, depending on the administered route, is of importance when making nutritional recommendations.[34]

The first study of parenteral nutrition for preterm infants was published in 1972.[35] Due to concerns of substrate intolerance, historically care professionals withheld or limited nutritional intake for ELGA infants for the first few postnatal days. In a randomized controlled trial (RCT) published 1997, Wilson et al. compared an "aggressive nutritional regimen" with a "conservative nutritional regimen."[36] The "conservative regimen" was compatible with contemporary guidelines and included initiation of 1 g/kg/day amino acids on postnatal day 3 and 0.5 g/kg/d of lipids on day 5. The interventions in the "aggressive regimen" included the initiation of 0.5 g/kg/day amino acids 12 hours after birth and 0.5 g/kg/d of lipids on day 2. Wilson et al. concluded that the "aggressive regimen" was safe.[36] Recommendations of initial intakes have increased during the last decades.[37] Guidelines published 2005 recommended higher minimal supply and initiation of amino acids and lipids the first postnatal day.[34, 38] Preterm infants have limited stores and high needs, and extremely preterm birth should be considered as a nutritional emergency. Present recommendations are to achieve full nutrition within four days of birth.[39, 40]

Nutritional guidelines aim at stating an acceptable range of intake.[40] Published 2014,[39] the most recent Swedish guidelines are based on international guidelines.[38, 41, 42] Different methods can be used to define nutritional needs. The factorial method is an example of a theoretical approach adding estimations of metabolism and growth.[43] Studies of controlled intervention or observational studies of dose response associations add to the evidence. The outcomes in these studies include both metabolic measurements and growth parameters. Data regarding ELGA and ELBW infants have been limited, but several recent studies have focused on this vulnerable group of patients.[42] Although the most recommended ranges of intakes are estimations based on a normally distributed population, preterm infants are not a homogenous population so individual needs must be considered in clinical practice. Certain groups of infants could need recommendations with specific considerations. For example, it has been hypothesized that IUGR could result in metabolic adaptations leading to differing nutritional needs.[44]

1.3.1 Energy

Growth, basal metabolism, and energy expenditure are used to estimate energy requirements in preterm infants. In Sweden, the current guidelines suggest that an ELGA infant needs 90-115 kcal/kg/d of energy from full PN or 115-135 kcal/kg/d from full EN.[39] However, certain conditions have been associated with increased energy expenditure and might warrant higher energy intake, although evidence is limited and contradictory.[45-48] Atwater's factors are commonly used to calculate energy content in macronutrients: 4 kcal/g protein, 9 kcal/g fat, and 4 kcal/g carbohydrates.

1.3.2 Amino acids and protein

Protein is the content in enteral nutrition products (including breast milk), whereas the subunits of protein, amino acids, are provided in parenteral solutions and some hydrolyzed formulas. To achieve growth of lean body components, the net protein accretion needs to be positive. That is, the rate of protein synthesis needs to exceed protein breakdown. Current recommendations, originating from studies of nitrogen balance, estimate that preterm infants need 1.5 g/kg/day for a neutral net protein accretion rate.[38, 49] Adding the need for growth, the total parenteral need is estimated to 3 g/kg/day.[50] Protein needs in infants suffering from active infection, inflammation and stress are not known. Swedish guidelines recommend an amino acid/protein intake of 3.5–4 g/kg/day in full PN or 4–4.5 g/kg/d in full EN.[39]

Several studies have highlighted the importance of early provision of amino acids to avoid a negative protein accretion rate.[51-54] Optimal starting dose and mode of increase of amino acids after birth have not been clearly shown. Current guidelines recommend 2.0-2.5 g/kg/day started as soon as possible after birth and 3.5-4.5 g/kg/day by postnatal day 4, depending on route of intake.[39, 49]

Oskar, born at 26 weeks and one day of gestation. ©Daniel Rådström

1.3.3 Protein to energy ratio

Energy can be divided into protein and non-protein energy. Protein is used as energy if other sources are lacking.[55] Protein is the determinant of lean body mass gain.[56, 57] Total energy and protein intakes as well as the protein to energy ratio are important for optimal utilization of protein and growth of lean body mass with limited fat mass deposition.[57-59] Results from these studies are the basis of current recommendations and state that an energy intake of 115-120 kcal supports a protein intake of 3.5–4.0 g/kg/day.[60]

1.3.4 Carbohydrates and lipids

Carbohydrates and specifically glucose are the principle source of energy for most metabolic processes, particularly for the brain. Lactose from human milk is converted into glucose by lactase in the intestines. In very preterm infants, the lactase activity may be only 30% compared to term neonates, but early feeds of human milk can induce lactase activity.[61] Swedish recommendations are 13-17 g/kg/day of carbohydrates in full PN and 9-15 g/kg/day in full EN.[39]

Lipids are effective as a source of energy. Intrauterine provision of nutrients is high in carbohydrates and amino acids but low in lipids.[62] The activation of mitochondrial oxidation is delayed in preterm infants.[63] Digestion and absorption of fat from the intestines are reduced in preterm infants and affected by the properties of the enteral solution.[64, 65] Long-chain polyunsaturated fatty acids (LC-PUFAs) are crucial for neurodevelopment. Beneficial effects of enteral supplementation with LC-PUFAs have been demonstrated in clinical studies.[66] Studies of parenteral lipid content have not shown consistent and convincing results.[67, 68] Current Swedish guidelines recommend lipids of 3-4 g/kg/day in full PN, starting at 1.0–1.5g/kg/day on the day of birth and 4-8 g/kg/day in full EN. Recommendations also include suggested intakes of LC-PUFAs arachidonic acid and docosahexaenoic acid.[39]

1.3.5 Other important factors for growth

The availability of nutrients is not the sole concern for growth and development. Growth factors and anabolic hormones are also crucial for fetal and postnatal growth.[69] It has been suggested that the hormone axis and nutrition interact in important ways. For example, growth factors affect nutrient utilization, and in older malnourished children nutrient intake affects levels of growth factors.[70, 71] In addition, low protein intake in preterm infants has been associated with low levels of insulin-like growth factor one (IGF-I) and its binding protein after 30 weeks postmenstrual age.[72, 73] The placenta has an important role in production and regulation of IGF-I.[74] After preterm birth, the circulating levels of IGF-I decreases in the neonate[75, 76] and endogenous production, mainly by the liver, does not provide sufficient IGF-I to reach corresponding fetal levels for several weeks.[77]

Multicellular organisms convert nutrients and oxygen to energy in the mitochondria via oxidative phosphorylation, a highly efficient aerobic metabolic pathway. Preterm infants need adequate tissue oxygenation for growth and development.

1.3.6 Enteral nutrition

The transition to enteral feeds is hampered by the immaturity of the preterm gut. At least minimal enteral nutrition is recommended from the first day of life.[39] Enteral feedings with human milk are associated with several beneficial effects in preterm infants such as the development of the gastrointestinal tract, improved neurodevelopmental outcome, and reduced incidence of necrotizing enterocolitis (NEC).[78-80] If available, mothers own milk (MOM) is the preferred choice.[81] In Sweden, the use of donor milk (DM) is widespread, and used for preterm infants born before 32 weeks of GA rather than preterm formula when MOM is lacking.[82, 83] Compared to formula, DM has been associated with reduced risk of NEC.[84] Mothers of preterm infants express breast milk with higher energy and macronutrient content compared to mothers to term infants. Both gestational age and postnatal age affect the nutritional content of MOM.[83] Pasteurization affects the bioactivity of components in human milk.[85]

Enteral feeds are advanced gradually. A 2017 meta-analysis concluded that increments of 30-40 ml/kg/day were associated with shorter time to full EN without increased incidence of NEC compared to slow enteral advancement.[86] In infants weighing less than 1000 g, feeding advancement of 15-25 ml/kg/day and full EN within 14 days is recommended.[87]

Fortifiers are used to supplement both MOM and DM to achieve recommended intakes of energy, protein, micronutrients and vitamins. A gradual initiation of fortification starting at enteral intakes of 50 ml/kg/day to full fortification at 100 ml/kg/day was been demonstrated to improve growth in infants with BW <1250g, and this protocol is currently recommended.[87, 88] Target fortification based on individual analyses of macronutrient content in MOM and DM has been demonstrated to improve growth.[89]

1.4 GROWTH

1.4.1 Intrauterine growth

Fetal growth depends on the fetal genome and the intrauterine environment. IGF-I, the most important hormonal driver of fetal growth,[69, 90] inhibits apoptosis and stimulates migration, cell division, and differentiation.[91, 92] The rapid growth of the normal fetus in the third trimester triples the weight and doubles the length of the fetus and is accompanied by a rise in the IGF-I level.[93]

1.4.2 Growth charts

Monitoring fetal and infant growth requires repeated measurements and a comparison to a suitable reference population as revealed in growth charts. A commonly used method to estimate fetal weight from intrauterine measurements is the Hadlock formula, which is based on measurements of the fetal head, abdomen, and femur.[94] Estimated fetal weight-derived charts use repeated ultrasound measurements of infants delivered at term, generating growth

charts considered to be representative of normal fetal growth.[95] Birth weight-derived fetal growth charts are based on birth weights of delivered infants in all gestational ages. However, because inclusion criteria vary between studies, they generate different curves and standard deviations.[96-98] Since preterm birth represents an un-physiological state, the charts are not representative of undisturbed intrauterine growth. Available fetal-based charts are based on limited samples and sonographic techniques, so birth weight-derived charts are in use in most neonatal care settings.

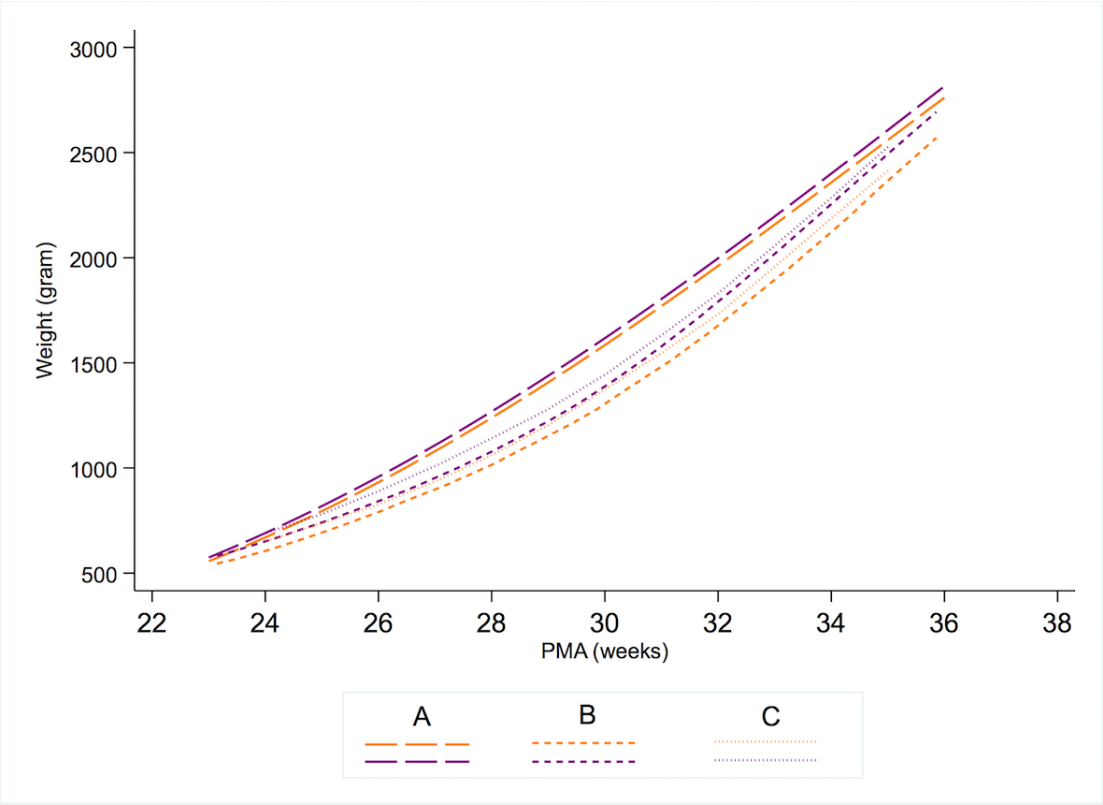

Figure 2. Illustration of the 50th percentile in three growth charts

A Marsal et al.[95] (estimated fetal weight-drived chart); **B** Fenton et al.[96] (birth weight-derived chart); **C** Olsen et al.[98] (birth weight-derived chart);
Orange: girls; Purple: boys

Gardosi et al. have suggested a method to adjust the intrauterine references provided by Hadlock et al. to individual factors.[99] This method may also be adjusted to parameters in a population. National data of mean BWs and standard deviations at term have been used to generate intrauterine-based country specific growth standards.[100] Zeitlin et al. used this model to construct 11 country-specific intrauterine derived growth standards.[101]

The INTERGROWTH-21st project is an attempt to generate globally valid growth charts from selected healthy populations. Charts developed from BW did not include ELGA or VLGA infants,[102] and charts from longitudinal growth of preterm infants only included a limited number of VLGA infants.[103] Estimated fetal weight-derived charts from ultrasound measurements have also been developed in the INTERGROWTH-21st project.[104]

1.4.3 Growth rate

Extrauterine growth can be expressed as deviation in standard deviation score (SDS) according to the used growth chart or as a growth rate. Growth rate is expressed as g/kg/day, and some studies report weight gain in g/day. After examining different methods for calculating growth rate in ELBW and VLBW infants, Patel et al. concluded that the exponential model is very accurate.[105, 106]

It has been proposed that the optimal growth of preterm infants should mimic fetal growth and body composition.[41] Fetal weight gain increases from 17 g/day in gestational weeks 24-28, to 24 g/day in gestational weeks 28-32 and 30 g/day during gestational weeks 32-34, followed by a decline in growth rate the last gestational weeks.[107, 108] Recalculated values from the publications give fetal growth rates of approximately 16–17 g/kg/day in gestational week 24, 18-19 g/kg/day in gestational weeks 26-28, 16 g/kg/day in gestational weeks 30-32, and 13 g/kg/day in gestational weeks 34-36.[107, 108]

Several studies have demonstrated that postnatal growth restriction is common in preterm infants.[109-112] The assessment of growth restriction depends on the choice of growth reference and percentile. Optimal postnatal growth for preterm infants has not been determined. After birth, weight loss and interrupted growth rate results in reduction in weight standard deviation score (WSDS). Some degree of weight loss due to redistribution of fluid is likely to be necessary, but optimal initial weight development has not been established. In a study by Senterre and Rigo, WSDS was reduced by 0.8 SDS the first three postnatal days in ELGA infants and 0.6 SDS in VLGA infants as determined by an ultrasound-derived growth chart.[113] In that study, growth was parallel to the growth chart during the 2nd and 3rd postnatal weeks followed by catch up growth and some regain in WSDS. The optimal degree of catch up has also been debated. Rochow et al. suggested that growth parallel to the revised growth chart by Fenton et al.[96] after an initial reduction in WSDS results in optimal growth and body composition.[114]

1.4.4 Intrauterine growth restriction

IUGR describes a fetus not reaching its genetic growth potential. No international consensus exists regarding the definition of IUGR. Suggested definitions include deviated growth either as measured with repeated ultrasound or compared to expected growth or in combination with affected blood flows in the umbilical cord.[115] In many studies and in clinical praxis, birth weight standard deviation score (BWSDS) as plotted on a preterm growth chart is used to define being born small for gestational age (SGA). BW below the 10th percentile [96, 98] or below two standard deviation scores (SDS) [95, 97] are considered SGA. The proportion of infants born SGA increases with increasing GA.[4, 101]

1.5 ORGAN DEVELOPMENT AND MORBIDITY

Important steps of organ development occur during the third trimester. Preterm birth alters the conditions for normal growth and maturation. VLGA and ELGA infants suffer from a diverse range of neonatal problems due to the immaturity at birth. Short- and long-term morbidity increase with decreasing GA.[8, 10, 116, 117] Lower BW compared to expected for GA is also a risk factor for morbidity.[118]

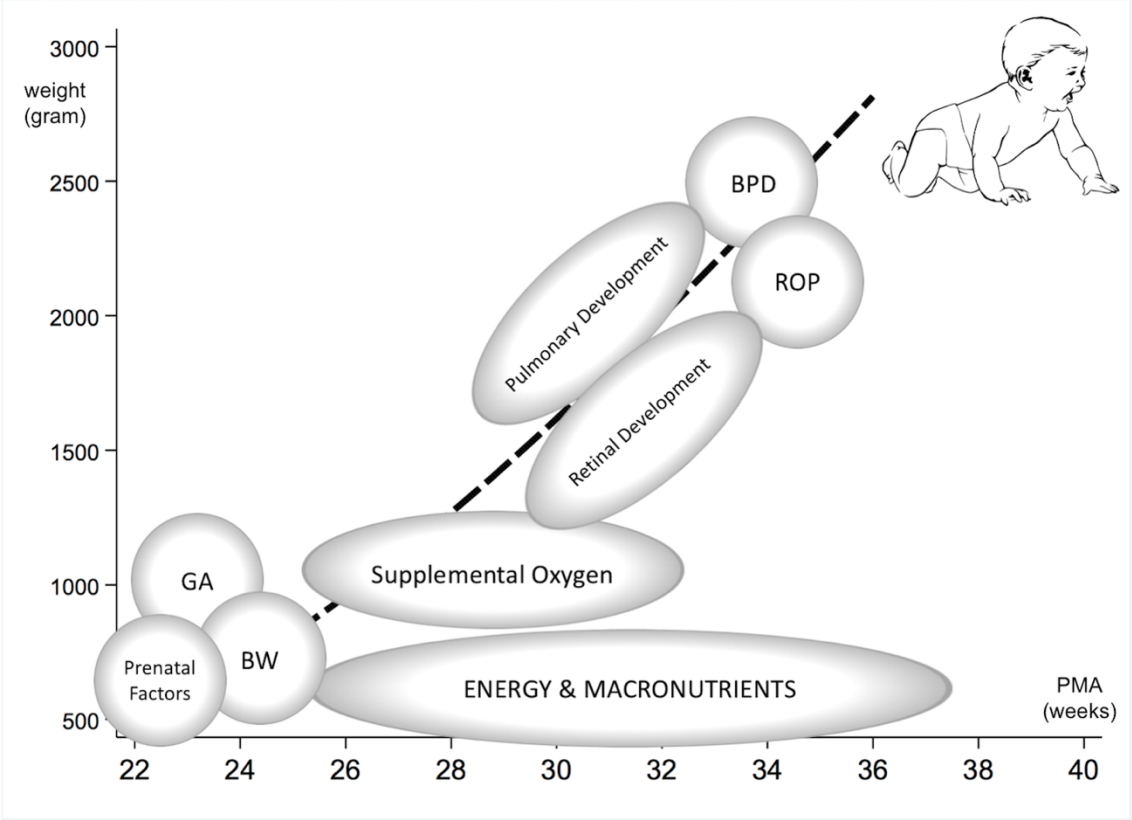

Figure 3. Changed conditions during an important period of growth and development

1.5.1 Retinal development and Retinopathy of prematurity

Vascularization of the retina starts from the center of the retina about 16 weeks into pregnancy and continues to term age.[119] Retinal neurons develop in parallel with the vessels and it has been proposed that neural growth drives vessel growth.[120]

Retinopathy of prematurity (ROP) is caused by disturbed neurovascular development of the retina. The disease is graded by severity (stages 1-5) detected during an eye examination.[122] Stage ≥3 is considered severe ROP. ROP develops in two postnatal phases[123] (Figure 4). Factors associated with preterm birth, such as placental infection and inflammation, may also affect retinal neurovascular development and predispose the fetal retina to ROP.[124, 125]

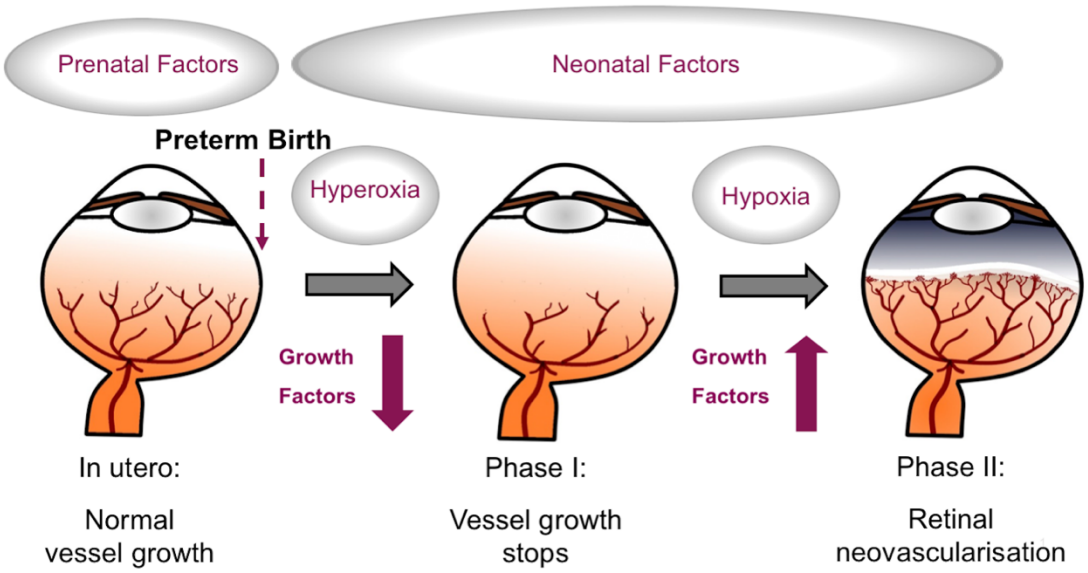

Figure 4. Development of ROP

Adopted from Hellström et al.[121]

Exposure to a hyperoxic environment and low levels of growth factors contribute to abrupt termination of vessel growth in the first postnatal phase of ROP development. Poor vascularization leads to local hypoxia, up-regulation of growth factors, and neovascularization in the second phase. The unregulated vessel growth can cause fibrosis, retinal traction, and retinal detachment.[126] Gestational age at birth is an important risk factor for ROP.[116, 127] The frequency and severity of ROP by GA in a Swedish preterm cohort is illustrated in Figure 5. Prenatal growth restriction is another well-known risk factor for ROP development;[127, 128] however, a more important risk factor in more mature infants.[129]

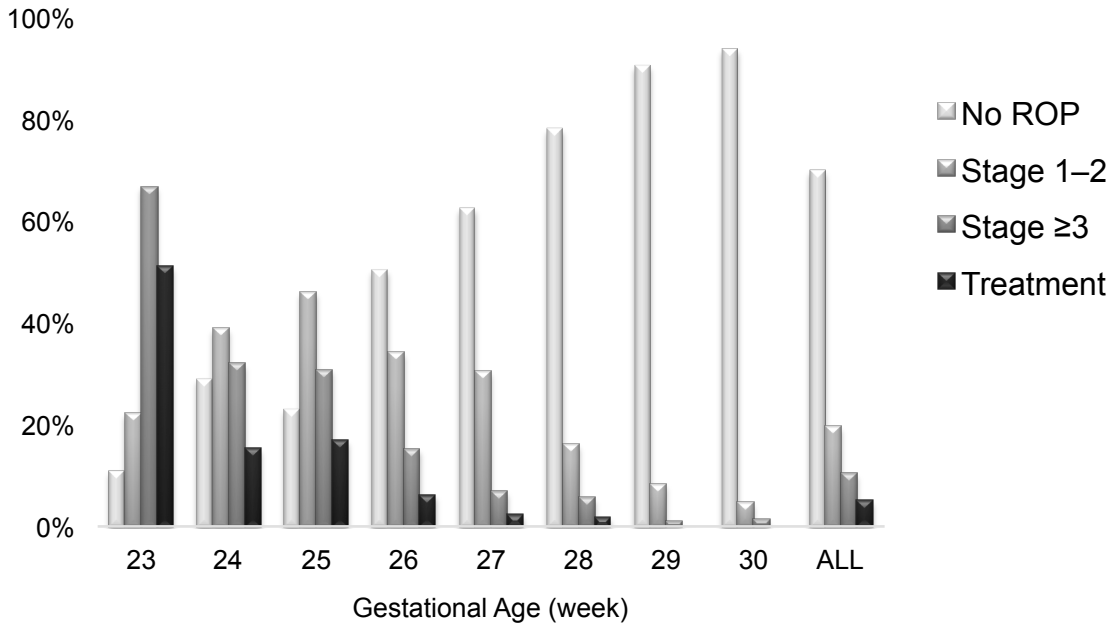

Figure 5. Frequency of different stages of ROP by GA in Sweden 2008-2011

Compiled data from (Holmström et al.)[130, 131]

ROP is not only a vascular disease but also a neural disease and it has been hypothesized that the disturbed processes leading to ROP are related to disturbed processes that impair brain development and affects long-term neurodevelopmental outcome. Children who have had severe ROP have been found to be more likely to have lower scores on neurodevelopment assessment at 2 and 5 years of age and lower IQ at adolescence.[132-134]

1.5.2 Pulmonary development and Bronchopulmonary dysplasia

The bronchiolar tree is established at GA 17 to 18 weeks. Lung capillaries emerge at about 20 weeks GA and continue to evolve and form a lung-air barrier that is mature at about 36 weeks GA. The production of surfactant starts at 25 weeks GA, but the system is immature until about 36 weeks GA.[135]

In 1967, Northway et al. described bronchopulmonary dysplasia (BPD) associated with barotrauma from mechanical ventilation (MV), and exposure to high concentrations of oxygen, "classic BPD".[136] "Classic BPD" affected more mature preterm infants after initial severe respiratory distress in an era before antenatal corticosteroid and surfactant therapy. In modern neonatal care, "new BPD" affects primarily ELGA infants and is related to disrupted pulmonary development.[137] It has been suggested that impaired angiogenesis is an important part of BPD development. Low levels of both vascular endothelial growth factor and IGF-I have been associated with BPD.[138-140] The need for supplemental oxygen at 36 weeks PMA, is one of the most accepted clinical definitions used to classify BPD in infants born at GA <32 weeks.[141] A physiological definition of BPD based on a test to confirm the need for supplemental oxygen has been proposed.[142] Known risk factors of BPD include complications of pregnancy, immaturity, gender, low BW, and low BWSDS.[143-146]

Infants with BPD are at risk for pulmonary vascular disease and pulmonary hypertension.[147] Long-term pulmonary, cardiovascular, and neurodevelopmental problems are more common in infants with BPD.[148-151]

1.5.3 Other morbidities

Spontaneous closure of the ductus arterious is often delayed in preterm infants. Patent ductus arteriosus (PDA) causing hemodynamic significant effects are treated with pharmaceuticals or surgical ligation. PDA is related to other morbidities, but it is unclear whether the association is with the hemodynamic effects of the left-to-right shunt, the treatment, or the immaturity.[152] Surgical ligation is also related to reduced energy and macronutrient intakes.[153] NEC is a potentially lethal complication in preterm infants. It is an inflammatory bowel necrosis and the most severe stage includes perforation of the gut. Modified Bell's stage criteria are commonly used to classify the severity of disease.[154] The pathology is not completely understood but the vulnerable under-developed gut is probably one of the underlying causes. Recommendations of treatment include suspension of enteral feeds, and in severe cases surgery that reduce the length of the intestines might be needed.[154] These treatments may lead to nutritional problems and reduction of total energy and macronutrient intakes. Use of human milk feeds can decrease the incidence of NEC.[155] MOM seems to have

a dose-dependent protective effect, but the protective effect of DM is less clear.[156] Preterm infants are vulnerable to infections, and sepsis is a common and dangerous condition. Septicemia was related to growth failure but not to GA or BW in the EXPRESS cohort.[116]

Neurodevelopmental impairment is common in ELGA infants and associated with GA.[157-159] In the Swedish EXPRESS cohort, 64% of the infants had some disability at six years of age, of which 34% had moderate or severe disability.[157] Several studies have shown that better postnatal growth is associated with improved neurodevelopmental outcome.[160-163] Association between increased nutritional intakes and neurodevelopmental outcome has been demonstrated in some studies,[164, 165] but not in others.[166, 167]

1.6 NUTRITION & GROWTH, ASSOCIATIONS WITH ROP & BPD

1.6.1 Growth and ROP

WINROP is a postnatal weight gain algorithm that uses GA at birth, BW, and weekly weight gain to predict risk of severe ROP. The development of this screening system has proven that postnatal growth is associated with disease development.[168-174] Absolute weight gain the first six postnatal weeks have been associated with severe and threshold ROP.[128, 175] Allegaert et al. did not demonstrate an association between ROP and relative weight gain,[128] but Fortes-Filho et al. showed that weight gain proportion after six postnatal weeks was a predictor for severe ROP.[176] Similarly, VanderVeen et al. demonstrated that low growth velocity between postnatal days 7 and 28 was associated with increased risk of ROP.[177] IGF-I is known to influence preterm growth and is important for vessel development. Severity of ROP has been correlated to serum concentrations of IGF-I and the duration of low concentrations of IGF-I.[121, 169]

1.6.2 Growth and BPD

Studies of postnatal growth and BPD have demonstrated differing results, and most studies do not investigate growth patterns the first postnatal weeks. Natarajan et al. identified that postnatal growth failure was common in preterm infants born before 27 weeks of GA with severe BPD referred to specialized neonatal intensive care units. The proportion of infants with weight below the 10th percentile was 20% at birth and 33% at 36 weeks PMA.[178] In a recently published study of growth among 25,899 VLBW infants born between 2005 and 2012, Griffin et al. showed that severe ROP and NEC, although not BPD, were associated with postnatal growth restriction at discharge.[179] In a 1999 study, Ehrenkranz investigated postnatal growth in infants stratified by BW. Infants with BPD demonstrated reduced weight gain compared to infants without BPD if the BW was above 700 g. Infants with BWs of 500-700 g with and without BPD did not demonstrate differences in growth patterns.[111] Nyp et al. did not show any association between growth rate in g/kg from birth to 36 weeks PMA and BPD in infants born before 28 weeks of GA.[180] Early weight loss has not been associated with increased risk of BPD.[181] Oh et al. demonstrated an association between high fluid

intakes, reduced weight loss during the first ten days of life, and increased risk of later respiratory morbidity. In that study, the mean fluid intake on postnatal days 4 to 6 was high (170 ml/kg/d) compared to recommendations.[182]

1.6.3 Nutrition and Growth

In a 2001 study, Embleton et al. demonstrated that feeding VLGA and ELGA infants according to current guidelines led to cumulative deficits compared to recommended intakes and resulted in postnatal growth restriction.[183] Senterre and Rigo conducted a similar comparison in VLGA and ELGA infants born between 2006 and 2007, demonstrating less deficits with more recent guidelines and recommendations. ELGA infants had an energy deficit during postnatal weeks 1 to 4 and VLGA infants had an energy deficit during the first and second weeks. All infants had a protein deficit the first week of life. Full nutrition was achieved within 8 days from birth for energy and 6 days for protein. Infants still developed postnatal growth restriction but less severe compared to what Embleton et al found. Senterre and Rigo found that WSDS decreased the three first postnatal days, to 0.8 SDS in ELGA infants and 0.6 SDS in VLGA infants. Catch up growth started between the 3rd to 4th postnatal week.[113]

RCTs of nutrition and growth in VLGA and ELGA infants have varied in intervention and primary outcome. Three RCTs examining different degrees and timing of increased protein intake without increase in non-protein energy did not demonstrate any significant effect on growth at 36 weeks PMA. [184-186] One of these studies also reported early weight development and showed no significant difference in growth to postnatal day 7 or 28.[186] Other trials have compared a combined intervention of increased energy and protein intake. Vlaardingerbroek et al. investigated a short intervention of increased amino acid intake day one and lipid intake day one and two. This study demonstrated improved nitrogen balance but not growth rate from birth to 28 days and discharge.[187] Tan et al. did not demonstrate any significant improvement in weekly growth rates with mean energy intake 99 vs. 94 kcal/kg/day and mean protein intake 2.6 vs. 2.3 g/kg/day during postnatal days 1 to 28.[188] Morgan et al. reported improved head growth at 28 postnatal days, which was sustained at 36 weeks PMA in an intervention group that received hyperaliminated PN from randomization at about three days after birth. Differences in protein and energy intakes were most pronounced in the 2nd week of life. Mean total energy intake was 102 vs. 95 kcal/kg/day and mean protein intake was 3.2 vs. 2.9 g/kg/day during postnatal days 1 to 28. The effect on head growth was more pronounced in the younger stratum of infants born at 24-26 weeks of GA.[189] In a trial including both parenteral and enteral interventions, Moltu et al. demonstrated improved growth rates the first four postnatal weeks with higher energy and protein intakes.[190] The trial was stopped early due to septicemia and electrolyte disturbances in the intervention group.

Moltu et al.'s RCT also reported growth the first postnatal week. Growth rates in the intervention group were higher already by the first postnatal week and WSDS started deviating from about day 4 to 5, with significant difference from postnatal day 8. Mean energy intake was 92 vs. 79 kcal/kg/day and mean protein intake was 3.7 vs. 2.5 g/kg/day the

first postnatal week. In this study, WSDS decreased 0.6 SDS from birth in infants who received higher amounts of protein and energy compared to -0.8 SDS in the control group.[190] In the study by Morgan et al., energy intakes the first postnatal week was 74 vs. 68 kcal/kg/day and protein intakes 2.8 vs. 2.4 g/kg/day. Weight day 7 was reported, but the difference between the groups was only explored at 28 days and not statistically significant, mean difference 0.14 WSDS (95% CI -0.11-0.38; p = 0.28).[18]

Several observational studies have demonstrated association between energy and protein intake and growth. In a study of infants born between 1999 and 2001, weight, length, and HC differed at 36 weeks PMA between infants who received over 3 g/kg/day of amino acids before or later than five days postnatal age. Differences in amino acid intake between the groups persisted for ten days, and infants with higher amino acid intake also had increased total energy intake. Mean energy intake on postnatal days one to five was only 45 kcal/kg/day.[191] In a cohort of 1187 infants born before 28 weeks GA between 2002 and 2004 (the ELGAN Study), Martin et al. demonstrated that infants who received the least amount of protein, fat, and carbohydrates during the first postnatal week had the lowest growth rates between days 7 and 28.[192] In the study by Senterre et al., WSDS from day three to six weeks was influenced primarily by protein intake the first weeks of life in a multiple regression analysis.[113]

Oskar, one year old. ©Daniel Rådström

Hansen-Pupp et al. detected no correlation between nutrition and growth in a first phase of growth restriction, which lasted until PMA 30 weeks. A relationship between protein and energy intake during later weeks and catch-up growth was shown, and a correlation between levels of IGF-I and growth was detected in both phases.[73] Association between nutritional intakes and growth the first postnatal week was not investigated in these studies. In most studies, recommended intakes were not fully met, and recommendations were lower compared to present recommendations.

Stoltz Sjöström et al. showed that energy and protein intakes were associated with weight change day 0-7, day 8-28, and day 29-70 in analyses adjusted for GA at birth, baseline measurements, and severity of illness in the EXPRESS cohort.[110] Mean intake on postnatal days 0-7 was for energy 66 kcal/kg/day and protein 2.1 g/kg/day. ΔWSDS from birth to postnatal day 7 was -1.4 SDS according to Swedish preterm growth reference.[97]
A 10 kcal/kg/day increase in energy intake the first postnatal week corresponded with 0.28 higher WSDS at postnatal day seven, and 1 SD increase in energy percent protein was associated with 0.11 higher WSDS.[110]

1.6.4 Nutrition and ROP

In the ELGAN study, VanderVeen et al. demonstrated that energy intake at the lowest quartile the first 28 postnatal days was associated with increased risk of severe ROP, adjusted odds ratio (OR) 2.1 (95% CI 1.4–3.2).[177] The association between nutrition and ROP development has also been investigated in the EXPRESS cohort, and in this study a 10 kcal/kg/d increase in energy intake the first 28 postnatal days was associated with decreased risk of severe ROP, OR 0.76 (95% CI 0.65–0.90), adjusted for GA, BWSDS, transfusions, and days of MV.[193] In a RCT of higher initial infusion rate of parenteral lipids, the rate of ROP was lower in the intervention group that had a higher energy intake the first postnatal week.[194] A recent case-control study of 106 infants treated for ROP did not show any differences in growth rate, energy intake, or protein intake the first postnatal week between cases and controls.[195]

1.6.5 Nutrition and BPD

Several animal studies have presented evidence of associations suggesting that malnutrition may interact with other causative factors of BPD. Higher susceptibility to oxygen induced lung damage have been demonstrated in both undernourished mice and lambs.[196, 197] Reduced energy and protein intakes were associated with decreased lung protein synthesis in rats.[198]

There are few well-performed epidemiological studies of the association between early nutritional intakes and BPD. Uberos et al. found that higher energy intake the first two postnatal weeks was associated with reduced risk of BPD, but this study did not take early respiratory morbidity into account.[199] Ehrenkranz et al. investigated association between initial severity of illness, nutrition, and development of morbidities. Higher energy intake during postnatal days 1-7 was associated with reduced risk of BPD, adjusted for MV, and a range of other variables. The regression model also included an interaction term between days of MV and energy intake that was not significant in the association with BPD.[200] In another observational study, infants who developed BPD had lower energy intakes the first four postnatal weeks, adjusted for days of MV.[201] Infants in both of these studies were born during a period of significantly lower intakes of energy compared to present

recommendations. The RCT by Wilson et al. from 1997 did not demonstrate any reduction in pulmonary morbidity with higher and earlier initiation of parenteral nutrition.[36] In a recent RCT designed to study change in head circumference, hyperaliminated PN did not result in any difference in rate of BPD.[189]

SUMMARY – NUTRITION & GROWTH, ASSOCIATIONS WITH ROP & BPD

Poor postnatal weight gain has been associated with increased risk of ROP,[128, 174-177] and conflicting results have been demonstrated regarding postnatal weight development and risk of BPD.[111, 179, 180]

Most previous studies of nutrition and postnatal growth have not reported weight development the first postnatal week.[184, 185, 187, 191] A RCT with >10 kcal/kg/day difference in mean energy intake the first postnatal week combined with an increased PE ratio reported higher WSDS from postnatal day 8 for infants with higher nutritional intakes.[190] A few other RCTs, with smaller differences in nutritional intakes, have reported growth to postnatal day 7 without significant difference in early growth.[186, 188, 189]

Higher energy intake has been associated with reduced risk of ROP.[177, 193, 194] A few observational studies but no RCT have demonstrated a positive association between early nutritional intake and BPD.[200, 201]

1.7 OXYGEN AND SATURATION TARGETS

1.7.1 Oxygen

Fetal development takes place in a hypoxic environment. Fetal hemoglobin (HbF) has a higher affinity for oxygen,[202] and in utero blood is shunted to the most oxygen demanding tissues.[203] At birth, there is a transition from fetal circulation and an increase in partial pressure of oxygen. Compared to the fetus, the neonate has a higher cardiac output, metabolic rate, and oxygen consumption.[204, 205] Oxidative stress is an imbalance between anti-oxidants and oxidants. Preterm infants have an immature antioxidant system and few defenses to counter oxidative stress. Reactive oxidants are increased by inflammation, infection, hypoxia, and hyperoxia.[206] Oxygen toxicity and oxygenation of the tissues depends on oxygen saturation, blood flow, hemoglobin levels, and fetal hemoglobin concentration. The proportion of HbF in ELGA infants is 70-90%.[207, 208] Transfusion of erythrocytes have been demonstrated to lower the proportion of HbF from 90% to 40% in ELGA infants.[209] In the hypoxic infant, a higher proportion of HbF results in better oxygenation of the tissues.[210]

1.7.2 Monitoring of oxygenation

Different methods are available to monitor the level of oxygen in preterm infants. Arterial partial pressure of oxygen (PaO_2) can be measured in blood drawn from an arterial line. Transcutaneous oxygen measurement is a non-invasive method measuring direct partial pressure of oxygen at the skin surface. Neither of these methods are used to continuously monitor oxygen levels and detect rapid changes in the neonatal unit. Pulse oximetry measures light absorption in red and infrared wavelengths. Oxygenated and de-oxygenated blood absorbs light in the different wavelengths and a peripheral oxygen saturation (SpO_2) value is derived from the ratios of absorption.[211] Pulse oximetry is routinely used to monitor infants in neonatal units. The method has a rapid response time, but also has some issues of uncertainty. The probe placement may be of importance while interpreting SpO_2 values. Pre- and postductal oxygenation might differ due to PDA and pulmonary hypertension, but also in healthy preterm infants.[212] Rosychuk et al. demonstrated greater uncertainty in lower values of SpO_2 in a study comparing oxygen saturation levels in arterial blood (SaO_2) to SpO_2 levels in preterm infants. SpO_2 in the range of 85-89% corresponded to 2.4% lower SaO_2 (95% CI 11.6-6.8).[213] Quine et al. demonstrated that SpO_2 in a range of 91-95% would corresponded to PaO_2 of 35-67 mmHg.[214] Higher values of SpO_2 correspond to a wider range of PaO_2 values,[214-216] and the proportion of HbF affects the association between SpO_2 and PaO_2. The same SpO_2 corresponds to higher PaO_2 if the proportion of HbF is lower.[209]

1.7.3 Saturation target

In preterm infants who receive supplemental oxygen therapy, it is important to provide sufficient oxygen for growth and organ development and avoid hypoxemia while at the same time avoid hyperoxemia and oxygen toxicity. Several observational studies have demonstrated lower incidence of severe ROP when targeting lower SpO_2 the first postnatal weeks.[217-221] Two of the studies reported mortality before and after intervention without significant change in mortality rates.[218, 220]

To address the research question of saturation targets in preterm infants, five coordinated RCTs were initiated between 2005 and 2007.[222] In total, almost 5000 infants born with a GA <28 weeks were included in the NeOProM trials SUPPORT,[223] COT,[224], and BOOST-II (UK, NZ, AU).[225, 226] The studies aimed to compare target ranges of 85-89% and 91-95%. Infants were included within 24 hours in all trials and the intervention lasted up to 36 weeks PMA. All studies used a masking algorithm in the SpO_2 monitors.

The original masking algorithm resulted in increased stability and instability at end-points of target range and gave false high values of SpO_2 from 87% and up.[227] Three studies revised the algorithm (COT, BOOST-II AU, and UK). Revision was supposed to improve saturation targeting. In all of the trials, median SpO_2 was higher than targeted and there was significant overlap between the groups (Figure 6). An interim analysis was the result of concerns about safety after the publication of the SUPPORT trial as well as considerations to increase sample

size due to the revision of the algorithm. Two studies were stopped early (BOOST-II AU and UK) due to the interim analysis, which demonstrated increased mortality in the lower saturation target group.[228] There is a risk to overestimate the treatment effect if a trial is stopped early due to benefit of treatment.[229]

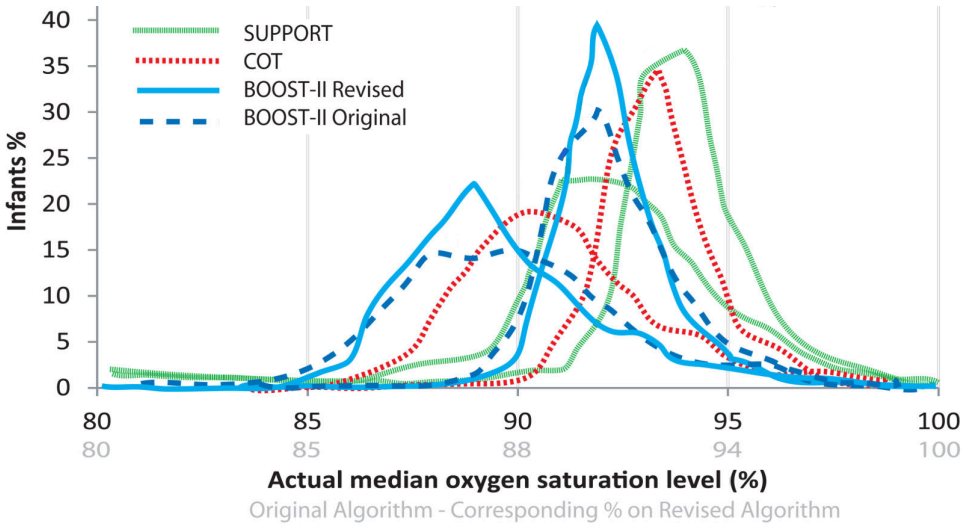

Figure 6. Distribution of median SpO_2 in the NeOProM trials

Figure adapted from Figure 4 in Lakshminrusimha et al.[230]

These issues have been the focus of some debate over the results. Several reviews and meta-analyses have been published.[231-236] Manja et al. graded the evidence as moderate to low in a review and meta-analysis from 2015.[232] In the most recent review, taking also previously unpublished information into account, Askie et al. rated the quality of evidence regarding mortality as high and quality of evidence regarding ROP as moderate.[234] Overall results from the five trials have demonstrated increased risk of ROP at higher saturation target and increased mortality at lower saturation target. Askie et al. found the RR to be 1.16 (95% CI 1.03–1.31) for death before discharge, the RR to be 0.72 (95% CI 0.61–0.85) for severe ROP, and the RR to be 1.24 (95% CI 1.05–1.47) for NEC.[234]

Other differences between the trials are enrollment and alarm settings. SUPPORT was the only trial that excluded infants born before 24 weeks GA. In SUPPORT, enrollment occurred before birth, which increased likelihood to include more vulnerable infants. In COT, more exclusion criteria were specified and included PPHN. Alarm settings differed in the five trials and were only mandated in COT.[236]

European guidelines were revised in 2013, adapting to the first results from the NeOProM trials.[237] The most recent guidelines, published in 2017, recommend saturation target range of 90-94% and suggest alarm limits of 89-95%.[238]

1.7.4 Adherence to target

In a review of compliance to oxygen saturation targeting by Van Zanten et al., time within target ranged between 31% and 75%.[239] Alarm limits closer to the prescribed targets increased the proportion of time spent within target range in a study by Hagadorn et al.[240] Nurse-to-patient ratio has been shown to influence adherence to target. More infants to care for resulted in more time above and less time within target range.[241, 242] In addition, educating nurses regarding guidelines and adverse effects of hypo- and hyperoxemia have been identified as a factor that may increase adherence to target.[243, 244] In a multicenter quality improvement effort, a structured implementation of policies was shown to have a positive effect on compliance.[245] Time within target can also be increased if there is an implemented guideline of response to SpO_2 outside of target range,[246] and several studies have shown that automated regulation of inspired oxygen increases the proportion of time spent within the target.[247-249]

Apnea is common in ELGA and VLGA infants and the incidence is higher in more immature infants.[250] Apnea in combination with bradycardia and desaturation might warrant an intervention of increased oxygen flow. Van Zanten et al. demonstrated that in 80% of the cases SpO_2 increased to ≥95% when extra oxygen was given following an hypoxic episode, and that the hyperoxia was of longer duration than the preceding hypoxia.[251] Fluctuations in oxygen tension might influence the development of disease. Di Fiore et al. have demonstrated an association between a higher number of hypoxic events and increased risk of ROP, requiring treatment in infants born in GA 24 to 28 weeks.[252, 253] Other studies have also shown increased variability of PaO_2 and TcO_2 the first postnatal weeks in infants developing ROP,[254-256] and in animal models of ROP development, higher variability in FiO_2 and PaO_2 have been associated with disease.[257, 258]

1.8 CONCEPTS OF EPIDEMIOLOGY

1.8.1 Causality

One major objective in medical research is to better understand the path leading to disease, and to use that understanding to try to prevent disease development. Causality is the relation of cause and effect, and in epidemiology exposure is the variable examined as a potential cause of an effect and the outcome is the result.[259] Reality is seldom as simple as only one exposure causing an effect. The causal mechanism can be illustrated as various sets of exposures acting in concert to cause an outcome.[260] Several different combinations of exposures can be sufficient to cause the outcome, and some might interact and depend on each other. A necessary cause is an exposure that must be present for the outcome to occur.[260]

1.8.2 Study design

The aim while planning a study is to set up the best possible design to answer a specific research question. A RCT is considered the best design to identify causal relationships and to

answer if an intervention is efficient in preventing or treating a disease. This design is not always feasible. To demonstrate effect in rare outcomes, a large number of subjects need to be included, and some outcomes develop over long periods of time and the cost to set up large trials might not be reasonable. Complex interrelated exposures might also be difficult to examine in RCTs, and results from a selected population included in a trial might not be generalizable to other populations.

Many studies in the field of neonatal research are cohort studies. In cohort studies, a defined group of people with different levels of exposure, is followed over time and influence of exposure on outcome is studied.[259] As in all observational studies, it is not possible to completely eliminate confounding factors. Careful selection of variables and statistical models increases the probability to find true or causal associations between exposure and outcome.[261] If well performed, cohort studies may contribute to improved quality of care and the results may increase the knowledge of disease development, information that can be used to improve the design of future studies.

1.8.3 Bias and confounding

Bias are systematic errors affecting the validity of a study. Covariates that are associated to both the exposure and the outcome and that are not intermediate factors are called confounders.[259] If these factors are known, it is possible to use statistical methods to evade the effect of the confounding variable from the studied association between exposure and outcome. Residual confounding factors – i.e., factors that are unknown or impossible to measure – may be handled in a well-designed RCT, but not in a cohort study. The randomization will distribute residual confounding factors evenly between the groups.

The exposure, by definition, always occurs before the outcome. In nutritional research, the exposure of interest (i.e., nutrient intake) is a varying series of events over time. Confounding factors may occur before or during that time. A problematic type of confounding is confounding by indication, when there is an inherent difference in those exposed and not exposed in an observational study.[259]

1.8.4 Interaction

If the association between exposure and outcome differs in relation to another factor, this factor modifies the effect, i.e., an interaction is present. The biological basis of interaction is that several causal components participate in a causal mechanism, and the effect of some causes may vary depending on the conditions.[261] Effect measure modification – i.e., how the effect changes over values of another factor – can be examined using an interaction term in the statistical model and evaluated by stratification. In statistics, interaction usually refers to the effect leaving the additive scale. The interpretation depends on the scale in the statistical model.[262]

1.8.5 Directed acyclic graphs

Directed acyclic graphs (DAGs) is a method to visualize variables that can be associated with exposures and outcomes. The network of possible associations as well as the time-line is not always easy to distinguish, but important while trying to identify possible confounders. The aim is a better understanding and a more correct selection of covariates to include in the statistical model. The DAG helps identify predictors that are important to include in the model and can also identify over-adjustment.[263, 264]

Each event in a DAG is illustrated as a circle and associations are illustrated as arrows. DAG is a simplified model that presumes associations with one-way directions; however, reality is often more complex and the associations are rarely known facts. Simple DAGs do not take interactions into account.[265]

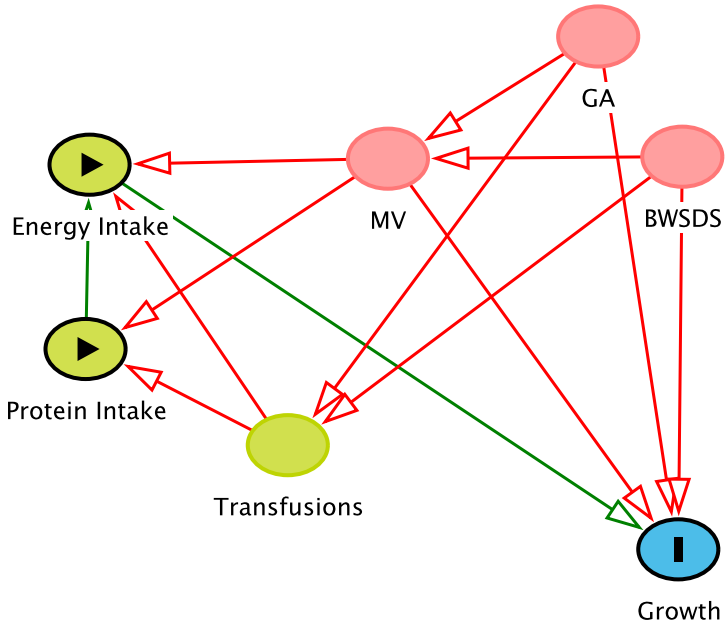

Figure 7. Example of DAG.

Exposure variables: energy and protein intake.
Outcome variable: growth.
Other covariates considered in the model: gestational age (GA), birth weight standard deviation score (BWSDS), transfusions, and mechanical ventilation (MV).
Arrows represent assumed associations.
In this framework, adjustment for GA, BWSDS, and MV or transfusions and MV would be sufficient.

1.8.6 Statistical concepts

Statistical methods are used to examine associations between exposures and outcomes or differences between groups. All analyses are subject to random error. The confidence interval gives the range within which the point estimate is, with a certain level of confidence. The p-value specifies the probability that the estimate from the statistical model would be the same or more extreme, given that the null-hypothesis was to be correct. A type I error is to reject the null-hypothesis when the null-hypothesis is true, and a type II error is to not reject the null-hypothesis when it is false. The risk of type I error is the significance level. A common significance level is 5%, at which the null-hypothesis is rejected if the p-value is below 0.05. Statistical models can give estimates of precision, but do not provide information regarding systematic error.

Regression models are used to estimate how the exposure is associated with the outcome, and regression models can be used to obtain estimates of associations or estimates of risk. Calculated regression coefficients can also be used to predict outcomes from given values of exposure. Predictions from regression models are mainly valid among values within the range of the studied data. Linear regression models can be used with continuous outcomes. A simple model assumes an equal association over the entire range, a straight line. One method to enable the model to adapt to non-linear associations is to introduce splines,[266] which gives the model pivot points in which an association is allowed to change direction.

Dependent data refer to dependence between observations within a variable. For example, in longitudinal data with multiple observations over time, the repeated measurements from one individual have an intra-individual dependence. Dependent data can be accounted for using several statistical models such as the Mixed-Effects model, a flexible regression model with several advantages. The model can handle multilevel dependence in the data, is flexible regarding missing observations, and enables estimation of differences in cluster-level variables.[267]

2 AIMS

The general aim of this thesis is to increase the knowledge regarding neonatal practices with the potential to improve outcome for extremely preterm infants. The thesis focuses on early nutrition and saturation targets and investigates implemented changes and associations with growth, ROP, and BPD.

Specific aims:

Paper I

- To describe postnatal growth in preterm infants and to examine variations related to gestational age, postnatal age, and birth weight standard deviation score.
- To examine whether infants with retinopathy of prematurity and bronchopulmonary dysplasia developed postnatal growth restriction compared to infants without disease.

Paper II

- To assess whether higher energy and protein intake the first week of life reduces the initial weight loss in extremely preterm infants.
- To investigate whether higher intakes of energy and protein the first week and month are associated with reduced risk of ROP and BPD in extremely preterm infants.

Paper III

- To describe nutritional interventions in Stockholm between 2004 and 2011 and to demonstrate if intakes of energy and macronutrients have increased in extremely preterm infants.

Paper IV

- To demonstrate whether higher saturation target was associated with higher SpO_2 and more time with hyperoxia in preterm infants.
- To examine whether target range and alarm limits were associated with variability and hypo- and hyperoxic episodes.
- To investigate whether altered saturation targets were associated with increased rates of ROP.

3 RESEARCH APPROACH

All four papers in this thesis are cohort studies. Paper II and III are based on a regional cohort of infants born in Stockholm between 2004 and 2011. Paper IV included infants cared for at two of the neonatal intensive care units in Stockholm between 2013 and 2015. Paper I included data from infants born in both North America and Sweden between 2004 and 2012. Paper I and IV included ELGA and VLGA infants with GA ≥23 weeks and <31 weeks. Paper II and III included ELGA infants with GA <27 weeks.

3.1 DATA COLLECTION

Infants in all studies had eye exams according to routine protocol, and ROP was classified according to the international system.[122] The basis for treatment were the recommendations from Early Treatment of Retinopathy of Prematurity Cooperative group.[268] BPD was defined as need for supplemental oxygen at a PMA of 36 weeks.[141]

3.1.1 Paper I

Paper I combined data from five cohorts of preterm infants born in North America and Sweden[171-174, 269]. The analyses included data from infants born at GA 23 0/7 to 30 6/7 weeks, alive to 40 weeks PMA, without severe malformations, hydrocephalous, or missing data regarding BW, ROP, or BPD. Data outliers were examined with the use of population and individual residuals and excluded if deemed unrealistic. Infants with more than two registered weight measurements considered to be unrealistic were excluded from analyses of postnatal growth (Figure 8).

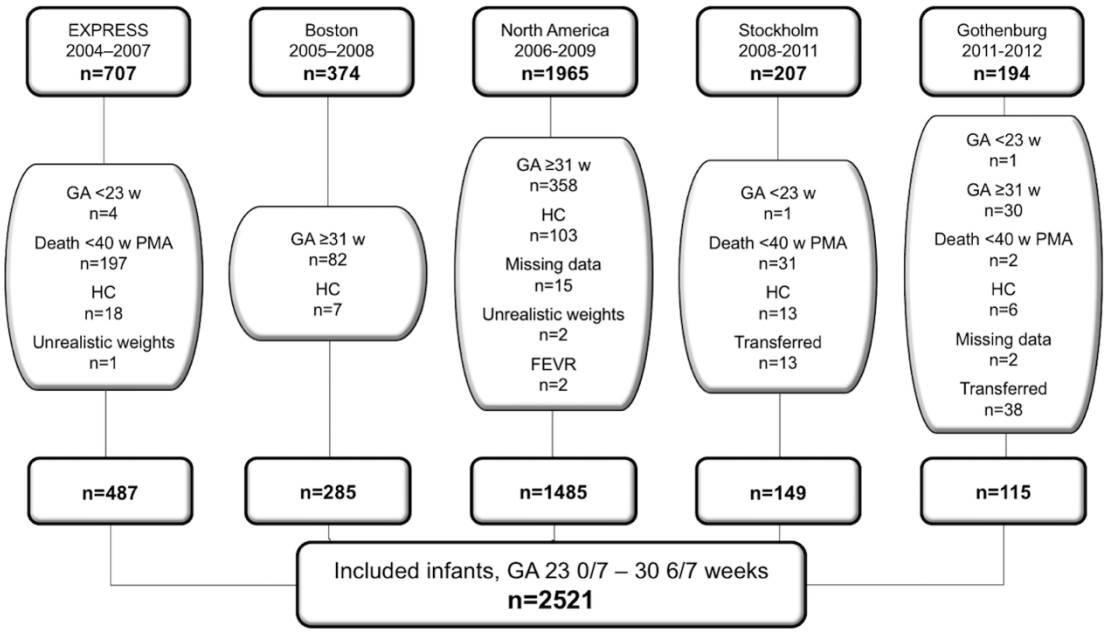

Figure 8. Flowchart of infants included in Paper I

HC: hydrocephalous; FEVR: familial exudative vitreoretinopathy

Paper I defined ROP as any stage of ROP as compared with no ROP. This thesis also presents additional results comparing growth of ELGA infants with severe ROP (stage ≥3) and no/mild/moderate ROP (stage <3). BWSDS was calculated from a Swedish growth reference based on intrauterine ultrasound measurements.[95] SGA was defined as BW below 2 SDS. Postnatal growth was evaluated as differences in weight and growth rates. Growth rates were calculated assuming exponential growth between measurements.[105] Mean number of weight measurements per infant was 14.3 (median, 11; 25th-75th pctl, 9-16), and mean duration of weight measurement registration was until PMA 37+6 weeks (25th-75th pctl, 36+0 to 39+5 weeks). NEC was defined as stage II or higher according to modified Bell's stage criteria.[154]

3.1.2 Paper II & III

Paper II and III included all infants born in the Stockholm region before 27 0/7 weeks of GA, who survived >24 hours. One tertiary unit in Stockholm handled all deliveries of ELGA infants and three additional units participated in the care for preterm infants. Infants who were born between April 1, 2004 and March 31, 2007, who were also included in EXPRESS,[4] and infants born between January 1, 2008 and December 31, 2011 were studied. Since PN compositions were inaccessible for infants born from April 2007 to December 2007, infants born during that period were not included in the cohort. Exclusion criteria in all studies were chromosomal anomalies, severe malformations, missing nutritional data, and death during postnatal days 0-3. Other exclusions depending on the studied outcome are outlined in the flowchart (Figure 9).

Perinatal and neonatal data were gathered from the quality register SNQ, Stage of ROP, BPD, NEC, and sepsis were confirmed by chart review. All parenteral and enteral intakes registered in hospital records as well as all anthropometric measurements were registered in nutrition calculation software (www.nutrium.se, Nutrium AB, Umeå, Sweden). Intakes were registered daily until day 27 and thereafter once a week until discharge, death, transfer to a hospital outside the Stockholm region, or unaccountable amounts of enteral feeds due to breast feeding. Amino acids were counted as protein in all analyses. Energy contents in macronutrients were calculated as 4 kcal/g protein, 9 kcal/g fat, and 4 kcal/g carbohydrates. Nutrient content of transfusions was included in analyses in Paper II. The content of energy was estimated as 18 kcal per 100 ml erythrocytes and 28 kcal per 100 ml plasma or thrombocytes and the content of protein was estimated as 4.1 g per 100 ml erythrocytes and 6.9 g per 100 ml plasma or thrombocytes.[270, 271] Paper III reported nutrient intake without considering transfusions.

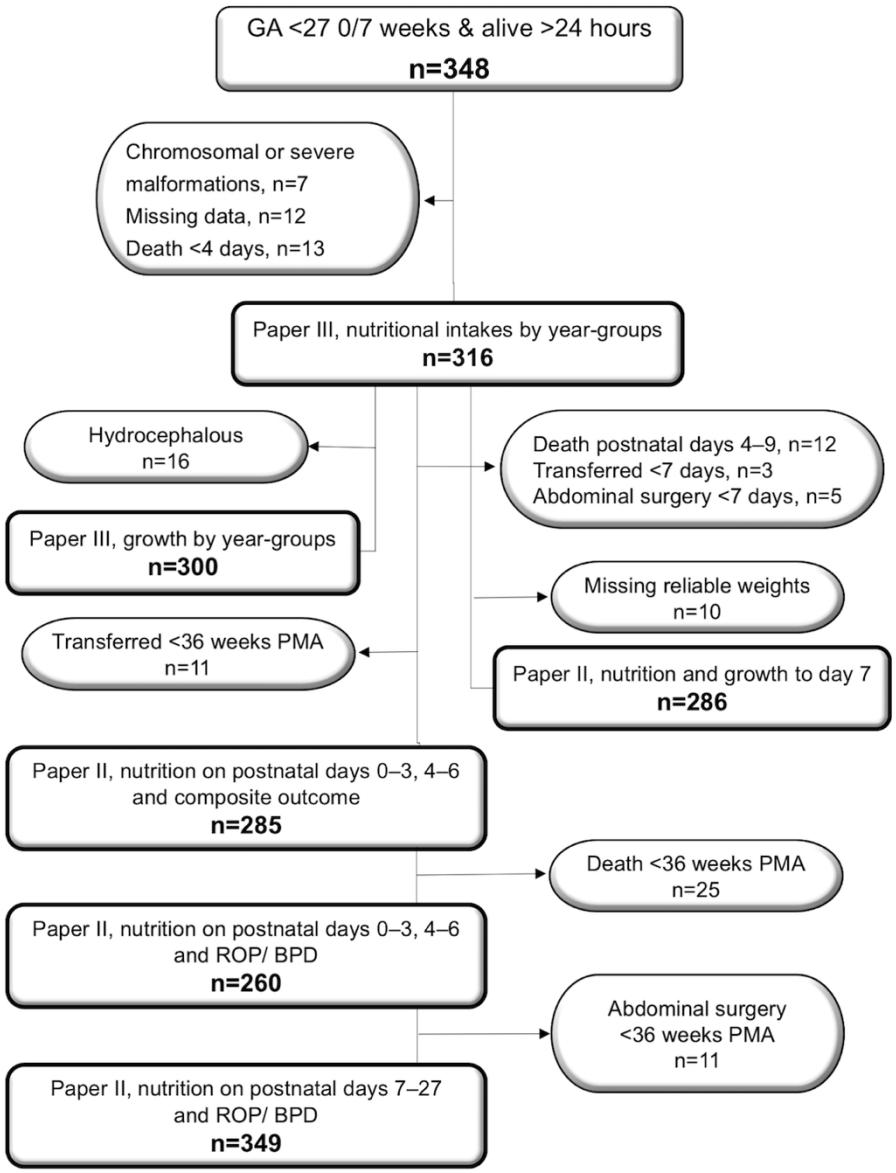

Figure 9. Flowchart of infants included in Paper II and III

Mid-infrared spectrophotometry was used to analyze human milk content (MilkoScan 4000, FOSS Hillerød, Denmark) at Eurofins Steins Laboratory AB, Jönköping, Sweden.[83] If MOM had not been analyzed, the average content of breast milk samples from mothers of ELGA infants, expressed before or after 28 postnatal days, were used in nutritional calculations.[83] Definition of full enteral feeds was cessation of parenteral nutrition or enteral volume 150 ml/kg/day. WSDS was calculated from the revised Fenton growth chart.[96] Postnatal periods of specific interest were days 0–3, days 4–6, and days 7–27.

3.1.2.1 Nutritional care

Local and international guideline updates as well as other interventions aiming to affect nutritional care between 2004 and 2011 were identified. Most changes were implemented as a continuum and at different time-points in the different sites. In Figure 10, interventions are stated from the first time-point implemented at any of the four neonatal care units. Local

guidelines were revised following international guidelines. One major change was the recommendations of higher amounts of amino acids and lipids from the first day of life. In The 2006 local guidelines recommended the initiation of 2.0 g/kg/day amino acids and 0.5-1.0 g/kg/day lipids from day 0. Increase to 4.0 g/kg/day of amino acids was recommended within 2-3 days and increase to 3.5 g/kg/day of lipids within 4-5 days. Parenteral solutions were individually subscribed by the neonatologist on call and ordered from the pharmacy on weekdays. Starting in 2009, a standardized parenteral nutrition solution was available to facilitate early start of parenteral provision of amino acids.

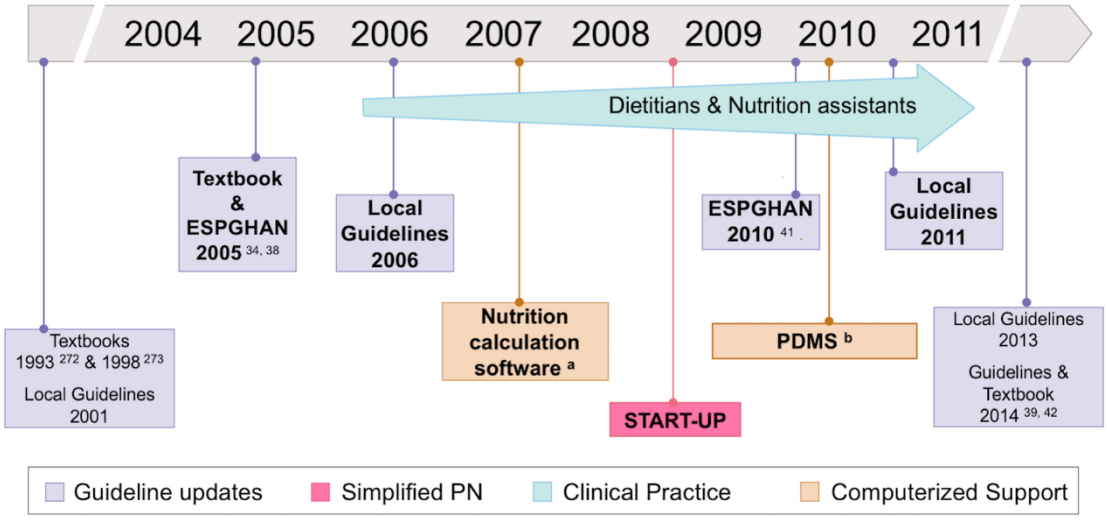

Figure 10. Interventions affecting neonatal nutrition between 2004 and 2011

[a] Nutrition calculation software, Nutrium™ (www.nutrium.se, Nutrium AB, Umeå, Sweden)

[b] PDMS: Patient data monitoring system, Clinisoft (Centricity Critical Care Clinisoft, GE Healthcare)

Trophic feeds were recommended from the first day of life during the entire study period. First choice of enteral nutrition was MOM; if unavailable, infants were fed DM. A first analysis of MOM was recommended at postnatal day 7 to 14, and thereafter every other week. The recommendations regarding fortification was altered in 2010 from initiation of fortification at full enteral feeds to initiation when enteral feeds contributed 75% of total intake. Fortification was calculated and prescribed by a neonatologist or a dietitian. From late 2007, a full time neonatal dietitian was employed at three of the four units, and improved education of nutrition assistants working in the ward kitchens was also initiated. Computerized support was enhanced during the later years. A web-based program (Nutrium™) was introduced starting in 2007 to facilitate nutritional calculations. Starting in 2010, two of the four units began using Centricity Critical Care Clinisoft (GE Healthcare), an electronic patient data monitoring system (PDMS). Parenteral and enteral intakes were registered in the PDMS, which simplified monitoring of nutritional intake.

3.1.3 Paper IV

Infants in this study were born between January 1, 2013 and December 31, 2015. Inclusion criteria were GA between 23 0/7 and 30 6/7 weeks and registration in the PDMS at Karolinska University Hospital sites Solna or Huddinge within 12 hours from birth. Infants with severe malformations of the heart or lungs, infants without supplemental oxygen, and infants with none of the studied target ranges or more than one alteration in target range were excluded (Figure 11). The analyses included time up to a postnatal age of three weeks or to completed supplemental oxygen treatment, transfer to another hospital, or 24 hours prior to death.

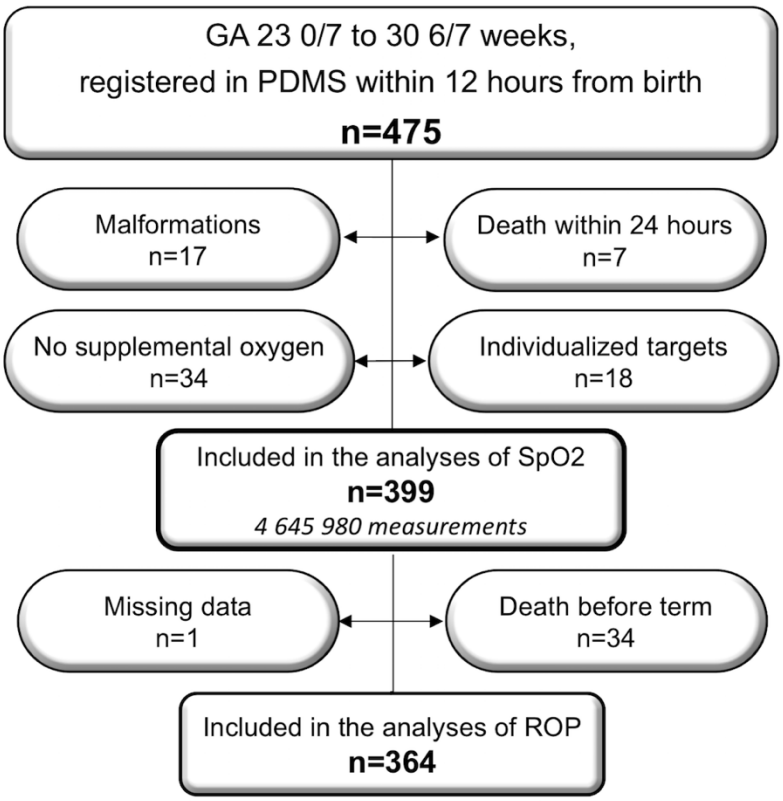

Figure 11. Flowchart of infants included in Paper IV

Data regarding GA, BW, malformations, time of death, and validated maximum stage of ROP were gathered from the Swedish quality registers SNQ and SWEDROP. In one infant, neonatal data were gathered from the chart. Pulse oximetry was used for continuous monitoring of SpO_2, and values were registered in the PDMS every other minute. Prescribed saturation target range, alarm limits, and SpO_2 at all registered time points were extracted from the PDMS. The principal target range prescribed in 2013 was 88-92% with associated alarm limits of 85-95%. Local guidelines were updated in November 2013 with a recommended target range of 90-94% with alarm limits of 89-95%. After updating guidelines, the target range of 90-95% with associated alarm limits of 89-96% was prescribed during 95% of the time. If supplemental oxygen were administered using nasal cannula with a flow lower than the weight of the infant, effective FiO_2 was calculated using the formula FiO_2=21+ (Flow(L/min)* (FiO_2given -21)/Weight(kg)) adopted from Benaron-Benitz[274].

3.2 STATISTICAL METHODS

All results are stated with 95% CI and p-values. P-values <0.05 were considered statistically significant.

3.2.1 Paper I

A linear regression model with robust standard errors was used to estimate differences in BWSDS. Mean weekly growth rates were calculated and used to identify weeks of highest growth rates and average growth rate during the neonatal period. Mean between-group differences in weight and growth rate over time were estimated using a mixed effects model, including all weight measurements and restricted cubic splines (knots at 2, 4, 6, and 10 weeks).[266, 267]

Covariates included in all analyses were exact GA in days, BW, sex, and center. BWSDS and NEC were considered as potential confounders in analyses of weight development and growth rate. Country and date of birth were also considered as potential confounders but did not alter the estimates and were not included in the final analyses. Interaction of BWSDS or country in the association between exposure and outcome was tested. Because none of the interaction terms were significant, they were not included in the final model.

The results were divided into three groups by GA at birth: 23 to 24 weeks; 25 to 26 weeks; and 27 to 30 weeks. The groups were selected based on results from analyses stratified by every gestational week.

3.2.2 Paper II

Paper II used Linear and Poisson regressions with robust standard errors to study the outcomes of interest.[275] If energy intake was significantly associated with outcome, association with protein intake was evaluated as energy to protein ratio and with an interaction term. Weight on postnatal day 7 was calculated assuming an exponential growth pattern between measurements within two weeks, if there was no measurement on postnatal day 7.[105]

The association with risk of ROP was examined as both risk of any ROP and severe ROP. Calculated differences in relative risk were expressed as risk ratios (RR). DAGs were used as a tool to select covariates to include in the regression models. Antenatal corticosteroids, exact GA in days, BWSDS, sex, fluid intake, transfusions of erythrocytes and plasma, and days of MV were covariates considered as potential confounders. Linearity in the models were tested using natural cubic splines.[266] Potential interaction of MV and of fluid intake in the association between exposure and outcome was tested and supplemented with stratified analyses if the interaction term was significant. Analyses including adjustment for period of birth were also reported. Time period (2004–2007 and 2008–2011) was included as a factor variable, and an interaction term between energy intake and time period was included to test differences in association between time periods.

3.2.3 Paper III

Data were analyzed in two-year periods. The median and the 10^{th} and 90^{th} percentiles were presented to best illustrate the data. Quantile regression with bootstrapped confidence intervals was used to examine differences in nutritional intakes.[276] Differences in growth were examined in a mixed effects model including restricted cubic splines.[266, 267]

3.2.4 Paper IV

Individual daily mean values of SpO_2 were calculated. Differences in SpO_2 and proportions of time with defined SpO_2 levels were analyzed using linear and quantile regression with cluster-robust standard errors. Analytic weights were used in the linear regression models giving more weights to infants with more time in a certain target range.[277] Average hourly absolute change, calculated as $T-1\Sigma t|SpO_2t\text{-}SpO_2t\text{-}1$, where the subscript t represents hours since birth and Σt indicates the sum over the T time-points, was used to measure variability. In the analyses of ROP, infants who survived to term age were allocated to the target range prescribed during the first postnatal week. The first postnatal week was selected to reduce potential influence from a later adaptation of saturation target to clinical conditions. Logistic regression was used to analyze differences in ROP and death, and these analyses were adjusted for GA and BW.

3.3 METHODOLOGICAL CONSIDERATIONS

Data were obtained retrospectively in all studies but registered in charts and PDMS prospectively. Data registered manually in charts is reliant on correct transcriptions. In paper IV, probe placement was not reliably registered in the PDMS. In paper II and III, nutritional data were visually reviewed for outliers, and extreme values cross-checked with all available information in the charts.

It is reasonable to assume that nutrition practices were continuously altered over time in Paper I. Differences in morbidity and growth between centers might reflect both differences in regional practice and in birth year. Adding date of birth as a covariate in the model did not alter the results. In paper II, associations between specific intakes of energy and protein were initially investigated with adjustment for known confounders, but without birth year. Date of birth covaried with intakes of protein and energy. No major changes in saturation targets or mode of ventilation were implemented between 2004 and 2011. The regression model enabled detailed and stratified analyses, but unknown factors related to neonatal care that might have changed between 2004 and 2011 were not adjusted for. To reduce potential residual confounding, time period was included as a factor variable in supplemental analyses.

A strength in paper I was the large number of infants, including a large number of ELGA infants, which enabled analyses stratified by gestational age group. In paper I, differences between growth and morbidity were examined in three strata of GA. Time was handled as a

continuum, and the graphic presentations illustrate the differences successively developing over time. A large cohort of preterm infants was studied in paper IV, but in relation to the NeOProM trials, the number of ELGA infants in our study was relatively small. The absence of significant difference might be due to a type II error.

In papers I and II, growth was evaluated as weight development, and no analyses regarding length, head circumference, or body composition were performed. Infants in the studies were not weighed daily. More severely ill infants may not be weighed as regularly as healthier infants, introducing uncertainty in the interpolated weights. The exponential model of growth, used to calculate growth rates in paper I and interpolate weights in paper II, have been demonstrated to fit neonatal growth data.[105] Papers I, II, and III used different methods of data modeling to study growth. The use of mixed effects models of growth is a strength in the studies, since missing measurements are less likely to affect the results. Papers I and III modelled the non-linear nature of growth using restricted cubic splines at selected weeks. Restricted splines were deemed to fit the data better than evenly distributed knots, based on knowledge of neonatal growth patterns with more variations during the first postnatal weeks, and a limited number of splines ensured a robust statistical model.

Two different pulse oximeter algorithms were in use during the study period in paper IV. In addition, the quantification of hypoxic and hyperoxic episodes is imprecise since data points were only registered every other minute. Furthermore, analyses of differences in shorter hypoxic episodes were not feasible.

The choice of growth reference may influence the results. In the study of BWSDS in paper I, a fetal growth reference was selected to reflect undisturbed fetal growth. The use of weight development and growth rates to study postnatal growth means there is no need to select a growth reference, but differences in growth rates are not as intuitive as divergence in WSDS. In papers II and III, the revised Fenton growth chart suggested by Cormack et al. was used.[278] In paper II, initial growth restriction was evaluated as growth to postnatal day 7. The selection of a specific day made it easier to select variables for the model, although this strategy might not reflect the true nadir of initial weight development.

Diagnosis of ROP is based on visual observation of disturbed vascular development of the retina. Pulmonary development is more difficult to study in similar detail. The diagnosis of BPD is based on physiological observation. An oxygen test to define the need for supplemental oxygen at 36 weeks PMA was not used in any of the studies in this thesis.

In Sweden, blood and plasma transfusions are given liberally and in higher volumes than estimated blood losses. Blood products – particularly albumin, plasma, and thrombocytes – have a high protein content. Because paper II aimed to examine the association between total energy and protein intake and outcome, blood products were included in nutritional calculations. We do not know to what extent protein from blood products is used in the protein metabolism of ELGA infants, and a limitation in paper II is the lack of information regarding blood losses. In paper III, blood products were not included in nutritional

calculations because the aim was to demonstrate change in prescribed and received nutritional intakes. A limitation in paper III is the lack of information regarding the exact timing of implementation of changes in nutritional practice.

Confounding by indication might be a problem in observational studies of nutritional intakes and associations with outcome. For example, healthier preterm infants may tolerate higher amounts of enteral nutrition. In paper II, we attempted to handle potential confounding by indication by including covariates related to severity of illness and by examining interactions.

A strength in papers II and III is that all ELGA infants that were born and cared for in the Stockholm region were included. The generalizability of the results might still be limited since infants were born between 6 and 14 years ago. Paper IV included a selected population from the two centers responsible for surgical and tertiary neonatal care in Stockholm and this might limit the generalizability of the results.

4 RESULTS AND DISCUSSION

4.1 RESULTS

4.1.1 Paper I, growth

In paper I, 52% of the infants were ELGA (Table 3). ELGA infants had 0.6 SDS (95% CI 0.5–0.7; p<0.001) higher mean BWSDS compared to the more mature infants. Mean growth rate from birth to 36 weeks PMA was 14 g/kg/d for ELGA infants and 13 g/kg/d for VLGA infants. ELGA infants had highest growth rates at PMA 30 to 31 weeks, and VLGA infants had highest growth rates the fifth postnatal week. SGA infants had higher mean growth rate the first three postnatal weeks compared to infants born AGA, a difference of 3.4 g/kg/day (95% CI 3.0–3.8; p<0.001).

Table 3. Characteristics of infants in paper I

	ELGA		VLGA
Infants, n (%)	GA 23–24 weeks 431 (17)	GA 25–26 weeks 881 (35)	GA 27–30 weeks 1209 (48)
BW, gram, mean (sd)	652 (97)	826 (158)	1185 (289)
BWSDS, SDS, mean (sd)	-0.6 (1.1)	-1.1 (1.3)	-1.5 (1.4)
No ROP, n (%)	26 (6) [a]	235 (27) [b]	824 (68)
ROP stage 1–2, n (%)	171 (40) [a]	451 (51) [b]	343 (28)
ROP stage ≥3, n (%)	234 (54) [a]	195 (22) [b]	42 (3)
BPD, n (%)	351 (82) [c]	597 (68) [d]	320 (26)

[a] Total 430 infants, information regarding ROP missing from one infant; [b] Total 880 infants, information regarding ROP missing from one infant; [c] Total 429 infants, information regarding BPD missing from two infants; [d] Total 874 infants, information regarding BPD missing from seven infants.

4.1.2 Paper I and II, growth and morbidity

4.1.2.1 ELGA infants

In infants born in gestational weeks 23 and 24, there was no difference in BWSDS between infants with or without ROP or BPD, but a difference in weight developed over time. Infants with ROP had lower growth rates during postnatal weeks 7 to 9 compared to infants who did not develop any stage of ROP (Table 4). Figure 12 depicts the growth trajectories for ELGA infants with ROP stage ≥3 and ROP stage <3. Mean weight was -49 gram (95% CI -83 to -16; p=0.004) lower at the 6th postnatal week, and -100 grams

(95% CI -145 to -54; p<0.001) lower at the 9th postnatal week for infants in gestational week 23 and 24 with ROP stage ≥3. The weight difference between infants with and without BPD born in gestational weeks 23 and 24 were not as evident. Infants with BPD had -60 grams (95% CI -110 to -9; p=0.02) lower weight at the 7th postnatal week and -80 grams (95% CI -141 to -20; p=0.01) lower weight at the 9th postnatal week in analyses adjusted for exact GA, sex, center, and NEC. There was no statistically significant difference in growth rates between infants who developed or did not develop BPD.

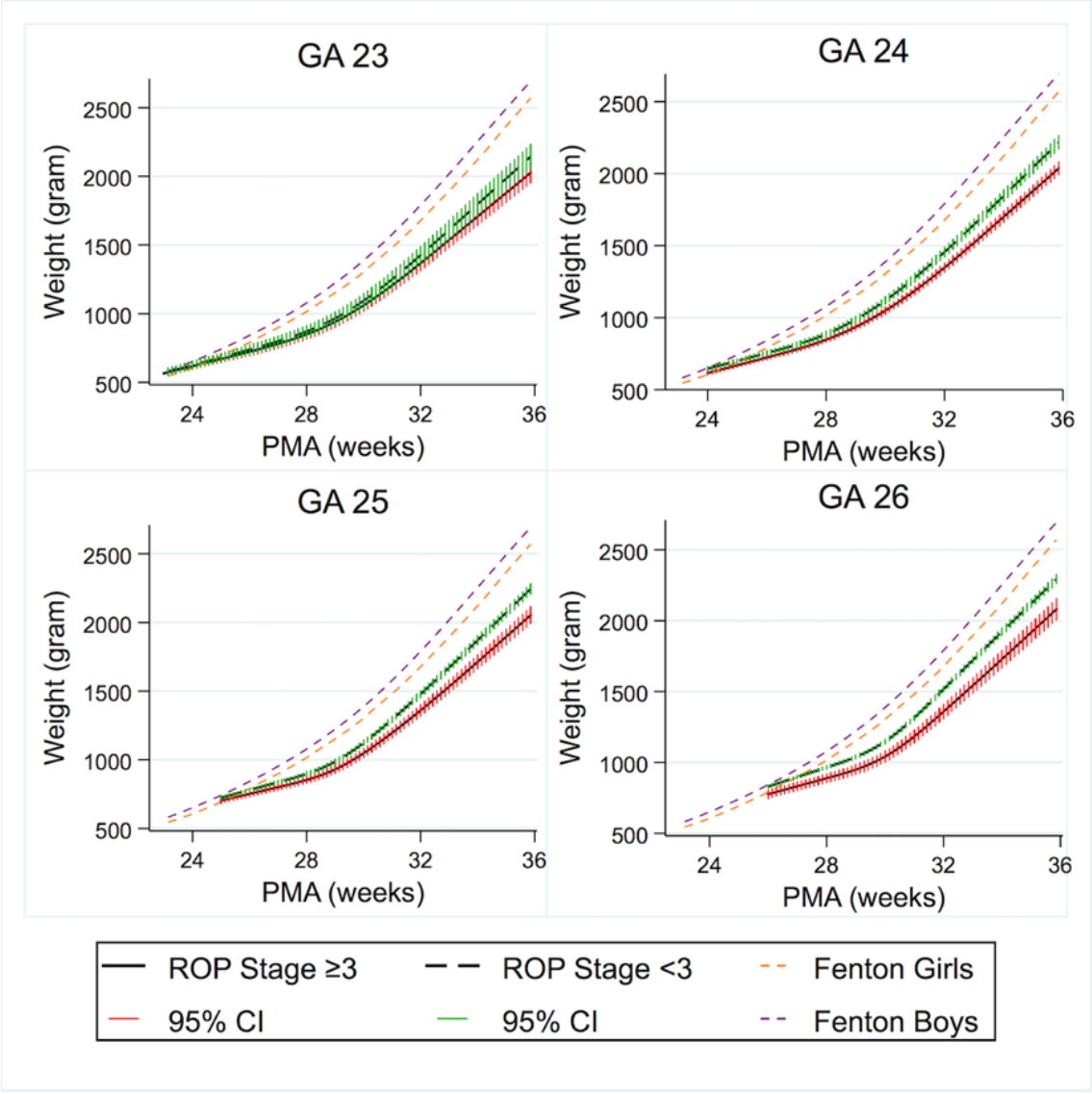

Figure 12. Growth trajectories by gestational week at birth demonstrate lower weight gain in infants with severe ROP (stage ≥3) compared to no/mild ROP (stage <3).

Reference values from the revised Fenton growth chart for girls (orange) and boys (purple).[96]

Infants born in gestational weeks 25 and 26 who developed ROP had -0.4 SDS (95% CI -0.6 to -0.2; p<0.001) lower BWSDS compared to infants who did not develop ROP. The growth rates for infants with ROP were lower during postnatal weeks 4 to 6

(Table 4). Infants born in gestational weeks 25 and 26 with BPD had -0.4 SDS (95% CI -0.5 to -0.2; p<0.001) lower BWSDS compared to infants without BPD. At birth, weight was -35 grams (95% CI -55 to -14; p<0.001) lower, and the 6th postnatal week the difference was -70 grams (95% CI -101 to -39; p<0.001), but there was no statistically significant difference in growth rates between infants who developed and did not develop BPD.

For ELGA infants, the weeks with statistically significant differences in growth rates between infants with and without ROP coincided with the postnatal weeks of highest growth rates at around PMA 30 to 31 weeks.

Table 4. Growth rates for infant with different stages of ROP born in gestational weeks 23 to 24 and 25 to 26 during the postnatal weeks of highest growth rates.

		No ROP	ROP stage 1–2	ROP stage ≥3	No ROP vs ROP stage ≥3	
	Postnatal week	Growth Rate (g/kg/day)			Difference (95% CI)	p-value
GA 23-24 weeks	6th	19.1	18.1	17.3	-1.8 (-4.2 to 0.7)	0.161
	7th	20.1	18.1	17.2	-2.8 (-5.2 to -0.4)	0.021
	8th	20.0	17.6	16.7	-3.2 (-5.9 to -0.5)	0.020
GA 25-26 weeks	4th	17.9	16.0	15.0	-2.9 (-4.3 to -1.4)	<0.001
	5th	21.6	19.2	18.0	-3.7 (-5.3 to -2.2)	<0.001
	6th	21.3	19.4	18.6	-2.7 (-4.0 to -1.5)	<0.001

Difference in growth rate between infants with no ROP and severe ROP stated with 95% confidence intervals. Results from analyses adjusted for exact GA in days, sex, center, NEC, and BWSDS.

In paper II, change in WSDS from birth to postnatal day 28 was calculated for the included ELGA infants. An increase in WSDS of 0.1 from birth to 28 days was associated with 7% (95% CI 2–11; p=0.004) lower risk of severe ROP. ΔWSDS to postnatal day 28 was not associated with risk of BPD.

4.1.2.2 VLGA infants

Infants born in GA 27 0/7 to 30 6/7 with any stage of ROP had -0.6 SDS (95% CI -0.8 to -0.4; p<0.001) lower BWSDS compared to infants with no ROP. Infants with BPD had -0.7 SDS (95% CI -0.9 to -0.5; p<0.001) lower BWSDS compared to infants without BPD. Figure 13 illustrates unadjusted weight development between infants who developed any stage of ROP or BPD and infants who did not develop either of these morbidities.

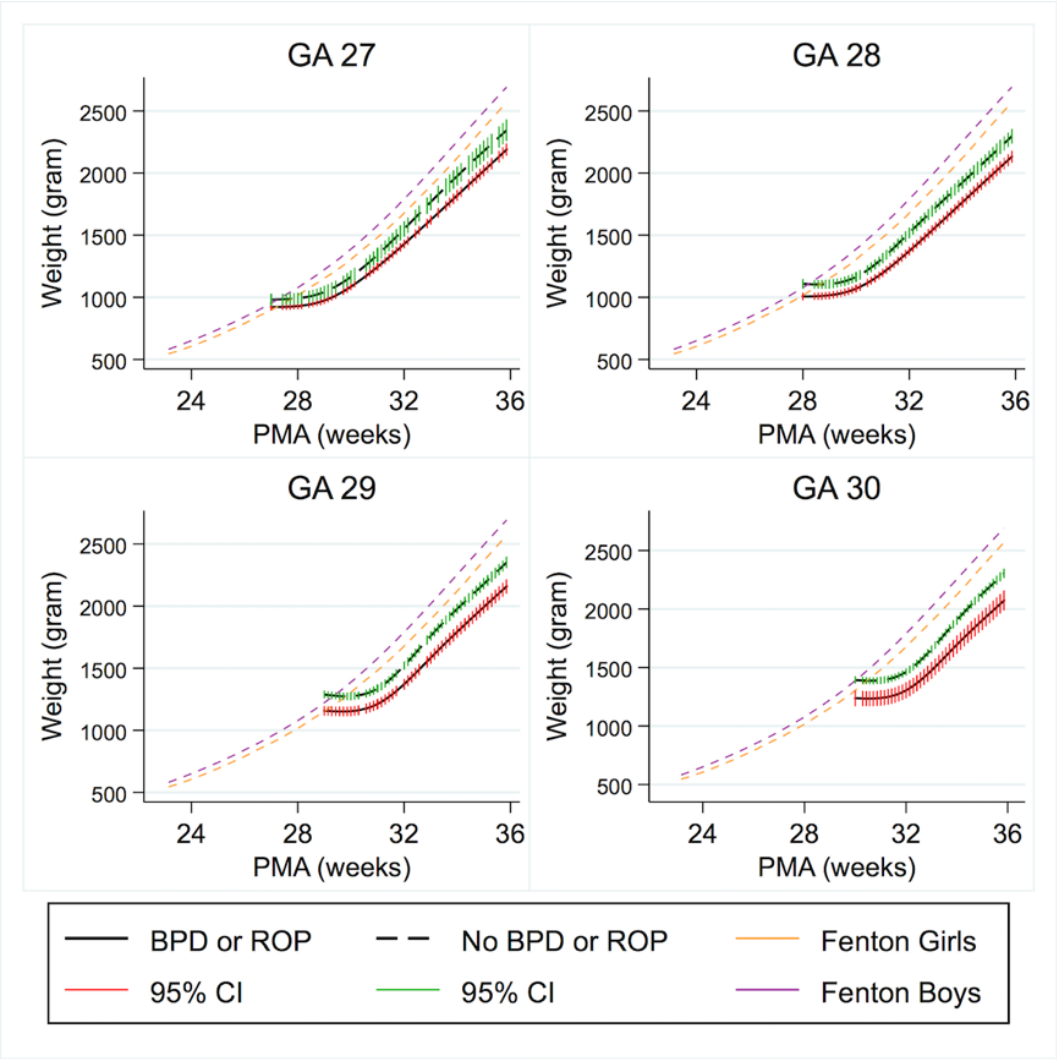

Figure 13. Growth trajectories for infants with any stage of ROP or BPD and no ROP or BPD by gestational week at birth.

Reference values from the revised Fenton growth chart for girls (orange) and boys (purple).[96]

4.1.3 Paper II & III, nutrition and growth

Higher intakes of energy and protein the first postnatal week were associated with reduced postnatal weight loss. Higher energy intake on postnatal days 0 to 3 was not statistically significantly associated with ΔWSDS (+0.05 WSDS (95% CI 0.00 – 0.10; p=0.076) in analysis adjusted for GA, BWSDS, time period, days of MV, transfusions, and fluid intake on days 0 to 3. At a mean energy intake of 60 kcal/kg/day, every 1 g/kg/day higher protein intake was associated with +0.05 WSDS (95% CI 0.00 – 0.09; p=0.041). On postnatal days 4 to 6, every 10 kcal/kg/day higher energy intake was associated with +0.05 WSDS (95% CI 0.02 - 0.09; p=0.004) in analysis adjusted for GA, BWSDS, time period, days of MV, and transfusions on days 0 to 6. At a mean energy intake of 100 kcal/kg/day, every 1 g/kg/day higher protein intake was associated with +0.14 WSDS (95% CI 0.07 – 0.21; p<0.001). The fluid intake the first week was not significant and did not alter the estimates in the model of energy and protein intakes on days 4 to 6.

Assuming nutritional intakes according to Swedish recommendations[39] the first postnatal week, the predicted reduction in WSDS from birth to postnatal day 7 was -0.5 WSDS (95% CI -0.6 to -0.4) in a model with mean values of GA, BWSDS, MV, and transfusions on days 0 to 6.

In paper III, infants born between 2004 and 2005 had lower WSDS at postnatal day 7 compared to subsequent years, a difference of -0.3 SDS (95% CI -0.5 to -0.1; p<0.001). This difference was sustained at postnatal day 56, a difference of -0.4 SDS (95% CI -0.7 to -0.2; p<0.001). At postnatal day 56, length, -0.5 SDS (95% CI -0.8 to -0.2; p<0.001), and head circumference, -0.5 (95% CI -0.8 to -0.2; p<0.001), differed between infants born between 2004 and 2005 and subsequent years.

4.1.4 Paper II, nutrition and morbidity

The multivariable regression model revealed no statistically significant association between energy intake on postnatal days 0 to 3 or days 4 to 6 with ROP or BPD. For the association between 10 kcal/kg/d higher energy intake and severe ROP, the adjusted RR was 0.90 (95% CI 0.81–1.00; p=0.056), and for the association between energy intake on days 4 to 6 and BPD, the RR was 0.96 (95% CI 0.88–1.04; p=0.293), adjusted for GA, BWSDS, antenatal corticosteroids, transfusions, and MV on days 0 to 6.

A 10 kcal/ kg/ day higher energy intake on postnatal days 7 to 27 was associated with 9% (95% CI 1–16; p=0.029) lower risk of BPD in analyses adjusted for GA, BWSDS, antenatal corticosteroids, days of MV, and transfusions. A 10 kcal/kg/ day higher energy intake on postnatal days 7 to 27 was associated with 6% (95% CI 2–9; p=0.005) lower risk of ROP of any stage, but not with a risk of severe ROP (RR 0.95 95% CI 0.87–1.05; p=0.341) in analyses adjusted for GA, BWSDS, MV, and transfusions.

The interaction term of energy intake and days of MV was significant in the association with ROP. In infants with ≤10 days of MV, higher energy intake on days 7 to 27 was associated

with reduced risk of ROP (RR 0.87 95% CI 0.80–0.95; p=0.003) in analyses adjusted for GA, BWSDS, MV, and transfusions. The reduction in estimated absolute risk of ROP was 10% with an increase from 110 to 120 kcal/kg/days and 8% with an increase from 120 to 130 kcal/kg/days. In analysis that included adjustment for time period, RR was 0.89 (95% CI 0.81–0.98; p=0.024) in infants with ≤10 days of MV. In infants with >10 days of MV, the association between energy intake and ROP was not significant (RR 1.01 95% CI 0.97–1.04; p=0.768) in the adjusted analyses. PE ratio on days 7 to 27 was not associated with risk of ROP in the adjusted analyses.

Without time-period in the regression model, the interaction-term of energy intake and days of MV was significant in the association with BPD. In infants with ≤10 days of MV, higher energy intake on days 7 to 27 was associated with reduced risk of BPD (RR 0.79 95% CI 0.65–0.95; p=0.011), in analyses adjusted for GA, BWSDS, MV and transfusions. The reduction in estimated absolute risk of BPD was 7% with an increase in energy intake on postnatal days 7 to 27 from 110 to 120 kcal/kg/day and 8% with an increase from 120 to 130 kcal/kg/day. In infants with >10 days of MV, the association between energy intake and BPD was not significant, but a combined higher intake of energy and protein was associated with reduced risk of BPD (Figure 14).

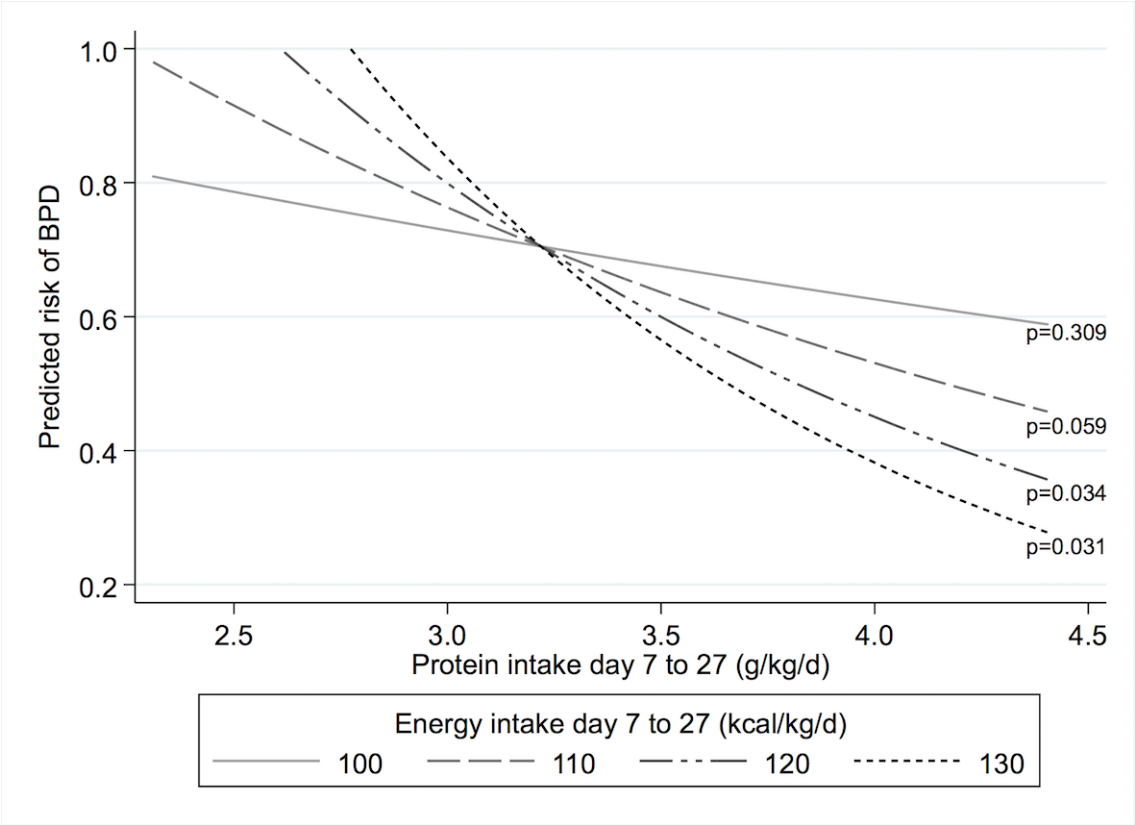

Figure 14. Illustration of protein/energy interaction and risk of bronchopulmonary dysplasia (BPD) in infants requiring >10 days of mechanical ventilation (MV).

Association between predicted risk of BPD and protein intake days 7 to 27 assuming different energy intake. Results from Poisson regression. Illustration assuming mean values of included variables of gestational age, birth weight standard deviation score, intake of antenatal corticosteroids, transfusions, and days of MV on days 0-27. Nutritional content in transfusions were included in the nutritional values used in the regression model.

If time period was included in the model, the interaction term of energy intake and days of MV was not significant (p=0.09), but interaction term between time period and energy intake was significant (p=0.03). There was no association between energy intake and BPD between 2004 and 2007 (RR 1.04 95% CI 0.93–1.17; p=0.496), whereas a higher energy intake was associated with a reduced risk of BPD between 2008 and 2011 (RR 0.86 95% CI 0.74–0.99; p=0.035) in the adjusted analyses. A combined higher intake of both energy and protein on postnatal days 7 to 27 was associated with reduced risk of BPD during the later time period: RR 0.84 (95% CI 0.73–0.98; p=0.021) for every 10 kcal/kg/d increase of energy at a protein intake of 3.5 g/kg/day and RR 0.62 (95% CI 0.41–0.92; p=0.019) for every 0.5 g/kg/d increase of protein at an energy intake of 120 kcal/kg/day.

4.1.5 Paper III, improved nutrition

In parallel with interventions to improve neonatal nutrition between 2004 and 2011, intakes of energy and macronutrients increased significantly (Figure 15). Energy and protein intakes were higher in 2010 and 2011 during days 0-3 and 4-6 compared to all previous years.

A majority of infants did not receive protein the first postnatal week according to the recommendations valid the respective two-year period, except for infants born in 2010 and 2011. Intakes of lipids were according to recommendations for the majority of infants during the entire period.

Advancement of feeds were faster between 2008 and 2009 compared to all other years. Median time to full enteral feeds was 15 days between 2008 and 2009, compared to 23 days 2004-2005 and 2010-2011, and 21 days 2006-2007. Enteral protein content was higher 2010-2011 compared to previous years, but not enteral energy intake. During the transition phase of 50-75% enteral intake, total energy intake was higher in 2010-2011 due to higher parenteral energy content.

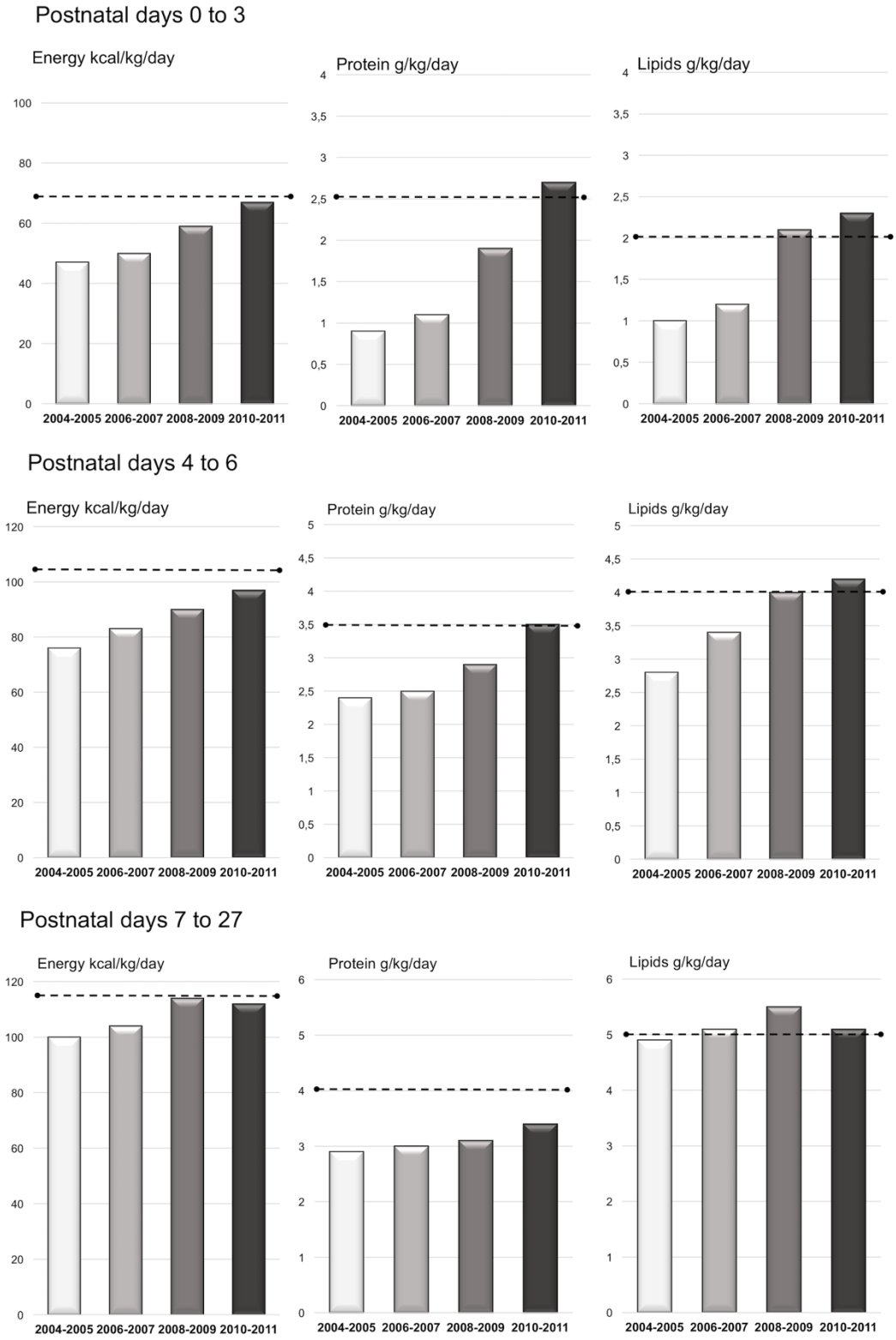

Figure 15. Mean intakes of energy, protein, and lipids during postnatal days 0-3, 4-6, and 7-27 in two-year periods.

The non-parametric test for trend demonstrated a statistically significant increase ($p<0.001$) of energy and protein during all studied postnatal periods and of lipids during postnatal days 0-3 and 4-6.

Dashed lines represent calculated mean intakes during the respective periods according to current Swedish guidelines.[39] Based on minimal recommended intake day 0, increased to minimal recommended intake day 4, and minimal recommended intake at full enteral nutrition during postnatal days 7 to 27.

4.1.6 Paper IV, altered saturation target guidelines and SpO_2

There was no statistically significant difference in GA, BW, BWSDS, sex, or antenatal corticosteroids between infants with the two studied target ranges. In the entire study population Median GA was 27 0/7 weeks (25^{th}-75^{th} pctl, 25 3/7 to 28 5/7), and median BW was 872 gram (25^{th}-75^{th} pctl, 701-1147). Fifty percent of the infants were ELGA. Median length of stay was 28 days (25^{th}-75^{th} pctl 11-58 days).

Compared to target range of 88-92% with alarm limits of 85-95%, a target range of 90-95% with alarm limits of 89-96% resulted in 1.3% higher (95% CI 1.0–1.6; p<0.001) mean SpO_2 the first three postnatal weeks. The distribution in SpO_2 over time is demonstrated in Figure 16. Proportion of time within target increased from 30% to 51%, a difference of 21% (95% CI 19–23; p<0.001); proportion of time within alarm limits decreased from 71% to 66%, a difference of -5% (95% CI -3 to -7; p<0.001). The proportion of time with SpO_2 >95% increased 9% (95% CI 7–11; p<0.001), from 20% to 28%, and the proportion of time with SpO_2 <85% decreased 3% (95% CI 2–4; p<0.001) with the higher target compared to the lower.

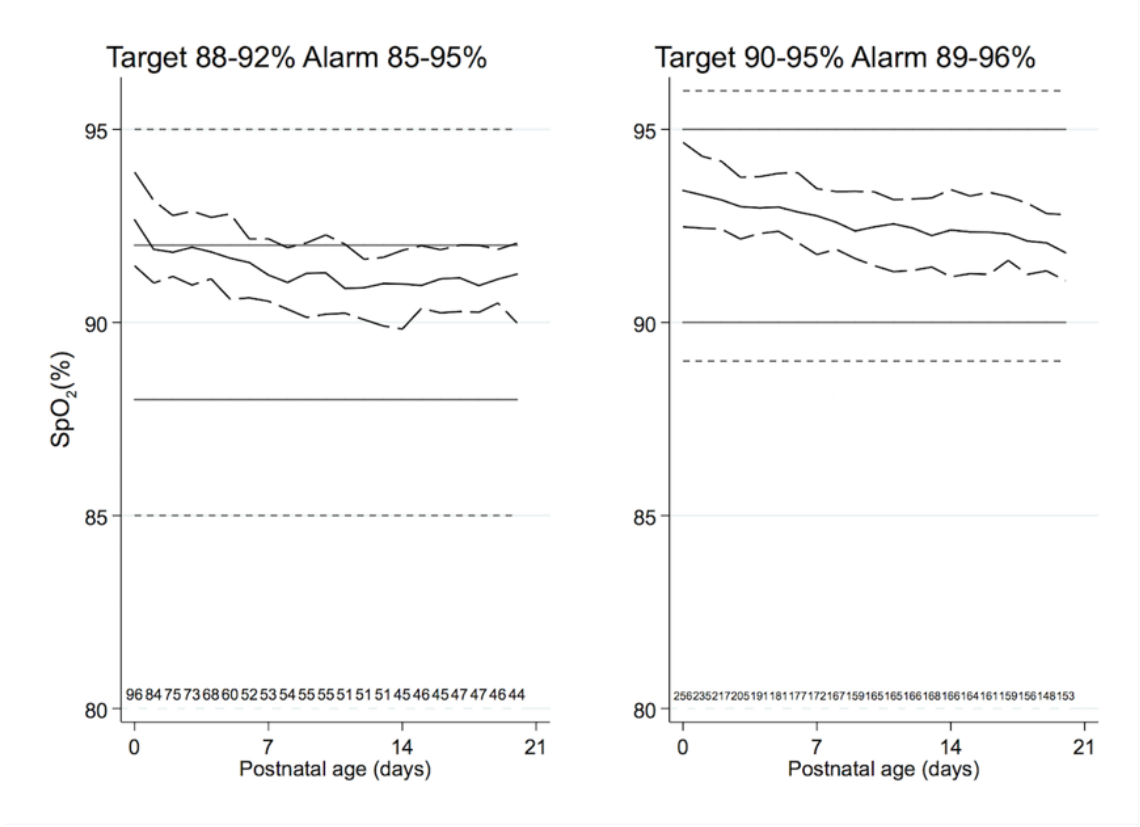

Figure 16. Oxygen saturation during the first three postnatal weeks with the studied target ranges and alarm limits.

Solid lines show median SpO_2 and dashed lines show 25^{th} and 75^{th} percentiles of SpO_2. Dotted lines mark alarm limits and solid lines mark target ranges. Numbers at the bottom refer to included infants.

Difference in the 25th percentile 1.1% (95% CI 0.8–1.4; p<0.001);
Difference in the 75th percentile 0.7% (95% CI 0.1–1.4; p=0.024)

The variability was higher with target range 88–92% and alarm limits 85–95%, as demonstrated in figure 17. The difference in "average hourly absolute change" the first three postnatal weeks was 8 units per hour (95% CI 3–13; p=0.001). Higher target range and tighter alarm limits were also associated with a 25% reduction (95% CI 13–35; p<0.001) in hypoxic episodes, SpO2 <80% up to 5 minutes, from 8.4 to 6.3 episodes per day.

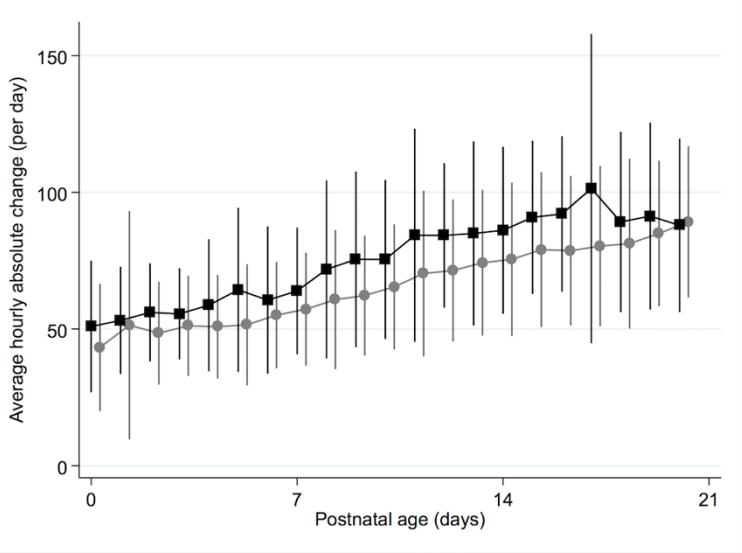

Figure 17. Variability of oxygen saturation the first three postnatal weeks with the studied target ranges

Black squares: target range 88–92% and alarm limits 85–95%; **Grey circles**: target range 90-95% and alarm limits 89-96%
Mean and standard deviations of "average hourly absolute change".

There was no statistically significant difference in fraction of supplemental oxygen between the different target ranges. Mean FiO_2 was 39% with the lower target, and 36% with the higher target, a difference of -3% (95% CI -6–1; p=0.13).

4.1.7 Paper IV, saturation targets, ROP, and mortality

There was no statistically significant difference in mortality or proportion of infants with any ROP, severe ROP, or ROP requiring treatment between the two target groups. Proportions and ORs in ELGA infants are presented in Table 5.

Table 5. Mortality and ROP in extremely low gestational age infants in paper IV.

	Proportion (%)		Unadjusted OR			Adjusted[a] OR		
	Target 88–92% n=48	Target 90–95% n=149	OR	95% CI	p-value	OR	95% CI	p-value
Any stage of ROP [b]	31(78)	112 (85)	1.63	0.67–3.93	0.280	1.33	0.53–3.34	0.543
Severe ROP [b] stage ≥3	13 (33)	58 (44)	1.63	0.77–3.43	0.200	1.11	0.48–2.53	0.811
ROP treatment [b, c]	7 (18)	32 (24)	1.51	0.61–3.74	0.375	0.88	0.31–2.48	0.807
Death before term age	8 (17)	17 (11)	0.64	0.26–1.60	0.344	0.54	0.21–1.44	0.221

197 infants with gestational age (GA) between 23 0/7 and 26 6/7 weeks, mean GA 25 2/7 weeks, mean BW 743 gram

[a] Adjusted for exact GA (days) and BW (gram).

[b] Out of 172 infants who survived to term age, n=40 with target 88–92% and n=132 with target 90–95%

[c] Infants treated for ROP all had ROP stage ≥3

4.2 DISCUSSION

Papers I and II demonstrate less weight gain among ELGA infants with morbidities such as ROP and BPD, and association between lower intake of energy the first month of life and increased risk of disease. Energy and protein intake the first postnatal week reduced initial growth restriction. Paper III and IV show that the implementation of new knowledge has resulted in significant changes in neonatal care.

Intake of energy and protein rather than fluid intake was important for weight development the first postnatal week (paper II). This result emphasizes the potential to reduce initial growth restriction through attentive nutritional care. Moltu et al. showed an association between an increased energy and protein intake and improved growth the first postnatal week with intakes comparable to the 60th and 90th percentiles of energy intake and the 30th and 70th percentiles of protein intake the first week in paper II.[190] Morgan et al.'s RCT, that demonstrated differences in head circumference but not weight, compared intakes of energy and protein the first postnatal week approximately at the 25th and 50th percentiles in our cohort with protein content in transfusions included in nutritional calculations. Without transfusions, protein intake the first week in the RCT corresponded to the 50th and 75th percentiles in our cohort.[189]

In 2005, an intake of 2.0 g protein/kg/day the first day of life was recommended.[34] An initial intake of 2 g/kg/day ought to result in a mean intake on postnatal days 0-3 above 2 g/kg/day. Less than 10% of the infants born 2006-2007, almost half of the infants born 2008-2009, and 90% of the infants born 2010-2011 had a protein intake ≥2 g/kg/day on postnatal days 0-3. Implementation of updated nutritional guidelines took several years. Availability of appropriate parenteral solutions might have limited the possibility to achieve a higher initial protein intake.

New saturation targets were implemented immediately following publication of updated local guidelines. Time with SpO_2 within target range improved with the higher saturation target and tighter alarm limits after guidelines were updated, as demonstrated in paper IV. Being within the prescribed target range 51% of the time is in line with previous studies,[240, 279, 280] but there is room for further improvement. There was no guideline regarding response to SpO_2 outside the target range in the included neonatal units.

Postnatal growth rates demonstrated in paper I are similar to previously reported growth rates in ELGA infants born during the same period,[281] and the growth pattern by GA resembles the trajectories illustrated by Ehrenkranz et al.[111] and Rochow et al.[114] Rochow et al. did not investigate growth patterns in infants with and without morbidity, but instead intended to investigate undisturbed postnatal growth in a select group of preterm infants without maternal and neonatal pathology. Reduction of extracellular fluid is the proposed cause of a physiological initial weight loss after birth. Rochow et al. proposed a reduction of 0.8 SDS in weight to postnatal day 7 followed by growth parallel to the Fenton growth chart. The recommendations of parenteral intakes from day 1 were lower in that study compared to the

most recent guidelines. In paper II, a reduction of 0.5 SDS in weight to postnatal day 7 is suggested with nutritional intakes per current guidelines. When determining appropriate growth trajectories in ELGA infants, the full potential of growth with improved nutritional provision the first postnatal week needs to be considered.

The developmental origins of health and disease (DOHaD) hypothesis suggests that early exposures have effects throughout life. The theory originated in studies by Barker showing that low BW was related to cardiovascular disease in adult life.[282, 283] Further studies have demonstrated that a high increase in body mass index during childhood also is an important predictor of later disease in low birth weight infants.[284] Preterm infants are born during what is thought to be a critical period of susceptibility, the period before and soon after birth. Disproportionate growth with weight gain that exceeds growth in length during the neonatal period has been associated with increased proportion of body fat, waist circumference, and signs of impaired glucose homeostasis in preterm infants.[285] It is unclear what significance the DOHaD hypothesis has for preterm infants and how this affects recommendations of growth and nutritional intakes.

Postnatal growth restriction has been previously associated with ROP. Paper I demonstrates associations related to specific postnatal weeks. ELGA infants who developed ROP had significantly reduced growth rates during PMA 30 to 31 weeks, coinciding with the period of maximum growth rate and transition from growth restriction to catch-up growth. The initiation of catch-up growth in this period has also been associated with lower concentrations of IGF-I.[73] In the studies that demonstrated an association between low energy intake and increased risk of severe ROP, mean energy intake the first 28 postnatal days was >10 kcal/kg/day lower compared to what we found (paper II).[177, 193] Paper II showed that low energy intake on postnatal days 7 to 27 was associated with an increased risk of any stage of ROP in infants with fewer days of MV. There was no statistically significant association between higher energy intake on postnatal days 4 to 6 and BPD or ROP, although the results were towards an association between higher energy intake on postnatal days 4 to 6 and lower risk of severe ROP.

The diagnosis of ROP is based on visualized differences in retinal vascularization, which makes comparisons between different stages of the disease possible. The diagnosis of BPD is less distinct and might not be a valid predictor of later pulmonary problems. Griffin et al. reported that severe ROP, NEC, and severe IVH (although not BPD) were associated with postnatal growth restriction.[179] In a study of infants born in GA 25 to 30 weeks, Nyp et al. did not find any association between postnatal growth rates and BPD.[180] In paper I, we examined growth as both growth rates and weight development stratified by GA. Our results were in line with previous studies, although we did report increasing differences in weight with increasing postnatal age.

Experimental studies provide a rational for the association between increased nutrition and lower risk of BPD.[196-198] Energy intake the first postnatal week was low compared to recent recommendations in both of the studies that previously demonstrated association between

low energy intake and increased risk of BPD.[200, 201] Optimal use of protein depends on adequate provision of non-protein energy.[58] As demonstrated in paper II, there was an association between higher energy and protein intake and reduced risk of BPD. This was significant during the later period with higher energy and protein intakes. A higher proportion of the infants who developed BPD had longer duration of MV during the later time period. The results indicate a positive effect of higher nutritional intake despite critical illness.

No previous studies have demonstrated detailed descriptions of growth patterns stratified by GA, considering the associations between growth at each postnatal week and the risk of morbidities in preterm infants. In papers I and II, the complex associations between nutrition, growth, and organ development were investigated using statistical models made possible because of availability of data from a large number of ELGA infants. In paper I, we examined growth patterns and development of disease. In addition to nutritional intakes, restricted fluid intake, inflammatory processes, and increased energy expenditure are processes suggested to be associated with poor weight development in infants with BPD. Postnatal corticosteroids have also been suggested as a possible explanation for poor postnatal growth and use of steroids has been demonstrated to influence weight gain during treatment but not over a longer period.[286] Several factors are likely to affect both growth and disease development and we were unable to differentiate how the associations were mediated. Irrespective of cause, the deviating growth patterns might serve as a marker for disease.

Paper IV examined the effect of updated saturation target guidelines on achieved SpO_2. Since two interventions were introduced at the same time, it is not possible to separate the effects of higher target range and tighter alarm limits on the results. The proportion of ROP has increased in some of the regions in Sweden after the introduction of new saturation targets.[287] Paper IV found no clear correlation between target group and proportions of ROP or mortality. Intermittent hypoxia, increased variability in oxygenation, as well as higher SpO_2 have been previously associated with an increased risk of ROP.[231, 233, 252, 254, 255, 257, 288, 289] In relation to the NeOProM trials, the alteration in peripheral SpO_2 as well as sample size in paper IV was limited, although Manley et al. demonstrated increased rate and severity of ROP after guideline update in a cohort of fewer ELGA infants.[290] The intervention was similar to ours. Saturation target 88-92% with alarm limits of 86-94% was altered to saturation target 91-95% with alarm limits of 89–95%, and the adjusted OR for any stage of ROP with the new target was 3.7 (95% CI 1.3–10.4; p=0.012) among infants born before 28 weeks of GA.[290]

Papers III and IV illustrate the clinical results of the continuous work to improve neonatal care. A versatile effort is needed to ensure proper implementation and lasting adherence to guidelines. Since results from studies and trials do not always reflect the clinical reality, a critical mind and recurring discussions are also important elements of quality improvement. Clinical situations and local conditions might warrant deviations from guidelines. Efforts to facilitate adherence to guidelines and monitoring of results are important in the continuous development of neonatal care.

4.3 CLINICAL IMPLICATIONS & FUTURE PERSPECTIVES

The results presented in this thesis demonstrate the significance of how neonatal care is provided. Optimized early nutrition improves the conditions for growth and development, reducing the risk of disease and increasing the chance of healthy growth and positive long-term outcomes. By monitoring our performance, we increased the possibility to optimize how care is delivered to reduce the risk of severe complications in a high-risk population. The results also demonstrate that further improvement of neonatal care is achievable.

The conditions in the neonatal care unit need to enable adherence to stipulated guidelines and facilitate implementation of new guidelines. Quality improvement is associated with management.[291] An organization that provides a structure where quality improvement efforts make use of the capabilities in the organization, alongside the clinical work, facilitates implementation of new practice.[292] Suitable tools to enable adherence to guidelines must also be available. Computerized systems provide an easy method to monitor performance and results.[293] These need to be well integrated and easy to use.[294] Limited manual administration results in more time with patients, and automated feedback can provide an easy to grasp visualization of the results, which increases awareness. Intelligent systems integrated in the health care systems might also offer warnings and support decision making. There is potential for improvement in development and implementation of technical interventions in the health sector.[294]

Factors important for adherence to nutritional guidelines also include availability of suitable nutritional solutions and supplements. Standardized PN for preterm infants are now available. Administration from multiple compartments increases flexibility. This reduces potential problems due to fluid restriction, changed electrolyte requirements, and paused infusions due to administration of drugs.[295] Areas with potential for further improvement include methods to better maintain the nutritional content in MOM and DM and development of supplements better adapted to the immature gut.[296] Quality of lipids also influence preterm development and is an evolving area of research.[297]

A phase 2 trial has been conducted and a phase 3 trial is planned to evaluate potential benefit of supplementation with the growth factor IGF-I to physiological intrauterine levels (ClinicalTrials.gov; NCT01096784). The aim is to reduce morbidity and improve growth in ELGA infants. Initial results did not demonstrate reduction in ROP or improved growth, but did demonstrate reduction in BPD and IVH.[298]

More research is needed regarding specific periods of growth and interactions between growth factors, nutrition, and morbidities. Future studies should consider the interplay between risk factors such as nutrition and mechanical ventilation. In addition, it is important to study the specific needs of special populations. Infants at the lowest gestational ages as well as growth restricted infants might benefit from specific nutritional recommendations and saturation targets.[299, 300]

Several recent publications have focused on the development of neonatal growth charts.[103, 114, 301] Many factors influence postnatal growth and need to be optimized in order to evaluate the potential for growth in preterm infants of different gestational ages. As suggested by the DOHaD hypothesis, pre- and postnatal growth influence the risk of metabolic and cardiovascular disease in adulthood. Body composition might prove to be a better determinant of long-term consequences.[302] Consistency in methods and reporting is needed to facilitate comparisons and evaluation of aggregated evidence.[278]

An interesting area of future research is the interplay between supplemental oxygen, oxygen transport, and development of ROP.[230] Also in the development of BPD, previous experimental studies as well as new evidence and results in this thesis suggest that further evaluation of potential interactions between metabolism and oxygen toxicity in the development of disease is warranted.[300]

5 CONCLUSIONS

This thesis demonstrates that higher nutritional intakes in the early postnatal period have the potential to improve growth and reduce morbidity in extremely preterm infants. The results show specific weeks of reduced growth rates in infants who developed ROP and demonstrate an association between higher nutrient intake and reduced risk of ROP and BPD. Furthermore, this thesis shows that infants only had SpO_2 within target range half of the time, even if adherence improved with updated saturation targets

Main findings:

- ELGA infants without ROP had higher growth rates around PMA 30 weeks and increased weight gain compared to infants with ROP.
- ELGA infants without BPD had increased weight gain compared to infants with BPD.
- A higher energy intake was associated with reduced risk of ROP in infants with less days of MV during the first four postnatal weeks.
- A higher energy intake and a combined higher energy and protein intake during the first four postnatal weeks were associated with reduced risk of BPD.
- Higher energy and protein intake during the first postnatal week was associated with reduced initial growth restriction.
- Energy and protein intake during the first four postnatal weeks increased in ELGA infants in Stockholm between 2004 and 2011.
- Higher saturation target and tighter alarm limits were associated with higher mean SpO_2, more time with hyperoxia, reduced variability, and less hypoxic episodes.
- The proportion of time with SpO_2 within target range increased from 30% to 51% with the new target and alarm limits.

In conclusion, neonatal care practices can improve outcome for preterm infants. Although several changes have been successfully implemented, further improvements are desirable and achievable.

6 SVENSK SAMMANFATTNING

En graviditet varar normalt i cirka 40 veckor. Ungefär 1% av alla barn i Sverige föds före 32 fullgångna graviditetsveckor. För tidig födelse förändrar förutsättningarna för tillväxt och organutveckling, och risken för sjuklighet är mycket hög hos extremt för tidigt födda barn (födda före 28 fullgångna graviditetsveckor). Två sjukdomar som drabbar dessa barn är prematuritetsretinopati (ROP) och bronkopulmonell dysplasi (BPD). ROP beror på störd utveckling av ögats näthinna och den allvarligaste formen kan leda till blindhet. BPD är en lungsjukdom som är förknippad med större risk för lungsjuklighet även senare i livet. Vissa studier har visat samband mellan näringsintag och risk för ROP respektive BPD, och riktlinjer för näringsintag har successivt uppdaterats de senaste årtiondena. I riktlinjer från 2005 rekommenderades högre näringsintag med start tidigare efter födelsen jämfört med tidigare rekommendationer. Extremt för tidigt födda barn behöver ofta extra tillförd syrgas, men syrgasexponering ökar risken för ROP. För alla barn med extra tillförd syrgas specificeras ett målområde med övre och nedre gränser, inom vilka syremättnaden bör hållas. Vilket målområde som är optimalt är fortfarande oklart, men resultaten från fem randomiserade prövningar ligger till grund för det målområde som rekommenderas sedan 2013.

Syftet med denna avhandling är att studera faktorer inom neonatalvården som skulle kunna påverka risken att utveckla ROP och BPD, samt att undersöka given vård i förhållande till nya rekommendationer. Det övergripande målet med projektet är att förbättra neonatalvården för att minska risken för sjukdomsutveckling och förbättra långtidshälsan hos för tidigt födda barn.

I studie I studerades skillnader i tillväxtmönster i en stor grupp barn födda före 31 fullgångna graviditetsveckor. Resultaten visade att extremt för tidigt födda barn med ROP och BPD hade mindre viktökning jämfört med barn utan sjukdom, och att tillväxtmönstret skiljde sig åt beroende på graviditetslängd och postnatal ålder.

I studie II undersöktes om energi- och proteinintag den första veckan och månaden påverkade tillväxten och risken för ROP eller BPD. Detaljerade data om näringsintag, från barn födda i Stockholm 2004 till 2011 före 27 fullgångna graviditetsveckor, analyserades. Resultaten visade att högre intag av energi och protein var associerat med förbättrad viktutveckling under den första levnadsveckan. Ökat energiintag under levnadsdag 7 till 27 var förknippat med en minskad risk för ROP hos barn med färre än tio respiratordagar, men inte hos barn med fler respiratordagar. Ökat energi- och proteinintag under levnadsdag 7 till 27 var förknippat med en minskad risk för BPD hos barn födda åren 2008 till 2011, men inte 2004 till 2007.

Studie III visade att given näring till extremt för tidigt födda barn har ökat kontinuerligt under 2004 till 2011. Under dessa år genomfördes flera insatser som syftade till förbättrat näringsintag. Riktlinjer för näringsintag uppdaterades vid ett par tillfällen dessa år. 2004 till

2009 hade de flesta barn ett lägre proteinintag de första levnadsdagarna än enligt de rådande rekommendationerna.

I studie IV studerades barn med två olika målområden för syremättnad samt olika larmgränser. Värden på uppnådd syremättnad från barn födda före 31 fullgångna graviditetsveckor 2013 till 2015 analyserades. Med det nya målområdet 90–95%, och larmgräns 89–96%, var andelen tid spenderad med syremättnad inom de rekommenderade gränserna högre jämfört med det tidigare målområdet 88–92% och larmgräns 85–95%. Svängningarna i syremättnad minskade och tiden med syremättnad över 95% ökade med det högre målområdet.

Sammanfattningsvis visar denna avhandling att dålig postnatal tillväxt är en markör för sjukdom, och att ökade tidiga näringsintag är associerat med minskad initial tillväxthämning och sjuklighet. Förbättrad näringsregim och ökat fokus på tillväxt kan förbättra utfallen för extremt för tidigt födda barn. Det är viktigt att övervaka följsamhet till riktlinjer och det finns utrymme för ytterligare förbättringar av neonatalvården.

7 ACKNOWLEDGEMENTS

Many people have contributed in making this thesis possible. It has truly been an educational and enriching adventure. I want to express my deepest gratitude to all of you.

Boubou Hallberg, my principal supervisor. You are always optimistic and visionary! You have influenced my development as a researcher and as a person during this project, and I really appreciate all opportunities you present. Thank you for this experience!

Anna-Karin Edstedt Bonamy, co-supervisor, you guided me into the field of epidemiological research. You have given me the tools to continue, and the belief in my own capability. You were also Director of Studies during many years of my residency, and I have enjoyed all of our collaborations and discussions.

Magnus Domellöf, co-supervisor, your enthusiasm to improve neonatal nutrition and outcomes for extremely preterm infants is the reason I pursued this field of research. I am grateful that you have shared your knowledge, and I have valued your guidance and support.

Ann Hellström, thank you for always offering your opinion and sharp analyses. I am inspired by your energy and generosity! I have really valued our collaborations, and look forward to future projects.

Mikael Norman, thank you for your welcoming attitude and insightful comments, and ***Mats Blennow,*** I have felt your support and commitment throughout the project.

Vera Westin, fellow PhD student, your devotion, clinical experience and hard work have been detrimental for this project. ***Elisabeth Stoltz Sjöström,*** thank you for sharing your expertise and enthusiasm, and for always carefully reviewing the details.

Ulf Hammar, you have been crucial in my projects and for my doctoral education. Thank you for all your efforts. I have enjoyed our deep statistical discussions.

Pia Lundgren, it is always pleasant to get an email from you with interesting results and cheerful comments, and co-authors ***Lois Smith, Chatarina Löfqvist,*** and ***Gerd Holmström*** it has been a privilege to collaborate with you.

Mireille Vanpée, co-author, thank you for interesting discussions and your devoted work on neonatal nutrition.

Berit Kristöm, mentor, your devotion as a clinical doctor and a researcher is inspiring.

I would like to thank ***Wiltrud Söderholm*** and ***Denise Jansson*** for administrative support, and all who have contributed in administration, data collection and data entering, the research nurses ***Kerstin Andersson, Michaela Melakari*** and ***Camilla Halzius,*** you are amazing at solving every issue.

Claude Marcus, Lisbeth Sjödin and all who have been of assistance at CLINTEC during my years as a PhD-student.

The research school for clinicians in epidemiology was an important part of my PhD studies, and I want to express my gratitude to director of studies ***Maria Altman,*** and all others involved in making the education great.

Emilija Wilson, I am glad I met you and got to share the experience of being a PhD student with you.

Katarina Grossman and ***Mikael Finder,*** fellow PhD-students, for great times during travels and for sharing joy and frustration. ***Dirk Wackernagel,*** you possess vast clinical knowledge and it is always a pleasure to engage in conversation with you. ***Ewa Henckel, Kajsa Bohlin*** and all the staff at the neonatal ward at Huddinge, thank you for always making me feel welcome. ***Ulrika Ådén*** and ***Nelly Padilla,*** thank you for helping me understand a little bit about brain development. ***Jenny Bolk*** and ***Lina Broström,*** I have really appreciated all the discussions and encounters, and that you invited me to the journal clubs with NeoBIG.

Matteo Bottai, Professor of Biostatistics, thank you for teaching me that statistics is interesting and making me curious to learn more.

Eva Berggren Broström, head of Sachs, and ***Fredrik Stenius,*** my boss, you are not alike but I value the same characteristics in both of you. You are engaged, supportive and distinct, open for suggestions and discussion. Thank you for providing a good research environment.

Bodil Schiller and ***Malin Rinder,*** thank you for bringing me to Sachs, and for great collaborations during residency and scheduling.

Inger Kull, Director of Research at Sachs. You do amazing work for all PhD students and researchers with your enthusiasm and sharp comments. Thank you for all the great support. ***Erik M, Lilly-Ann, Tobias, Charlotta F, Ola, Mirja, Helena MH, Susanne, Maria Ö, Natalia, Per T,*** and all others in different stages of research education and career at Sachs, I love that we help and inspire each other independent of field of research. A special thanks to ***Caroline Fransson*** and ***Anita Stålsäter*** at KI SÖS and Sachs for administrative support in planning this dissertation.

Cecilia, you provide a calm reliability and emit a feeling that everything can be solved. I am happy that you have taken on CNN. ***Nicolas,*** my clinical supervisor, you encouraged my interest in neonatology, and with ***Anders D, Caroline A, Ishan, Josefin, Petra, Thomas A, Thomas B, Annika, Stefan,*** and all the staff at the neonatology unit, you made me feel at home when I started at Sachs 2010 and you still do.

Helena T, your text messages in the middle of the night during the intensive period of breast feeding kept me sane. I love your ironic, educational, comments. ***Josef,*** I have enjoyed working alongside parallel paths with you, and I can always count on you to be engaged in both important work environment issues and song- or dance performances. ***Lina,*** you have the ability to say the exact thing that lifts my spirits when research feels overwhelming. ***Jonna*** and ***Sanam,*** surprisingly inclusive, and always fun. ***Emma,*** Don't walk, dance!

Karin R, Josephine, Lotta, Helena R, Erik B, Olle, Karolina, Sofia T, Jocke and ***Noni,*** you made me feel very welcome from my first day at Sachs, ***Ulrika, Helena L, Samuel, Sara M, Sofia B, Björn, Gotte, Karin B, Reza, Fredrik L, Sanna***, and all co-workers at Sachs, thank you for conversations, laughs and serious discussions during morning report, lunch, after work, parties and skiing. And for awesome dancing!

All friends in the world outside of work and research, thank you for bringing joy. In particular ***Erik*** and ***Maria,*** always the best of times, and ***Karin*** and ***Daniel,*** from ski bum delux to barnsemester delux.

The talented ***Lisa Öhman,*** thank you for painting the cover, and your wonderful family for being welcoming and inspiring.

Ulla-Britta, aunt, godmother and nanny. Always ready to get on a train, push your way through the subway and help out.

Ewa and ***Thomas,*** thank you for all the love and help. You are amazing with the kids. I am really happy that you are my parents-in-law.

Magnus, and ***Hanna,*** it is great to share experiences and to discuss everything in life with you. I feel lucky that you and your kids are in my life.

Gerd and ***Lennart,*** Mamma och Pappa, for all the love and support! for encouraging curiosity and telling me that nothing is impossible.

Svante and ***Folke,*** you are the most amazing persons! I am fortunate to have you in my life.

Fredrik, I love you, our family, the team that is us, and everything that we do together and for each other. I am looking forward to our new adventures.

Fundings

I also want to acknowledge the economic support that I have received working on this thesis. Thanks to the combined clinical residency and PhD training program provided by Stockholm County Council, I have been able to finish this thesis still feeling like research is fun.

I have also received grants from Lilla Barnets Fond, Stiftelsen Samariten, Föreningen Mjölkdroppen and Sachs FoUU.

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