Nutritional support for preterm infants: a study of current perceptions and practices of parenteral and enteral nutrition and complementary foods

By

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Abstract

The incidence of preterm birth is increasing globally. In the UK, approximately 7% of live born infants are born prematurely. Premature birth is one of the most important issues in perinatal medicine, leading to a considerable global burden of diseases due to high mortality and morbidity in these vulnerable infants. Suboptimal nutritional intakes during the early postnatal and post-discharge period, including inappropriate weaning practices contribute to malnutrition, suboptimal growth and poor neurodevelopment outcome among infants born preterm.

The aims of this thesis were: (1) to explore the early nutritional support of preterm infants during the first two weeks of life, (2) to investigate the current routine nutritional practice for intra-uterine growth restriction (IUGR) infants with abnormal antenatal Dopplers during their hospital stay, (3) to evaluate families' practices and perceptions regarding the introduction of complementary feeding (CF), and (4) to critically appraise the current evidence for the provision of nutrition education to families on weaning of infants born preterm and full-term infants.

To achieve these aims, this thesis was divided into four studies. The first study (Chapter Two) utilised raw data from 59 infants admitted to the Neonatal Units at Nottingham University Hospitals to explore nutritional support for preterm infants in the first 14 days of life. To investigate how close the nutritional support for preterm infants was to published nutritional recommendations, further data were obtained for 119 preterm infants admitted to Neonatal Units within the UK Central Newborn & Trent Perinatal Networks. The study determined that overall, nutritional intakes were close to recommendations for infants in Neonatal Intensive Care Units, although the intakes were below the recommended range for infants from Special Care and Local Care Units.

The second study (Chapter Three) utilised data of 1085 IUGR infants with abnormal antenatal Doppler studies identified from a national database to account for the possible impact of the evidence on the clinical practice. I have explored change in nutritional practices between two

cohorts, before and after the publication of the Abnormal Doppler Enteral Prescription Trial (ADEPT). I have also investigated the nutritional practices of those units who recruited, and those who did not recruit for the ADEPT study. The study demonstrated that there has been significantly earlier introduction of enteral and parenteral nutrition after the publication of the ADEPT study. Growth outcomes also improved for infants from the cohort after results were published from the ADEPT. However, it appears that there was no influence on the infants' clinical outcomes.

The third study (Chapter Four) involved a survey to evaluate parents' practice and perception of the support provided on weaning of preterm infants along with providing contextual, demographic data. A total of 100 questionnaires were completed and analysed. The survey findings revealed that the majority of parents were satisfied with the support provided on weaning although a large minority were not. This support was associated with later commencement of weaning, compliant with the few available recommendations.

The fourth study (Chapter Five) involved two Cochrane systematic reviews as a means of critically appraising published randomised controlled trials of family nutrition education interventions on weaning preterm and full-term infants. Systematic literature searching identified 1174 unduplicated records. No studies met the inclusion criteria of the review involving preterm infants, however, there was one ongoing trial. Therefore, there was no evidence to inform the potential impact of nutrition education intervention in preterm infants. The second review involved full-term infants. Nine studies were included in this review. The reviewed randomised controlled trials showed that nutrition education has an impact on infant growth outcomes. However, the available trials were of low to moderate quality, therefore, further high-quality research in this area is needed.

This programme of research concludes by highlighting the implications of a new body of research evidence for early postnatal and post-discharge nutrition support clinical practice, guidelines and future research.

Dedication

I wish to dedicate this thesis to:

- the memory of my beloved father. Abdulla, who passed away during my study and whom I miss very much. He was the source of my inspiration to succeed throughout both my professional and personal life

- my family with all my love.

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The work in this thesis was undertaken at the Academic Division of Child Health, Obstetrics and Gynaecology at Nottingham University Hospital, Queens Medical Centre, Nottingham, between November 2013 and July 2018.

Unless otherwise stated, this thesis presents my own work completed with the supervision of Professor Helen Budge, Professor Michael Symonds, Dr Jon Dorling of the University of Nottingham.

This thesis has not, whether in the same or a different form, been submitted to this or any other university in support of an application for any degree other than that I am now a candidate.

Zenab Abdullah Elfzzani
April 2019

Presentations

Oral presentations

Elfzzani, Z.; Ojha, S. Jarvis, C, Dorling, J. Symonds, M. Budge, H. "Nutritional support for preterm infants: a study of current practices of parenteral and enteral nutrition". Sue Watson Postgraduate Presentation Prize, School of Medicine, University of Nottingham. October 2015.

Poster presentations

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Elfzzani, Z.; Ojha, S. Jarvis, C, Dorling, J. Symonds, M. Budge, H. "Nutritional support for preterm infants: a study of current practices of parenteral and enteral nutrition". Trent Perinatal Network Research, Audit & Quality Improvement Day, giving a poster presentation, March 2016.

Publications

Elfzzani Z, Kwok TC, Ojha S, Dorling J. Education of family members to support weaning to solids and nutrition in infants born preterm. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD012240. DOI: 10.1002/14651858.CD012240.pub2.

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List of Abbreviations

Abbreviations	Definition
AEDF	Absent end-diastolic blood flow
AREDF	Absent or reversed end diastolic flow
AAP	American Academy of Paediatrics
ADEPT	Abnormal Doppler Enteral Prescription Trial
BW	Birth weight
BPD	Bronchopulmonary dysplasia
BAPM	The British Association of Paediatric Medicine
CF	Complementary feeding
CFs	Complementary foods
CGA	Corrected gestational age
CRIB-II	Clinical Risk Index for Babies
CPAP	Continuous positive airway pressure
CI	Confidence interval
CNN	Central Newborn Network
DH	The Department of Health
EDF	End-diastolic blood flow
ELBW	Extremely low birth weight
EUGR	Extra-uterine growth restriction
EBM	Expressed breastmilk
ESPGHAN	The European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FTT	Failure to thrive
GA	Gestational age
GIT	Gastrointestinal tract
GV	Growth velocity
GRADEpro	The Grading of Recommendations Assessment, Development and Evaluation approach
HR	Hazard ratio
HB	Haemoglobin
HAZ	Height-for-age z-score
ID	Iron deficiency
IDA	Iron deficiency anaemia
IQR	interquartile range

IVH	Intraventricular haemorrhages
IPN	Individualised parenteral nutrition
IUGR	Intra-uterine growth restriction
ITT	Intention-to-treat analysis
ISO	International Organisation for standardisation
LBW	Low birth weight
NNAP	National Neonatal Audit Programme
NGT	Nasogastric tube
NICU	Neonatal Intensive Care Unit
NEC	Necrotising enterocolitis
PDA	Patent ductus arteriosus
PN	Parenteral nutrition
QI	Quality improvement
RCT	Randomised controlled trials
RR	Risk ratio
REDF	Reversed end-diastolic blood flow
RBC	Red blood cell
SGA	Small for gestational age
SSEF	Standardised slow enteral feeding protocol
SD	Standard deviation
SEM	Standard error of mean
SPN	Standardised parenteral nutrition
TPN	Trent Perinatal Network
UNICEF	The United Nations Children's Fund
UA	Umbilical arteries
VLBW	Very low birth weight
WAZ	Weight-for-age z-score
WHZ	Weight-for-height z-score
WHO	World Health Organisation

Chapter 1: Introduction

1.1 A general overview of the programme of research

This thesis investigates the nutrition care of preterm infants. In the first study, the changes in nutrition practice in the first fourteen days of life in three different eras were assessed through the analysis of protein and energy intakes. The nutrition intakes for infants from the Trent Perinatal and the Central Newborn Networks were further examined by analysing growth outcomes of the population. In the second study, the change in parenteral nutrition (PN) and enteral feeding practices since the Abnormal Doppler Enteral Prescription Trial (ADEPT) for babies with Abnormal Doppler's was assessed. The third study investigated support provided for families of preterm infants on weaning through analysis of families' practices and perceptions. Finally, the fourth study synthesised trial evidence on the effectiveness of nutrition education on weaning delivered to families of preterm infants as well as full-term infants. Outcomes of interest were an infant and young child nutrition status, growth, and neurodevelopment. This introductory chapter summarises current knowledge on the nutrition of infants in the neonatal unit and later during the period of weaning from milk to solid foods.

1.2 Premature births

A premature infant, as defined by the World Health Organization (WHO) (10), is one born before 37 weeks of gestation. Based on the gestational age (GA), preterm infants are categorised into three sub-categories:

- extremely preterm (<28 weeks)
- very preterm (28 to <32 weeks) and
- moderate to late preterm (32 to <37 weeks)

Since the growth and development of many of the systems take place at some stage in the last trimester of pregnancy (11), preterm infants may have low birth weight (LBW: birth weight <2500g) and immature functions of the major organs and systems. LBW is caused either by premature birth or by the infant being small for gestational age (SGA), or a combination of both. Birth weight (BW) and GA each have an important effect on perinatal morbidity and

mortality, especially in very low birth weight (VLBW: birth weight <1500g) and extremely low birth weight (ELBW: birth weight <1000g) infants (12).

Inadequate intrauterine fetal growth affects approximately 3-10% of pregnancies (13-15). Such pregnancies result in physiologically normal SGA infants or intra-uterine growth restricted (IUGR) infants where a pathological process interferes with growth. SGA is usually defined as birth weights <10th percentile for infants of the same GA (16). IUGR occurs when the fetus does not receive adequate nutrients and oxygen needed for appropriate growth and development of tissue and organs (17, 18). Based on the aetiology of impaired fetal growth, IUGR fetuses can be divided into two groups: non-placental and placenta-mediated growth restriction. The second group is the much more common type of IUGR, and causes include pre-eclampsia, placental anomalies, multiple pregnancies (Twin-to-Twin) (19).

IUGR can be a severe medical problem in the perinatal period. In developed countries, 3-15% of neonates are classified as IUGR (14, 15, 20). These fetuses are at high risk of hypoxic events, hypoglycaemia acidaemia and premature birth (21, 22). Moreover, IUGR is found to be the second cause of perinatal mortality after prematurity and estimated to be a contributing factor in 43-52% of stillbirths (23, 24); therefore, IUGR is an important clinical entity. However, the severity of perinatal comorbidities related to IUGR may vary by the case definition.

Generally, premature birth can influence how infants grow and develop, and the earlier a child is born, the higher the risks, so it is crucial to address the areas that could contribute to improved outcome. A large range of factors, including nutrition and medical conditions, might affect the growth and development of each infant. This research thesis explores some of these in detail to expand knowledge and ultimately inform optimal nutritional practices.

1.3 The problems and challenges of preterm birth

Across 184 countries, the rate of premature birth ranges between 5% and 18% (10). Low- and middle-income countries (25) endure a disproportionate burden of this medical condition. Approximately 60% of preterm births occur in developing countries (South Asia and Sub-Saharan Africa), where the highest mortality also occurs (5). In the UK, approximately 7% of

liveborn infants are born prematurely (26). Premature birth is one of the major issues of perinatal medicine and creates a considerable global burden due to its high mortality and morbidity. Each year, approximately one million preterm infants die due to complications of prematurity and many of those who survive face lifelong disability (5). Figure 1.1 illustrates the global causes of deaths in children under 5 years of age in 2015.

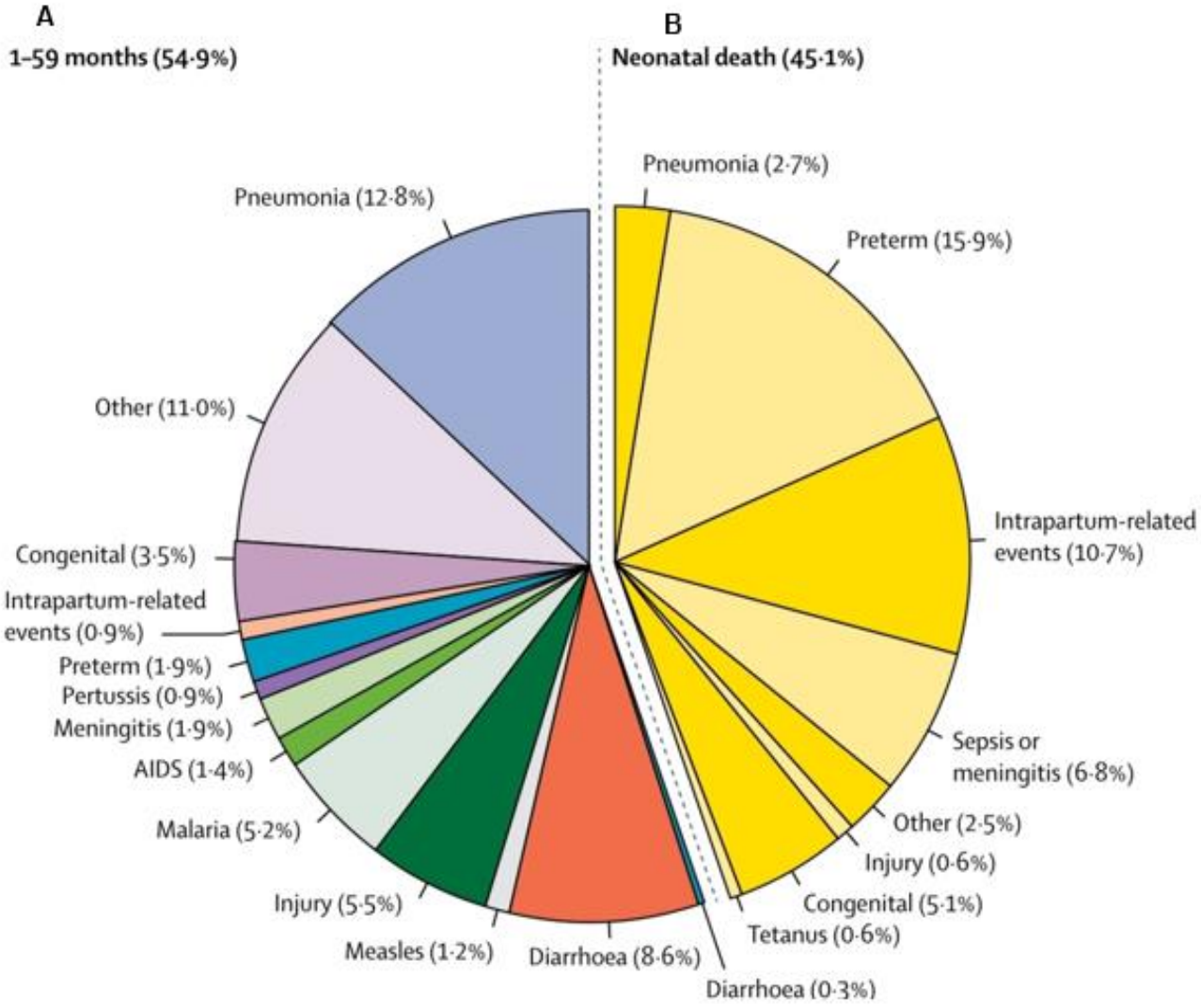

Figure 1.1 The estimated child mortality by cause: Global causes of deaths in children under 5 years of age in 2015 (5)

The chart depicts the causes of under-5 death (A) and neonatal death (B). Each sector is proportional to the percentage of total under-5 death

Preterm infants are prone to serious illness, impaired growth and development. Numerous studies have attempted to evaluate the effect of premature birth on later growth and

development at different stages of life (27-29). It has been estimated that three-quarters of these complications could be prevented with current, cost-effective interventions (10). Optimising early life nutritional support is one of the main interventions available to improve the clinical sequences of premature birth. However, currently, to the best of my knowledge, there are no standard nutritional policies for infants born preterm.

Standards for nutrition support for full-term infant have been based on logic and accuracy measures, which include nutrient intake and growth of healthy, breastfed infants (30). However, the main problem with the nutrition of preterm infants particularly those who were born with LBW has been to define what "normal" nutrition should be. Suboptimal nutrition support may increase the risk of complications related to prematurity. My study addresses some issues of preterm infants during admission to neonatal units and the later period of weaning to solid foods.

1.4 Complications of prematurity

In comparison to full-term infants, preterm infants have a greater risk of postnatal complications (31). The first large population-based cohort study in the UK (32), which explored the relationship between GA at birth and later health outcomes, showed a gradient of worsening health outcomes with decreasing gestational age. Preterm birth is the major risk factor for neonatal mortality, with 73% of infant deaths in the UK occurring in preterm infants (33). In addition to high mortality, this population is at high risk of short and long-term morbidities.

Premature birth is associated with underdeveloped organs and systems; manifested in prematurity-related medical complications. Some complications are manifested in the early neonatal period (12) such as:

- respiratory complications:
    - i- respiratory distress syndrome
    - ii- mechanical ventilation associated complications
    - iii- respiratory infection
    - iv- aspiration pneumonia
- gastrointestinal complications

i- feeding problems including feeding intolerance and immaturity of sucking, swallowing reflexes and their coordination
ii- the need for PN which may be associated with nutritional deficiencies, metabolic bone disease, infections, and liver diseases
iii- necrotising enterocolitis (NEC) (Section1.4.1)

- brain injuries such as intraventricular haemorrhages (IVH)
- anaemia of prematurity and need for blood transfusion.

Although the survival of preterm babies is improving, survivors are at increased risk of long-term complications. It has been estimated that the percentage of preterm infants who would have long-term complications in England and Wales is 4.2% rising to 7.9% for babies born less than 28 weeks postconceptional age (34). These complications include extra-uterine growth restriction (EUGR) (discussed in Section 1.4.2), respiratory problems, motor and sensory impairment, learning difficulties (34). Premature birth is also associated with negative psychosocial and emotional effects on the family (35), in addition to its implications for public-sector services, such as health and education (34). Some of these complications may be related to nutritional insufficiency.

1.4.1 Necrotising enterocolitis

NEC is a disease that affects the gastrointestinal tract (GIT), characterised by inflammation and injury of the intestinal wall that may progress to necrosis and, potentially, perforation of the gut (36). The disease is thought to arise from a triad of ischaemic injury, milk feeding and bacterial invasion of the intestinal wall (37). NEC is much less common in term infants in comparison to preterm infants with ninety percent of cases occurring in preterm babies (38).

The incidence of NEC varies among countries and neonatal units. Recently, the incidence of NEC across the neonatal networks in England has been estimated (39). Severe NEC, defined as cases that confirmed at laparotomy, post-mortem, or resulting in death, was found to affect 3.2% of infants born <32 weeks (39). However, restricting the analysis to infants with cases of NEC confirmed at laparotomy may not represent the population for which the case-definition is intended. On the other hand, the Vermont Oxford Network, defined a NEC case as an infant with at least one clinical sign (bilious aspirate or emesis, abdominal distension or occult or

gross blood in stool) and at least one radiological finding (pneumatosis, hepatobiliary gas, pneumoperitoneum) in addition to cases identified by inspection during surgery or at post-mortem (40). It is noteworthy that less severe cases of NEC have many non-specific features. The Vermont Oxford definition requires only one clinical and one radiological finding and may be too loose a case-definition. Therefore, data on the incidence of NEC at the population level are unreliable and may lead to overestimation of the disease burden.

Prevalence of NEC ranges from 1.6 to 12% (41-45). Surgical intervention is required for 20–40% of NEC cases (46). Furthermore, NEC is one of the leading causes of death in neonatal units. Mortality rates associated with NEC range from 10 to 40% (47, 48). However, these estimates were based on data from local neonatal networks. Hence, the possibility of incomplete case ascertainment of NEC cannot be excluded.

The estimated length of NICU stay and the cost of medical and surgical treated NEC is above the average cost incurred for extremely preterm infants without NEC. Infants with NEC stayed in NICU 11.7- 43.1 days longer than infants without NEC. Accordingly, the cost of hospitalisation was estimated at medical treated NEC: US$74.004 [95% confidence interval (CI): 47.051 to 100.957]; surgical treated NEC: $198.040 [95%CI: 159.261 to 236.819] per infant (49), and $6.5 million per year for treating infants with NEC (50). Of note, these estimates were based on length of hospital stay, which may not directly estimate the cost of NEC. Furthermoore, NEC causes long-term costs to society, the individual, and their families due to lifelong physical and mental impairment are substantial.

The morbidity and mortality in NEC are inversely related to the infant's GA and BW. Although NEC was described several decades ago, the exact mechanism of NEC is not well understood. It has been observed that more than 90% of NEC cases occur after feeding (38). This might be due to the fragility of the immature intestinal wall which could predispose to bacterial invasion after milk exposure (12). Moreover, hypoxic-ischemia of the intestine stimulates the release of inflammatory mediators, such as platelet activating factors and tumour necrotic factors, that mediate inflammatory processes and, hence, mucosal injury and

the damaged intestinal barrier is a result. Factors increase the risk of NEC in preterm infants illustrated in Figure 1.2.

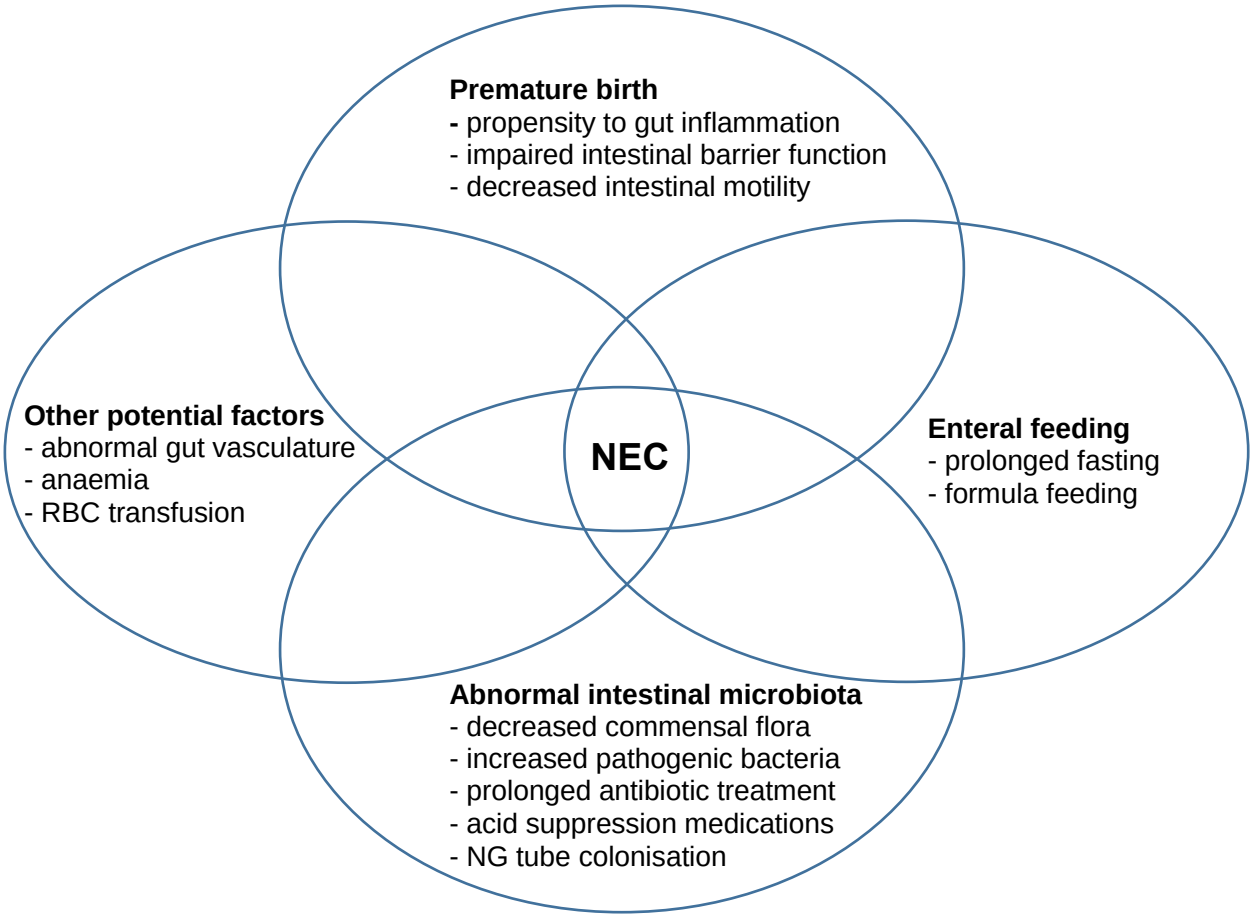

Figure 1.2 Necrotising enterocolitis: A multifactorial medical condition. Adapted from Patel et al. (6)

Necrotising enterocolitis: NEC; Red blood cell: RBC; Nasogastric tube: NG

Generally, NEC is a common cause of postnatal morbidity in premature infants with a higher possibility of advanced disease in those most premature (51). The outcomes of infants with NEC are highly dependent on the severity of the case. Based on clinical presentation, NEC can be classified into three stages as described by Bell and colleagues - Stage I: suspected NEC; Stage II and III: definite NEC (52). This classification was developed to guide surgical management after the diagnosis was confirmed (52). In 1987, Bell's staging was modified and adapted to be used for case definition (53) (Table 1.1).

Table 1.1. Modified staging criteria of necrotising enterocolitis Adapted from Kliegman and Walsh (53)

Modified Bell's Staging	Clinical Findings	Radiographical Findings	Gastrointestinal Findings
Stage I	Temperature instability, apnoea, and bradycardia	Normal gas pattern or mild ileus	Mild abdominal distention, gastric residuals, faecal occult blood,
Stage IIA	Temperature instability, apnoea, and bradycardia	Ileus with dilated intestinal loops and focal pneumatosis	Abdominal distention, haematochezia, absent bowel sounds
Stage IIB	Metabolic acidosis with thrombocytopenia	Portal venous gas, widespread pneumatosis, and ascites	Oedematous abdominal wall and tenderness
Stage IIIA	Hypotension, coagulopathy, mixed acidosis and oliguria	Moderate to severely dilated intestinal loops, ascites, no free air	Oedematous abdominal wall, erythema, and induration
Stage IIIB	Shock, deteriorating vital signs and laboratory values	Pneumoperitoneum	Bowel perforation

High morbidity rates are associated with definite cases of NEC, especially in ELBW infants (54). Given the role of inflammatory cytokines in NEC and the associated nutritional deprivation, infants may be at high risk for long-term neurodevelopment and growth impairment. Many studies have shown associations between NEC and neurodevelopment, using a variety of neurodevelopmental assessment scales at various ages (55-57), However, much of the prior research has been retrospective in nature, which does not allow one to know whether these complications are directly from having NEC. For example, Hintz et al. (57) evaluated growth and developmental outcomes of 2948 infants at age at age of18 to 22 months. This study showed poor growth and neurodevelopmental outcomes in infants who had surgically treated NEC in comparison to infants with medically treated NEC and also those infants without NEC. It is noteworthy that the association between NEC and neurodevelopmental outcome may be affected by many other factors that were not considered in the Hintz et al. study (57), such as malnutrition. Suboptimal nutrient intakes may occur during the acute stage of NEC or, subsequently, due to short bowel syndrome in infants managed by surgical bowel resection (58).

To reduce the incidence of NEC in preterm infants, many protective measures have been tried (59), such as prophylactic antibiotics (60), delayed enteral feeding, slower incrementing of enteral feeds and parenteral nutrition administration (61), and probiotic administration (62, 63).

Nonetheless, based on current research evidence, early introduction of enteral feeding does not appear to increase the risk of NEC (64).

1.4.2 Extra-uterine growth restriction

Although the survival rate of preterm infants has increased, these infants still experience several co-morbidities at the time of discharge from hospital. One of these co-morbidities is EUGR (65). EUGR is defined as a growth value ≤10th percentile estimated for GA (66). Clark et al. (67) defined EUGR as a growth value ≤10th percentile estimated for GA at discharge from hospital. The incidence of EUGR in infants born between 23 and 34 weeks GA of 28% for weight and 34% for length (67). Shan et al. (68) reported an incidence in infants < 37 weeks gestation of 56.8% for weight and Stoll et al. (69) reported an incidence of EUGR in infants 22 to 28 weeks' GA of 79% for weight. However, there are limits to how the concept of EUGR has been taken. It is noteworthy that comparing the incidence of EUGR may be hindered by differences in case definitions, variation in feeding practices, and inclusion criteria.

. EUGR is commonly observed in small preterm infants due to insufficient early nutrition that results in protein and energy deficits during early postnatal life (70). Growth assessment serves for evaluating the nutritional status of children and provides an indirect measurement of the quality of life of an entire population (71). An infant with low weight for age measurements needs to be assessed for malnutrition or any illnesses that may lead to slow growth. For population-based assessment, WHO suggests that z-score as the best system for analysis and presentation of anthropometric data and it is one of the most commonly used anthropometric indices to assess infant's nutritional status and growth (72).

Z-score is a numerical measurement of a value's relationship to the mean of a dataset, which quantifies the distance of standard deviations (SDs) from the mean (71). The WHO Global Database on Child Growth and Malnutrition uses a z-score cut-off point of <-2 SD to categorise low weight-for-age (WAZ), low height-for-age (HAZ) and low weight-for-height (WHZ) as moderate and severe undernutrition, and <-3 SD to define severe undernutrition. The cut-off point of >+2 SD categorises high WHZ as overweight in children (71).

The most recent growth charts were developed based on the growth patterns of fetus (as has been determined by infants' size at birth in the large population-based studies) and the term infant (based on the WHO Growth Standard) (73). It is noteworthy that ultrasound studies and comparison of subgroups of preterm infants suggest that the fetal studies, including those used in this development, may be biased by the premature birth. Fetuses who remain in utero are likely differing in growth from babies who are born early (74, 75). Nonetheless, fetal size from these imperfect observational studies may be the best data available evidence at this point for comparing the growth of preterm infants.

1.4.2.1 Factors associated with extra-uterine growth restriction

EUGR is a common problem that might be a result of complex interactions between many factors, such as low GA and BW; suboptimal nutrient intake; and prematurity-related co-morbidities. The following section describes these contributors in more detail.

1.4.2.1.1 The effect of gestational age and birth weight on growth outcomes

The consistently reported risk factors for EUGR in the literature are prematurity and LBW (67, 70). In fact, in 2003, an administrative database study reviewed 24,371 preterm infants admitted to 124 NICUs (67). The study aimed to assess postnatal growth outcomes of infants at the time of discharge from NICU in relation to GA. Impaired postnatal growth was observed in 71% of infants born at 23 weeks compared to 23% for those born at 34 weeks. Although the investigators considered many factors that may affect growth outcomes, such as the infants age and the ongoing medical condition, their findings might be limited by site-specific differences in nutritional approach, which may also have an impact on growth restriction incident rates (67). Similar findings were observed in Ehrenkranz et al. (76) study. This large, multicentre, prospective cohort study (76) assessed growth outcomes in preterm infants and showed that the majority of infants born between 24 and 29 weeks gestation failed to achieve the median BW of their fetal counterparts at the time of discharge from hospital. However, these findings may also be limited by the lack of information on the infants' nutritional intakes. It has been found that nutrition intake had a large impact on explaining growth differences between preterm infants (70, 77).

EUGR is commonly seen in VLBW and ELBW infants (28, 65). Cooke et al. (65) studied 659 infants from different levels of neonatal units in the UK and found that there were variations in z-scores for weight at birth. These variations accounted for 45% of the change in z-score between birth and discharge. Although the adjusted changes in weight outcomes at discharge were not reported in details by Cooke et al. (65), the relationship between BW and growth outcomes at 36 weeks GA was also observed by others (28). Lemons et al. (28) studied 4438 infants weighing between 501 and 1500 g born at the 14 centres of the National Institute of Child Health and Human Development Neonatal Research Network. EUGR observed in 97% of VLBW infants and 99% of ELBW. It is likely that poor in-hospital growth aggravated by suboptimal nutrition support and medical conditions. In particular, a significant number of co-morbidities were observed among the study population (28). Therefore, LBW and low GA at birth are major clinical risk factors for co-morbidity that may affect growth outcome and the magnitude of nutritional support provided may partially mediate this effect.

1.4.2.1.2 The effect of co-morbidities on growth

Impaired growth of infants may result from premature birth associated co-morbidities. These morbidities are known to be one of the strongest contributing factors to failure to thrive (76) and affect the nutritional status of infants (27). However, providing sufficient amounts of nutrients in the first period of life could be crucial to prevent growth restriction among this high-risk group (78).

The severity of the illness of infants admitted into neonatal units affects the intensity of the therapy, the prognosis for the infant and the hospital costs of infants' care. For example, birth weight-specific neonatal diseases such as IVH and severe group-B streptococcal pneumonia may contribute to poor outcome (79) because infant's nutritional support is most likely influenced by the neonatal team's impression of infant's medical condition. It is common practice for infants thought to be more critically ill, to be managed differently than infants thought to be less critically ill (78). For example, infants with high Clinical Risk Index for Babies (CRIB-II) score require longer time to achieve full enteral feeding (80). The CRIB-II score is a commonly used model in neonatal units to assess the clinical condition of infants with the first

12 hours after birth (81). It is useful in identifying high-risk neonates, auditing neonatal units and provides a standardised mortality rate for performance comparison among neonatal units.

The CRIB-II score considers BW, GA, base excess, body temperature at admission, and gender of the infant to determine the initial mortality risk. The score provides a valid and simple method of risk-adjustment for neonatal intensive care. The total CRIB-II score ranges from 0 to 27. The higher the score, the poorer the prognosis (81).

The association between co-morbidities and growth outcome has been investigatedin a prospective controlled trial (82) of 13 preterm infants with bronchopulmonary dysplasia (BPD). There was an increase in the duration of oxygen supply and elevated energy expenditure in infants with BPD, which probably contributed to impaired growth, though, infants with protein-losing enteropathy or malabsorption were excluded (83). Also, there was no statistical difference in the calorie and protein intakes between the study groups. Kurzner's et al. (82) analysis does not take account of the amount of nutrients provided, nor do they examine postnatal steroid exposure, growth measurements and infants' gender. It is noteworthy that, despite the small sample size and the insufficient information of factors which may have an impact on growth outcomes of preterm infants (77), the findings are consistent with others (84-86).

Early and progressive nutrition support including PN and enteral feeding is associated with improved outcomes without an increased risk of adverse events in particular NEC (87-89). The relationship between critical illness during the neonatal period and later growth and other outcomes is found to be mediated by the early nutritional support provided to preterm infants during the first few weeks of life (88).

1.4.2.1.3 The effect of early nutrition on growth

Neonates usually lose weight in the first week of life regardless of the type of nutritional support provided, but BW is usually regained after that (90). The development of EUGR during hospitalisation is thought by many to be inevitable in small preterm infants who do not receive early and adequate amounts of protein and calories during the first few weeks of life. Embleton

et al. (70) showed that approximately 45% of the variation in growth is related to nutritional intake. Further retrospective study (77) observed 564 infants from 6 NICUs between 1994 and 1996, and assessed weight growth velocities of infants born <30 weeks gestation, between day 3 and day 28 of postnatal age. Multiple regression models showed that differences in nutritional practices, particularly mean protein intakes, were strong contributors to the variation in growth outcomes among the participating units.

A similar finding was obtained from a secondary analysis of data collected (91) on 1018 infants, ≤1000 g BW who were included in a randomised clinical trial (RCT) of glutamine supplementation between 1999 and 2001. A noticeable influence of protein and caloric intake on growth outcomes was observed. Moreover, there was a significant improvement in growth at 36 weeks gestation when infants were provided with at least 3g/kg/day of parenteral protein early within the first five days after birth. Of note, variability in nutritional practices may be influenced by the severity of prematurity associated illnesses (78), particularly of those illnesses concerned with the early initiation and increment of PN or enteral feedings, such as chronic lung disease and NEC, and this may explain the difference in postnatal growth.

Taken together, clinical practice decisions about early nutritional support provided to preterm infants appear to be related to the perceived severity of illness and the magnitude of early nutritional support provided to infants plays a role in mediating the effects of co-morbidities on later outcomes including growth and development.

1.5 Nutritional management

Most preterm infants remain in the neonatal unit during the time equivalent to the third trimester. During this time, one of the aims of the neonatal unit team is to deliver nutrition to an infant to attain a growth velocity (GV) like intrauterine GV. Nonetheless, infants' growth and organ development create a challenge in nutritional management during early neonatal life. The fear of critical illness further complicates the delivery of sufficient nutrients (92). Nutrition support for preterm infants is divided into parenteral and enteral routes. Although enteral feeding has several advantages over PN, there are specific cases when PN is given as a

concomitant or sole therapy, to meet nutritional requirements. These include BW, GA, respiratory and cardiovascular function, and acquired intestinal morbidity such as NEC (2). PN is used to meet nutrition requirements as 'bridging' whilst enteral feeding is established. The average duration of 'bridging' PN is typically 1-2 weeks (2).

PN use is associated with benefits and complications, and clinicians must balance these benefits and risks. Figure 1.3 illustrates the common benefits and risks associated with PN use in neonates.

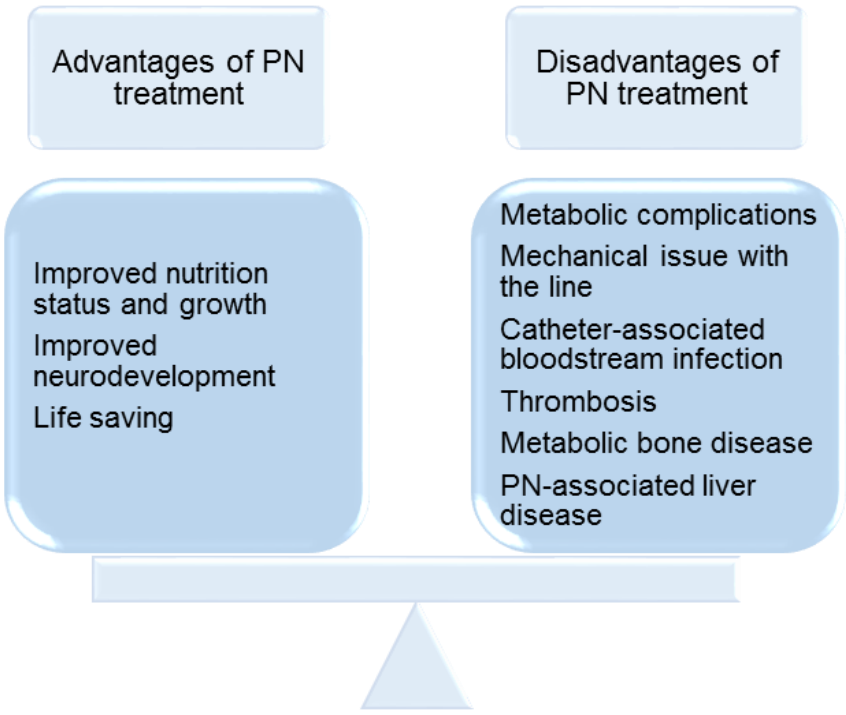

Figure 1.3 Common benefits and risks associated with parenteral nutrition use in neonates. Adapted from Embleton et al. (2)

Parenteral nutrition: PN

PN can be prescribed as individualised PN (IPN) or standardised PN (SPN). IPN formulations have nutrients (± acetate) that are individually prescribed based on each infant's requirements, whereas SPN contains a fixed amount of nutrients that cannot be modified. Recently, a concentrated SPN (fixed amount of nutrients in a low volume) become available in some units (93). The concentrated SPN allows delivery of the required nutrients when fluid is restricted or during the transition period (transition from PN to enteral feeding). The main drawback of the

IPN is the time between prescription and PN administration, which vary from hours to a few days, e.g. during weekends. Furthermore, sufficient nutritional knowledge is required to prescribe IPN adequately. Generally, SPN is effective in optimising nutrient intakes, it also has advantages of rapid availability, cost savings, fewer prescription and administration errors (94) compared to IPN (95).

Early PN is well tolerated by preterm infants including those who have BW of <1500 g (96). However, many infants do not receive the calorie and protein expected from the prescribed PN. Although the reasons for this are complex and multifactorial; co-administration of other drug infusions, fluid restriction, changing electrolyte requirement and sudden unexpected changes in fluid and electrolyte balance all play a part (97).

Enteral feeding in preterm infants is challenging, especially in ELBW infants (98). Suspected feeding intolerance and the potential risk of NEC are common gastrointestinal problems observed in preterm infants with LBW (39). These concerns often lead to delayed initiation of enteral feeding, slow progression of feeds and unsatisfactory nutritional delivery (99). Under-utilisation of the GIT is associated with a prolonged need for PN and its associated complications (64). Furthermore, delayed enteral feeding induces GI mucosal atrophy, weakens the intestinal barrier, increases permeability, decreases regenerative capabilities, inducing GI dysfunction and increasing the risk of feeding intolerance and NEC (100).

Several feeding regimens have been developed for preterm infants which are usually determined by local knowledge, experiences, and traditions (98, 101). There is wide variation in feeding practices internationally and between and within neonatal units (98), which may reflect the uncertainty of best practice. Although evidence-based enteral nutrition guidelines suggested that feeds should be rapidly initiated within 6–48 h after birth (102), the practice of delayed introduction of enteral feeding is frequently observed, particularly in VLBW infants (98) due to fear of feeding intolerance and NEC. Other reasons for delayed introduction of enteral feeds have been reported such as waiting for expressed breastmilk (EBM), the presence of an umbilical artery or venous catheter, significant patent ductus arteriosus (PDA), and postnatal haemodynamic instability requiring inotropes (98, 101).

Early initiation of enteral feeding is currently applied in several NICUs associated with significant improvement of infant outcomes (98). Full enteral feeding could be achieved in most preterm infants within the first two weeks after birth (103). However, establishing enteral feeding in high-risk infants, such as those who are extremely preterm and very preterm, might be delayed due to concern that earlier introduction may not be tolerated and may increase the risk of NEC (98).

1.6 Nutrient requirements and recommendations

Nutrition is important for survival, growth and development, and therefore, a considerable focus on it is needed in neonatal care. Nutrient requirements of preterm infants have been defined by two approaches, the factorial approach, and the empirical approach. The former approach estimates nutrient requirements by considering that the total requirement for a nutrient is equal to accretion rates of nutrients derived from the chemical analysis of fetal body composition at different stages of gestation. A model from GA, weight gain and the absolute amount of nutrient were used to construct a reference fetus (104). Most of the international recommendations used the reference fetus concept to estimate nutrition requirements. Although the studies used to develop this concept were selected with caution, a question that arises is should a stillborn fetus included have normal intrauterine growth?. Stillbirth may occur due to many causes, which may interfere with nutrient transfer to the fetus, and consequently, would affect growth and body composition. Furthermore, this approach may be limited by the fact that there are major physiological differences between the neonate and fetus (105).

The empirical method was developed based on manipulation of nutrient intakes and observation of the biochemical or physiological responses, including growth, comparing actual nutrient intakes with growth (106). Of note, the empirical approach provides an estimate of nutrient requirements, but such studies have rarely included very small infants for whom no empirical estimates are therefore available.

Several expert groups have contributed their views and discussed the latest developments to formulate international consensus recommendations for the nutritional support of preterm

infants (106-108). These recommendations have been designed to help neonatal unit teams develop nutrition guidelines to improve standards of nutritional care. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the first set of recommendations on nutrition support of preterm infant in 1987 (109). The recommendations were re-evaluated by Tsang et al. (107) and presented in “Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines”. Tsang et al. (107) recommendations are taking into account the factorial and empirical approaches to define infants nutritional needs. These guidelines have recently been updated by Koletzko et al. (106). The ESPGHAN published recommendations on PN in 2005 (110). These recommendations give general guidelines on PN requirements; neither specific details on what daily prescriptions should be nor the incremental rate of PN in early neonatal life were described. In 2010, the ESPGHAN published enteral feeding guidelines (108). These recommendations suggest sensible ranges for nutrient intakes for stable-growing preterm infants weighing ≤1800 g. No specific recommendations for ELBW were given because data are lacking for most nutrients in this group apart from protein. Over the past few decades, considerable progress has been made on the early nutrition support of infants born preterm.

Nonetheless, the optimal nutritional requirements of preterm infants are still not yet fully known. Limitations in the available recommendations are:

- based on low- to moderate-quality evidence
- mostly based on infant’s BW, and do not consider GA. Preterm infants are a heterogeneous group in their nutritional, growth and physiological development status. Nutrition requirements of infants born early preterm are different from those form infants born late
- some of these recommendations are based on the requirements for maintenance and growth and do not consider the need for catch-up growth

The nutritional requirements of preterm infants have not been extensively investigated; to my knowledge, there are no published studies stratifying infants by both BW and GA. More research is required to determine if recommended intakes should consider both GA as well as BW.

1.6.1 Recommendations of Tsang versus Koletzko

1.6.1.1 Recommended protein intakes

Proteins are the major functional and structural component of cells and are key factors for growth (111). Therefore, during the early neonatal period, infants require the highest levels of nutrient intakes in life to meet the requirements. Both recommendations emphasise the importance of early initiation of protein supply of 2 g/kg/day in the first 24 hours of life. Koletzko et al. (106) described an even higher upper limit of 2.5 g/kg/day for the initial dose. Both agreed that the amount of protein provided for transition should be approximately 3.5 g/kg/day. However, Tsang guidelines (107) suggested that the transition period may be extended up to 7 days, where Koletzko guidelines (106) suggested this period should be shortened to 1-2 days. The amount of 3.5–4 g/kg/day should be provided for catch-up growth.

1.6.1.2 Recommended energy intakes

Energy is needed for all vital functions of the body at molecular, cellular, organ, and systemic levels. Premature birth is associated with high energy requirements, because of the relatively large body proportions of metabolically active organs compared to term infants (112), including the heart, liver, kidney, and especially the brain (113). Recognising that maintaining internal stores depends on balancing total energy intakes with energy expenditure (114), both guidelines recommend starting with amounts that are close to the expended energy. Tsang guidelines (107) recommend starting with 40-50 kcal/kg/day, where Koletzko guidelines (106) recommend starting with slightly a higher amount 60-80 kcal/kg/day. Rate of increment of energy supply is another area where there are marked differences between the two recommendations. The Tsang recommendation (107) for transition is a range between 75 and 85 kcal/kg/day, whereas the Koletzko recommendation (106) for transition is between 80 and 100 kcal/kg/day. When catch-up growth is needed, Tsang (107) recommended that the intake should be increased up to 105-115 kcal/kg/day, whereas Koletzko (106) suggested that providing 85-100 kcal/kg/day to infants should be sufficient. Both guidelines recommend an energy intake of 110-130 kcal/kg/day to support basal metabolism, protein/fat balance and growth for an enteral fed infant.

1.7 Concerns arising from current nutritional management

Gaps between nutrition recommendations and clinical practice have been extensively reported (98, 115-117), confirming failure to achieve the recommended amount of nutrient intakes (118), cumulative nutrient deficits (70, 87) and inadequate growth (70). A large discrepancy often exists between prescribed and actual nutrient intakes (3, 115, 119). Although the introduction of more appropriate nutrition guidelines in NICUs associated with higher nutrient intakes, VLBW infants often did not receive nutrients which meet protein and energy requirements (120, 121).

Many preterm infants are too ill to receive sufficient amounts of enteral feeds and require prolonged PN. Delaying enteral feeding is associated with prolonging the need for PN with PN-associated complications, prolonged time to achieve full enteral feeding (64), and trace element deficiencies (122). Table 1.2 illustrates the common reasons for delayed nutrition delivery for preterm infants.

Table 1.2 Common reasons for delayed nutrition delivery for preterm infants. Adapted from Ziegler et al. (123)

	Reason for delayed feeding	Source of concern or fear
Enteral	Abdominal distention	NEC
	Gastroesophageal reflux	Apnoea
	Hyperglycaemia	Poor metabolism and infection
	Low peripheral oxygen saturation	Slow metabolism
	On CPAP	Air entering the stomach
	On mechanical ventilation	Slow digestion
PN	Umbilical artery or umbilical vein catheter	Gut ischemia & NEC
	High blood urea	Urea & amino acid toxicity
	Hypo or hyperkalaemia	Interfere with poor gut function

Abbreviations
Continuous positive airway pressure: CPAP; Necrotising enterocolitis: NEC

1.8 Early enteral feeding in the high-risk preterm infants

Variations exist in when clinicians start enteral feeds and what is used to feed high-risk infants born preterm. Weighing the risks of early commencement of enteral feeding with those of PN is not easy. Moreover, high-risk preterm infants are extremely heterogeneous with respect to the prevalence of comorbidities as well as in the developmental stage of their organs

including, the maturation of their GIT (124). Enteral feeding comprises many confounding interventions such as commencement age, the frequency of administration, the volume is given, the rate of increase in milk volumes, and, not least, the choice between donor milk and formula to complement or substitute mother's breast milk. Given that the complexity of the situation, the small sizes of most randomised controlled trials (RCT), difficulties with blinding, defining and measuring outcomes, it is not surprising that best practice remains uncertain.

Premature birth commonly occurs as a result of a complicated pregnancy often due to impaired placental function (124). Increased placental resistance in the presence of placental failure leads to a reduction in end-diastolic blood flow (EDF) through the umbilical arteries (UA), which may progress to absent (AEDF) or reversed flow (REDF) (4) (Figure 1.4). This situation is often complicated by growth failure of the fetus and considered to be an indication of early delivery (22).

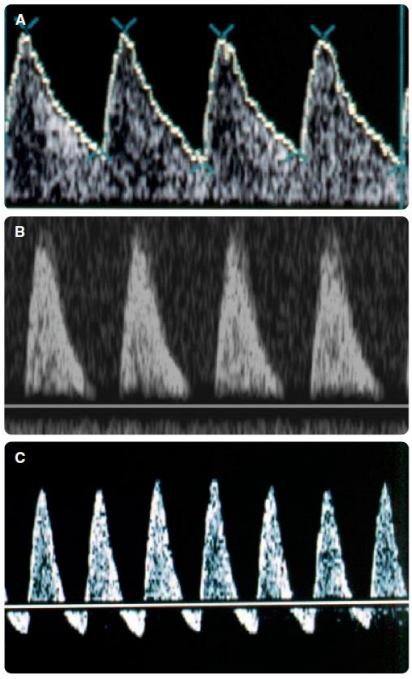

Figure 1.4 Examples of umbilical artery Doppler flow waveforms

Adopted from: SMFM. Doppler assessment of foetus with IUGR (4)
A: Normal umbilical artery Doppler flow waveform. B: Absent and C: reversed end-diastolic Doppler flow in the umbilical artery

1.8.1 Effect of absent or reversed end-diastolic flow in the umbilical artery on the gastrointestinal tract

Absent or reversed end-diastolic flow (AREDF) is a phenomenon which occurs due to increased placental vascular resistance in response to both acute and chronic hypoxia (17). Fetal adaptation to hypoxia involves preferential shunting of blood to the brain, adrenal glands and the heart at the expense of the splanchnic circulation (125). Oxygen deficiency results in IUGR (18); therefore, an infant is often born premature and SGA. AREDF occurs in almost 6% of infants of high-risk pregnancies (126). Premature birth is further complicated by IUGR and antenatal AREDF, such infants having a poorer prognosis compared to those with normal antenatal Doppler studies (127). Premature birth is associated with an immature mucosal barrier including immature tight junctions between epithelial cells resulting in increased permeability, bacterial translocation, and inflammation (128). Preferential shunting of blood in placental dysfunction may also result in impaired motor, secretory, and mucosal development of the GIT during postnatal life (129). IUGR infants with abnormal antenatal Doppler studies often develop abdominal problems with delayed meconium passage, abdominal distension, bilious vomiting and delay in tolerating enteral feeding within the first days after birth (130). This may occur due to postnatally persistent redistribution of regional blood flow and results in gastrointestinal problems and may adversely affect gut motility (131).

1.8.2 Feeding intra-uterine growth restricted infants with abnormal antenatal Dopplers

The introduction of enteral feeds to IUGR infants with AREDF in the UA is often delayed due to concern that early feeds may not be tolerated and may increase the risk of NEC (61). Regarding the advantages of early initiation of enteral feeding (≤ 5 days of life) for LBW infants, studies (9, 89) have shown a shorter time to achieve full enteral feeds, lower bilirubin concentrations, improved growth outcomes and shorter duration of hospital stay in the early feeding groups. Also, there appears to be no increased risk of feeding intolerance or NEC in infants who receive early enteral feeding, in particular, when mothers' milk is used (49, 64).

Generally, early initiation of enteral feeding is preferable to delays, but this is still controversial for infants who have AREDF in the UA (64).

The timing of the commencement of enteral feeding is thought to be an important modifiable risk factor for the development of NEC (36). There are advantages and disadvantages for both early and late introduction of enteral feeds and no conclusive consensus has been obtained. Early commencement may improve nutrition and growth, but it may also be associated with increase intestinal morbidity (61). Conversely, late introduction of feeding may be detrimental. Delaying feeds could diminish the functional adaptation of the immature GIT because gastrointestinal hormone secretion and motility are stimulated by enteral feeds (132). Also, delayed enteral feeding may cause hyperbilirubinemia via increased enterohepatic recirculation of bilirubin and delaying hepatic enzyme maturation (133). Furthermore, prolonged PN use may be associated with sepsis and metabolic complications (2). These complications often associated with adverse consequences for survival, duration of hospital stay, and growth (134).

Most cases of NEC develop in infants who have received enteral feeding (38). However, there is no good evidence to support the beneficial effect of delayed initiation of enteral feeding (64). A retrospective study (99) was established to examine when to start enteral feeding for ELBW infants. The study reviewed the incidence of NEC before and after implementation of a standardised slow enteral feeding protocol (SSEF). The SSEF is to delay the initiation of enteral feeding. Pre-SSEF group included infants admitted between 2003 and 2009 and SEFF group included infants admitted between 2009 and 2012. Four hundred and nineteen ELBW infants from NICU at the MetroHealth Medical Centre, USA were studied. The study showed that the incidence of NEC was significantly reduced in infants who followed the SSEF. However, the researchers did not consider pre-existing comorbidities. A significantly higher proportion of infants had comorbidities in Pre-SSEF compared to SSEF groups. These morbidities have been regarded as risk factors of NEC (135-137). Moreover, there was a significantly higher percentage of infants who had PDA within the Pre-SSEF group, and this may have contributed to their increased risk of NEC (138).

The same group (61) assessed the effect of SSEF on ELBW infants with BW <750g and found a significant reduction of incidence of NEC. However, this practice was associated with a longer time to achieve full feeds, duration of PN and total central line days. Furthermore, not surprisingly, infants from SSEF had more cholestasis and higher peak alkaline phosphatase levels. A higher proportion of infants who were fed breast milk from SSEF group was also observed, which might partially explain the decreased rates of NEC among these infants.

On the contrary, other studies have demonstrated that prolonged withholding of enteral feeding does not decrease the incidence of NEC. The evidence of NEC risk reduction strategies in IUGR preterm infants, in the context of the timing of introduction of enteral feeding, were reviewed and summarised in Table 1.3. Early enteral feeding was defined as starting <5 days and late feeding as starting feeds ≥ 6 days after birth. All these trials showed no difference in the incidence of NEC between infants receiving early, compared to late enteral feeding. Evidence for the optimal time to initiate enteral feeding for IUGR infants when insufficient, remains inconclusive. In this thesis, I will examine nutrition practices in neonatal units in two epochs, before and after the ADEPT study was published, to determine if the trial has changed the practices.

ADEPT (Abnormal Doppler Enteral Prescription Trial) is a multicentre randomised controlled trial (RCT) was undertaken in the UK (9). The ADEPT study included 404 preterm infants (< 35 weeks; median 31 weeks), who were IUGR and diagnosed with abnormal antenatal UA Doppler waveforms. Infants were allocated randomly to commence enteral feeds “early’’, i.e. within the first two days of life, or “late,” i.e. after the first six days of life. The same incremental rate of feeding was used for both groups, according to a “feeding prescription” tailored to BW, aiming to achieve 150 ml/kg/day within 9-13 day according to the infant’s weight. Mother’s milk was recommended as the first choice followed by donor human milk than infant formula milk.

Full, continued, enteral feeding was achieved at an earlier age in the group which received feeds early; the median age was 18 days compared with 21 days (hazard ratio (HR): 1.36 [95% CI: 1.11 to 1.67]). Therefore, the early feeding group had a shorter duration of PN (Risk ratio (RR): -3 [95% CI: -4 to -2]). From these findings, the authors concluded that early

initiation of enteral feeds in IUGR infant results in the earlier achievement of full enteral feeding. Although there was a high risk of performance bias as caregivers were not blinded to the allocation groups, early feeding did not appear to raise the incidence of NEC.

The findings of the ADEPT study are supported by a Cochrane systematic review (64). The review showed that delayed initiation of enteral feeding does not decrease the incidence of NEC development amongst SGA infants, including IUGR preterm infants with abnormal antenatal Dopplers.

Table 1.3 Randomised controlled trials that assessed the effects of early enteral feeding compared to the period of enteral fasting in small for gestational age (SGA) preterm infants

Study ID	Setting	N	Participants	Intervention	Outcomes	notes
Abdelmaaboud and Mohammed (139)	Single centre **Qatar**	117	28-36 weeks' gestation with BW <10th centile	Early initiation of progressive enteral feeds on day 3 vs late initiation of enteral feeds on day 6	The incidence of NEC (stage II/III), time to achieve full enteral feeds, rates of feed intolerance, mortality and duration of hospital stay	-Carers were not blinded -No information on blinding assessors
Arnon et al. (89)	Single centre **Israel**	60	BW <10th centile	Early enteral feeding on day 2 after birth vs late progressive enteral feeding on day 4-5 after birth	The incidence of NEC, time to achieve full enteral feeds, mortality, nosocomial infection and duration of hospital stay	- No information on random sequence generation as well as allocation concealment -Infants received expressed breast or formula or both - Carers were not blinded -No information on blinding assessors
Karagianni et al. (140)	Single centre **Greece**	84	27- 34 weeks' gestation and BW <10th centile	Early enteral feeding introduced on ≤5 days after birth vs late progressive enteral feeding introduced on >6 days after birth	The incidence of NEC	-Minimal enteral feeding was continued until day 7 after birth and then feed volumes were advanced at daily targeted increments of 15 mL/kg - Carers were not blinded -No information on blinding assessors
Leaf et al. (9)	54 neonatal care centres the **UK and Ireland**	404	< 35 weeks' gestation and BW <10th percentile	Early enteral feeding on day 2 after birth vs late progressive enteral feeding on day 5 after birth	The incidence of NEC (all stage), time to achieve full enteral feeds, rates of feed intolerance, mortality and duration of hospital stay	- Protocol for advancing feed volumes was the same in both groups - Carers were not blinded
van Elburg et al. (141)	Single centre **Netherlands**	56	< 37 weeks' gestation and BW <10th percentile	Early enteral feeding on day 2 after birth vs late progressive enteral feeding on day 5 after birth	The incidence of NEC (stage II/III), time to achieve full enteral feeds, functional integrity of the small bowel, growth, and whether fetal blood flow pulsatility or intestinal permeability predicts feeding tolerance	- Carers were not blinded - The high attrition rate (25%) of infants were not included in the final analysis - sample size estimation not reported, and was not powered to detect the effect of the intervention on NEC, feeding tolerance or growth

Study	Setting	N	Participants	Intervention	Outcomes	notes
Tewari et al. (142)	**India**	62	< 35 weeks' gestation and BW <10th percentile	Early enteral feeding on day 1-2 after birth vs late progressive enteral feeding on day 5-6 after birth	The incidence of NEC, time to achieve full enteral feeds (150-180ml/kg/d), rates of feed intolerance, mortality, nosocomial infection, duration of hospital stay and time to regain BW	- Open-label RCT

Abbreviations:
Small for gestational age: SGA; Necrotising enterocolitis: NEC; Randomised controlled trial: RCT; birth weight: BW

1.9 Nutritional support – post-discharge from hospital

Preterm infants may be discharged from hospital care with body weights below the usual body weights of healthy term infants. The ESPGHAN Committee on Nutrition recommended close monitoring of growth during the hospital stay and after discharge to permit the provision of adequate nutrition support (143).

Adequate nutrition during infancy is a substantial contributor to the overall well-being of children and may also have a great impact on long-term development (144). Increased nutritional needs in preterm infants may persist beyond the neonatal period (145). Much early parental anxiety and uncertainty concerns infant feeding, in particular with new parents seeking advice from family/ friends, books and the media, which may be associated with early commencement of weaning (146, 147). This is the case because evidence-based research on the association between weaning preterm infants and subsequent growth, development, and health during childhood and adulthood is limited.

Generally, inadequate weaning practices may be associated with poor carers' knowledge, being influenced by traditional beliefs and lack of information and support (148). Improving carer knowledge may have an impact on the nutrition and growth of infants and young children. Health professionals or lay people (including families and friends), trained or untrained, in hospital or community settings offer advice on commencement of weaning in a range of ways. Advice might be offered to women in groups or one-to-one. Advice also may involve peer support, and it can include family members (149).

Carers' perceptions about appropriate size, growth and feeding patterns have an important role in the development of inappropriate weaning practices. Families have strong beliefs that heavy infants are desirable because weight is often perceived as the best marker of health and successful parenting (150). Carers' perceptions are crucial determinants of infant feeding practices and behaviour. Hence, any intervention should consider these views. Parents need practical and the most accurate information so they can make appropriate choices for their

particular circumstances utilising advice from health professionals and other sources of information perceived as ‘official’ such as a leaflet produced by the BLISS charity (151).

1.10 Weaning preterm infants

-Weaning is defined as "the process starting when breast milk and/or infant formula alone are no longer sufficient to meet the nutritional requirements of an infant, and therefore, other foods and liquids are needed, along with breast milk or a breast-milk substitute" (152). More broadly, the term is used to describe the period of introduction of weaning foods to complement human or formula milk. A guideline-based focus is needed on feeding strategies for preterm infants to promote optimum nutritional status, growth, and development. For this research study, I use the term ‘‘complementary feeding or weaning’’ to encompass feeding an infant with any solid and/or liquid foods other than breast milk and/or infant formula.

1.10.1 Guidelines on the introduction of complementary foods

The appropriate time to commence weaning is a matter of debate. United Nations Children's Fund (UNICEF) and the WHO recommend that breastfeeding should be continued for the first six months of life, with the introduction of weaning foods thereafter (153, 154). The ESPGHAN suggested that, in developed countries, weaning foods should be introduced not earlier than four, and no later than six months of age (155). Similarly, the American Academy of Paediatrics (AAP) advises that infants should be exclusively fed mother’s breast milk or formula milk until at least four months of age. Solids may be introduced in formula-fed infants if the infant is physically ready, after four months of age and all infants should be given weaning foods after six months of age (156). However, both ESPGHAN (155) and AAP (157) suggest that weaning may be commenced when an infant has achieved developmental milestones, i.e. between the ages of four and six months.

While national and international guidelines provide recommendations about how and when to commence weaning to full-term infants (154, 157, 158), there is a scarcity of evidence to support any such recommendations for preterm infants (151, 159, 160). In 1994, the Department of

Health (DH) in the UK provided guidance which addresses weaning of preterm infants (159). This guidance proposes that the following signs of infant readiness should be considered:

- the infants' weight should be at least 5kg
- they should have lost the extrusion reflex; infant forces the tongue outward when it is touched or depressed, and
- be able to eat with a spoon

In general, therefore, this would mean that weaning cannot be commenced until 8-11 months of actual age before they reach this weight (161) and would be particularly delayed in those who had premature birth associated co-morbidities (29).

In 2011, the British Association of Paediatric Medicine (BAPM) updated a joint consensus statement on weaning of preterm infants. The statement suggested that complementary foods could be safely introduced between five and eight months after birth, on recognition of appropriate readiness cues from the child (160). Similarly, in 2014, a leaflet produced by the charity BLISS suggested that the best time for commencement of weaning is between five to eight months after birth (151). It is noteworthy that all the available recommendations provided so far suffer from the fact that they were not evidence-based, and they address weaning of stable preterm infants.

1.10.2 The timing of weaning

DH reported that nearly seven in ten mothers weaned their children by the age of three months in 1990 (159). This proportion is markedly fell over time to 24% in 2000, 10% in 2005 and only 5% in 2010. Between 1990 and 2010, the proportion of infants who first received complementary foods after the age of four months markedly increased from 6% in 1990 to 15% in 2000 and 69% in 2010 (149).

In the most recent infant feeding survey conducted in the UK in 2010 (149), generally, about one third (30%) of mothers commenced weaning by the time their infants reached four months of age, and three quarters (75%) had done so by the age of 5 months. The survey also showed that there were many factors influencing families' decision on the timing of commencement of weaning, including advice from health professionals (149).

With increasing recognition of the importance of weaning of preterm infants as a crucial dietary event, the debate has focused on the optimal timing (162). Appropriate timing of commencement of weaning is essential for healthy growth, development, and survival (152). The transition from milk to complementary foods is very vulnerable period. Hence, weaning should be adequate (timely, in nutritional content, and safe) to meet the age-specific needs of a child (152). In addition to the effects on growth and neurodevelopment in childhood, recent evidence suggests that, in preterm infants, high and low nutrient intakes, as well as fast or slow rates of growth in infancy, could have long-term adverse effects on metabolic health (163, 164). Inappropriate weaning practices may contribute significantly to the high prevalence of malnutrition in children under five years of age worldwide (165). In 2016, 155 million children under 5 were estimated to have stunted growth, 52 million were estimated to be wasted, and 41 million were overweight or obese (165). These proportions could be even more in preterm infants (85).

Preterm children are a diverse population, varying from those born extremely preterm to moderate to late preterm infants (10), their nutritional needs are different from those infants born at term, particularly for energy (166), protein (145), long-chain polyunsaturated fatty acids (167), and iron (168). Preterm infants require additional macro- and micronutrients to compensate for their relatively low stores at birth and, subsequently, increased consumption is needed in the rapid growth phase (169).

A single centre RCT (162), conducted in the Royal Hampshire County Hospital Neonatal Unit, UK, evaluated the effect of timing and nutrient content of weaning foods on infants' nutritional intake, growth, serum iron and haemoglobin. Sixty-eight preterm infants with a mean (SD) BW of 1470 (430) g and GA of 31.3 (2.9) weeks were studied. Infants were randomised into two groups. The intervention group was advised to commence weaning from 13 weeks after birth, and to use energy and protein-rich foods: 70-105 kcal/100 g and 2.3-5.0 g/100 g, respectively, in addition to providing preterm formula. The control group was advised to commence weaning from 17 weeks postnatal age and to use foods with energy and protein contents in ranges of 60-105 kcal/100 g and 1.5-5.0 g/100g, respectively. Infants from the intervention group had greater length gain per week from term to 12 months corrected gestational age (CGA) than infants in control group

(mean (SE) of 5.1 (0.07) mm/week versus 4.9 (0.10) mm/week, p=0.04), respectively. The intervention group had a greater increase in length standard deviation scores from term to 12 months of CGA (mean difference (MD) in the intervention group was 1.3 and the control group was 0.9). No differences were observed in the other growth parameters. However, the sample size in the study population was small (n=68) and more of the intervention group had received breast milk fortifier than in the control group. Hence these infants were provided with increased nutrients in their early diet. It is noteworthy that the suggested weaning strategy in this RCT (162) cannot be implemented for preterm infants to optimise growth and neurodevelopment since the study investigators did not consider short- or long-term harms which may relate to early exposure to complementary foods.

In contrast, another RCT (170) across three hospitals in India assessed the effect of commencement of weaning at four versus six months CGA. Four hundred three infants born <34 weeks gestation were studied. The investigators observed that earlier weaning had no measurable impact on growth parameters, metabolic or neurodevelopment outcomes at 12 months CGA, but early weaning was associated with an increased rate of hospital admission primarily due to diarrhoea and lower respiratory tract infection. Hence, the authors concluded that the introduction of complementary foods should be initiated later at six months CGA rather than four months CGA. Of note, the high rates of infectious diseases could be related to the low rate of breastfeeding in the study population or to poor food hygiene. The trial was adequately powered (n=403), however, the findings may not be generalisable to preterm infants cared for in other healthcare settings or higher income countries.

Inappropriate timing and method of weaning can introduce further problems in the already fragile nutritional status of preterm infants (171). As previously mentioned, preterm infants are a heterogeneous group. The heterogeneity of preterm infants may be further aggravated by differences in growth rates, on-going medical conditions and differing rates of neurodevelopmental progress. Furthermore, preterm infants have immature gastrointestinal tracts with insufficient digestive and absorption functions (100). Premature birth is associated with poor mechanical function, such as suck-swallow- breathing incoordination (172), delayed gastric empty

(173) and disorganised intestinal emptying (100). In addition to the lack of sufficient evidence, the decision to introduce weaning foods to preterm infants should be safe and perhaps best made on an individual basis, considering GA, gross motor development and nutritional status as well as requirements.

1.10.3 The importance of age of weaning

Diet in the first two years of life may have an immediate effect on the health of infants because it may be associated with the provision of unsuitable alternatives to breastmilk, contaminated foods and lack the availability of suitable foods (174). A WHO review of the scientific knowledge on appropriate child feeding (174) showed that there is plentiful evidence supporting the continuation of exclusive breastfeeding through the first six months of life. The evidence showed a protective effect of breastfeeding, which reduces the risk of morbidity and mortality particularly among children from low- and middle-income countries. The risk of infection from the introduction of complementary foods is high in low- and middle-income settings due to exposure to contaminated water, foods or feeding equipment. In a cohort study (175) in Belarus involving 17046 infants, there was decrease in the incidence of gastrointestinal infection in infants who were exclusively breastfed for six months compared to infants exclusively breastfed for three months.

With specific regard to infants born preterm, data from five prospective RCTs conducted in the UK between 1993 and 1997 were analysed (176). Two of these five trials involved preterm infants (total n= 467). There was no significant association between the number of episodes of gastroenteritis or acute respiratory tract infections and whether weaning started at ≤12 or >12 weeks CGA. Thus, the available UK data do not support an association between the timing of weaning preterm infants and the incidence of infections.

Evidence of the protective effects of the delayed commencement of weaning on the risk of atopic diseases and food allergy is controversial. A significant decrease in the incidence of childhood wheezing in association with prolonged exclusive breastfeeding was observed in children at age six years (177). A meta-analysis of 12 prospective studies implies a protective effect of exclusive breastfeeding, for at least three months, against the development of asthma between 2 and 5

years of age. The protective effect of breastfeeding was even stronger when the analysis was limited to children with a positive family history of atopic disease (178). Of note, the review (178) included observational studies and was restricted to the English language. This may explain the difference in conclusions from the Cochrane review (153) which did not find a benefit of exclusive breastfeeding beyond three months on the incidence of asthma in families not selected for history of atopic disease.

Importantly, these studies involving term infants cannot be directly translated to preterm infants, who are more vulnerable than their term-born peers are.

Morgan and colleagues (179) found that there is an association between the age of commencement of weaning (≤12 or >12 weeks CGA) of preterm infants and the incidence of eczema. Approximately thirty-five percent of the entire cohort had eczema by 12 months CGA. Introduction of complementary foods before 10 weeks CGA was associated with an increased incidence of eczema (OR: 2.94 [95%CI: 1.57 to 5.52]). However, most of the study infants who had eczema had atopic background (57.3%) and the findings might be limited by the high loss of follow-up (21.9%) among the entire cohort.

1.10.4 Families' knowledge, attitude, and practices of weaning

Generally, the current recommendations (159, 160) are not detailed and giving advice may present difficulties. Therefore, families are challenged with the lack of clarity about when and how to start weaning. Social and family pressures to start weaning early and give unhealthy foods (180), and gaps in understanding healthy diet (181) may also have an impact on weaning practices.

Weaning is an important event in each preterm infant's life. However, very little research has addressed the introduction of complementary foods for this population and few RCTs have been published. In the literature, studies investigating the attitude and practices of weaning in preterm infants are limited (Table 1.4).

A multicentre cohort study in England involving two hundred fifty-three preterm infants was undertaken nearly 20 years ago (146). Nearly half (49%) of the infants were weaned before four months. Infants with LBW, low GA weaned early. Furthermore, older (>30 years old), educated mothers tended to introduce weaning foods at a later age than younger mothers. However, the findings of the study (146) cannot be generalised as the study population was skewed towards the higher social class.

Another, more recent, multicentre study in England described feeding patterns and mothers' perceptions of desirable feeding practices in LBW infants after hospital discharge (182). A wide range of infant feeding practices, varying levels of knowledge and differing attitudes about infants' feeding amongst mothers were observed. LBW, lower social class, and multiparity were associated with inappropriate feeding practices in terms of early weaning and providing low fat/calorie diet. Of note, the study was not limited to preterm infants, but all LBW infants (preterm and term) were included.

Fanaro et al. (147) found that the percentage of Italian infants who received complementary foods before four months after birth was markedly lower compared to the British study (146) (described earlier in this section). Only 6.5% of the cohort study received complementary foods before the age of four months. Considering CGA, the proportion increased up to 60.9%. There was significant correlation between weaning age and weight at the time of weaning. Maternal age was directly related to the age of introduction of complementary foods. However, there was some concern about the high losses of follow-up (>30%). Furthermore, insufficient details were available in the study such as the validity of the questionnaire used for the study and the inclusion and the exclusion criteria of the included subjects.

Braid et al. (183) investigated the odds of early weaning in preterm infants and compared them with full-term infants. More preterm infants were weaned early (before four months CGA) than term infants (64.5% vs 23.8%). Variations in weaning were significantly affected by the same factors as shown in previously mentioned studies (146, 147) in terms of the degree of

prematurity, BW, and maternal age. Maternal ethnicity and smoking were also found to be associated with the age of weaning.

Another study (184) assessed the introduction of complementary foods to 375 preterm infants from three countries (Chile, n= 49; the United Kingdom, n= 51, and the United States, n= 275) and compared against recommendations for term infants. By four months CGA, 98% of the infants in the UK, 67% in the US and 41% in Chile were weaned. Also, multiple types of foods were introduced at one time.

Improving inappropriate weaning practices and narrowing the gap in knowledge need effective interventions beginning during the perinatal period. Several strategies have been undertaken to improve weaning practices (185). These include nutritional education to encourage healthy feeding practices.

Table 1.4 Summary of studies investigating weaning practices

Author	Type	Country	Size	Group I	Group II	Main finding	Notes
Norris, Larkin (146)	Observational study	The UK	253	Preterm infants, born Jan 1997 to Dec 1998	-	- Mean (±SE) age of commencement of weaning was17.1±0.23 weeks from birth; corresponding to mean age 11.5±0.21 weeks CGA	- 95% of the infants received weaning food prior to 4 months CGA. - 21% of the infants received weaning foods when they were <5kg
Morgan, Williams (182)	Multicentre observational study	The UK	183	Low birth weight infants	-	- Median (range) age of commencement of weaning was 17 weeks (8 to 36) weeks from birth; corresponding to the median age 11 weeks (–1 to 27) CGA	- 50% of the infants received weaning foods when they were <5kg
Fanaro, Borsari (147)	Observational study	Italy	230	Preterm infants, born Jan 2004 to Dec 2005	-	- Mean (±SE) age of commencement of weaning was 22.2±0.4 weeks from birth; corresponding to mean age 15.1±0.39 weeks CGA	- 61% of the infants received weaning foods prior to 4 months CGA. - 18% received weaning foods before 5kg
Braid, Harvey (183)	Secondary data analysis	The USA	7650	Preterm infants, born in 2001-2002	Term infants, born in 2001	- Preterm infants received weaning foods at a mean of 13 weeks CGA - Preterm infants had a 9.90 [95% CI: 5.54 to18.0] odds to receive weaning foods before 4 months compared to term infants	- 65% of the infants received weaning food prior to 4 months CGA

Abbreviations:
Standard error: SE; confidence interval: CI; corrected gestational age: CGA

1.11 Nutrition education

Nutrition education has been defined as "any combination of educational strategies, accompanied by environmental support, designed to facilitate voluntary adoption of food choices" (186). 'Environmental support' is complex and can include many components such as emotional (including reassurance and praise), practical and informational support (including the opportunity for an individual to discuss problems and ask questions) and social support (including signposting women to support groups) (187, 188).

Nutrition education on weaning is an intervention that has a multifaceted challenge of enabling carers to breastfeed and optimise weaning practices. The WHO-UNICEF strategy for infant and young child feeding (189) suggested that adequate weaning practice should include four elements:

- introduction of complementary foods should occur when the energy and nutrient needs of infant exceed what is provided through exclusive breastfeeding
- food diversity that provides sufficient energy, protein, and micronutrients to meet the growing child's nutrition need
- hygiene, an important consideration during preparation, storing and feeding, and
- having responsive feeding approach

Nutrition education is needed to deliver these messages, but not all approaches to education are successful in having the impact (185).

1.11.1 Theoretical models of behaviour change in nutrition education

There are four theoretical models, which explain and help to understand the determinants of dietary behaviour and the process of changing eating patterns (190). These models include Consumer Information Processing, Health Belief Model, Social Cognitive Theory and Diffusion of Innovation. The first three models deal with the role of people's cognition (thoughts and judgment) and how this cognition influences their behaviour (190). Whereas the Diffusion of Innovation Model explains how the nutrition educator can be more effective in spreading the adoption of new healthier eating habits through a specific population (190).

1.11.2 Nutrition education and complementary feeding

Nutrition education either combined with or without, other strategies can improve the dietary intake and growth of young children (191), particularly in areas where access to food is not a limiting factor (192). Randomised trials, mostly from low- and middle-income countries, have demonstrated that providing culturally-suitable educational interventions is associated with improved growth rates, decreased prevalence of malnutrition (193-195), increased quality of parent-child interaction and improves child's cognitive development in low- and middle-income countries (196). Nutrition education may also have a positive effect even on infants from high-income countries as it may act as a preventive measure of childhood overweight and obesity (197).

1.11.2.1 Effect of nutrition education on infant growth

Studies addressing educational interventions use different indices to assess nutritional status by relating weight and length gain (198), WAZ and LAZ scores (199). Educational interventions on weaning with an emphasis on regularly providing animal-derived food to infants with low WAZ scores at baseline also have a positive impact on both weight and length gain (199, 200). The Roy et al. (200) study did not focus on educational interventions only but looked broadly at different types of weaning strategies, including education with, or without, food supplementation. Others (201, 202) showed significant improvements in child weight, WLZ, and WAZ scores in the intervention group compared to controls.

Differences observed in the effect of nutrition education on growth outcomes (192, 198, 199). For example, differences in the effect of the intervention on LAZ scores might be partly due to the shorter intervention duration in some studies (192) compared to others (198, 199). Furthermore, weight changes were observed in the short term, compared to changes in length (203). This may indicate that interventions need to be carried out over a longer period to achieve linear growth.

1.11.2.2 Effect of nutrition education on breastfeeding

The current general recommendations are that infants should be breastfed from the first day of life, be exclusively breastfed for the first six months and be breastfed along with complementary feeding after that (154, 165). Globally, 45% of infants have early initiation of breastfeeding (within the first hour of life), 43% are breastfed exclusively for the first six months of life and 46% continue to be breastfed up to 2 years of age (204).

The predictors of exclusive breastfeeding duration among women have been investigated. Incorporation of peer support (205), encouraging behavioural changes and improving knowledge regarding the duration of exclusive breastfeeding, and increasing the utilisation of pre and postnatal counselling about exclusive breastfeeding may increase the prevalence of exclusive breastfeeding and the rate of breastfeeding in the first two years of life (206).

Starting early nutrition counselling for parents has been shown to produce long-term dietary improvements, by decreasing early weaning (206), increasing rates of breastfeeding and preventing the onset of unhealthy feeding practices (207). Postnatal nutrition counselling is also significantly associated with a longer duration of exclusive breastfeeding (206). Women who were not counselled during postnatal care were five times more likely to stop exclusive breastfeeding before their child reaches six months of age compared to mothers who received counselling (208). The Cochrane systematic review showed that breastfeeding support had increased the duration and exclusivity of breastfeeding (209).

Nutrition education supporting breastfeeding can work in different ways for different women. Timely, skilled support may help families overcome breastfeeding problems that can lead to early cessation of breastfeeding (206). In settings where breastfeeding is not a social norm, education can increase parental belief in breastfeeding, give them the confidence to continue breastfeeding and overcome social pressures that might undermine breastfeeding (206, 210).

Intensive early nutrition counselling for caregivers, during the perinatal period, has been shown to produce long-term dietary improvements, by preventing the early weaning (206).

1.11.2.3 Effect of nutrition education on infant iron status

Anaemia in infancy is a common health problem with global prevalence of 42.6% among children under 5 years old (211). The highest prevalence rates are observed among children less than 24 months old, in preterm infants from low-income and middle-income countries (211). The principal cause of anaemia among children less than 5 years old is iron deficiency (ID) (42%) (211). In full-term infants, iron deficiency typically occurs during the second half of the first year of life. Infants with lower GA and BW are at greatest risk for developing iron deficiency at an earlier age, within the first six months after birth (212-214). Anaemia is considered one of the largest public health issues in low- and middle-income countries as well as high-income countries as it can be prevented by dietary measures (211). Inexpensive, mainly cereal-based foods available in poor communities are of low quality, with low protein and micronutrient content that lead to deficiencies in infants and children (215).

Furthermore, diets may also contain elements that inhibit iron absorption. Consumption of phytates and inositol phosphate, commonly found in cereals and whole grains affect serum iron (216). Polyphenols, commonly found in tea, inhibit iron absorption by causing ferric iron to precipitate and form molecules which cannot be absorbed (216).

Iron deficiency commonly occurs during the period of introduction of complementary foods, particularly in preterm infants (213) and those consuming human milk exclusively without supplementation (217). Breast milk is a complete food containing everything infants need for around the first six months of life, including iron (218). Iron present in breastmilk is highly bioavailable. However, preterm infants who are exclusively breastfed for six months are at high risk of ID, because of high iron consumption needs for rapid growth and relatively low stores at birth (212). Therefore, preterm infants require iron-rich complementary foods, either directly from foods or as supplements (219).

Nutrition education intervention has been used to improve children's nutritional status, including ID and iron deficiency anaemia (220). Dietary counselling along with complementary

foods supplements are effective in improving caregivers' feeding practices and reducing the prevalence of ID (220).

A limited number of studies have addressed the effect of nutrition education on iron status in preterm infants and the findings are not consistent (described in Section 1.10.2). A RCT conducted in the UK suggested that nutrition educational intervention can have a significant effect on iron status in preterm infants at six months CGA (162). Another study in India showed that nutrition education did not significantly affect serum iron in infants at 12 months CGA (170). Of note, in the later study (170), iron supplementation was provided as standard until 12 months of CGA. Therefore, the results cannot be easily extrapolated. Moreover, both groups in the study received nutrition education based on WHO guidance.

1.11.2.4 Effect of nutrition education on infant neurodevelopment

The WHO practical manual for improving mother-child interaction suggests that whilst carers have the capacity to love and care for their children, a number of reasons such as poverty, stress, illness, or just lack of awareness of the need for such care are stopping some from doing so (221). Improved quality of mother-child interactions enhance children's cognitive development and have been linked to educational achievement, in both high-income (222) and in low- and middle-income countries (223, 224). One of the pathways through which educational interventions might affect child nutrition and care practices is through the impact on maternal responsiveness. Maternal responsiveness is associated with social competence and fewer behavioural problems at 12 months, increased intelligence quotient (IQ), cognitive growth at four years (225) and cognitive skills across 3-10 years of age (226). School achievement at seven years, as well as higher IQ, self-esteem and fewer behavioural and emotional problems, were also seen (225). Some of these studies focused on LBW infants (226) or other at-risk populations (227) and found that maternal responsiveness had a protective effect on health and development.

Suboptimal nutrition in early life, during a "vulnerable" phase of brain development, the period between the third trimester and three years after birth, could affect later cognitive function

(228, 229). During this period, the brain is very sensitive to factors that may interfere with brain growth and development, such as low energy intake, macro- and micronutrient deficiency (230). Although it could be difficult to separate the effects of malnutrition from other deprivations to which children living in poverty are exposed, early malnutrition has been linked to the lowered cognitive functioning and poorer school performance (231). The effect of malnutrition in early childhood may also result in partially irreversible structural and functional brain changes (232), lower educational attainment and lower economic productivity in later life (233). Therefore, interventions that improve dietary intakes also offer improved neurodevelopment outcomes.

1.12 Aims and rationale

Nutrition is a major contributing factor in children's health and well-being. Malnutrition is an underlying cause of mortality and morbidities among children under five years of age globally. The effects of malnutrition on somatic and neurodevelopment of children are well established. The consequences of impaired growth and development during early childhood persist throughout life, negatively influencing the quality of life of individuals.

PN is established as an integral component of care for preterm infants. Most extremely premature infants take a few weeks to tolerate full enteral nutrition. Therefore, the composition of PN should be designed to complement any enteral feeding and to ensure that the infant receives all essential nutrients during this period. Despite the widespread use of PN, a diverse range of practices exists across the UK. Therefore, reviewing current nutrition practice, recording how much energy and protein babies were received and comparing them with current nutrition recommendations was the first aim of this thesis.

The timing of introduction and rate of advancement of enteral feeds is an area of clinical uncertainty. Feeding infants born preterm, particularly those with IUGR is challenging. Early introduction of enteral feeding may improve nutrition and growth, but it may increase the risk of NEC. On the other hand, delayed enteral feeding may be detrimental and may be associated with prolonged use of PN. This study aims to firstly identify the current parenteral and enteral

feeding practices for IUGR infants' care, regarding the onset of enteral feeding and PN, the duration of PN and the time needed to achieve full enteral feeding. Secondly, it aims to evaluate the change in feeding practice since the publication of the ADEPT study to assess the impact of the trial on clinical practices.

Weaning earlier than recommended has been reported, but little is known about the timing or factors affecting the introduction of complementary foods to infants born preterm. The available recommendation advocates that complementary foods should not be introduced before the age of 5 months to ensure optimal child feeding. Early initiation and exclusive breastfeeding practices has been improved over recent years. In contrast, complementary feeding issues have not received a similar level of attention.

Understanding the differences in beliefs and practices relating to infant feeding support is important for the successful delivery of health messages and health care to diverse populations. There has been little research into parents'/carers' experiences and satisfaction with the introduction of complementary foods to infants born preterm. The aims of this study were, therefore, to explore families' experiences and satisfaction with their care on weaning preterm infants, and to identify the domains associated with positive and negative weaning experiences.

Nutrition education interventions have been reported as improving nutrient intakes and growth among infants and young children. Reviews of previous studies showed modest effects on growth and nutrition status. However, in these reviews, improving caregiver nutrition knowledge was combined with food supplements to observe their impact on growth and nutrition of full-term children. An approach that includes nutrition education delivered to families of preterm infants is likely to provide an effective way of addressing suboptimal complementary feeding, which in turn could lead to improved young children growth and nutrition. The aims of this study were, therefore, to investigate the role of nutrition education of family members on complementary feeding with respect to growth, neurodevelopment, and nutritional status.

1.13 Hypotheses

Many previous studies and reviews of current clinical practice have concluded that the early commencement of parenteral nutrition and the early introduction of enteral feeding is important and offers positive health benefits. Furthermore, the early introduction of complementary foods does not appear to add any risks for preterm infants. I, therefore, hypothesise that:

- there was considerable change in nutrition support in preterm infants admitted to the neonatal unit at Nottingham University Hospitals NHS Trust (NUHs) through three epochs; 2007, 2012 and 2014. However, current nutritional practices on NICUs do not meet recommendations for nutrient intakes
- Furthermore, still, there is an area for improvement in the nutrition support provided in neonatal units across the UK Trent Perinatal and Central Newborn networks in relation to the available recommendations
- since 2007, enteral and parenteral feeding is started sooner after birth for IUGR infants with AREDF. This has been addressed by assessing the change in PN and enteral feeding practices for babies with Abnormal Doppler's since the ADEPT trial was published
- the healthcare professionals are meeting the needs and expectations of families on weaning their preterm babies. This has been addressed by surveying and analysing families' practices and perception on weaning
- there is insufficient evidence to make firm recommendations on how and when to wean infants from evaluations of educational and other family support interventions during the period of weaning in late infancy (6-12 months). This has been addressed by a metanalytic appraisal of the evidence.

1.14 Ethical considerations

During the design and implementation of this research project, the researcher was aware of and ensured that the studies were conducted in adherence to the professional and ethical standards. To support this, the following published guidelines were applied:

- University of Nottingham (UoN, 2013) Code of Research Conduct and Research Ethics (234)
- UK policy framework for health and social care research (235)

A summary of the specific ethical considerations, which relate to this project, is discussed below.

Chapters 2 and 4 are including quality improvement (QI) projects; clinical audit and service evaluation, respectively. The clinical audit study (Chapter 2) involves analysis of existing data and comparing them to international nutritional recommendations and the service evaluation study (Chapter 4) involves the use of a survey questionnaire. Very often these types of projects highlight gaps in care practices, which in turn stimulate further research activity. To address the ethical consideration of these studies, the Health Research Authority tool was used, which has been developed to help to decide if the activity requires ethical review (236). Accordingly, these studies did not require Ethics Committee review.

Ethical approval for the exploring the nutrition management for infants diagnosed with AREDF study (Chapter 3) was granted by the Medical School Ethics Committee at the University of Nottingham (Ref: M16042015 SoM CHOG BADGER) and the North of Scotland Research Ethics Service (Ref: 16/NS/0040).

Chapter 2: Comparing early nutritional practices between neonatal care settings in two Neonatal Networks

2.1 Background and rationale

A sizeable number of preterm infants become growth restricted with parameters below the 10th percentile by 36 weeks' gestational age (28, 29, 70, 76). This extra-uterine growth restriction (EUGR) is attributable, at least in part, to inadequate nutrition in the first weeks of life (91). Although the accurate nutritional needs of preterm infants are still unknown, the available recommendations suggest providing sufficient energy and nutrients to prevent tissue catabolism and support growth (106, 107, 237). Nonetheless, still there is differences between the nutrient supply that the normally growing fetus receives and that received by the postnatal peer. In other words, despite these recommendations, nutritional deficits are still not uncommon (238). These deficits are greatest in the first week of life but continue to accumulate through the first month (70).

The continued prevalence of EUGR despite changes in published recommendations requires systematic assessment. Appropriate nutritional management in the pre-discharge period may prevent nutrient deficits occurring or persisting at discharge from hospital. If adequate nutrition is being achieved, there may be little or no catch-up needed. Improved nutrition practices have been previously reported. Nonetheless, nutrient intakes remained below goals (101, 239), therefore, the current chapter contains two studies assessed nutritional support of preterm infants in two Neonatal Networks.

Data for the current chapter were obtained from the UK Trent Perinatal (TPN) and the Central Newborn Networks (CNN). The TPN and the CNN are large neonatal networks in the Midlands and East of England regions in terms of geographical area covered (Figure 2.1). These networks are two of 22 clinically managed Operational Delivery Networks for neonatal services. Neonatal networks were established following recommendations from the Department of Health in 2003 (240).

The objective of these networks is to ensure that infants and their parents/caregivers receive high-quality care that is accessible to all. Neonatal networks play a key role in improving standards of neonatal care by supporting professionals involved in neonatal practice to optimise their skills and knowledge, to deliver and share high-quality and safe practices and to undertake research (241).

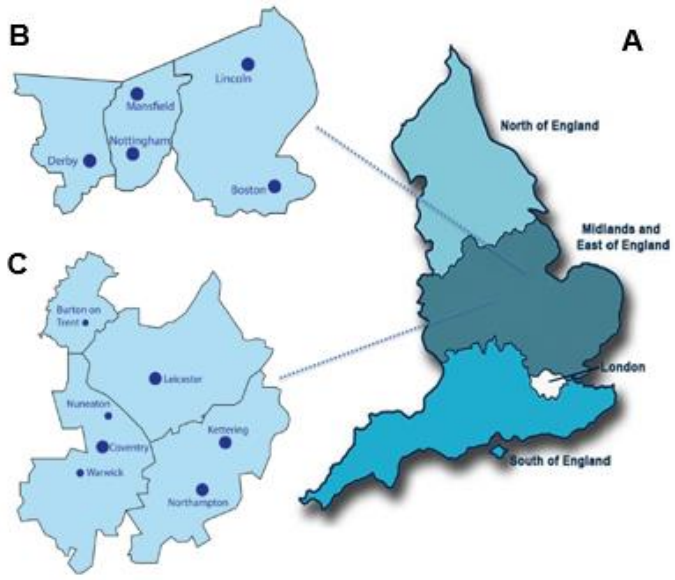

Figure 2.1 The Trent Perinatal Network and the Central Newborn Network Areas

Adapted from Central Newborn (CNN) &Trent Perinatal (TPN) Operational Delivery Networks; available from: http://www.centralandtrentneonatalnetwork.nhs.uk/index.php/about-us/our-network-areas
A is the geographic locations of the networks within England. **B** shows the geographical locations of units within the TPN, and **C** shows the geographical locations of units within the CNN

While there are two units geographically situated in Nottingham they are operated as one service, babies transfer to Nottingham City Hospital for Level II care and to the Queens Medical Centre for surgical care where necessary and the units operate to a single set of care guidelines. Due to the nature of the neonatal services in Nottingham, infants may have transferred across two sites during the first two weeks, the data for the two individual units have been combined for reporting purposes.

Units within these Neonatal Networks work closely together to provide care to infants born within their areas and require specialist neonatal services. There is a total of eight neonatal

units within the CNN and six neonatal units within the TPN. Three of these are designated as Neonatal Intensive Care Units (NICUs): previously known as Level III units; six are designated as Local Neonatal Units (LNUs): previously known as Level II units and three are designated as Special Care Units (SCUs): previously known as Level I units.

2.1.1 Types of care provided by Neonatal Units

The three types of neonatal unit are providing different levels of care; these are:

- NICUs provide care for babies who need:
  i. ventilation support
  ii. additional support due to low birth weight of less than 1,000g
  iii. continuous positive airway pressure (CPAP) and are extremely preterm (born at < 28 weeks gestation)
  iv. support due to severe respiratory disease
  v. surgery

- LNUs provide care for babies who need:
  i. short-term intensive care support, e.g. following apnoeic attacks
  ii. CPAP
  iii. parenteral nutrition

- SCUs provide care for babies who need:
  i. continuous monitoring of their breathing or heart rate
  ii. additional oxygen
  iii. tube feeding, phototherapy
  iv. recovery and convalescence from other care

2.1.2 Networks nutrition guidelines

The recommendations in the networks guidelines (242) are based on the international guidelines (106, 107) that explicitly stress the importance of minimising the delay between infant's birth and optimising nutrition. The guidelines suggested that PN should be administrated early where full enteral feeds are not likely to be achieved within 5 days. All extremely preterm (<30 weeks) and low birth weight infants (<1250g) should routinely receive

PN. Also, infants born at 30 weeks onwards who are unable to establish significant volumes of enteral feed by 5 days either through illness, immaturity should receive PN.

The guidelines cover many aspects of nutrition management of neonatal, and for this study, I am focusing on protein and energy requirements. The guideline suggests that to give 3.5g/kg/day protein and energy intake increased from 74 to 104g/kg/day (Appendix 8.3). The network guideline may be allied to other local guidelines relating to nutrition of preterm infants

Given the potential benefits of early initiation of high doses of protein and energy provision during the first few days of life (106) and based on findings from previous studies (70, 120), the question arises; was the introduction of energy and protein intakes improved compared with current recommendations?

For this study, a quantitative study approach was applied to achieve the objectives of the studies. Population-based secondary data analysis was undertaken to obtain relevant information, which was used to assess the nutritional support of infants in neonatal units. A secondary data is defined as an analysis of data gathered not specifically for a research question but used for another purpose (e.g. medical records and registry data) (243).

2.1.3 Advantages and disadvantages of using secondary data

A trend over time analysis can be difficult for academic researchers because data collection may require long period and significant financial commitment (1), therefore, secondary data was used in the current studies. The economic aspects of secondary data have been discussed in previous studies, as this type of analysis allows for enormous savings in both time and costs (1). However, secondary data must be treated carefully because errors can lower the reliability and validity of results. These errors include sampling errors, errors that invalidate the data and errors that require data reformulation (1). Give that potential errors can affect the accuracy of secondary data; these errors have been considered when the current studies were undertaken.

Sampling errors occur when the chosen sample does not accurately reflect the whole population that is studied. The error occurs when the researcher either inaccurately includes or excludes potential participants (244). To avoid this form of bias, a clearly defined target group and determine a sampling frame for selecting study populations to specifically outline the type of study population (244) was predefined in the study's instructions for completing individual infant data. This would eliminate misunderstandings or errors in the population definition (1).

Secondary data might be manipulated, contamination being caused by inappropriateness, confusion, carelessness or concept errors. Data collected and organised without properly specifying the details of the collection process are likely to be less reliable (1). Therefore, in the current study, a clear explanation of techniques used to collect the data, including data collection instruments have been designed and provided in the present study to ensure the validity and reliability of collection methods (1).

It is not uncommon that some important variables are not available for analysis. Multiple sources of secondary data may help to overcome this limitation (1). For example, nutrition support data are available from nursing charts as well as in medical notes.

2.2 Hypotheses

Nottingham University Hospitals NHS Trust (NUHs) as major neonatal surgical units have large numbers of infants who require PN. Nutrition guidelines are frequently reviewed, almost every three years, within the unit as well as the networks. Based on the international guidelines, the local PN regimens have been updated in 2007, 2012 and 2014 (Appendix 8.3). Furthermore, the level of compliance with guidelines is not known and it is unclear to what extent the recommendations for early PN and enteral feeding have been translated into clinical practices. Therefore, this study examined the hypotheses that:

- nutritional practice improved over time from 2007 to 2014
- the current nutritional practices on neonatal units do not meet the international recommendations for nutrient intake, and there is still an area for improvement

- current nutritional practices have an impact on growth of preterm infants during hospitalisation. Low nutrient intake is associated with poorer somatic growth.

2.3 Aims

The aim of study 1 (Comparing the nutritional practices at Nottingham Neonatal Units in 2007, 2012 and 2014) was to evaluate the trend in nutrient intakes of preterm infants born in three different cohorts, 2007, 2012 and 2014. Also, compare nutritional intake with the Tsang recommendations (107). The aims of the second study (assess nutritional practices in neonatal care settings in two Neonatal Networks) were to gain an overview of current nutritional practices in 12 neonatal units from the CNN & TPN and describe parenteral and enteral protein and energy intakes in relation to published recommendations (106, 107). Also, to determine what the implications of current PN and enteral feeding practices were for preterm infants, in terms of nutrient deficits, weight outcomes and growth in head circumference.

2.4 Outcome measures

2.4.1 Study 1

The outcomes were to assess the amounts of protein and energy intakes and deficits during the first two weeks of life for infants from three cohorts; 2007, 2012, and 2014.

2.4.2 Study 2

2.4.2.1 Primary outcome measures

The outcomes were to assess the amounts of protein and energy intakes and deficits during the first two weeks of life.

2.4.2.2 Secondary outcome measures

- weight gain during the first 14 days after birth
- weight and head circumference gain from birth to discharge from the neonatal unit
- the change in weight for age z-scores (WAZ) between birth and 14 days of age, and
- the change in WAZ between birth and discharge from neonatal unit.

2.5 Materials and methods

2.5.1 Study design

Multicentre observational study.

2.5.2 Setting, study population and sampling

Study 1 was undertaken at NUHs. The Trust has two Neonatal Intensive Care Units (level III neonatal units), which operate as one Neonatal service. Study 2 was undertaken at 12 neonatal units from CNN and TPN.

Eligible infants born <35 weeks gestation (i.e. up to and including 34^{+6} weeks), were admitted to the neonatal unit for 14 days and had intravenous access during the first 14 days of life. Babies transferred out of a unit after the first 24 hours of life were excluded.

2.5.2.1 Selection of participants and representativeness

The selection of participants in current studies was based on consecutive sampling; babies were consecutively selected in order of appearance according to their presence in the neonatal unit. The sampling process came to an end when the total amount of participants (sample saturation) was reached (245). The study population was prospectively identified as the ten eligible infants consecutively admitted to the neonatal unit in the study period, providing a random sample. Birth weight and gestational age were compared to the target population who were born in the corresponding year. For example, 2007 cohort were compared to all infants who were born <35 weeks in 2007 and admitted to NUHs.

2.5.3 Process

Detailed instructions were provided to the participating units, to ensure rigorous data collection. Local respondents identified the study population. Data was collected using a standard proforma, using routinely collected data recorded daily in the hourly nursing records of babies in neonatal units. Data were collected for the first 14 days of life from nursing charts in their medical recording. As the nursing nutrition records commence at 08:00 am, day 1 was

defined as from the time of birth to the first next 08:00 am. As day 1 may not represent a complete 24-hour period, the intake was measured at 08:00 am and the nutrients given in that period was corrected from the time of birth. Growth outcome data were collected from the database.

Data were collected using a spreadsheet, designed by Professor Helen Budge and Dr Shalini Ojha. The spreadsheet was adapted by ZE and used to collect data for study 2. On the adapted form, nutrient intakes in the first 14 days were recorded for 10 babies per unit. A local respondent in each of the 12 units collected data on early nutrient provision across the Networks. The local respondent collected Eighty-five percent of the data. A medical student and ZE collected the rest. Inter-observer and intra-observer coefficient of variance used to assess agreement between observers. The inter-observer coefficient of variance was 6.5%; the intra-observer coefficient 1%.Data collection

Completeness of data has been achieved by the support of neonatal dietitian (Chris Jarvis), who encouraged complying with data collection tool directly to local neonatal units.

2.5.3.1 Study 1

This study designed to monitor changing trends in nutrition therapy in three eras 2007, 2012 and 2014. Therefore, routine nutrient intake data of infants who were admitted to the neonatal units at NUHs were collected

2.5.3.2 Study 2

Routine nutrient intake data were collected on infants admitted to the neonatal units within CNN &TPN. Information was collected for each infant including:

- date and time of birth
- post-menstrual age at birth (in whole completed weeks, i.e. 22 weeks^{+6} days = 22 weeks)
- BW
- daily body weight
- weight and postnatal age at discharge
- occipitofrontal head circumference at birth and at discharge, when available

- the volume of glucose solutions and any other infusions
- the volume of enteral feeding; including EBM, fortified EBM, formula milk
- name of formula milk
- the volume of starter PN
- the volume of standard PN solutions.

Body weights were recorded (to allow for oedema/fluid overload) at the day of admission and over the first 14 days of life. Day-to-day weight changes were recorded to evaluate fluid balance and growth, and where no body weight was recorded, the last available weight within the 14 days was used. International Organisation for Standardisation (ISO) equipment was used in the participating units. Postnatal age was calculated using the estimated gestational age (GA) at birth and length of hospital stay, i.e. GA at birth + (length of hospital stay in days/7). Actual weight at birth, weight at 14 days of age and discharge weight were converted to z-scores (246). Newborns were considered small for gestational age (SGA) when the gender and age-adjusted weight at birth was below the 10th percentile according to reference standards from Fenton 2013 (246). Changes in z-score were calculated as the difference between birth z-score and z-score at day 14 and again at discharge.

Daily enteral and parenteral fluid intakes were obtained from contemporaneous hourly nursing charts and medical records. The data collection period was the first 14 days of life (24 hours every day). Intravenous fluids (IV), either glucose solutions, saline or PN were recorded as well as enteral fluids including infant formula used, mother's own expressed breast milk (MBM), and whether this was fortified. The total daily volume of each solution given and its diluent was used to calculate the actual total daily fluid intake for all infusions, such as inotropes, insulin, heparin. The total fluid intake per kilogram per day (kg/d) was calculated.

Daily fluid, protein and calorie intakes were calculated for all babies for each day during the first 14 days of life.

Human milk (HM) was considered to contain 70 kcal/100 ml and 1.8 g of protein/100 ml. MBM + fortifier was considered to contain 86 kcal/100 ml and 2.6 g/100 ml (247). The nutrient contents of the different types of formula milk used are listed in Appendix 8.1. The actual

intakes were calculated per kilogram per day and the intakes were subtracted from the recommended dietary intake to calculate the daily deficit or excess. These were summed to calculate the cumulative energy and protein deficit over the two weeks. The cumulative deficits were calculated using the following equation:

$$\text{Cumulative defect}_n = \text{deficit on day}_1 + \text{deficit day}_2 + \ldots\ldots\ldots + \text{deficit day}_n$$

n= postnatal age

To understand the differences between the two sets of recommendations, cumulative deficits were calculated based on:

1- recommendations that were modified from the Tsang guidelines (107). Calorie intake should be started at 55kcal/kg/day on day 1 and increased up to 130 kcal/kg/day and protein intake of 2 g/kg/day on day 1 and increased up to 3.5 g/kg/day
2- recommendations from Koletzko recommendations (106). Calorie intake should be started at 60 kcal/kg/d on day 1, increased up to 105 kcal/kg/day and protein intake of 2 g/kg /day on day 1, and increased up to 3.5 g/kg /day.

The increment rate of energy and protein varies between the two recommendations (Appendix 9.2).

2.5.4 Statistical analysis

All statistical analyses were conducted by myself, under guidance from a statistician (Dr Andrea Venn), using SPSS v22 for Windows (248) and GraphPad Prism v6.0 for Windows (249)). Values were presented as mean (±SEM) for normally distributed data; otherwise, data were presented as median (IQR). Normally distributed continuous data were analysed using Student t-test and analysis of variance (ANOVA) with post-hoc (Tukey test). Otherwise, Mann-Whitney test and Kruskal-Wallis test were used. Where needed, data were transformed to normality using square root transformation. Unlike logarithmic transformation, square root transformation was used (250) because:

- it is commonly used for reducing right skewness, and also
- it can be applied to zero values
- it is commonly applied to counted data, especially if the values are mostly rather small.

Scatter plots and Person's correlations were used to assess relationships between the variables. Univariate linear regression analysis was performed to detect factors influencing WAZ scores at discharge. The univariate analysis included the following predictors: BW, GA, body weight at day 14, cumulative energy deficit, cumulative protein deficit and gestational age at discharge. Variables found to be significantly associated with WAZ scores in the univariate analysis ($p<0.05$) were considered candidate variables for the multiple linear regression.

Some candidate variables are likely to be correlated; therefore, I used scatterplot and Person's correlation test to assess the correlations.

The variables were then assessed in combination using a multiple linear regression analysis. Variables were only entered into the models if they had a significance level of <0.05 for an association with the combined outcome of WAZ scores. As there were correlations between some predictors (BW, GA, body weight at day 14 and GA at discharge), to check that the model was predicting WAZ scores each one of these variables was assessed with the other significant predictors. The variable was then removed if the p-value became not significant.

Statistical analysis was considered significant when $P<0.05$.

2.6 Results

2.6.1 Study 1: Comparing the nutritional practices at Nottingham Neonatal Units at 2007, 2012 and 2014

Data were collected for 52 infants from the neonatal units at the NUHs to evaluate how the feeding practices changed from 2007 to 2014.

2.6.1.1 Body weight and gestational age at birth

Infants in the three cohorts were considerably lighter and of earlier gestation than the entire target population born in the corresponding years (Table 2.1). This finding indicates that the study population is representative of the group of high-risk infants.

Table 2.1 Sample characteristics compared to the target population born in the corresponding year

Year		The study population		The target population born in the corresponding year		P-value
2007	BW	n= 16	1.2 (± 0.1)	n= 185	1.5 (±0.04)	0.006
	GA at birth	n= 16	28 (26-30)	n= 266	31 (27-33)	0.009
2012	BW	n=17	1.1 (±0.1)	n=461	1.4 (±0.03)	0.008
	GA at birth	n= 17	28 (27-30)	n= 466	30 (27-33)	0.004
2014	BW	n= 19	0.9 (±0.1)	n= 510	1.5 (±0.03)	<0.001
	GA at birth	n= 19	27 (26-28)	n= 510	31 (27-33)	<0.001

Values are given as mean (± SEM) or median (IQR); (n)
Abbreviations:
Birth weight: BW; gestational age: GA

The average (±SEM) birth weights and the median (IQR) GA of the study population presented in (Table 2.1). No significant differences in BW (p=0.1) or GA (p=0.3) were observed between infants from the three cohorts; 2007, 2012 and 2014..

2.6.1.2 Total calorie intakes

The current study showed that all infants, admitted during the three cohorts, were provided with different amounts of energy on the first day of life. The median (IQR) square root of energy intakes on day 1 of life was: 2007: 5 (4-5); 2012: 6 (4-6); 2014: 5.3 (5-6) kcal/kg/day. The mean (±SEM) square root of calorie intakes in the first week of life was: 2007: 8.2 (±1); 2012: 9 (±1) and 2014:9 (±1) kcal/kg/day. The mean (±SEM) square root of calorie intakes in week two of life was: 2007:11 (±0.1); 2012: 10.2 (±0.1) and 2014:10 (±0.1) kcal/kg/day (Figure 2.2).

On day one, calorie intake was considerably higher in the 2012 cohort compared to the other cohorts. During the first week of life, there were improvements in energy intakes from 2007 to 2012 and 2014. The intakes became considerably higher in the following 5 days of life in the 2012 and 2014 cohorts compared to the 2007 cohort, and at some time points, the intakes were very close to the recommended amounts. Calorie intakes were significantly higher in 2012 and 2014 cohorts compared to 2007, p= 0.036. Nonetheless, by the end of the first week of life, energy intakes did not increase and fell below the recommendations for all and without any significant differences between the three cohorts.

Overall the second week of life, the calorie intake was closer to the recommended amount in 2007 compared to 2012 and 2014. There was no significant difference between the three cohorts (Figure 2.2).

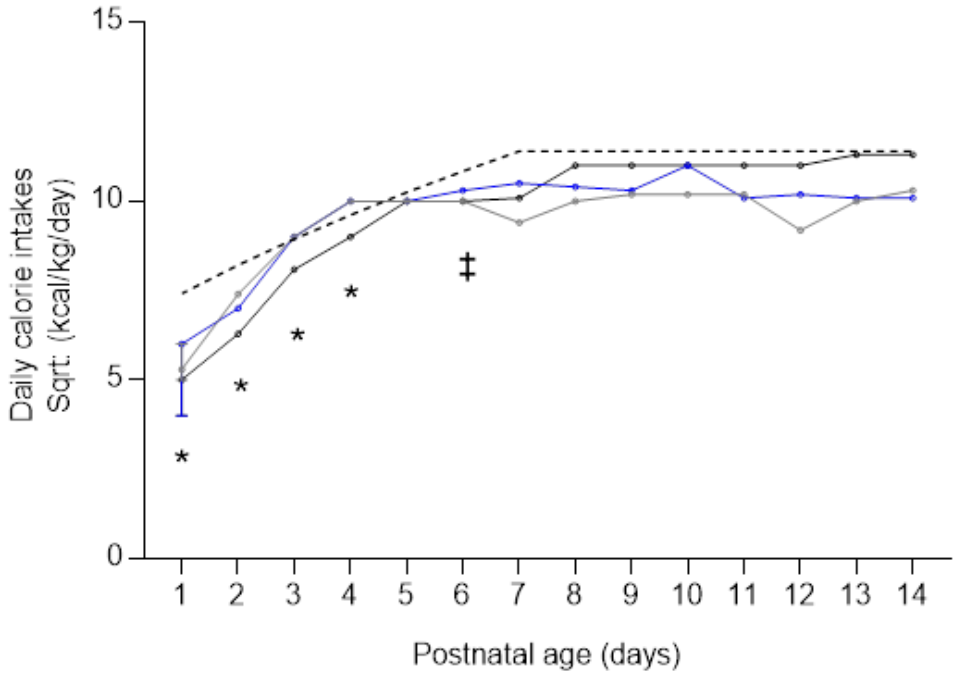

Figure 2.2. Average daily calorie intakes (kcal/kg/day) in 2007, 2012 and 2014 at the Nottingham University hospitals

First day calorie intake displayed as median (IQR), from day 2 to day 14, data were displayed as mean (±SEM). Black: represents intakes during 2007, n=16; Blue: represents intakes during 2012, n=17; Grey: represents intakes during 2104, n=19, dashed black: daily calorie intakes adopted from Tsang recommendations. Error bars represent SEM. Statistical differences between 2007&2012 and between 2007&2014 denoted by * correspond to $p<0.05$ and statistical differences between 2007&2012 only denoted by ‡ correspond to $p<0.05$ (Kruskal-Wallis test and One-way ANOVA, Tukey post-hoc test)

2.6.1.3 Total protein intakes

Of the study population, there was significant increase in the proportion of infants who received protein on the first day of life from 2007 to 2014 (2007: 31% (5/16); 2012: 71% (12/17); 2014: 79% (15/19), p=0.005). The median (IQR) square root of protein intakes on days 1 of life were: 2007: 0 (0-0.5); 2012: 1 (0-1.2); 2014: 0.9 (0.4-1) g/kg/day. The mean (±SEM) protein intakes in the first week of life was; 2007: 1.2 (±0.2); 2012: 1.5 (±0.2); 2014:

1.2 (±0.1) g/kg/day. The mean (±SEM) protein intakes throughout the second weeks was; 2007: 1.8 (±0), 2012: 1.8 (±0) and 2014: 1.7 (±0) g/kg/day (Figure 2.3).

The current study showed a trend toward considerable increase in protein intake during the first week, from 2007 to 2014. In the first two days of life, protein intakes were below the recommendations, however, the intakes were significantly higher in 2012 and 2014 cohorts compared to 2007. Figure 2.3 showed that the mean square root of protein intakes of infants from 2012 and 2014 cohorts are meeting the recommendation from day 3 to day 8. There were significant differences in protein delivery, for infants from the three cohorts, during the first week of life, $p<0.0001$. The differences were mainly between 2007 and 2012, $p<0.0001$ and between 2007 and 2014 cohorts, $p=0.003$, but there was no significant difference between 2012 and 2014 cohorts, $p=0.2$. Almost throughout the second week of life, the amounts of protein achieved were higher in 2007 and 2012 compared to 2014.

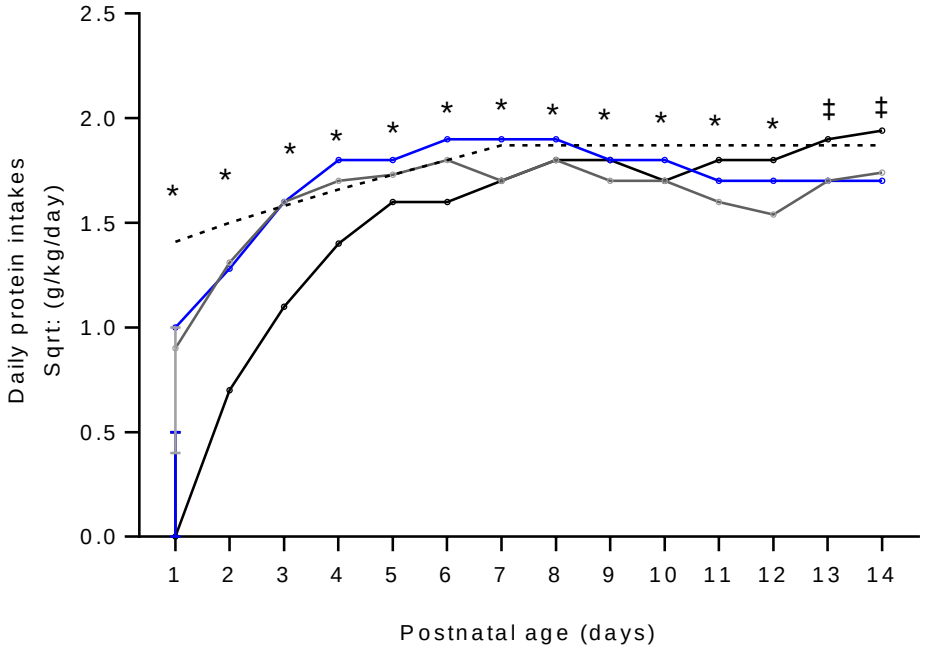

Figure 2.3. Average daily protein intakes (g/kg/day) in 2007, 2012 and 2014 at the Nottingham University hospitals

First day protein intake displayed as medians (IQR), from day 2 to day 14, data were displayed as means (±SEM). Black: represents intakes during 2007, n=16; Blue: represents intakes during 2012, n=17; Grey: represents intakes during 2104, n=18, dashed black: daily calorie intakes adopted from Tsang recommendations. Error bars represent SEM. Statistical differences between 2007&2012 and between 2007&2014 denoted by * correspond to $p<0.05$. Statistical differences between 2007&2012 only, denoted by ‡ correspond to $p<0.05$ (Kruskal-Wallis test and One-way ANOVA, Tukey post-hoc test)

2.6.1.4 Cumulative calorie deficit

The mean (±SEM) cumulative calorie deficits throughout the first week of life was: 2007: 83 (±13); 2012: 51 (±7); 2014: 44 (±10) kcal/kg/day. These deficits were mounting throughout the second week up to 2007: 185 (±7); 2012: 169 (±18); 2014: 207 (±23) kcal/kg/day. The cumulative deficits were considerably more in 2007 compared to 2012 and 2014 in the first week (Figure 2.4). A trend toward improvement in the cumulative deficit was observed in 2007 by the end of the second weeks of life, but not in 2012 and 2014 cohorts. Nonetheless, significant differences in cumulative calorie deficits were observed only on day 2 of life between the three cohorts, p=0.03.

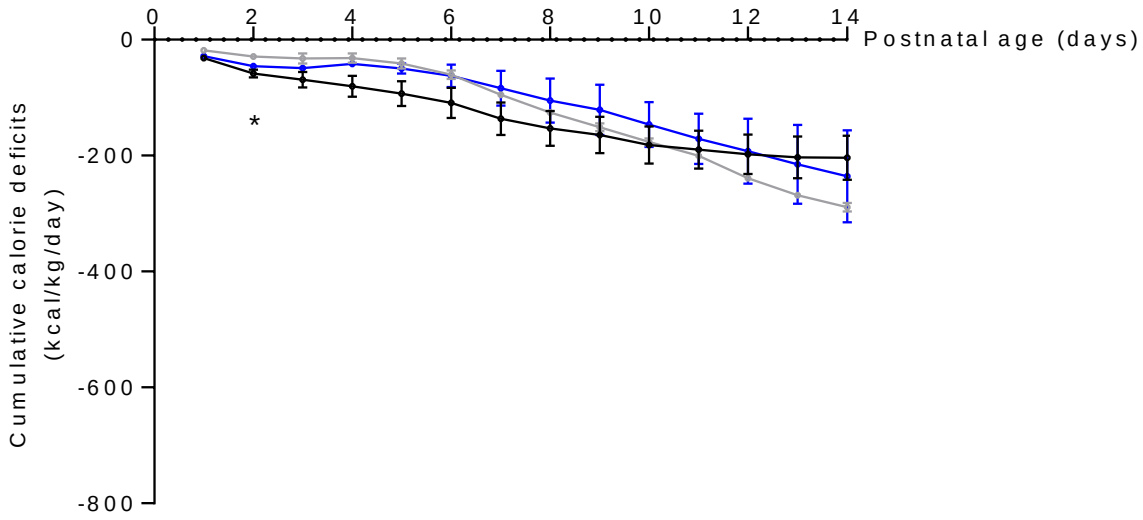

Figure 2.4. Average cumulative calorie deficits (kcal/kg) in 2007, 2012 and 2014

Black: represents deficits during 2007, n=16; Blue: represents deficits during 2012, n=17; Grey: represents deficits during 2104, n=18. Error bars represent SEM. Statistical differences between 2007&2014 denoted by * correspond to $p<0.05$ (One-way ANOVA, Tukey post-hoc test)

2.6.1.5 Cumulative protein deficit

The mean (±SEM) cumulative protein deficits throughout the first week of life was considerably lower for infants from the 2012 and 2014 cohorts compared to the 2007 cohort (2007: 6.6 (±0.6); 2012: 0.8 (±0.2); 2014: 0.9 (±0.1) g/kg. The cumulative deficits became considerable throughout the second week of life mainly in 2007 and 2014 (2007: 7.5 (±0.1); 2012: 0.7 (±0.2); 2014: 2.5 (±0.4) g/kg (Figure 2.5). Nonetheless, a trend toward improved cumulative deficit was observed in 2012 and 2014, but not in 2007 cohorts. Significant differences in cumulative protein deficits were observed throughout the study period between the three cohorts, $p<0.001$.

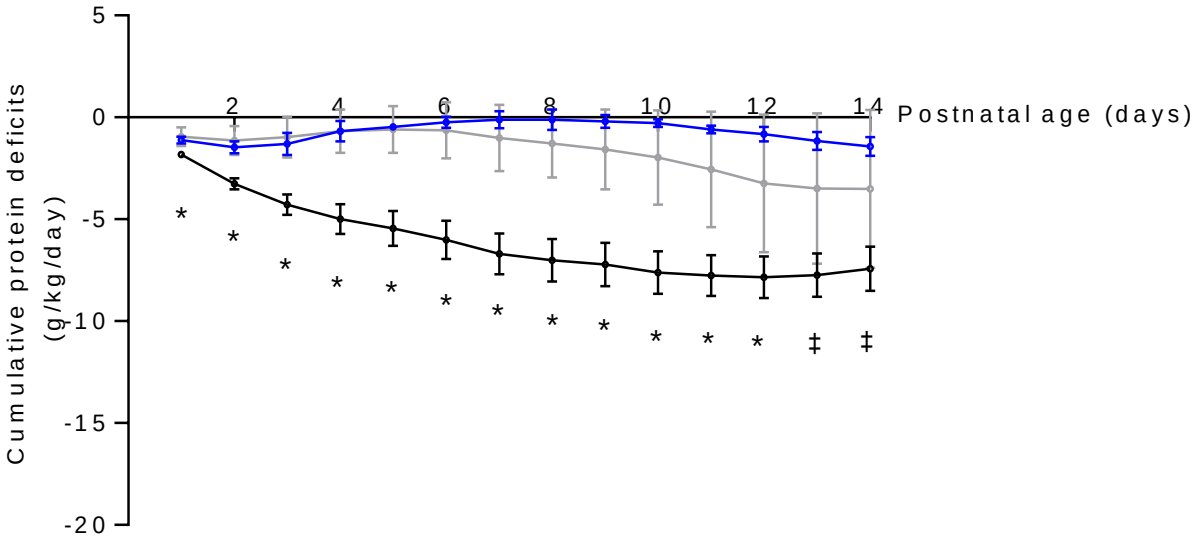

Figure 2.5. Average cumulative protein deficits (g/kg) after birth in the years studied

Black: represents deficits during 2007, n=16; Blue: represents deficits during 2012, n=17; Grey: represents deficits during 2104, n=18. Error bars represent SEM. Statistical differences between 2007&2012 and between 2007&2014 denoted by * correspond to $p<0.05$. Statistical differences between 2007&2012, only, denoted by ‡ correspond to $p<0.05$ (One-way ANOVA, Tukey post-hoc test)

2.6.2 Study 2: Comparing early nutritional practices in neonatal care settings in a Neonatal Networks to the international recommendations

The current study included all neonatal units within CNN and TPN that provide PN. Therefore, the study included population who are representative of the group units that are caring for high-risk preterm infants. Data were collected from 12 neonatal units, of which three units designated as SCUs, six units designated as LNUs and 3 units designated as NICUs, from the UK CNN & TPN. A hundred and nineteen infants admitted between 2013 and 2014 into neonatal units were studied. Infants were excluded from the analysis when there was missing detailed nutritional information (n=1, from LNU). This included information was about the Day of Aqueous Phase, which was required when calculating the nutrient contents of PN given.

2.6.2.1 Demographic features of the study population

The demographic features of infants entered into the study presented in Table 2.2. The attendant care team randomly chose infants and, therefore, demographic characteristics were varied. A hundred and nineteen infants were studied; of which seventy-two had incomplete information on head circumference at birth, at discharge from hospital or both and for six infants the gender was not recorded.

2.6.2.2 Body weight and gestational age at birth

Average (±SEM) birth weights of the current study population were SCUs: 1.97±0.6; LNUs: 1.37±0.04; NICUs: 0.87±0.04 kg. Average BW was significantly different between infants from LNUs, $p<0.001$, but there were no significant differences in BW between infants from SCUs, $p=0.1$ and NICUs, $p=0.1$. Birth weights of infants according to admission units are summarised in Table 2.2 and Figure 2.9 - Figure 2.11.

Of the study population, the median (IQR) GA of infants were admitted was SCUs (n=27): 32 (31-34); LNUs (n=55): 30 (29-31); NICUs (n=37): 26 (25-28) weeks. As expected, the GA in the units were very different, because this reflects management practices in the neonatal network. Within the group of neonatal units, there were significant differences in GA between units designated as SCUs, $p<0.001$ (Figure 2.6), and LNUs, $p=0.01$ (Figure 2.7). No significant differences in the GA were seen between NICUs, $p=0.3$ (Figure 2.8).

Table 2.2 Demographic characteristics of the study population

Characteristics	SCUs (n=27)	LNUs (n=55)	NICUs (n=37)
Infant gender, n (%) Boy [a]	12 (44%)	27 (49%)	18 (49%)
Gestation (weeks) median (±IQR)	32 (31-34)*	30 (29-31)*	26.5 (25-28)
Birth weight (kg)	1.97 (±0.06)	1.36 (±0.04)*	0.89 (±0.04)
Weight (kg) at day 14 of life	1.98 (±0.06)*	1.38 (±0.04)*	0.99 (±0.04)*
Weight (kg) at discharge	2.2 (±0.06)	2 (±0.05)	2.5 (±0.1)*
Gestation (weeks) at discharge median (IQR)	34 (32-36)*	35 (35-37)	38 (36-40)*
WAZ at birth	0.02 (±0.2)	-0.3 (±0.1)	-0.2 (±0.1)
WAZ at day 14	-1.1 (±0.1)	-1.2 (±0.1)	-0.8 (±0.1)
WAZ at discharge	-1.0 (±0.1)	-1.4 (±0.2)	-1.5 (±0.3)
HCZ at birth [b]	0.1 (-0.3, 0.8)	-0.3 (-0.9, 0.5)	-0.1(-1.5, 0)
HCZ at discharge [b]	-0.9 (-1.1, -0.3)	-1.1 (-1.7, 0.6)	-1.7 (-2.3, -0.4)

Abbreviations
Special Care Units: SCU, Local Neonatal Units: LNU, Neonatal Intensive Care Units: NICU.
Weight for age z-score: WAZ, Head circumference z-score: HCZ.
Values are mean (±SEM), unless specified.
Statistical differences between units within the same level of care denoted by *correspond to $p<0.05$
[a]Values are n (%); n=26/27, 53/55, 34/37 for SCUs, LNUs and NICUs, respectively
bValues are median (±IQR); n=18/27, n=22/55, n=7/37 for SCUs, LNUs and NICUs, respectively

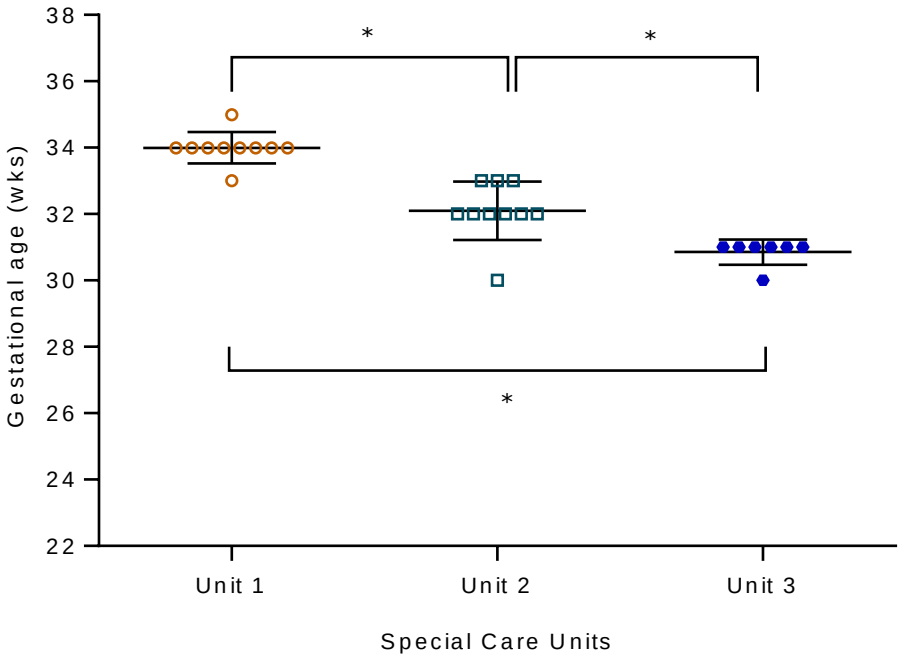

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Figure 2.6 Mean (±SD) gestational age of infants from Special Care Units (SCUs) according to admission unit

Each symbol represents an individual infant; Unit 1: n=10, Unit 2: n=10, & Unit 3: n=7. Statistical differences denoted by *correspond to p<0.05 (One-way ANOVA, Tukey post-hoc test).

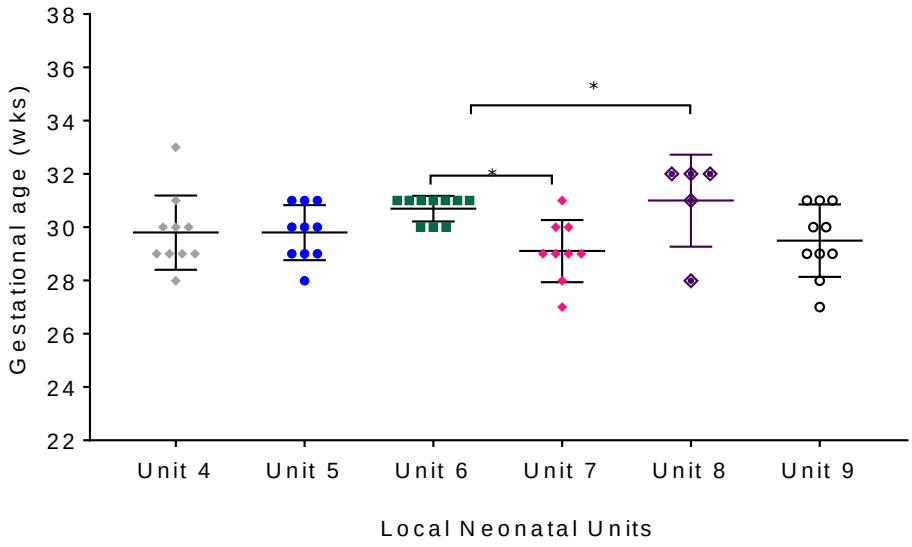

Figure 2.7. Mean (±SD) gestational age of infants from Local Neonatal Units (LNUs) according to admission unit

Each symbol represents an individual infant; unit 4: n=10, Unit 5: n=10, Unit 6: n=10, Unit 7: n=9, Unit 8: n=5, Unit 9: n=10. Statistical differences denoted by *correspond to p<0.05 (One-way ANOVA, Tukey post-hoc test).

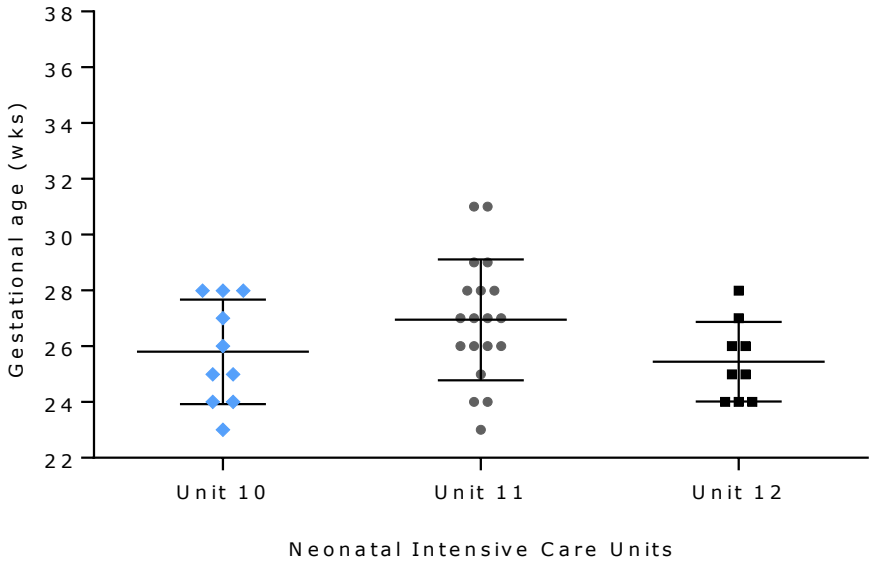

Figure 2.8. Mean (±SD) gestational age of infants from Neonatal Intensive Care Unit (NIUs) according to admission unit

Each symbol represents an individual infant; Unit 10: n=10, Unit 11: n=19, Unit 13: n=8

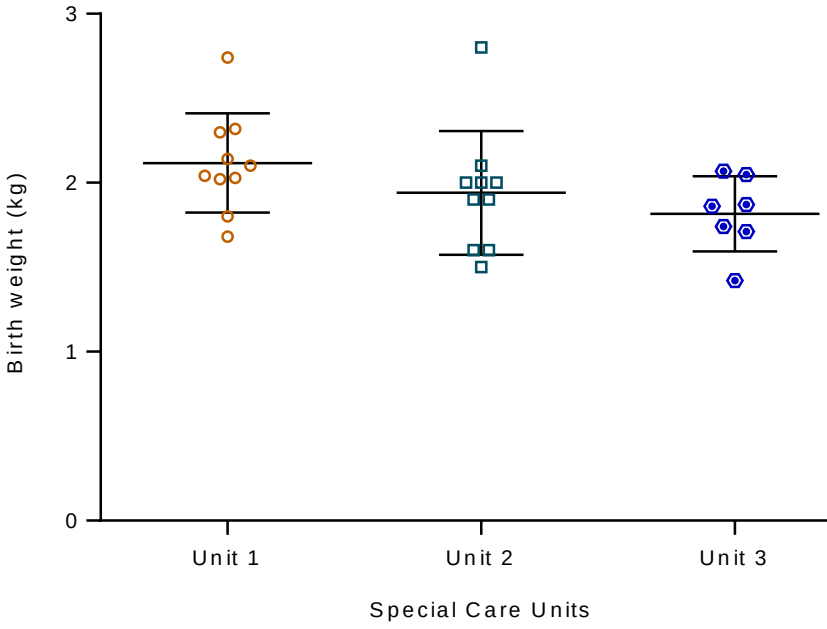

Figure 2.9. Mean (±SD) birth weights of infants from Special Care Units (SCUs) according to admission unit

Each symbol represents an individual infant; Unit 1: n=10, Unit 2: n=10 & Unit 3: n=7

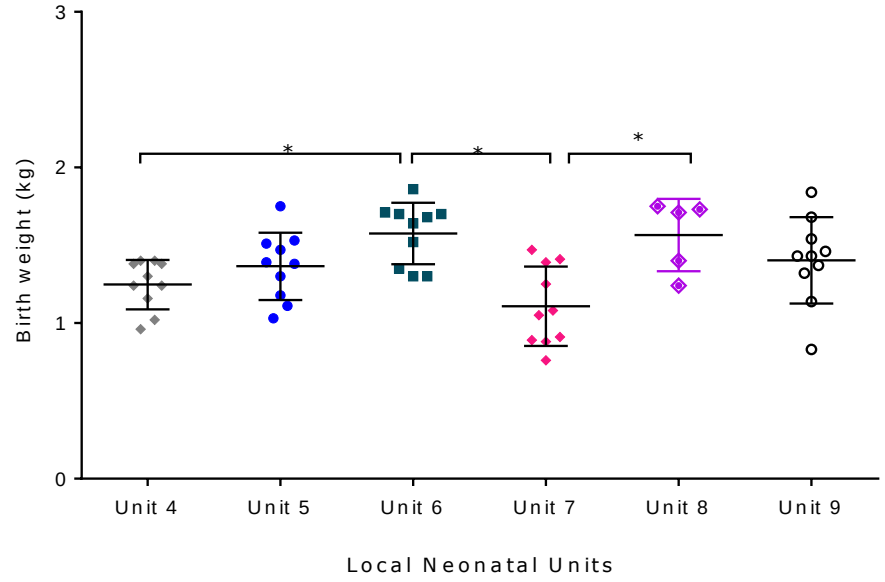

Figure 2.10. Mean (±SD) birth weights of infants from Local Neonatal Units (LNUs) according to admission unit

Each symbol represents an individual infant; Unit 4: n=10, Unit 5: n=10, Unit 6: n=10, Unit 7: n=9, Unit 8: n=5, Unit 9: n=10. Statistical differences denoted by *correspond to $p<0.05$ (One-way ANOVA, Tukey post-hoc test)

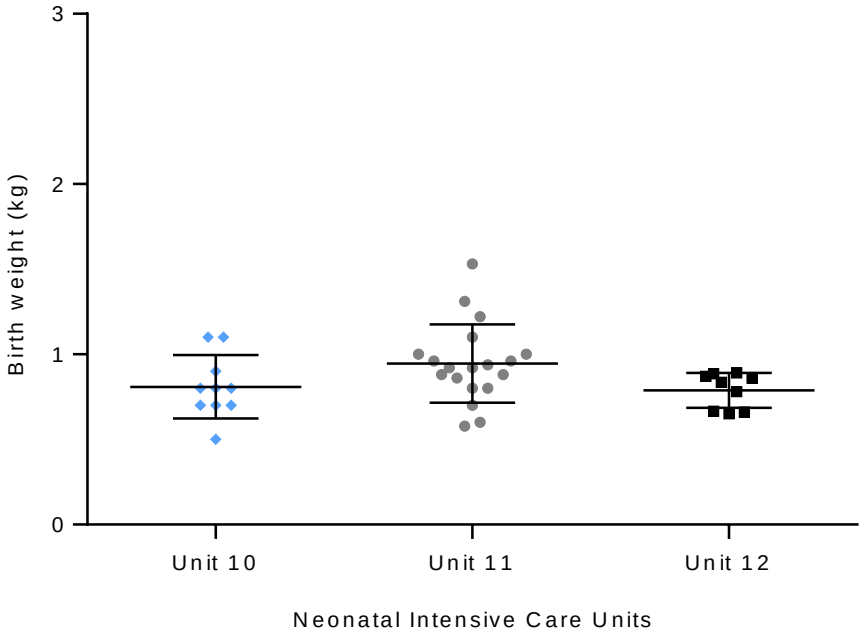

Figure 2.11. Mean (±SD) birth weights of infants from Neonatal Intensive Care Units (NICUs) according to admission unit.

Each symbol represents an individual infant; Unit 10: n=10, Unit 11: n=18, Unit 13: n=9

2.6.2.3 Nutritional practices

Early nutritional support was provided according to each neonatal unit's nutrition guidelines and was, therefore, variable between units. Within units of the same level, some infants received PN from the first day of life whilst in others did not receive PN.

2.6.2.3.1 PN intakes

In general, PN was prescribed for all infants were born at, or below, 30 weeks gestation. Therefore, infants from SCUs usually do not need PN. GA of infants received PN varied in the current study, between 27 and 33 in LNUs and 23 and 31 in NICUs (Figure 2.12 & Figure 2.13). In LNUs, only 15% (8/55) received PN on the first day and 22% (12/55) started on day 2 of life. Seventy percent (26/37) of infants in the study from NICUs started PN on day 1 and 22% (8/37) started on the second day of life. Day of starting PN presented in Figure 2.14 & Figure 2.15.

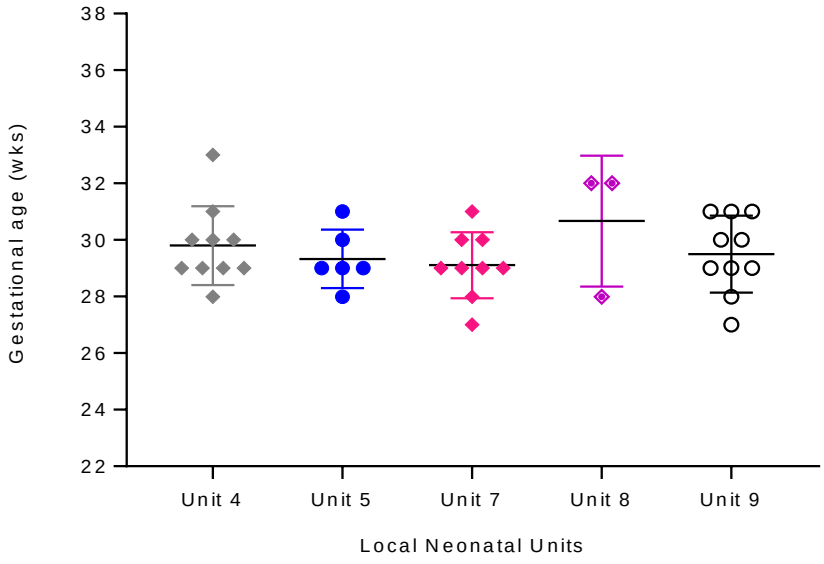

Figure 2.12. Gestational age of infants from Local Neonatal Units (LNUs) had PN during the first two weeks of life

Each symbol represents an individual infant; Unit 4: n=10, Unit 5: n=6, Unit 7: n=9, Unit 8: n=3, Unit 9: n=10

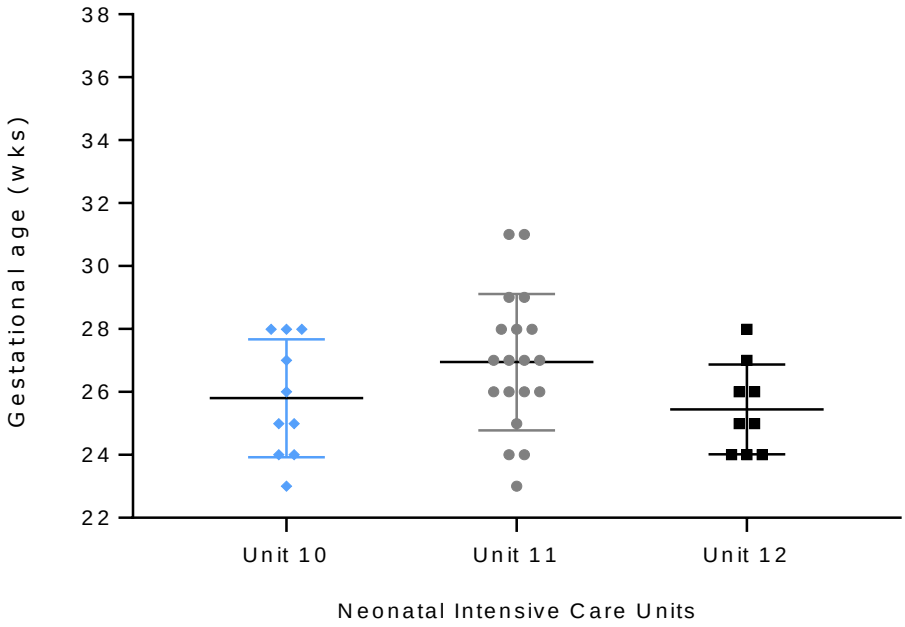

Figure 2.13. Gestational age of infants from Neonatal Intensive Care Units (NICUs) had PN during the first two weeks of life

Each symbol represents an individual infant; Unit 10: n=10, Unit 11: n=18, Unit 13: n=9

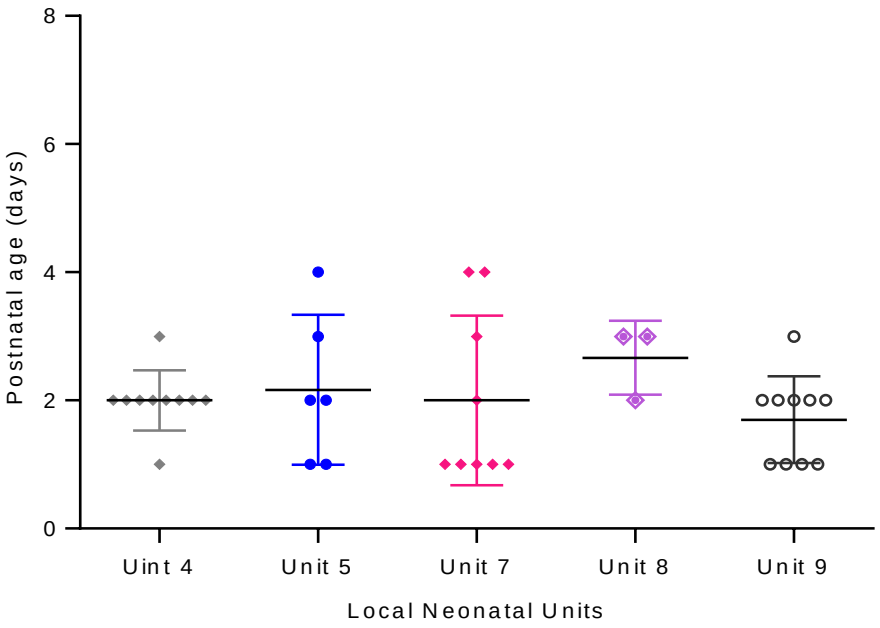

Figure 2.14. Day of starting PN for infants from Local Neonatal Units (LNUs)

Each symbol represents an individual infant; Unit 4: n=10, Unit 5: n=10, Unit 6: n=0, Unit 7: n=9, Unit 8: n=5, Unit 9: n=10

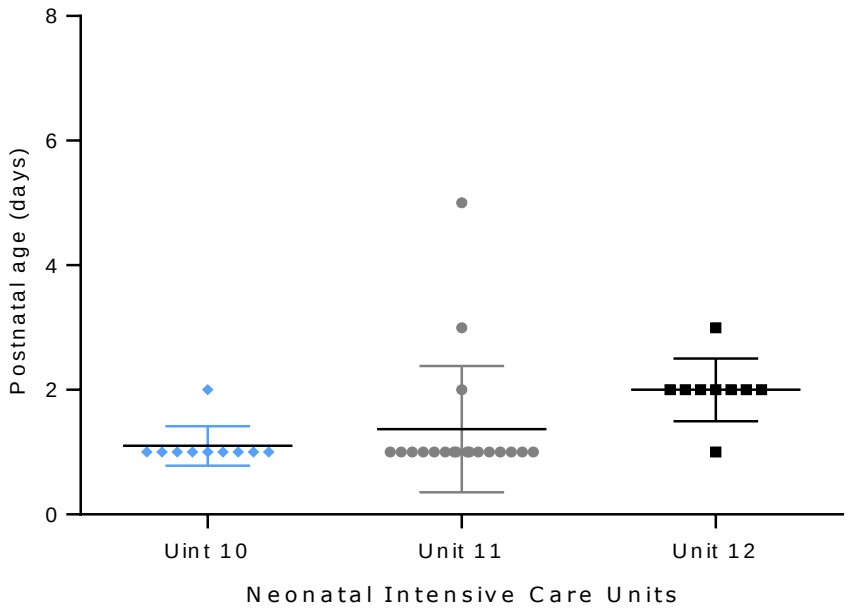

Figure 2.15 Day of starting PN for infants from Neonatal Intensive Care Units (NICUs)

Each symbol represents an individual infant; Unit 10: n=10, Unit 11: n=18, Unit 13: n=9

2.6.2.3.2 Enteral feeding

Enteral feeding was commenced on the first day of life in 37% (10/27) and 11% (6/55) & 3% (1/37) of babies from SCUs, LNUs & NICUs, respectively. On the second day, the percentage of babies who received enteral feeding increased up to 48% (13/27), 40% (22/55) & 30% (11/37), in SCUs, LNUs & NICUs, respectively. The median (IQR) days of starting enteral feeding was: SCUs: 2 (1-2); LNUs: 2 (2-3); NICUs: 3 (2-4) day of age; (Figure 2.17 & Figure 2.18). Fifty-eight percent of infants were tolerating an enteral intake of ≥150 ml/kg/day in the second week of life.

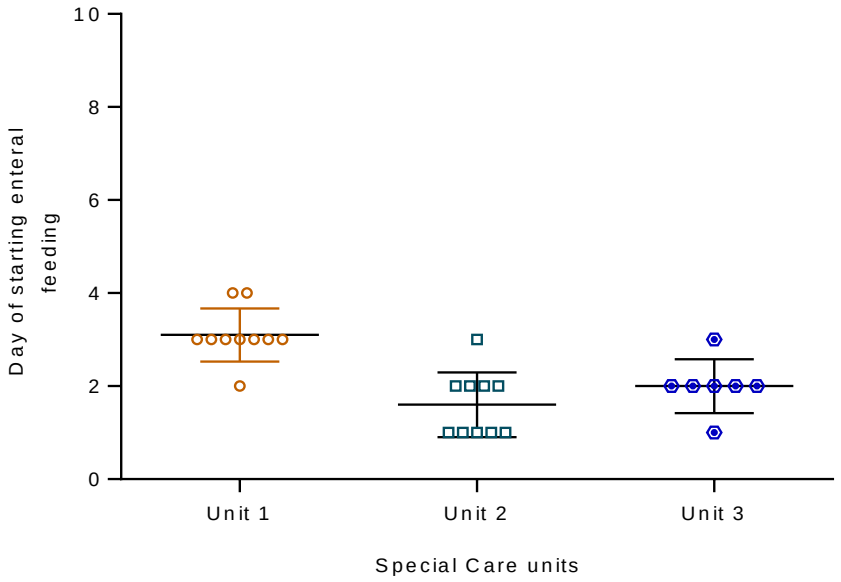

Figure 2.16 Day of starting enteral feeding for infants from Special Care Units (SCUs)

Each symbol represents an individual infant; Unit 1: n=10, Unit 2: n=10 & Unit 3: n=7

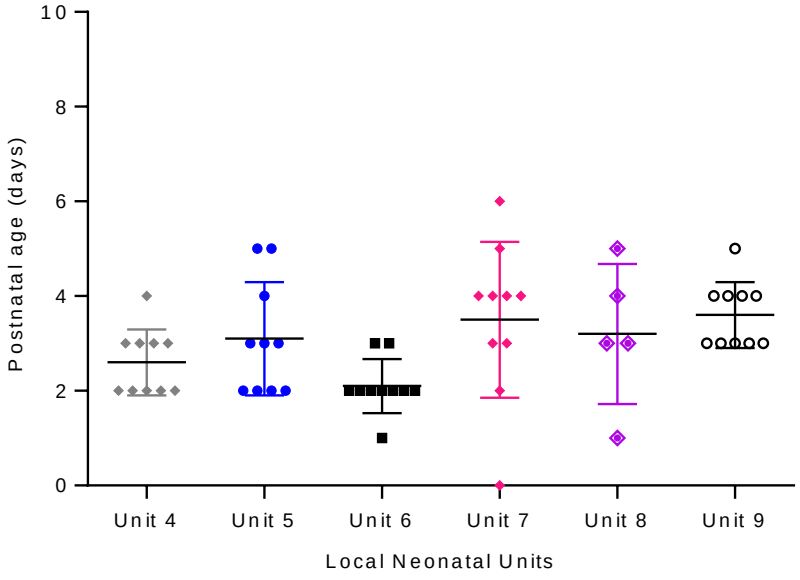

Figure 2.17 Day of starting enteral feeding for infants from Local Neonatal Units (LNUs)

Each symbol represents an individual infant; Unit 4: n=10, Unit 5: n=10, Unit 6: n=10, Unit 7: n=9, Unit 8: n=5, Unit 9: n=10

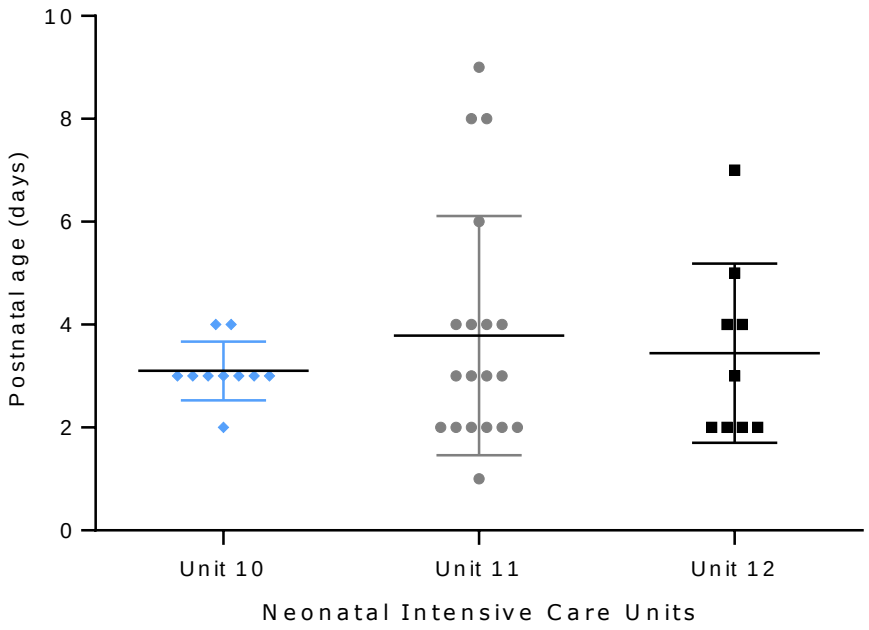

Figure 2.18 Day of starting enteral feeding for infants from Neonatal Intensive Care Units (NICUs)

Each symbol represents an individual infant; Unit 10: n=10, Unit 11: n=18, Unit 13: n=9

2.6.2.3.3 Total energy intakes

The average recommended energy intake was 130 kcal/kg/day, however, some severely ill infants may require a higher amount of calories. The target energy intake was achieved in some units. Enteral and parenteral energy intakes illustrated in Table 2.3. The median (IQR) square root of energy intakes on the first day of life were different between the units from different designation (SCUs: 4 (3-5); LNUs: 4 (3-5); NICUs: 5 (4-6) kcal/kg/day). As expected, higher amounts of energy were delivered to infants from NICUs while receiving PN (Figure 2.19 - Figure 2.24). The mean (±SEM) square root of cumulative energy intakes for infants in the first week was: SCUs: 71 (±3); LNUs: 63 (±2); NICUs: 72(±3) kcal/kg/day. By the end of the second week after birth, the mean (±SEM) square root of cumulative energy intake increased to SCUs: 92 (±2); LNUs: 86 (±2); NICUs: 85 (±2) kcal/kg/day.

2.6.2.3.4 Total Protein intakes

Average protein intakes (enteral and parenteral) presented in Table 2.3. The median (IQR) square root of protein intakes on the first day of life was: SCUs: 0 (0-0.3); LNUs: 0 (0-0.1); NICUs: 0.5 (0-0.9) g/kg/day. Whilst some infants were on glucose or normal saline solution; the median protein intake was 0 (Figure 2.25, Figure 2.27 & Figure 2.29).

A small number of the study population received protein on day 1 from SCUs and LNUs (SCUs: 37% (10/27); LNUs: 27% (15/55); NICUs: 70% (26/37) of infants). The means (±SEM) square root of protein intakes for the first week were similar between SCUs and LNUs, and higher for infants from NICUs, because all infants from NICUs had PN (SCUs: 1.7 (±0.1); LNUs: 1.6 (±0.1); NICUs: 2.2 (±0.1) g/kg/day). By the end of the second week of life, the mean (±SEM) square root of protein intakes were close to the recommendations in some neonatal units (SCUs: 3.1 (±0.2); LNUs: 2.9 (±0.1); NICUs: 2.8 (±0.1) g/kg/day). Throughout the first two weeks of life, infants from individual SCUs, LNUs and NCUs had low mean protein: energy ratios as illustrated in Table 2.3. .

Table 2.3 Total protein and energy intakes in the first two weeks of life

	SCUs		LNUs		NICUs	
Postnatal age	Protein (g/kg/d)	Energy (kcal/kg/d)	Protein (g/kg/d)	Energy (kcal/kg/d)	Protein (g/kg/d)	Energy (kcal/kg/d)
Day 1‡¥	0 (0-0.3)	4 (3-5)	0 (0-0.1)	4 (3-5)	0.5(0-0.9)	5 (4-6)
Day 2	0.7 (±0.1)	7 (±0.2)	0.6 (±0.1)	6 (±0.1)	1 (±0.1)	7 (±0.2)
Day 3	1 (±0.1)	8 (±0.3)	1 (±0.1)	7 (±0.2)	1.4 (±0.1)	8 (±0.2)
Day 4	1.3 (±0.1)	9 (±0.3)	1.3 (±0.1)	8 (±0.2)	1.5 (±0.1)	9 (±0.2)
Day 5	1.5 (±0.1)	9 (±0.2)	1.5 (±0.05)	9 (±0.1)	1.6 (±0.1)	9 (±0.2)
Day 6	1.7 (±0.1)	10 (±0.2)	1.6 (±0.04)	10 (±0.2)	1.6 (±0.04)	10 (±0.2)
Day 7	1.7 (±0.1)	10 (±0.2)	1.6 (±0.04)	10 (±0.1)	1.7 (±0.05)	10 (±0.2)
Mean intake from day 1 to 7 of life	1.7 (±0.1)	71 (±2.5)	1.6 (±0.1)	63 (±2)	2.2 (±0.1)	72 (±3)
Mean intake from day 1-14 of life	2.4 (±0.1)	92 (±2)	2.3 (±0.1)	86 (±2)	2.5(±0.1)	85 (±2)
Protein: energy ratio throughout the first two weeks (g/kcal)	1:6		1:6		1:5	

Values are square root transformed data, presented as mean (±SEM), unless specified
‡values are presented as median (IQR)
¥day of birth

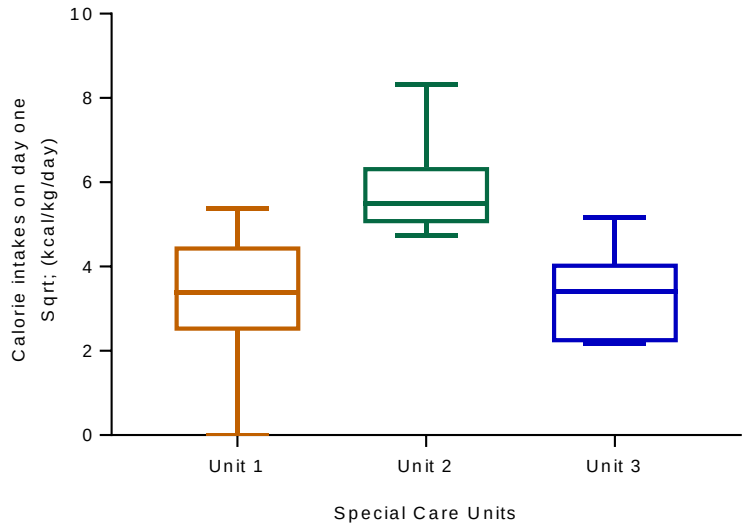

Figure 2.19 First day calorie intake from both parenteral and enteral sources by neonatal units for infants from Special Care Units (SCUs)

Data displayed as medians (IQR). Brown: Unit 1, n=10; Green: Unit 2, n=10; Blue: Unit 3, n=7.

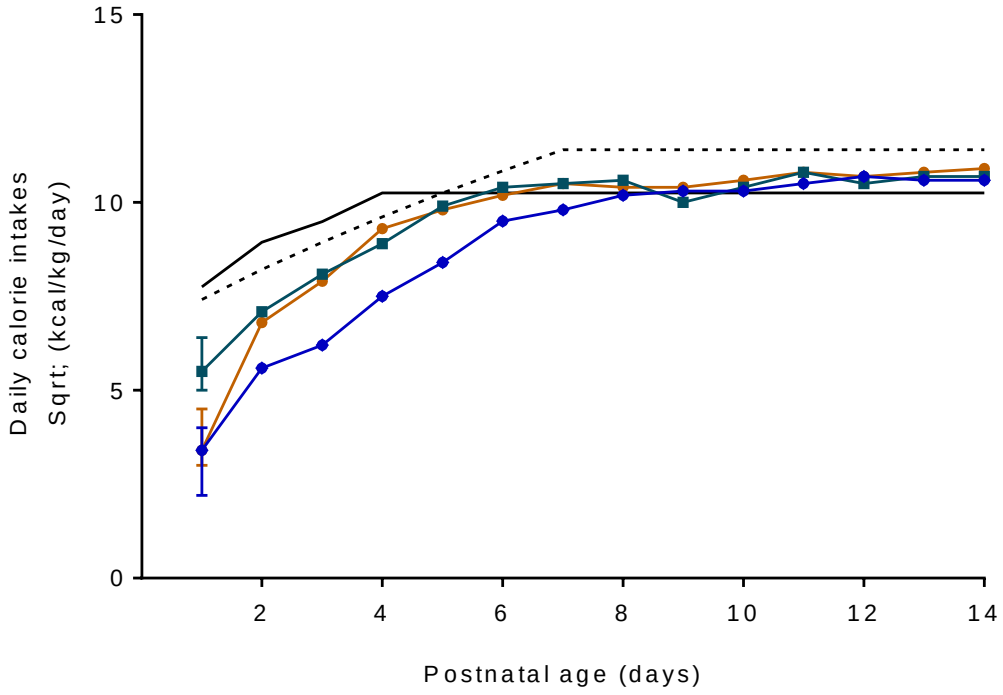

Figure 2.20 Daily calorie intake from both parenteral and enteral sources in the first 2 weeks of life by neonatal units for infants from Special Care Units (SCUs)

Data displayed as medians (IQR) on day 1 and means (±SEM) from day 2 to day 14. Brown: Unit 1, n=10; Green: Unit 2, n=10; Blue: Unit 3, n=7, dashed black: daily calorie intakes adopted from Tsang recommendations, solid black: daily calorie intakes adopted from Koletzko recommendations.

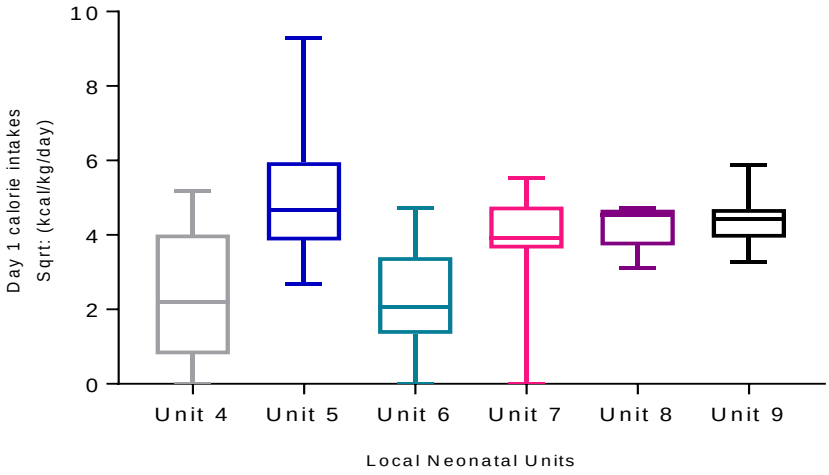

Figure 2.21 First day calorie intake from both parenteral and enteral sources by neonatal units for infants from Local Neonatal Units (LNUs)

Data displayed as medians (IQR). Grey: Unit 4, n=10; Blue: Unit 5, n=10; Green: Unit 6, n=10, Pink: Unit 7, n=9, Purple: Unit 8, n=5, Black: Unit 9, n=10

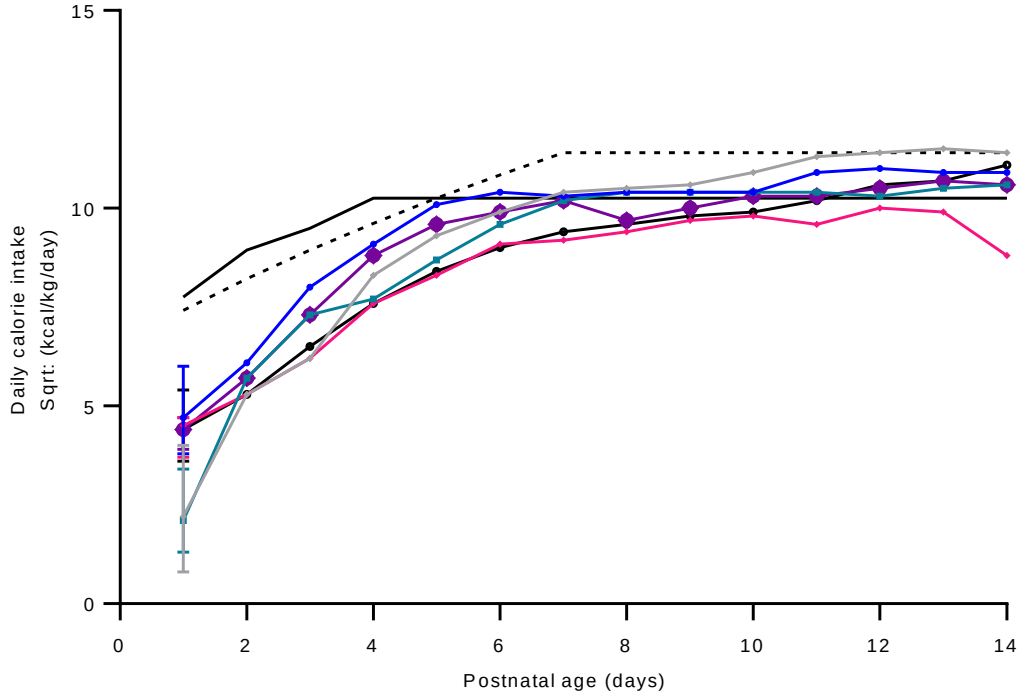

Figure 2.22 Daily calorie intake from both parenteral and enteral sources during the first 14 days of life by neonatal units for infants from Local Neonatal Units (LNUs)

Data displayed as medians (IQR) on day 1 and as means (±SEM) from day 2 to day 14. Grey: Unit 4, n=10; Blue: Unit 5, n=10; Green: Unit 6, n=10, Pink: Unit 7, n=9, Purple: Unit 8, n=5, Black: Unit 9, n=10, dashed black: daily calorie intakes adopted from Tsang recommendations, solid black: daily calorie intakes adopted from Koletzko recommendations.

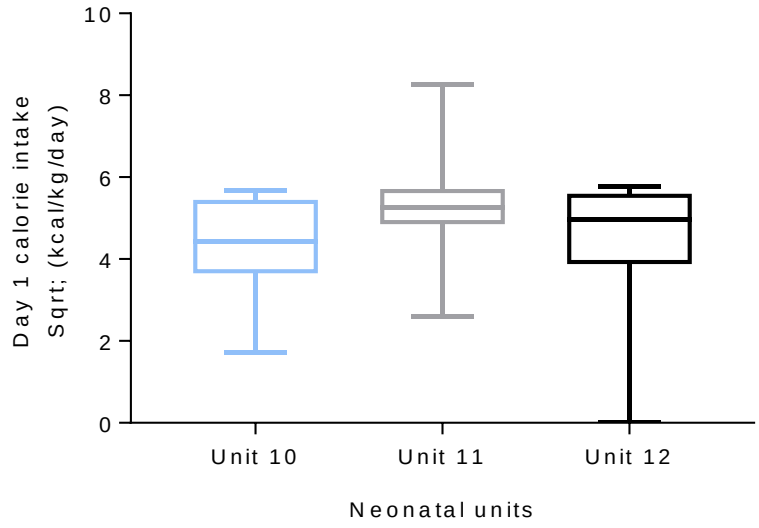

Figure 2.23 First day calorie intake from both parenteral and enteral sources by neonatal units for infants from Neonatal Intensive Care Units (NICUs)

Data displayed as median (IQR). Blue: Unit 10, n=10; Grey: Unit 11, n=19; Black: Unit 12, n=8

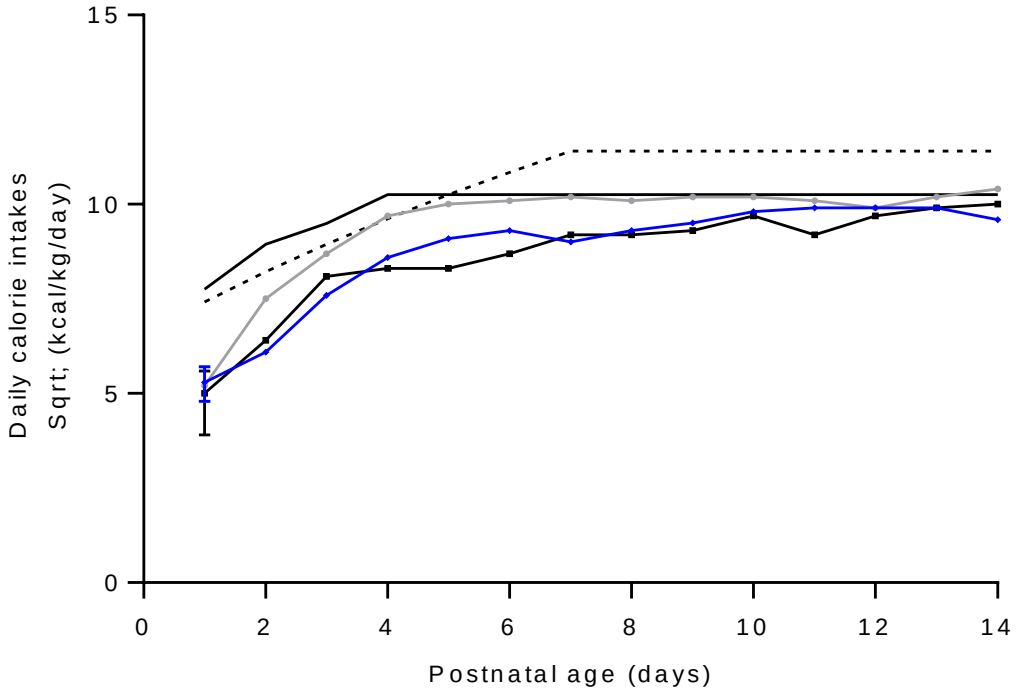

Figure 2.24 Daily calorie intake from both parenteral and enteral sources from day 2 to day 14 of life by neonatal units for infants from Neonatal Intensive Care Units (NICUs)

Data displayed as medians (IQR) on day 1and as means (±SEM) from day 2 to day 14. Blue: Unit 10, n =10, Grey: Unit 11, n=19; Black: Unit 12, n= 8, dashed black: daily calorie intakes adopted from Tsang recommendations, solid black: daily calorie intakes adopted from Koletzko recommendations.

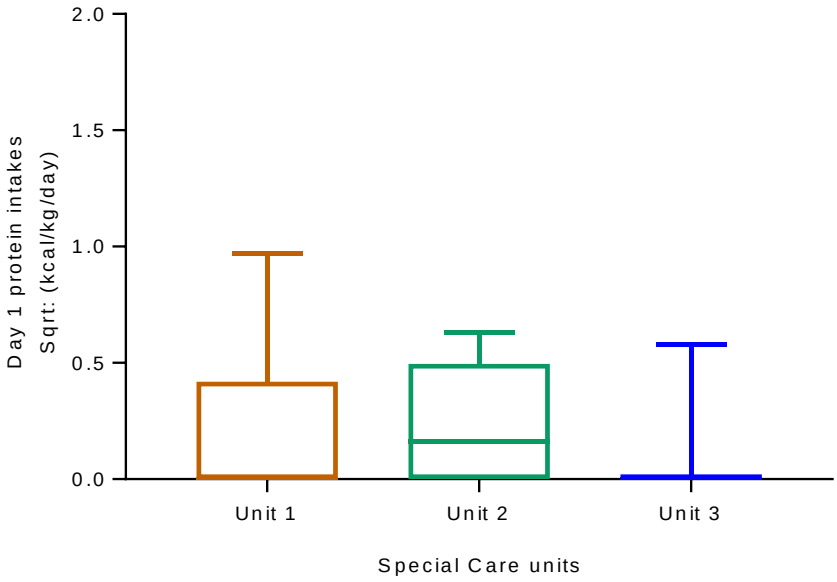

Figure 2.25 First day protein intake from both parenteral and enteral sources by neonatal units for infants from Special Care Units (SCUs)

Data displayed as medians (IQR). Brown: Unit 1, n=10; Green: Unit 2, n=10; Blue: Unit 3, n=7

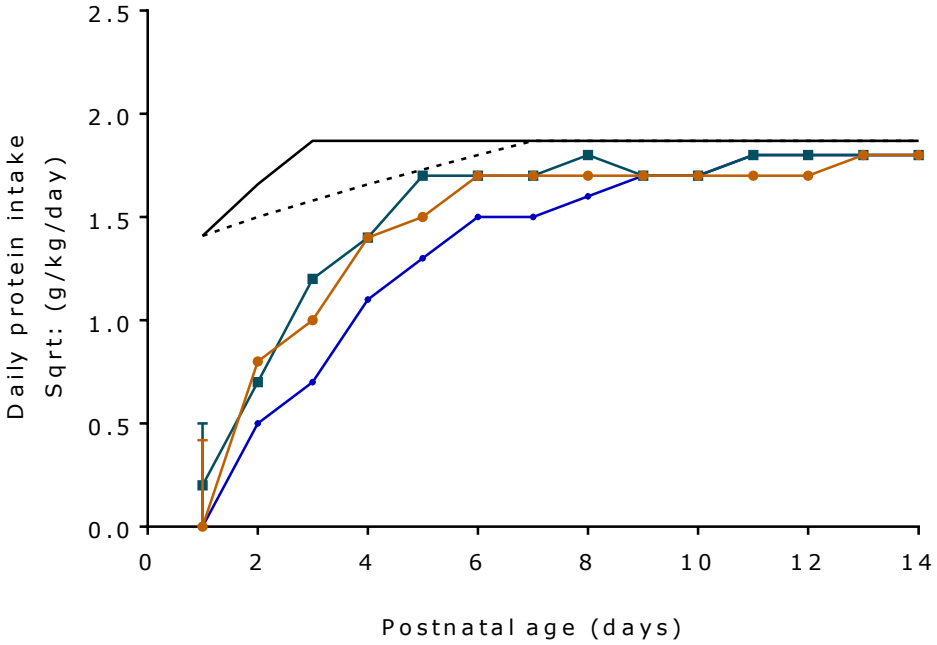

Figure 2.26 Daily protein intake from both parenteral and enteral sources in the first 14 days of life by neonatal units for infants from Special Care Units (SCUs)

Data displayed as medians (IQR) on day 1 and means (±SEM) from day 2 to day 14. Brown: Unit 1, n=10; Green: Unit 2, n=10; Blue: Unit 3, n=7, dashed black: daily calorie intakes adopted from Tsang recommendations, solid black: daily calorie intakes adopted from Koletzko recommendations

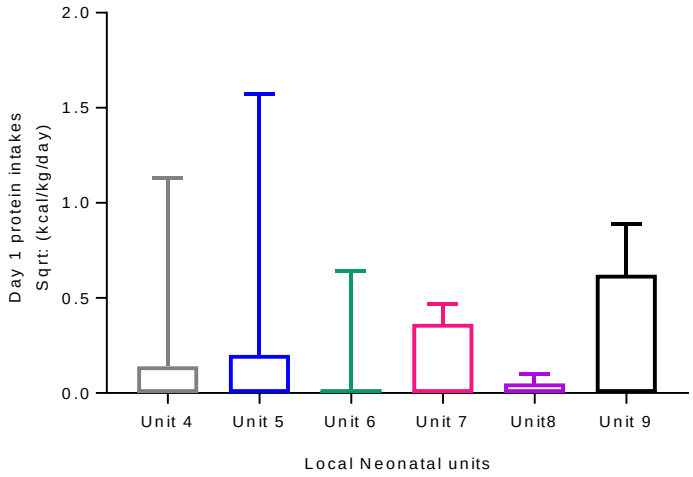

Figure 2.27 First day protein intake from both parenteral and enteral sources by neonatal units for infants from Local Neonatal Units (LNUs).

Data displayed as medians (IQR)
Grey: Unit 4, n=10; Blue: Unit 5, n=10; Green: Unit 6, n=10, Pink: Unit 7, n=9, Pink: Unit 7, n=9, purple: Unit 8, n=5, Black: Unit 9, n=10

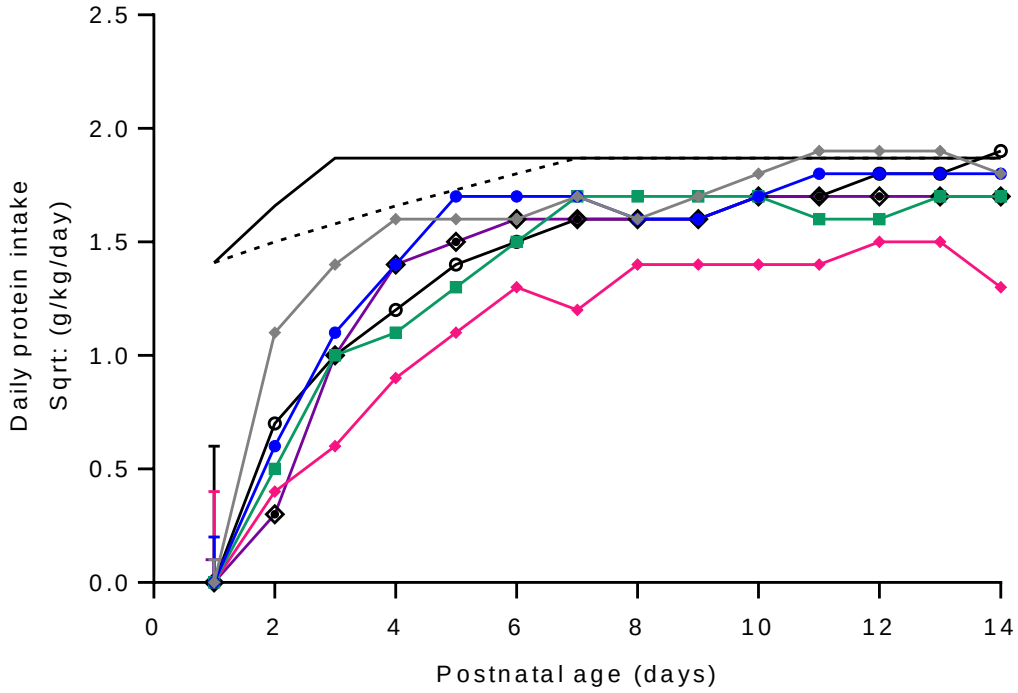

Figure 2.28 Daily protein intake from both parenteral and enteral sources in the first 14 days of life by neonatal units for infants from Local Neonatal Units (LNUs)

Data displayed as medians (IQR) in day 1 and as means (±SEM) from day 2 to day 14 of life. Grey: Unit 4, n=10; Blue: Unit 5, n=10; Green: Unit 6, n=10, Pink: Unit 7, n=9, Purple: Unit 8, n=5, Black: Unit 9, n=10, Dashed black: daily calorie intakes adopted from Tsang recommendations, solid black: daily calorie intakes adopted from Koletzko recommendations.

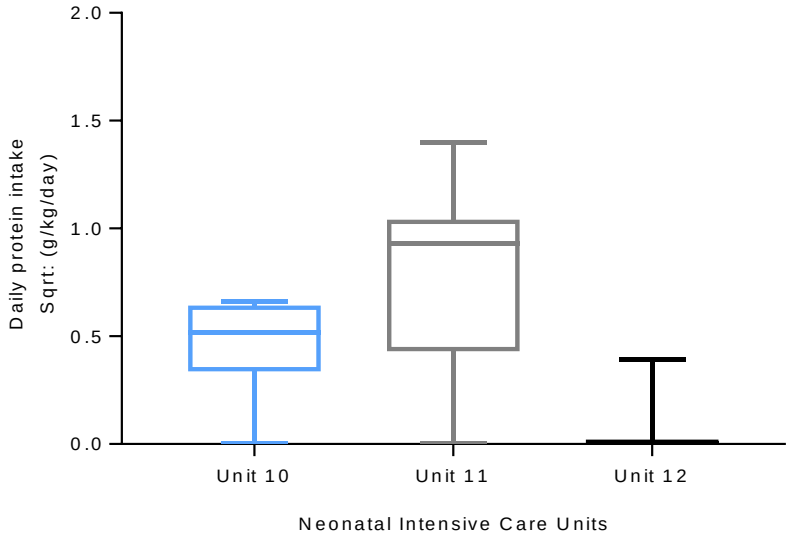

Figure 2.29 First day protein intake from both parenteral and enteral sources by neonatal units for infants from Neonatal Intensive Care Units (NICUs)

Data displayed as medians (IQR). Blue: Unit 10, n=10; Grey: Unit 11, n=19; black: Unit 12, n=8

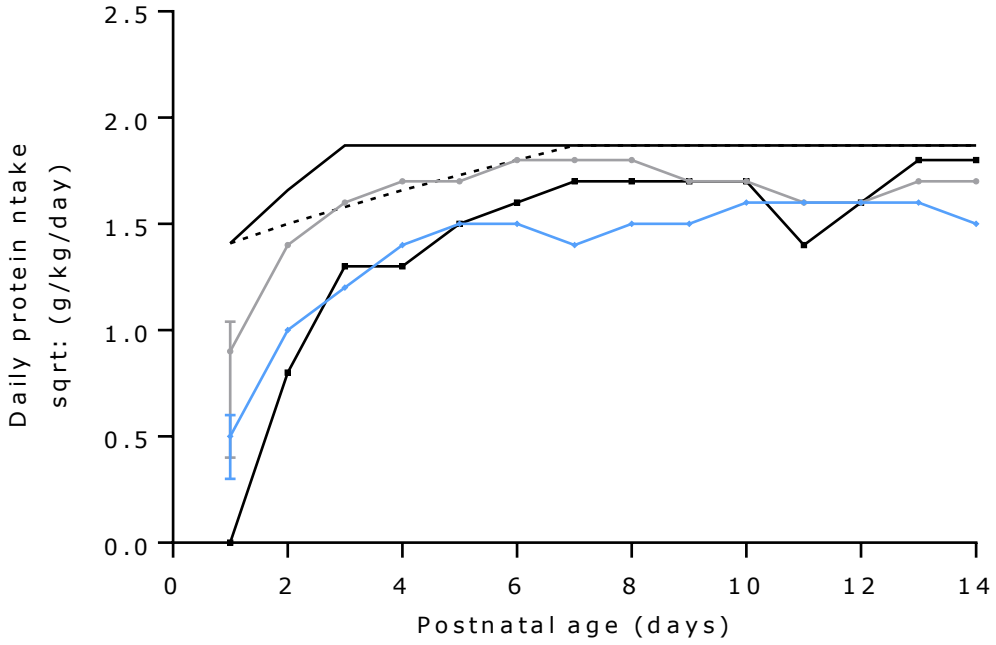

Figure 2.30 Daily protein intake from both parenteral and enteral sources in the first 14 days of life by neonatal units for infants from Neonatal Intensive Care Units (NICUs)

Data displayed as medians (IQR) in day 1 and as means (±SEM) from day 2 to day 14. Blue: Unit 10, n =10, Grey: Unit 11, n=19; Black: Unit 12, n=8, Dashed black: daily calorie intakes adopted from Tsang recommendations, Solid black: daily calorie intakes adopted from Koletzko recommendations.

2.6.2.3.5 Cumulative calorie deficits

Using interpretations of Tsang recommendations (107), by the end of the second week of life, the mean(±SEM) cumulative calorie deficits was: SCUs: 277(±27); LNUs: 347(±23); NICUs: 355 (±33) kcal/kg, Figure 1.31– Figure 1.33. The mean (±SEM) deficits decreased using Koletzko recommendations (106) to SCUs: 93(±29); LNUs: 175(±23); NICUs: 212(±28) kcal/kg. As expected, cumulative deficits based on Koletzko recommendations (106) were significantly less when compared to the cumulative deficits based Tsang recommendations (107) for infants from SCUs; $p<0.001$, LNUs; $p<0.001$, and NICUs; $p<0.001$.

2.6.2.3.6 Cumulative protein deficits

When protein deficits were calculated using values adapted from Tsang recommendations (107), by the end of the second week of life, infants had mean (±SEM) cumulative protein deficits of SCUs: 9.1 (±2); LNUs: 11.4 (±1.2); NICUs: 8.1 (±9) g/kg (Figure 2.34-Figure 2.36). The mean (±SEM) cumulative deficits increased using Koletzko recommendations (106) up to SCUs: 13.3 (±1.7), LNUs: 15 (±1.1); NICUs: 11.9 (±1.3) g/kg.

As expected, cumulative deficits based on Koletzko recommendations were significantly more when compared to the cumulative deficits based Tsang recommendations for infants from SCUs; $p=0.001$, LNUs; $p<0.001$, and NICUs; $p<0.001$.

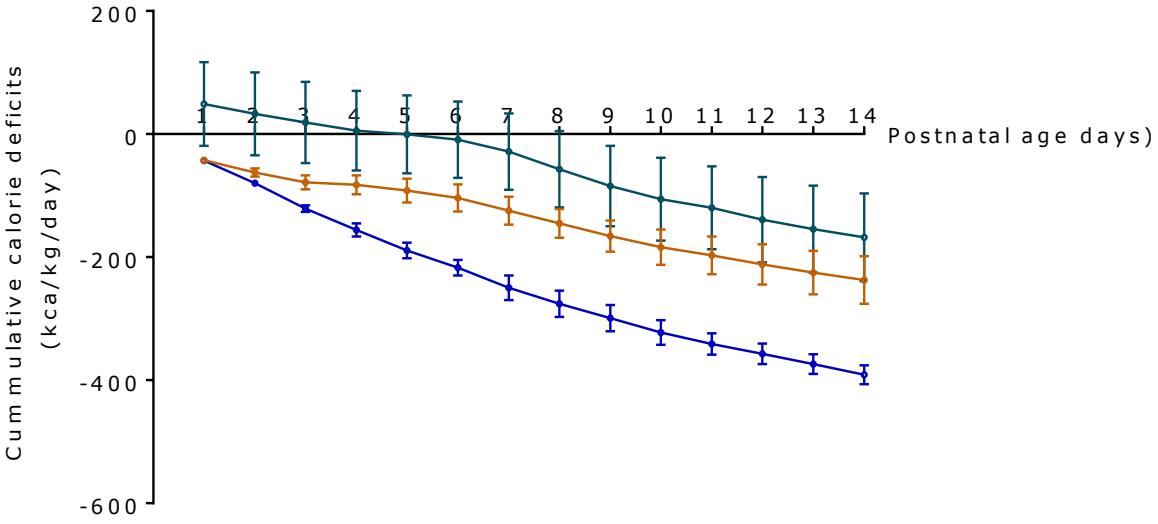

Figure 2.31. Average cumulative calorie deficits (kcal/kg) for babies from Special Care Units (SCUs)

Brown: unit 1, n=10; Green: unit 2, n=10; Blue: unit 3, n=7. Error bars represent SEM.

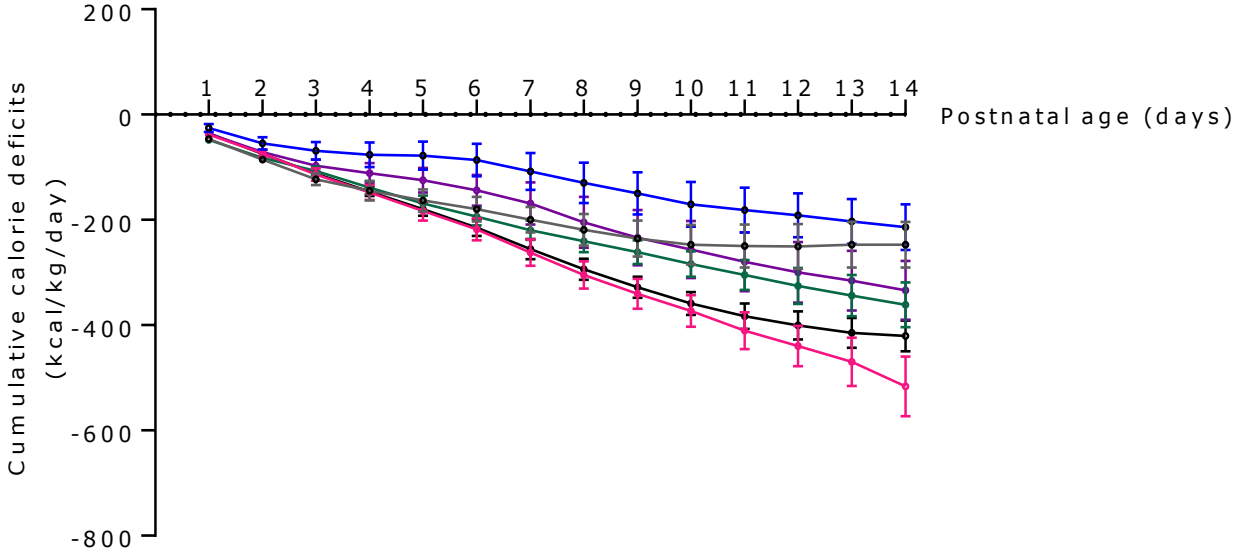

Figure 2.32. Average cumulative calorie deficit (kcal/kg) for babies from Local Neonatal Units (LNUs)

Grey: unit 4, n=10; Blue: unit 5, n=10; Green: unit 6, n=10, Pink: unit 7, n=9, Purple: unit 8, n=5, Black: unit 9, n=10. Error bars represent SEM.

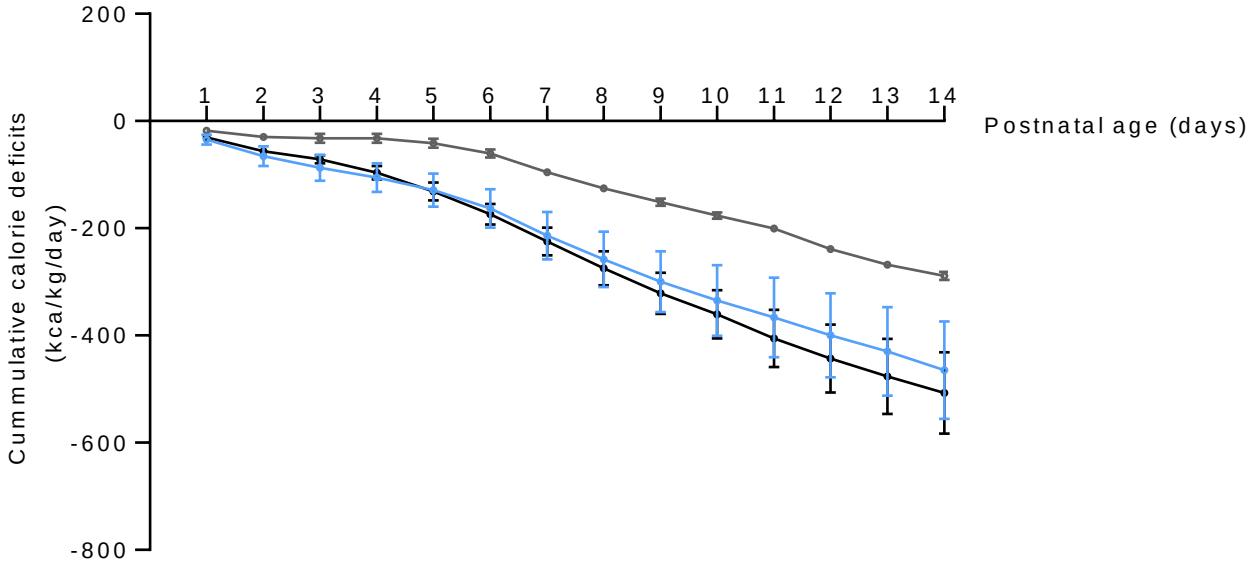

Figure 2.33. Average cumulative calorie deficit (kcal /kg) for babies from Neonatal Intensive Care Units (NICU)

Blue: unit 10, n =10, Grey: unit 11, n=19; Black: unit 12, n=8, Error bars represent SEM.

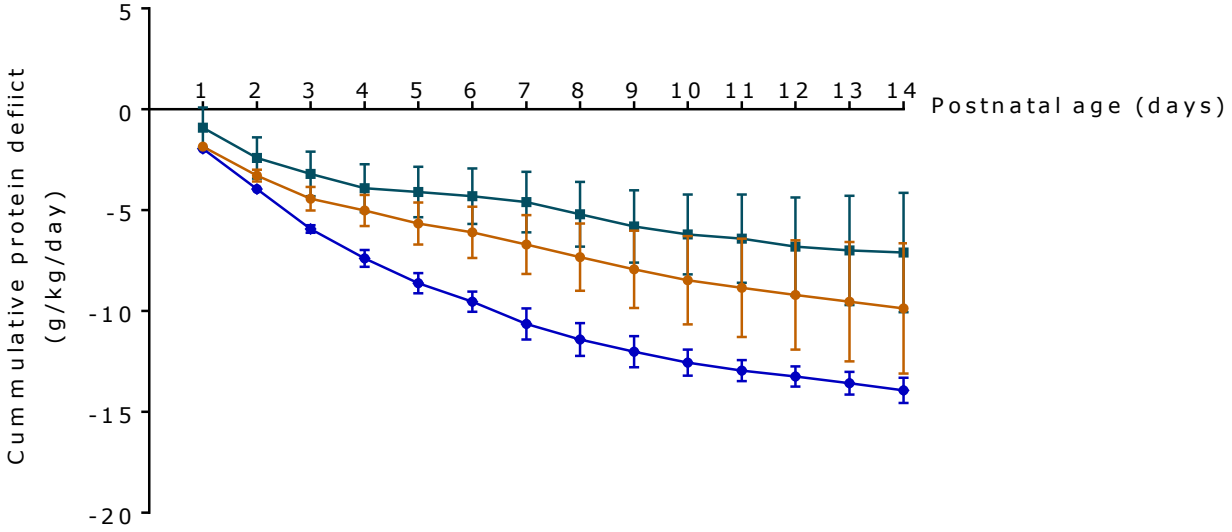

Figure 2.34. Average cumulative protein deficit (g/kg) for babies from Special Care Units (SCUs)

Brown: unit 1, n=10; Green: unit 2, n=10; Blue: unit 3, n=7, Error bars represent SEM.

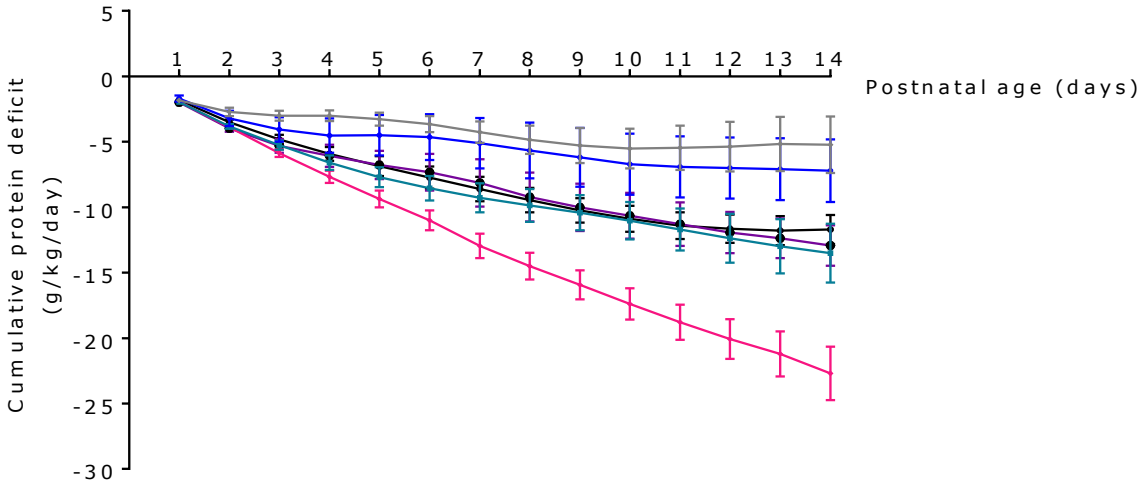

Figure 2.35. Average cumulative protein deficit (g /kg) for babies from Local Neonatal Units (LNUs)

Grey: unit 4, n=10; Blue: unit 5, n=10; Green: unit 6, n=10, Pink: unit 7, n=9, Purple: unit 8, n=5, Black: unit 9, n=10. Error bars represent SEM.

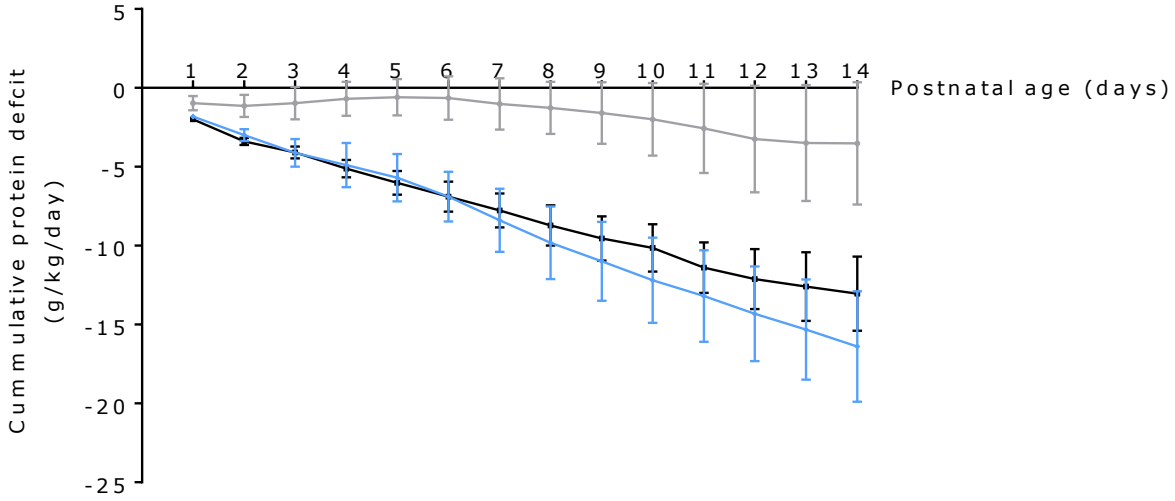

Figure 2.36. Average cumulative protein deficit (g /kg) for babies from Neonatal Intensive Care Units (NICU)

Blue: unit 10, n =10, Grey: unit 11, n=19; Black: unit 12, n=8, Error bars represent SEM.

2.6.2.4 Age at discharge

The median GA (IQR) at discharge was: SCUs: 34 (32-36) and LNUs: 35 (35-37) weeks gestation. Infants from NICUs had longer hospital stay period. The median (IQR) age at discharge was 38 (36-40) weeks.

2.6.2.5 Changes in body weight

2.6.2.5.1 Body weight at day 14 of life

Compared to BW, the mean (±SEM) body weights at day 14 of life did not show marked changes (SCUs: 0.01 (±0.02); LNUs: 0.01 (±0.02): NICUs: 0.1 (±0.01) kg). At birth, different designations of neonatal units had different proportions of infants that were SGA: SCUs: 4% (1/26); LNUs: 20% (11/51); NICUs: 8% (3/36). Not surprisingly, as babies are expected to lose weight the first few days after birth due to loss of extracellular fluid, by day 14, the proportion of infants who had EUGR increased to: SCUs: 41% (11/26); LNUs: 32% (18/51); NICUs: 24% (9/36). Of these infants, 4% (1/26) from SCUs, 10% (5/51) from LNUs and 8% (3/36) from NICUs, were SGA at birth, whereas, 38% (10/26), 17% (9/51) and 17% (6/36) of infants from SCUs, LNUs and NICUs, respectively, were body weights appropriate for gestational age (AGA). AGA defined as weights between the 10th and the 90th centile for gestational age). Low protein and energy intakes for infants from SCUs and LNUs may have resulted in the increased proportion of infants with EUGR.

2.6.2.5.2 Body weight at discharge

The average (±SEM) change in weight at discharge was: SCUs: 0.2 (±0.04); LNUs: 0.7 (±0.1); NICUs: 1.5 (±0.1) kg. At discharge, the proportion of infants who had EUGR was 33% (9/26) for infants from SCUs. More than fifty percent of infants from LNUs and NICUs had postnatal growth restriction (LNUs: 54% (30/50); NICUs: 62% (23/34)). Of these infants, 19% (5/26), 22% (11/51) and 11% (4/36) from SCUs, LNUs and NICUs, respectively, were SGA at birth. Whereas, 27% (7/26), 31% (16/51) and 50% (18/36) of infants from SCUs, LNUs and NICUs, respectively were weights between the 10th and the 90th centile for GA at birth showed growth failure at discharge from hospital.

2.6.2.6 Change in weight for age z-score

Generally, after birth, most preterm infants show slow initial weight gain or weight loss. In other words, they appear to fall in z-scores, and then they tend to regain BW by the end of the second week. The mean (±SEM) changes in WAZ scores between birth and day 14 of life

was: SCUs: -1.1 (±0.1); LNUs: -0.9 (±0.1); NICUs: -0.7 (±0.1). The mean (±SEM) change in WAZ scores from birth to discharge were SCUs: -1.0 (±0.1); LNUs: -1.1 (±0.1); NICUs: -1.5 (±0.2).

2.6.2.7 Head circumference z-scores

The median (IQR) changes in head circumference z scores (HCAZ) from birth to discharge was: SCUs: -1.0 (-1.1 to -0.5), LNUs: -1.0 (-1.7 to -0.6); NICUs: -1.1 (-2.6 to -0.1). Overall, the study population, 3% (2/65) of the infants were symmetrical SGA.

2.6.2.8 The potential factors affecting weight for age z-scores at discharge

Scatterplots of WAZ scores and the potential confounders showed roughly linear relationships (Figure 2.37 -Figure 2.42). There were weak positive correlations between WAZ scores and weight, body weight at day 14 and calorie deficit. An inverse relationship with GA at discharge was observed. Correlations between WAZ score to GA at birth and protein deficit were not observed.

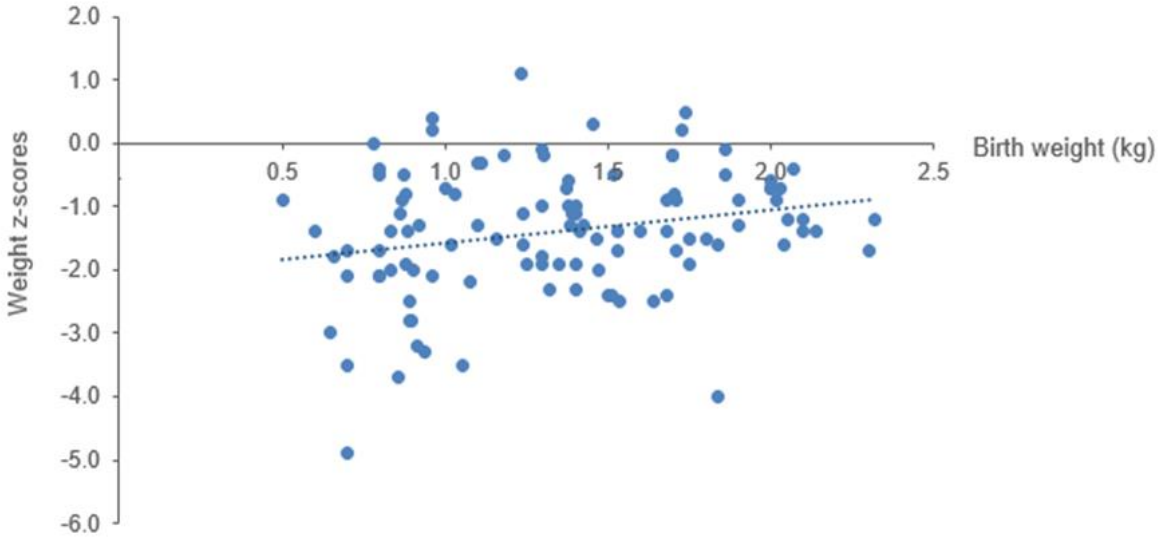

Figure 2.37 The association between weigh for age z-scores and birth weight (kg)

Pearson correlation coefficient (r) = 0.24, p = 0.01
Each symbol represents an individual infant. Dotted line represents the linear fit of data

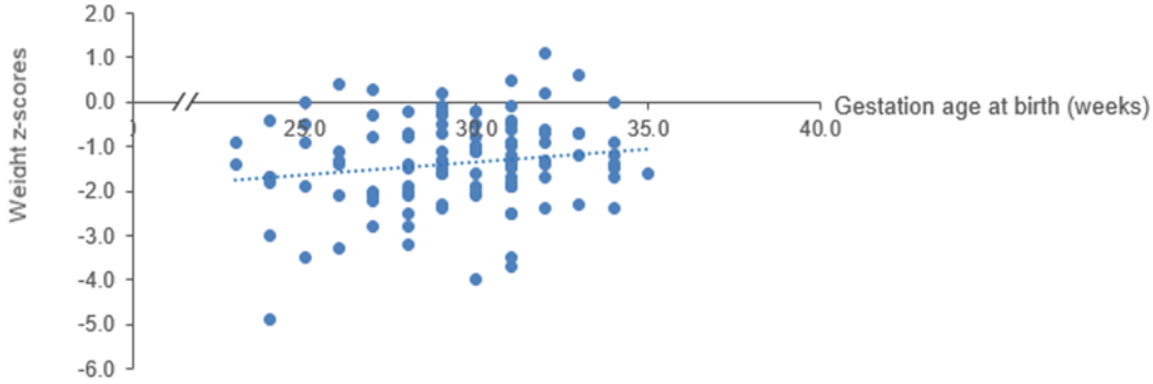

Figure 2.38 The association between weigh for age z-scores and gestation age at birth (weeks)

Pearson correlation coefficient (r) = 0.16, p = 0.09
Each symbol represents an individual infant. Dotted line represents the linear fit of data

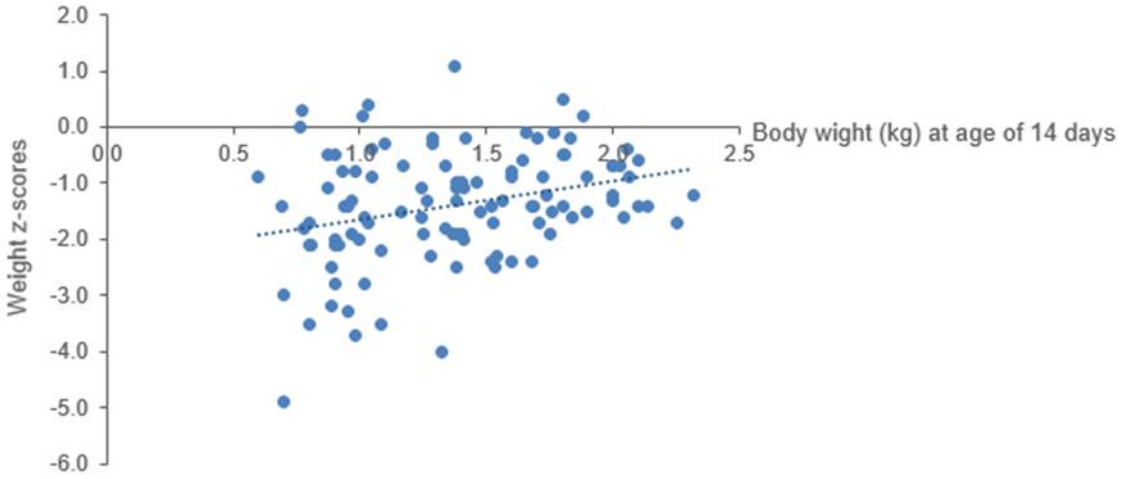

Figure 2.39 The association between weigh for age z-scores and body weight at day 14 of life (kg)

Pearson correlation coefficient (r) = 0.35, p <0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

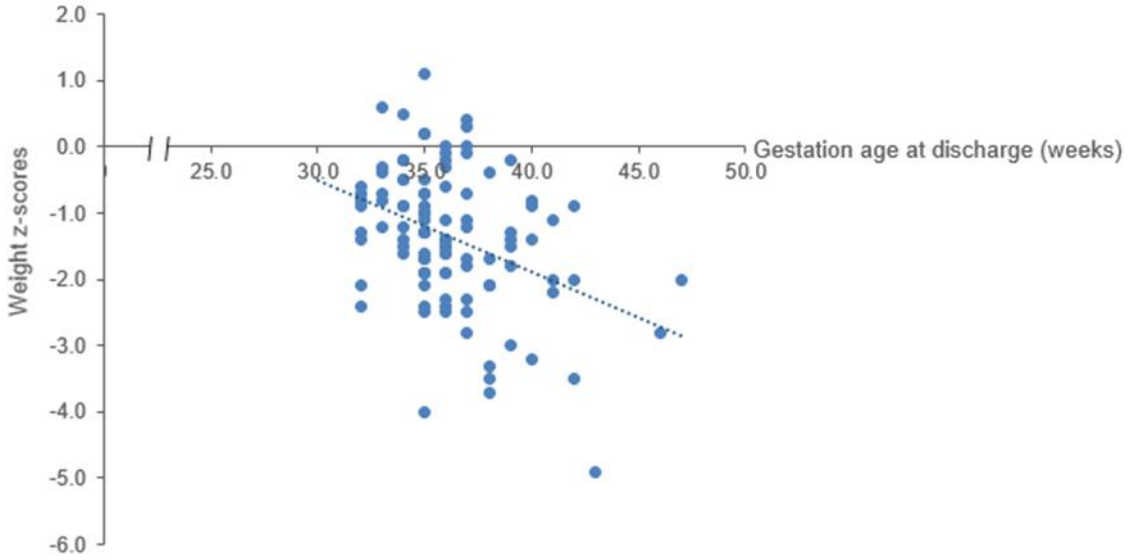

Figure 2.40 The association between weigh for age z-scores and gestation age at discharge (weeks)

Persons correlation r= -0.4, p< 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

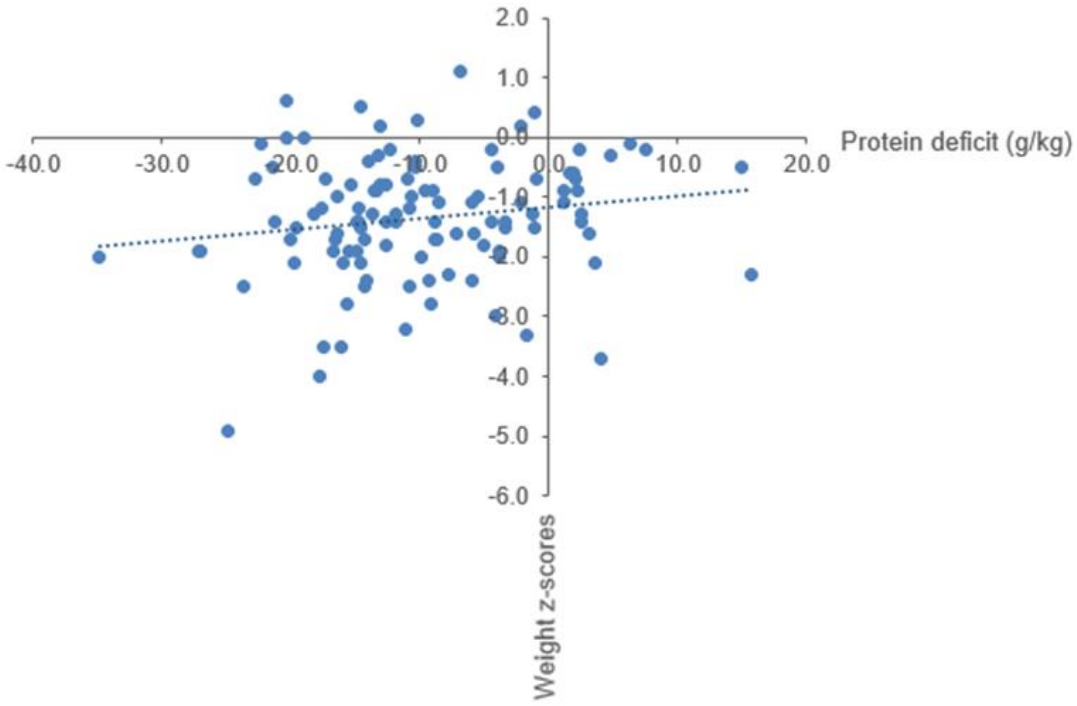

Figure 2.41 The association between weigh for age z-scores and protein deficit (g/kg)

Pearson correlation coefficient (r) = -0.2, p = 0.09
Each symbol represents an individual infant. Dotted line represents the linear fit of data

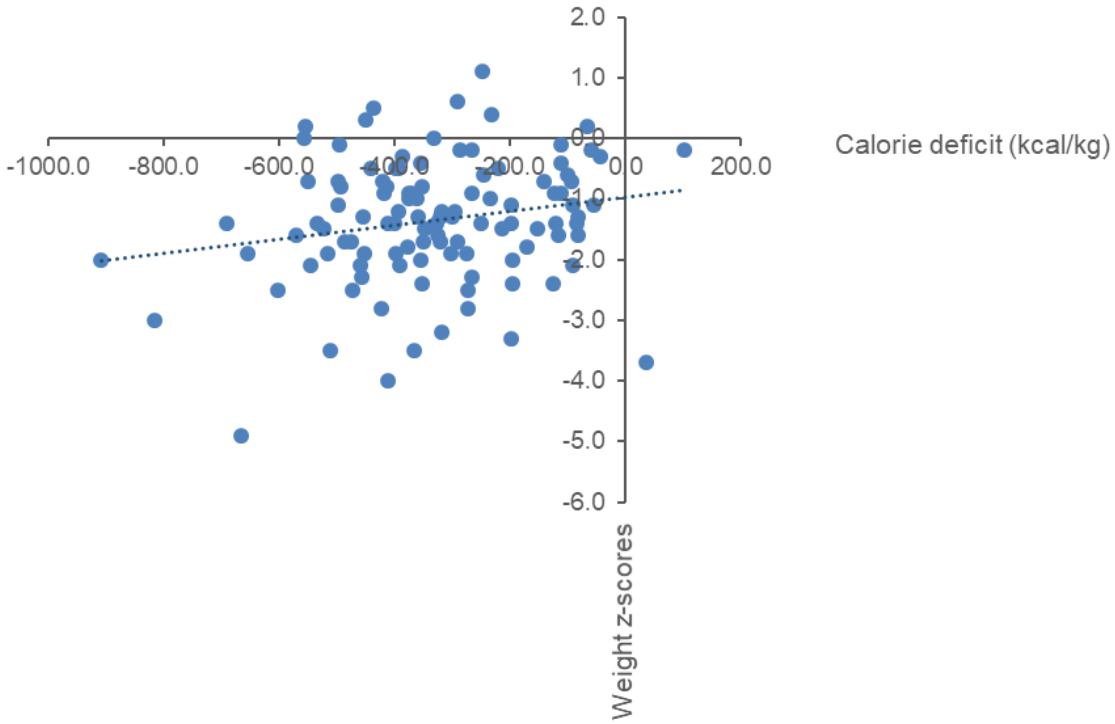

Figure 2.42 The association between weigh for age z-scores and calorie deficit (kcal/kg)

Pearson correlation coefficient (r) = -0.2, p = 0.037
Each symbol represents an individual infant. Dotted line represents the linear fit of data

Univariate analysis showed that BW, body weight at day 14 of life, cumulative calorie deficit and GA at discharge are significant predictors. Table 2.4 illustrates the univariate analyses.

Table 2.4 Univariate analysis to determine which variables were associated with weight for age z-scores

Variables	B	95%CI		P-value
		Lower	Upper	
BW (kg)	0.632	0.248	1.016	0.001
GA at birth (weeks)	0.058	-0.010	0.126	0.09
Body weight at day 14 (kg)	0.765	0.374	1.155	<0.001
Protein deficit (g/kg)	-0.09	-0.003	0.040	0.09
Calorie deficit (kcal/kg)	-0.001	0.00007	0.002	0.037
GA at discharge (weeks)	-0.134	-0.198	-0.071	<0.001

Abbreviations:
Birth weight: BW; gestational age: GA; confidence interval; CI

The next step in the analysis was concerned with possibility of that there were correlations between some predictors. I looked at correlations between BW, GA, body weight at day 14, and GA at discharge. As expected, there were strong positive correlations between GA BW; body weight at day 14 BW; body weight at day 14 and GA. Weak negative correlations were observed between GA at discharge and BW; GA at discharge and GA at birth and GA at discharge and body weight at day 14 (Figure 2.43 - Figure 2.48).

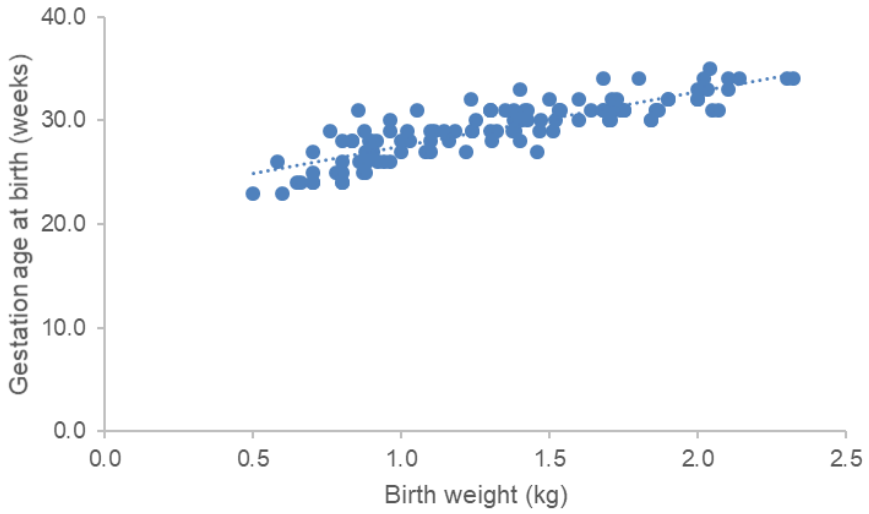

Figure 2.43 The association between gestational age at birth (weeks) and birth weight (kg)

Pearson correlation coefficient (r) = 0.953; p = 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

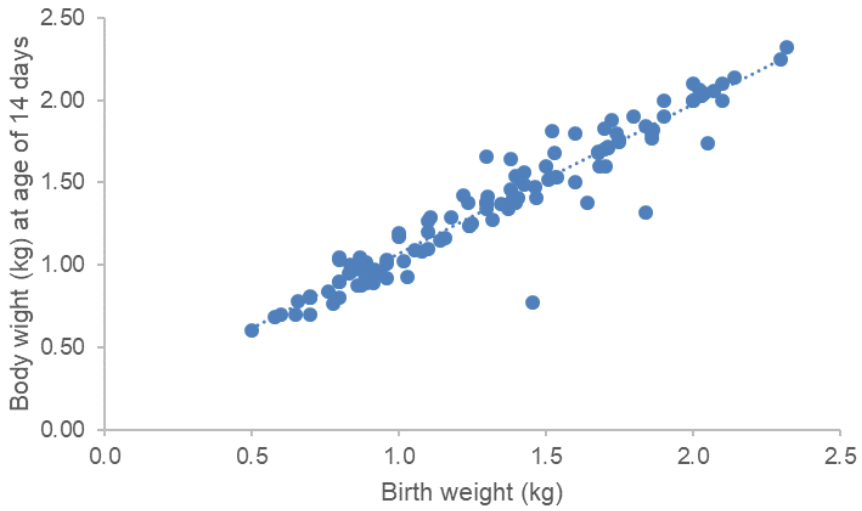

Figure 2.44 The association between body weight at day 14 (kg) and birth weight (kg)

Pearson correlation coefficient (r) = 0.958; p = 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

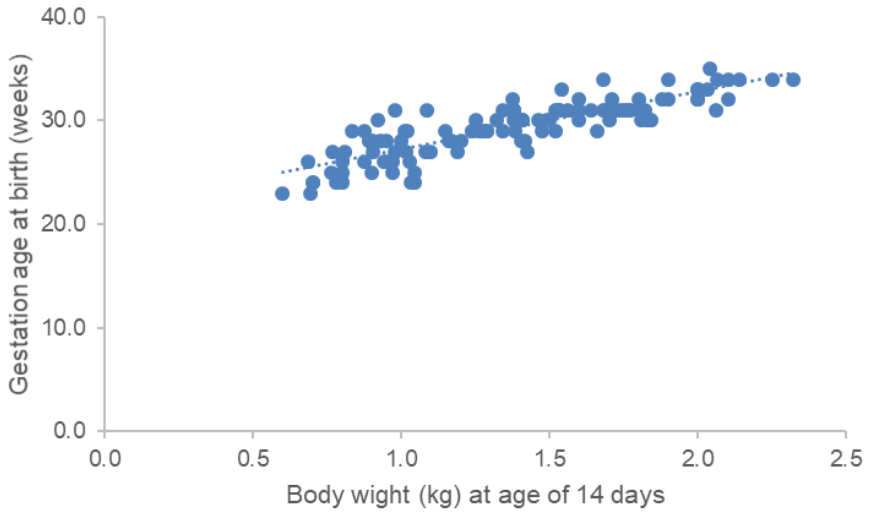

Figure 2.45 The association between gestational age at birth (weeks) and body weight at day 14 of life

Pearson correlation coefficient (r) = 0.842; p< 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

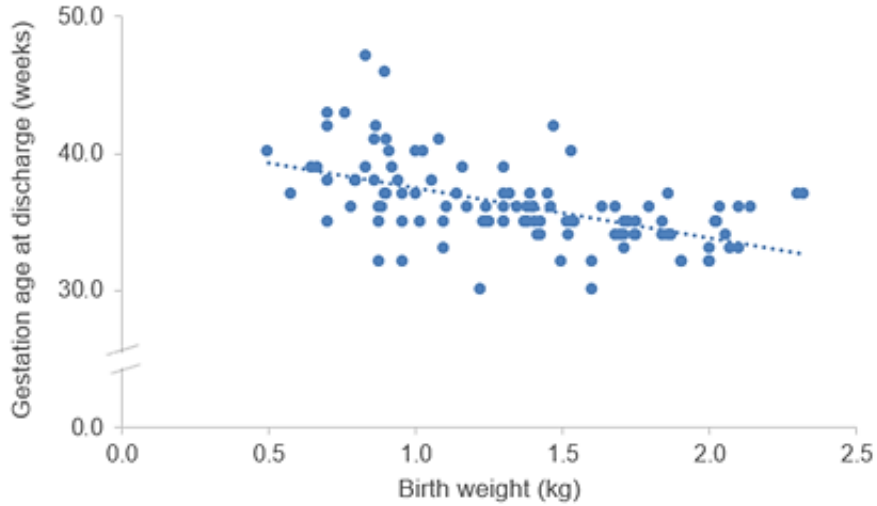

Figure 2.46 The association between gestational age at discharge (weeks) and birth weight (kg)

Pearson correlation coefficient (r) = -0.495; p< 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

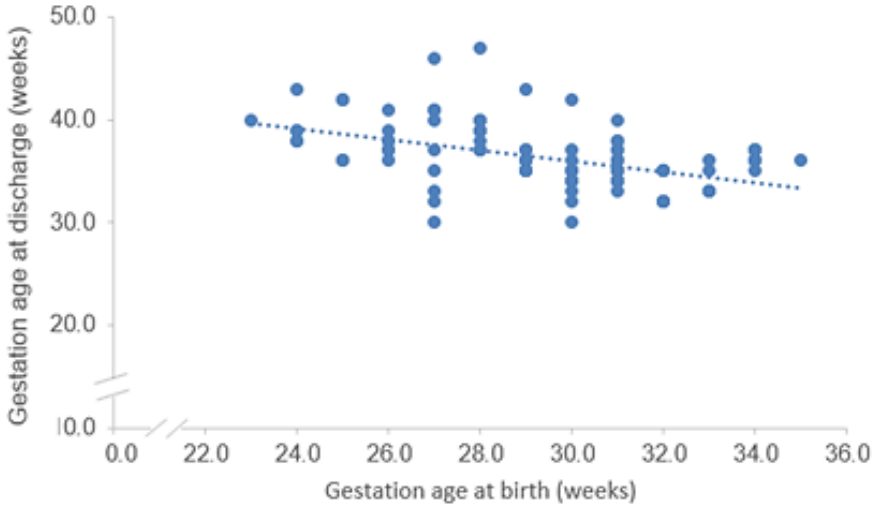

Figure 2.47 The association between gestational age at discharge (weeks) and gestational age at birth (weeks)

Pearson correlation coefficient (r) = -0.425; p< 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

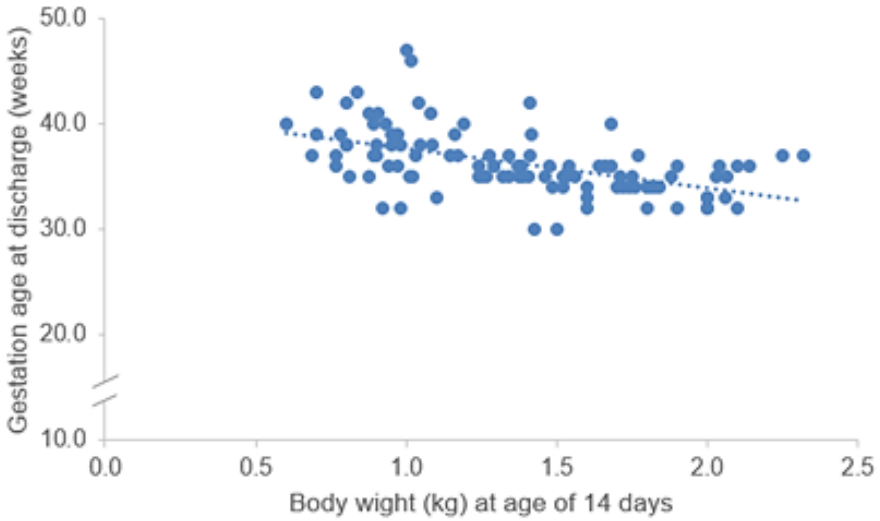

Figure 2.48 The association between gestational age at discharge (weeks) and body weight at day 14 of life

Pearson correlation coefficient (r) = -0.466; p< 0.001
Each symbol represents an individual infant. Dotted line represents the linear fit of data

The predictive ability of the model at each step detailed in Table 2.5. Multiple linear regression was performed where WAZ scores were the dependent variable and the independent variables entered into the model were: body weight at day 14, GA at discharge and calorie deficit; only body weight at day 14 and GA at discharge were found to be significant predictors.

WAZ scores are 0.765 higher per 1 Kg increase in weight at day 14, having adjusted for GA at discharge. Also, the estimate WAZ scores are 0.134 lower per 1 week increase in GA at discharge, after adjusting for weight at day 14.

Table 2.5 The steps of regression modelling for predicting WAZ at discharge

Step 1: BW entered				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
BW (kg)	0.418	-0.037	0.874	0.072
Calorie deficit (kcal/kg)	-0.001	-0.0003	-0.002	0.19
GA at discharge (weeks)	-0.097	-0.168	-0.025	0.009

Step 2: Body weight at day 14 entered				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
Body weight at day 14 (kg)	0.418	-0.037	0.874	0.072
Calorie deficit (kcal/kg)	-0.001	-0.0003	-0.002	0.19
GA at discharge (weeks)	-0.097	-0.168	-0.025	0.009

Step 3: GA entered				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
GA	-0.029	-0.108	0.050	0.47
Calorie deficit (kcal/kg)	-0.001	-0.0008	-0.002	0.06
GA at discharge (weeks)	-0.139	-0.211	-0.067	<0.001

Step 4: Protein deficit entered				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
Body weight at day 14 (kg)	0.469	0.002	0.936	0.04
Calorie deficit (kcal/kg)	-0.0002	-0.002	0.001	0.74
Protein deficit	-0.014	-0.041	0.014	0.32
GA at discharge (weeks)	-0.094	-0.166	-0.022	0.01

Step 5: protein deficit removed				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
Body weight at day 14 (kg)	0.418	-0.037	0.874	0.072
Calorie deficit (kcal/kg)	-0.001	-0.0004	-0.002	0.19
GA at discharge (weeks)	-0.097	-0.168	-0.025	0.009

Step 6: Final model				
Variable	**B**	**95% CI**		**p-value**
		Lower	Upper	
Body weight at day 14 (kg)	0.488	0.046	0.931	0.008
GA at discharge (weeks)	-0.097	-0.168	-0.027	0.031

2.7 Discussion

2.7.1 Study 1

2.7.1.1 Summary of main results

The study included infants who had significantly lower birth weight and gestational age than the target population. Infants with low birth weight and low gestational age at birth are at high-risk, therefore, the finding could be generalise to the entire population of infants born ≤ 35 weeks gestation.

While the overall GA and BW were comparable between the groups, evolving trends in neonatal nutrition management were demonstrated in the current study. Comparing the nutritional practices from 2007 to 2014, there was a considerable increase in protein and

energy intakes from 2007 to 2014 for infants from neonatal units at the Nottingham University Hospitals. This increase was seen mainly in the first week of life.

There were improvements in calorie and protein intakes during the first week of life from 2007 to 2014, but nutrient intakes became below the recommendations (107) throughout the second week. In the former, increased nutrient intakes probably reflected the increased use of PN, whereas in the second week, lower intakes may have reflected the period of transition from PN to enteral feeding. Similar findings were reported by Hans et al (101), who reported that clinicians initiate PN and enteral feeding earlier and in a larger volumes than in the past (101). This may reflect the increased knowledge about recommended nutrition practices for preterm neonates.

The transition from PN to enteral feeding in preterm infants is a period where malnutrition may develop easily because of tapering off parenteral protein and energy intakes might not be compensated by enteral feeding (251). The transition phase was found to be most vulnerable to inadequate nutrition (252). Barriers to achieving nutrient goals during transition period include slow advancement in enteral feeding with a volume-based PN transition (239), may explain the current study findings. It has been observed that moving from “volume-based” transition protocol to “nutrient-based” transition protocol improves nutrient intakes and infants’ outcomes.

The nutritional practices, in the three groups, were associated with cumulative protein and calorie deficits when compared to international recommendations available since 2005 (107). Not surprisingly, protein deficits appear to be greater in infants born in 2007 compared to infants born in 2012 and 2014, as infants born in 2007 received lower amounts of protein. The change in nutrition practices could be explained by the fact that in the traditional nutrition practice, for extremely premature and ill preterm infants such as whom with respiratory distress syndrome, PN and enteral feeding were often delayed. Commonly, protein are not given immediately after birth, and when provided, they are given in low amounts and then increased slowly, taking several days to reach the required amount (70). In addition, there

were several causes for delayed feeding such as fear of NEC, respiratory distress syndrome and need for mechanical ventilation, (123).

Advances in postnatal interventions during the past decades have resulted in dramatic improvement in nutritional practices. This improvement has been demonstrated in the current study and previous studies (101, 116).

To determine the current nutritional practices for the PN and enteral feeding infants preterm and to compare nutritional practice differences according to levels of care, further data were collected from neonatal units across the two Neonatal Networks.

2.7.2 Study 2

At the inception of this study, Tsang recommendations (107) was the main source of relevant nutrition guidelines. As the nutrition recommendations changed during the past decade, to a new international guideline, Koletzko recommendations (106), published based on more recent evidence. This study designed to compare the current feeding practices against the two sets of recommendations and to see how the actual intakes achieved compared with the most recent guidelines.

The neonatal units that participated in this study were classified according to the level of care they provide. SCUs provide level III care; LNUs provide level II care and NICUs, provide level I intensive care. The median (IQR) GA of infants from these units was: SCUs: 32 (31, 34); LNUs: 30 (29, 31); NICUs: 26 (25, 28) weeks.

The current study demonstrated that nutrient intakes meeting recommended intake remain difficult in some neonatal units across the two networks. During the first week of life, protein and energy intakes were less than that recommended. After the first week of life, the recommended protein intakes were achieved for infants from individual SCUs, LNUs and NICUs. Inevitable cumulative protein and calorie deficits resulted and this was associated with and not excessive weight gain and head growth at hospital discharge.

2.7.2.1 Current nutrition practices

2.7.2.1.1 PN

Reflecting health care organisation in these neonatal networks, all infants born < 30 weeks gestation had PN. None of the infants from SCUs has PN, whereas 15% infants from LNUs and 70% infants from NICUs received PN on the first day. The current study showed a higher proportion of infants from NICUs had PN on the first day of life compared to a Canadian study (253) which evaluated nutritional intake during the first week of life in very low birth weight infants (VLBW). Only 28% of the study population had PN on the first day of life (253).

Extremely preterm or low birth weight (LBW) infants should usually receive PN soon after birth so that the nutritional needs can be achieved early in neonatal life (254, 255). Nonetheless, many neonatal units delay the initiation and rate of progression of energy and macronutrients delivered to this group of infants (119). Although there was a high proportion of infants, in the current study, who had PN on the first day of life, particularly those infants from NICUs, there was a delay in PN commencement of two days or more for many of the infant required PN. The causes of delay may include acute neonatal illness, concerns over tolerance of parenteral macronutrient (protein, carbohydrate, and lipid) intakes (12), desire to minimise morbidities related to fluid overload such as CLD and PDA (90) or there was no central access for PN. Furthermore, catheter insertion may be associated with complications such as thrombosis, sepsis, catheter malfunction and fluid extravasation. Other factors were identified in the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) survey (3); an observational study of PN use conducted in the UK. This report showed that even though the advisors judged that the indication for PN was appropriate in the majority of neonatal units, there was unreasonable delay in recognising the need for PN in 28.2% of the cases. Most of the delays were in the order of a few days from birth. However, in some cases, the delays were up to a week or more during which inadequate nutritional support had been provided. While a high proportion (162/248 (72%)) of infants included in the NCEPOD study (3) had PN started within a day of the decision to start, there was a delay of two days or more in some

cases (14/248 (6%). Reasons for these delays included PN not being available at the weekend, difficult intravenous access and awaiting stabilisation of the patient (3).

2.7.2.1.2 Enteral feeding

There has been a shift in neonatal practice towards an earlier and more rapid use of enteral feeding in preterm infants compared with results of similar published previously (70). The Embleton et al. study (70) showed that enteral feeding was commenced at a mean (±SD) of 3 (±1) days of life, whereas in the current study enteral feeding started sooner. The median (IQR) day of starting enteral feeding, in the current study, varied between infants from the three designated types of neonatal units was SCUs: 2 (1-2); LNUs: 2 (2-3); NICUs: 3 (2-4) days of life. Similar findings were observed in a study conducted in Australia (256) in which, infants received enteral feeding on the median (IQR) 1 (1-3) day of life.

Enteral feeding is often delayed for several days in extremely preterm, LBW, and infants with IUGR (123, 257). This may partially explain the findings with 24% (29/119) of the study population being extremely preterm and 29% (35/119) extremely low birth weight (ELBW). Given that the controversy exists regarding the timing and speed of enteral feed advancement and the associated risk of feeding intolerance and NEC (discussed in Chapter Three) could explain the delayed enteral feeding in the current study. Delayed enteral feeding could be related to decision making in considering enteral feeding. In the NCEPOD report (3), approximately fifth of the responders thought that inadequate consideration had been given to enteral feeding.

2.7.2.1.3 Nutritional practices and their consequences

There were inter-site differences in initiation of protein and calorie delivery in the 12 neonatal units participated in the study. According to the available recommendations, protein delivery can be initiated within the first 24 hours of life, and it is safe, even in very premature infants (106, 107). The current study demonstrated that a large proportion (70%) of infants from NICUs received protein and calorie on the first day of life, whereas, nearly one-third of the infants from SCUs and LNUs had protein and calorie on day one of life. Generally, the amount

of the nutrients delivered fell below the recommendations (107). The median (IQR) square root of protein intakes of SCUs: 0 (0-0.3); LNUs: (0-0.1); NICU: 0.5 (0-0.9) versus the recommended 1.41 g/kg/day and the Median (IQR) square root of calorie intakes on the first day of life were different between the units from different designation (SCUs: 4 (3-5); LNUs: 4 (3-5); NICUs: 5 (4-6) kcal/kg/day) versus the recommended 7.42 kcal/kg/day. However, the advancement of protein and calorie intakes approximated to the recommendations in some neonatal units by the end of the second week. This might be explained by nearly two-thirds of the current study population tolerating an enteral intake of ≥150 mL/kg/day before 14 days of life. Achieving these volumes allows the achievement of recommended nutrient requirements from fortified human milk, preterm formula or both (258).

Given that heterogeneity of population, summary measures of protein intake, and the time point of reported protein intakes in previous studies, it is difficult to compare the protein attainment in the current study. In spite of this limitation, our cohort seems to have received protein intakes higher than has been reported in many other studies (120, 253, 259). In a cohort study (120) included 14 institutions, studied infants born at 23 to 27 weeks gestation, the median (IQR) protein intakes on day one was protein: 1.0 (0-1.0) g/kg/day and calorie: 26 (25-26) kcal/kg/day. The amount of nutrients delivered increased. By day seven of life nutrient intakes were: protein: 3.5 (3.3-3.9); calorie: 79 (70-84) kcal/kg/day) and by day 14 of life nutrient intakes were: protein 3.4 (3.5-3.6) g/kg/day calorie: 92 (84-92) kcal/kg/day. More recently, another study of infants born 30 to 33 weeks gestation from 29 NICUs, the average protein intake was 1.1 (± 0) g/kg/day on day one and increased to 2.9 (± 0.9) g/kg/day on day 7 of life and the calorie intake 94 (± 18) on day 7 of life (259). Similarly, in another study (253), infants <1500g received a median of 3.5 g/kg/day of protein by day 7, however, neither IQR nor the upper and lower limits were reported in the study (253).

In addition to the clinical and practical factors that may affect the initiation of protein, one plausible reason for this variation could be the difference in the method of estimation of the macronutrients of human milk during the first few weeks postpartum and how researchers have defined the first day of life. For example, Ng et al. (253) proposed that the estimated

protein and energy contents of human milk during the first seven days postpartum as high as protein: 2.4 ± 0.3 g/dl and calories: 63 ± 4 kcal/dl (253). Whereas, Iacobelli et al (259) suggested that the mean nutrient contents of human milk was: protein: 1.4 g/dl and calories: 64 kcal/dl. In comparison, the estimated nutrient contents of human milk used in the current study were protein: 1.8 g/100 ml and calories: 70 kcal/100 ml calories (247). However, the values we used for nutrient concentrations in human milk in the first 2 weeks of life are virtually identical to those Gidrewicz and Fenton (260) recently reported. These differences could partially explain the variation of protein intake as we found that lower amounts of protein were delivered in the current study.

Variations in the timing and the amount of nutrients delivered to infants have also been observed between individual clinicians working in the same neonatal unit adhering to the same nutritional guideline (261). This may be due to varying degree of reluctance of physicians in regards to fluid overload, intolerance to PN and vascular catheterisation issues (3).

Low nutrient intakes, particularly in the first few days of life, might be related to other factors. For instance, infants' medical condition. Compared with more critically ill, less critically ill preterm infants are significantly more likely achieving protein and energy recommendations on any given day (78, 262). Critically ill infants may have a reduction in the volume of PN while other intravenous medications were given such as antibiotics that may take some time and fluid allowance to deliver. Thus, PN volume would be less than the calculated requirements were charted over 24 hours. Similarly, in the case of metabolic abnormalities such as metabolic acidosis. In this case, the amount of protein delivered might be reduced in order to compensate the acidosis by adding carbohydrates. Unfortunately, ascertain the reasons for suboptimal nutrient intake is not within the scope of the current study.

A gradual increase or a delayed commencement of nutrient delivery will inevitably be associated with considerable deficits during the first few days of life. Cumulative nutrient deficits may continue to increase during hospital stay (70). The current study showed that cumulative deficits developed were not replaced even when the recommended nutrient intakes

were achieved in some individual units. These deficits have proven to be very hard to correct and efforts should be made to avoid their occurrence (263).

Given that different sets of recommendations were used to assess nutritional management in the different studies, it is difficult to compare the cumulative nutrient deficits in the current study. However, many studies (70, 120, 253) were consistent in the fact that the nutritional practices did not meet the recommendations and this was associated with cumulative nutrition deficit before hospital discharge.

The current study showed that cumulative protein deficits were markedly lower in infants of lower GA, which agrees with previous research (115). Infants of later GA received lower amounts of protein compared to lower GA infants (115). This could be explained by the fact that lower GA infants are more likely to be given PN. For example, the Nottingham early care guideline (264) emphasises the importance of early commencement of PN for extremely preterm (<30 weeks).

The variation in intakes may also be related to PN duration. Moderately preterm babies may be different from those extremely preterm. Moderate preterm may have limited nutritional intakes, especially during the transition from PN to enteral feeding dependent, when PN volumes are weaned with advancing enteral feeding (265). Thus, suboptimal nutrient intakes usually occur during this time (251).

2.7.2.1.4 Effect of nutrients intake on growth

There were significant differences in growth outcomes at discharge, even for infants from different units of the same level; therefore, it was important to investigate the factors that may contribute to these outcomes.

Regression analysis was used to understand whether WAZ scores could be predicted based on BW, GA, body weight at age of 14 days, GA at discharge, protein and calorie deficit among the study population. WAZ scores increased with an increase in body weight at day 14 of life and decreased with increase in gestation age at discharge. These variables have significant

effects on WAZ scores at discharge even when controlled for other confounders. A higher attained WAZ scores for infants discharged from SCUs and LUNs compared to infants discharged from NICUs. These findings may be explained, in part, by larger body weight at day 14 of life and smaller GA at discharge achieved by infants from SCUs and LNUs compared to infants discharged from NICUs. It is noteworthy that differences in WAZ scores could not be explained by protein or energy deficit. This could be because the study was underpowered. . Nonetheless, Yang et al.(266), showed no relationship between either protein or calories on growth outcomes at 2 years corrected postnatal age. In contrary, Embleton et al. (70) found that the cumulative energy deficit could explain variation in z-scores and cumulative protein deficit had no significant effect. However, it was not clear on which day of life infants received protein and energy. It has been observed that early provision of balanced protein: energy supplements on the first day of life may help to prevent early loss of body protein stores (267-269) and increasing protein intake increases protein retention (270). Furthermore, although Embleton et al. (70) demonstrated significant variation in z-scores related to calorie intakes, the p values for differences in nutritional status were not presented.

Protein and energy deficits could be directly related to growth outcomes, however, the current study showed that the variation in growth could not be explained by nutrient intake. Non-nutritional factors, such as illnesses (78, 86) were also found to have a significant effect on growth outcomes. This is not surprising since illnesses may significantly affect nutritional status (78), increase nutrient requirements and utilisation.

An observational study (261) evaluating early protein in the first four weeks showed no correlation between nutrient intakes and growth at the age of 18 months. This could be because some babies in this study received very low protein intakes (0.5 g/kg/d) concomitant with low amounts of energy, delivered during the study period. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition guideline (ESPGHAN) (110) recommends ≥25kcal non-protein energy should be administered for each gram protein. This should provide a protein energy ratio that allows for synthesis of new tissue.

The current recommendations (106, 107) suggest that higher nutrient intakes would improve growth outcomes. However, higher doses of energy and macronutrients did not significantly enhance infants' growth, as shown in two recent studies (271, 272). Recently, the NEON (Nutritional Evaluation and Optimisation in Neonates) study (271) examined the effect incremental introduction of protein (Inc-AA; 1.5 g/kg/d on day 1, 1.9 on day 2, and 2.4 from day 3 thereafter) compared with immediate administration of the recommended daily intake (RDI) of 3.2 g/kg/d from day 1 thereafter (Imm-RDI) on growth outcomes at term age. The study showed that Imm-RDI of protein did not benefit growth outcomes. However, these findings could not be generalised as there were baseline differences between groups, such as sex and antenatal steroid use between the study groups. It has been observed that in preterm infants, boys appear to be much more sensitive than girls to poor postnatal growth (273, 274), and probably have different growth patterns/requirements. Furthermore, the mean week one energy: protein ratio was lower in the immediate group compared to the incremental group. Nonetheless, similar findings were reported in Balakrishnan et al.(272), who evaluated weight outcomes at 36 weeks postconceptional age from high dose parenteral protein 3-4g/kg/d advanced to 4g/kg/d by day 1 vs 1-2g/kg/d advanced by 0.5g/kg/d up to 4g/kg/d. It is possible that there are no significant effects of higher doses of protein on weight outcomes, but these findings may be because the two studies were underpowered and a larger number of infants are required to detect any effect. Furthermore, in the Balakrishnan et al. (272) study, there was a significantly higher proportion of SGA at birth in the intervention group and 4 infants from the intervention group had their protein dose reduced (50% lower than the proposed amounts). Once again, delivery of low amounts of energy: protein ratio may have the potential to influence growth in these two studies (271, 272).

The current study showed that different HCAZ scores were observed at the day of discharge. Interestingly, mean HCAZ scores were low for infants from units who received higher doses of protein and energy in the first two weeks of life. More alarming are reports showing that higher doses of protein may have a negative impact on head growth (271, 272, 275). The Balakrishnan et al.(272) study (described above) showed that the high protein group had lower

head circumference at 36 weeks CGA(CGA) than the low protein group. Similar findings were observed in the NEON study (271). Once again, the possible explanation of these findings is related to protein: energy ratio. Synthesis of new tissue needs energy. Therefore, provision of low protein: energy may have the potential to affect tissue synthesis, including brain tissue (276).

Similarly the study of Blanco et al. (277) assessed the effect of nutritional intakes on growth and neurodevelopment. Sixty-one infants were randomly assigned to starting 0.5 g/kg/d of protein in the first 24–36 hours and advanced by 0.5 g/kg/d to a maximum of 3 g/kg/d vs starting at 2 g/kg/d at enrolment and advanced by 1 g/kg/d to a maximum of 4 g/kg/d. The study showed lower MDI scores for children from the high protein group at 18 months, but the difference was no longer seen at 2 years corrected age. It is important to note that there was a high loss of follow-up (30%). Furthermore, lipid, glucose and minerals were given according to the nursing protocol as tolerated, but it was not clear if there were significant differences between the study groups, therefore the findings of this study cannot be confidently generalised. Furthermore, none of the identified trials reported sufficient power to detect this outcome.

Opposite findings were reported in the SCAMP (Standardised, Concentrated with Added Micronutrients Parenteral) study (278), in which PN containing a maximum protein of 3.8 g/kg/day and lipid 3.8 g/kg/day, was compared to maximum protein 2.8 g/kg/day; lipid 2.8 g/kg/day. An increased change in head circumference at 28 days and 36 weeks corrected age was observed in the intervention compared to the control group. Once again, variations in baseline criteria such as more SGA being included in the SCAMP group compared to control may have influenced the outcome. Infants who were born with growth restriction have often been reported as benefitting more from nutritional interventions than AGA infants (76).

Taken together, these studies suggest that starting at >2 g/kg/d parenteral protein may not provide an incremental benefit when lower amounts of energy are provided and achieving a target of 4 g/kg/d protein incrementally after birth may be a safer approach.

2.7.3 Strengths

To my knowledge, this is the first study that has evaluated how closely current practices approximate energy and protein recommendations from recently published recommendations. The study group was a representative sample of a heterogeneous population of preterm infants cared for in three different levels of the neonatal care units in the Midlands of England. Detailed instructions regarding the completion of the standard proforma were given to all participating units, which should minimise the risk of incomplete/inaccurate data collection. Furthermore, anthropometric measurements might be site-specific, but standard use of ISO equipment should reduce inter-site variations.

2.7.4 Limitations

There are several limitations that should be acknowledged. I looked for preterm infants who might need PN and I looked at their intakes that could be achieved, were or were not achieved by the study 2 population. Therefore, I cannot be certain that those babies were truly representative. As in many research studies involving human populations, one of the limitations lay in the collection of an adequate number of samples to reach substantial clinical evidence. Another limitation could be sampling errors, which may occur when the chosen sample does not accurately reflect the whole population that is studied. The error occurs when inaccurately includes or excludes potential participants (1). A detailed protocol was sent to the individual units (detailed in Section 2.1); nonetheless, sample selection could be biased.

Due to the nature of observational studies, the current study cannot determine the causation of suboptimal macronutrient and total energy intakes, such as limited central line access, the presence of metabolic abnormalities, volume boluses to support blood pressure, drug infusions and maintenance of vascular access (78, 253), which may result in administration of non-nutritional fluids.

If nutritional data in this study had been taken for a longer period of time a significant difference between the neonatal units may have been reached, for instance, the protein deficits in one of the NICU appear close to 0 (no deficit). If the sample size of infants studied

was larger, it is possible that a greater number of infants who remained in hospital for longer periods of time would be studied to give more results at later time points.

Although the nutrition intake measurements were corrected for time of birth, these findings are likely to be limited by the fact that delay in commencing PN may occur whilst an infant was in a delivery room. This is usually the case when an infant needs immediate care; therefore, PN cannot be commenced promptly.

2.7.5 Conclusions

The novel contribution of this study is to assess how close nutrition practices were to current recommendations. In addition, the available data facilitated the analysis and interpretation of growth outcomes related to these nutritional practices.

Study 1 showed a trend towards improved protein and energy intakes in the first week of life from 2007 to 2014. Despite the early introduction of enteral and parenteral nutrition, by the end of the second week of life, energy and macronutrients delivery did not meet current recommendations. From these findings, one could conclude that although large energy and macronutrient deficits remain, there have been significant improvements in the delivery of nutrition in preterm infants than in the past.

Study 2 showed that body weight at day 14 and GA at discharge are independent predictors of WAZ at discharge. Although the data showed that energy and protein deficit were not predictor of weight outcomes, a role for it in protein deposition cannot be ruled out.

The current study demonstrated that nutrition regimes take time to establish; therefore, infants develop nutritional deficits before achieving the recommended intakes that required to support their growth and development.

Adequate nutrition is fundamental for good growth (110). Nonetheless, the administration of the required volume of PN can be challenging, particularly in the first few days of life. It is important to determine the correct nutritional and fluid needs, provide appropriate PN

constituents, obtain adequate vascular access and undertake careful biochemical and clinical assessment (110).

In this study, the Tsang (107) and Koletzko (106) recommendations were used for calculating the deficits. These guidelines are based on the nutrients needed to achieve intra-uterine growth rates, and they are not entirely based on high-quality evidence (as described in Section 1.6). Further, adequately powered research studies with a specific focus on protein: energy ratios may, therefore, be valuable to provide such evidence.

It would be beneficial to ensure that each infant has a nutrition plan from the first day of life. Milk feeds should be started as soon as possible and if not, PN should be started. In addition, reviewing nutrition status on daily bases by the medical team may have a positive effect on nutrition practice and ensure that feed increments and parenteral regimens are in keeping with the guidelines, as previously reported (3).

Given the reported relationship between nutrition during neonatal life and long term growth and neurodevelopmental outcomes (231, 261), a prospective study with longer follow up and calculation of nutritional intakes throughout the hospital stay should be performed with relevant anthropometric and developmental assessments to better understand the impact of early life nutrition on the growth and development in this specific group of infants.

Chapter 3: Exploring the current management of infants diagnosed with AREDF, using the national neonatal database

3.1 Background and rationale

Physiological studies on neonates with absent or reversed end-diastolic flow (AREDF) in the umbilical artery (UA) have shown persistent flow abnormalities in the superior mesenteric artery during the first few days of life (130, 279, 280). Hence, the reduced intestinal blood perfusion during early neonatal life provides a rationale for a modest delay in enteral feeding. On the other hand, there is little, if any, evidence that this delay is beneficial, and it might further compromise the nutrition and growth of IUGR infants with AREDF in the UA (9).

Premature birth and growth restriction with abnormal blood flow in the UA increase the risk of developing necrotising enterocolitis (NEC) (126) (Section 1, 1.4.1). NEC is multifactorial; the disease affects 90% of infants who have received milk feeds before NEC develops (281).

In current clinical practice, infants receive 'modern' perinatal care including exposure to antenatal corticosteroids, exogenous surfactant, early nutritional support and other interventions have improved outcomes and reduce death in preterm infants (282).

Early PN, within the first 48h, is becoming the standard of care for the low birth weight (LBW) infant in many Neonatal Intensive Care Units (NICUs) (116). Most organisations caring for this population have developed their guidelines for nutrition management, and nutrition practices vary widely (3). However, to my knowledge, there are no widely accepted guidelines for feeding IUGR preterm infants whose antenatal Doppler measurements are abnormal.

In respect of enteral feeding, early (≤5 days of life) enteral feeding of infants with IUGR infants has been suggested as a strategy to prevent complications of prolonged PN and enhance early achievement of full enteral feeding (140, 142). Early commencement of enteral feeding has been shown to improve the clinical outcome with no additional increase in NEC (9, 89, 139, 142). However, some of these trials were poorly powered to assess NEC (9, 139).

Limited information are currently available regarding the effect of early versus delayed introduction of enteral feeding on feeding intolerance or NEC in IUGR infants with abnormal antenatal Doppler studies (289). Additionally, conflicting results have been shown in clinical studies assessing enteral feeding in this high-risk group (9, 61, 142).

In the absence of accepted standards for feeding preterm infants with IUGR and AREDF, the present study aimed to explore the current management of infants diagnosed with AREDF, using the national neonatal database (Badger.net). This study aimed to identify current PN and enteral feeding practices, in terms of the onset of PN and enteral feeding, the duration of PN and the time needed to achieve full enteral feeding. It also evaluated the change in feeding practice since the publication of the Abnormal Doppler Enteral Prescription Trial (ADEPT) (described in 1.8.2) (9) to assess the impact of the trial on clinical practice.

Evidence exists (283, 284) to suggest that centres involved in trials are more likely to change their clinical practice in general. Sites with high RCT enrolment may have approaches to patient care that consequently leads to better outcomes. These approaches may include more or better staffing resources, an overall greater ability of the site to assign appropriate treatment and provide appropriate care. Given that, RCT care is subject to trial protocols, which involve the evaluation and monitoring of patients this is likely to influence clinician behaviour. Therefore, the current study also evaluated the change in feeding practice in hospitals who did or did not recruit to ADEPT (9).Based on the objectives of the current study and the timeline of data collection, a descriptive, quantitative, observational study was conducted using a database-based study design.

3.1.1 History of neonatal databases

For more than 25 years, neonatal data have been collected in regional databases. The availability of national neonatal electronic data is a relatively recent phenomenon in the UK as well as internationally (285). The use of electronic patient records across the UK neonatal units started in 2004 as a regional initiative. Subsequently, the platform, Badger.net database, expanded nationally (285). The database is now used by many neonatal units to record

activity and plan services (285), used for audits (286), service evaluations (287) and quality improvement projects (288). Badger.net can link datasets related to healthcare. In other words, while connecting to all other Badger.net records available for the same patient in other units, which allows units real-time, contemporaneous recording of all daily events (289). The UK has also established an early reputation for producing quality database-based research through the publication of some studies that evaluated the validity and quality of electronic data (290).

3.1.2 Badger.net neonatal database

Badger.net neonatal database is a single record of care for all babies within neonatal services, which is designed to support full paperless working within a neonatal unit (289). The platform is currently in use in over 250 hospitals throughout the United Kingdom, New Zealand, and Australia (289). The Badger.net is provided by Clevermed Ltd (Level 6, Edinburgh Quay, 133 Fountainbridge, Edinburgh, EH3 9QG, www.clevermed.com). Clervermed is an authorised NHS hosting commercial medical software company that provides a platform stored on a secure server. Badger.net contains records for all admissions to UK neonatal units.

Badger.net database is designed to collect information on babies during their neonatal unit admission and generates a discharge summary. The database has number of key features, such as the platform allows real-time, simultaneous recording of all daily events ad hoc event forms for events during the admission, interfaces to patient monitors with real-time trend data recording fluid charting and full line management, results in interfaces and charting (289). Very few centres utilise all benefits of the database system however.

Databases are mainly used to support health carers (291). Therefore, records may not be structured in a way that facilitates the research process. However, many features have been implemented in the Badger.net database that would make it more applicable for research use (289). Databases including the badger.net database have number of key features (289), such as:

- databases provide the user with some options where the same information can be stored. Therefore, researchers can find the data of interest in different areas
- information entered in defined fields or could be found as a structured list of medical terms instead of being entered as free text. The use of medical terms decreases variability in patients' information (291)
- abbreviations are clear to users because a data dictionary that documents each element in the database with descriptions is provided.

3.1.3 A dvantages and disadvantages of database-based study design

The use of database-based study design has many advantages. The use of the database is considered to be a promising step towards reducing research costs, increasing patient-centred research and expediting the rate of new medical discoveries (292). Database-based studies are less expensive and less time-consuming compared to studies that use primary data, especially when data can be downloaded from a database as files that are compatible with analysis software. The use of downloads provides more time to analyse and interpret the results (245). Also, the size of databases makes research on low-incidence diseases logistically impossible to study in any other way (303). The database also provides quick access for researchers and reduces the time and expenses required to recruit target populations and search for controls, which provide a unique opportunity and source of data for the academic community (293). Database-based studies also allow gaining insights into the medical care, status and outcomes of a diverse population including vulnerable populations that researchers ordinarily may have trouble recruiting, such as infants born extremely preterm. Therefore, the data are representative of actual patients.

Moreover, because the data already exist, therefore, researchers can evaluate the data before using them for research (294). Therefore, the time spent to evaluate any potential data source is time well spent because rejecting unsuitable data early on can save a considerable amount of wasted time later. Electronic data ensure privacy in terms of who has control of what is recorded in the record, who has access, who should have access and for what purposes. Badger.net database was found to be a suitable, convenient and cost-effective data source that could be used to answer the current study's research question and to meet the objectives.

On the other hand, one of the drawbacks is data extraction, which is a key issue in using information from a database for research studies (291). Nonetheless, on Badger.net, this issue has been considered. There are basic options for searching for specific information in the Badger.net database. There are pre-determined queries, by which users select a query option preloaded in the software. These queries ease the use of the dataset. For instance, one type of query can produce a report that lists patients, for instance by diagnoses, admitted during a certain period. Also, labelled 'simple customisable queries' are preloaded in the software, for which users can enter input into the queries to generate reports. For example, a user may select a patient by gestational age who was born within a specific start date and end date.

At times, the storage location of data may also limit the use of database for research. This was not the case when the Badger.net database. In the Badger.net database, data are stored offsite by Clevermed (289); therefore, data can be accessed by users remotely over a secure network. However, offsite users require authorisation to access the database.

Generally, the advantages of basing research on Badger.net database include:

- the use of medical information collected by individual practices across the UK provides a representation of the local population, and the geographical coverage of the databases also allows for broad generalisations within the UK population
- many neonatal patients have complete data available since 2007, providing a good source of longitudinal data for researchers
- the size of databases allows for conducting research on low-incidence diseases logistically impossible to study in any other way
- the electronic database provides quick access for researchers and reduces the time and expenses required to recruit target populations and search for controls
- electronic recording of medical data facilitates the ability to target specific vulnerable populations that researchers ordinarily may have trouble recruiting, such as infants born preterm
- database ensure privacy in terms of who has control of what is recorded in the record, who has access and who should have access and for what purposes.

3.1.4 Hypotheses

The hypotheses were:

- feeding practices have changed for IUGR infants with AREDF in the UA since the inception of the database in 2007 and that these changes are identifiable in time to the presentation and publication of the ADEPT results
- there is an improvement in the use of PN in IUGR preterm infants with AREDF in the UA
- early enteral feeding in IUGR infants with AREDF does not increase the risk of NEC
- change in nutritional practices is associated with improved growth outcomes of IUGR preterm infants with abnormal antenatal Doppler studies
- nutrition practices have changed for IUGR infants with AREDF in the UA in the ADEPT Hospitals in comparison to the non-ADEPT hospitals.

3.1.5 Aims

This study aimed to:

- review and evaluate current PN and enteral feeding practices and the impact of research evidence on the care of preterm infants
- evaluate evidence-linked changes in feeding practice since the publication of the ADEPT results (9) to assess the impact of the trial on clinical practice in neonatal units
- evaluate evidence-linked changes in feeding practice in the ADEPT and the non-ADEPT hospitals

3.1.6 Outcome measures

3.1.6.1 Primary outcome measures

- Age, in days, at which enteral feeding is commenced and age at which full enteral feeds are sustained for 72 hours is achieved
- age in days at which parental nutrition (PN) was commenced and duration of PN
- necrotising enterocolitis, using modified Walsh criteria, stage I, II or III (Modified Bell's Staging).

3.1.6.2 Secondary outcome measures

- the type of milk feeding
- confirmed sepsis
- cholestasis jaundice
- gastrointestinal perforation, surgery or both
- continuous supplemental oxygen at 36 weeks postconceptional age and at hospital discharge
- death before hospital discharge
- duration of hospital stays
- duration of intensive care (IC)
- duration of high dependency care
- duration of special care stay

- change in infant's anthropometric measures (weight and head circumference) from birth to discharge.

3.2 Methods

3.2.1 Study design and data source

Multi-centre, 2 x 2 analysis evaluating two comparisons. The first part compared outcomes of IUGR infants over two epochs, before and after the presentation and publication of the ADEPT study (9). The second comparison evaluated changing practices in the ADEPT hospitals versus the Non-ADEPT hospitals.

Data were obtained from the Badger.net national neonatal database.

3.2.2 Data quality

The Badger database has been used to assess whether infants admitted to neonatal units in England, Scotland and Wales receive consistent, high-quality care in relation to the National Neonatal Audit Programme (NNAP) measures. These measures are aligned to assess performance against a set of professionally agreed guidelines and standards and used to ascertain areas for quality improvement in neonatal units in relation to the delivery and the outcomes of care (286). From 2010, the NNAP project team have produced quarterly reports to provide regular updates on completeness and adherence to the NNAP standards of data on the Badger system. Data validation studies were carried out as part of data quality assessment to determine agreement between the database and medical notes (295). The annual report showed that data completeness for the majority of the NNAP audit measures is at an extremely high level and provide a trusted source of information (295).

3.2.3 Setting

The study involved twelve neonatal units. Of these, five were neonatal units in England and Wales from units who recruited to the ADEPT study and seven were neonatal units in England and Wales and Scotland who did not recruit to the ADEPT study.

3.2.4 Study population

3.2.4.1 Inclusion criteria

The inclusion criteria for the eligible patients were:

- born at or less than 34^{+6} weeks gestation, and
- small for gestational age (birthweight < 10th centile for gestational age, using a table of eligible birth weights adapted in the ADEPT study (Table 3.1) (7, 8), and
- abnormal antenatal Doppler studies are comprising AREDF in the UA.

Table 3.1 Table of eligible birth weights

An infant is eligible if their birthweight is < 10th centile for week of gestational age at birth, adapted

Gestational age range		**Birth weight (g)**	
Weeks/days	Weeks/days		
Lower	Upper	Male	Female
34+4	34+6	<1978	<1908
33+4	34+3	<1802	<1723
32+4	33+3	<1622	<1548
31+4	32+3	<1454	<1382
30+4	31+3	<1299	<1231
29+4	30+3	<1159	<1093
28+4	29+3	<1033	<970
27+4	28+3	<919	<861
26+4	27+3	<814	<760
25+4	26+3	<718	<666
24+4	25+3	<626	<577
23+4	24+3	<537	<491
22+4	23+3	<450	<406

3.2.4.2 Exclusion criteria

Infants were excluded if they had any of the following criteria:

- died within the first 72h
- major congenital abnormality, including a known chromosomal abnormality
- twin-twin transfusion
- intrauterine transfusion or exchange transfusion

- rhesus isoimmunisation
- significant multi-organ failure

3.2.5 Process

Data were extracted from the Badger.net database in an anonymised format. The participating centres provided an anonymous data download or access to download the anonymised spreadsheet from their unit. A schematic diagram of constructing the study cohort illustrated in Figure 3.1.

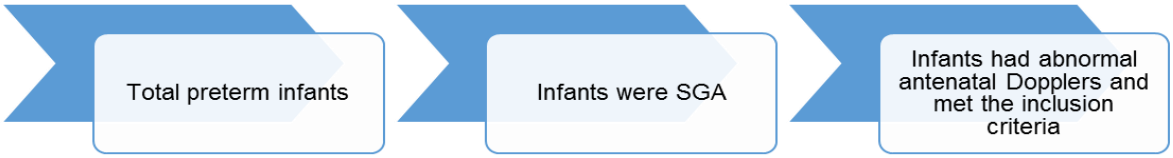

Figure 3.1 Summary of building the study cohort

SGA: small for gestational age

The study population was comprised of neonates who were born between 1st January 2007 and 31st December 2015. Data before 2007 were not included because of the small number of units contributing to the Badger.net database at that time. Data regarding the infant's stay in any neonatal unit and including the day of discharge to home were collected. Data including enteral feeding history, PN received and other interventions and outcomes were also collected. Important missing data that were required for the study analysis were collected from nursing charts, fluids and feeding or the discharge letter, where available.

Information collected for each infant included:

- birth weight (BW)
- gestational age (GA)
- gender
- age, in days, when parenteral and enteral feeding started
- duration of PN
- the day at which full enteral feeding was achieved and sustained for 72 hours (full feeding defined as the time required to attain sufficient feed volume leading to discontinuation of PN)

- type of initial feed milk (mothers' milk, donated breast milk, or infant formula milk)
- ventilation status
- NEC episode (was diagnosed at surgery, or by using key clinical and radiographic criteria)
- bronchopulmonary dysplasia (BPD) defined as oxygen dependence at 36 weeks gestation
- confirmed sepsis defined as at least one episode of positive blood or/and CSF culture during the episode of care
- GIT perforation/surgery
- cholestasis
- patent ductus arteriosus (PDA) treated by medical/surgical intervention
- type of milk at discharge
- anthropometric measurements at discharge
- oxygen dependency at discharge
- length of hospital stay (calculated as the sum of the number of days since birth until death or hospital discharge) and
- duration of IC, HDC, and SC in running days.

In addition, information on any serious events was obtained, such as all deaths and any severe central venous line complication, such as cardiac tamponade, or major vessel thrombosis.

3.2.6 Ethical considerations

Although ethical issues relating to the study were not envisaged as anonymised data were used, approval for this study was obtained from the Medical School Research Ethics Committee (REC) at the University of Nottingham (Ref: M16042015 SoM CHOG BADGER: Appendix 8.4). An ethical amendment was obtained on 19 Jan 2016 to permit the data collection to be extended to include 2015, i.e. the study period was from 2007 to 2015 (Appendix 8.5).

Some neonatal units requested NHS research ethics approval, so additional approval was obtained from the North of Scotland Research Ethics Service (Ref: 16/NS/0040: Appendix 8.6).

3.2.7 Confidentiality

Anonymous downloads were held securely in line with UK data protection and confidentiality legislation. Medical information obtained as a result of this study were considered confidential. Participant confidentiality was further ensured by using identification code numbers to correspond to study data in the electronic files. Data generated as a result of this study were available for inspection on request by the Sponsor and the REC.

The confidential information were held on a password-protected laptop, provided by the University of Nottingham. The data were analysed, by the researcher, at the investigator's site at the University of Nottingham.

3.2.8 Data analysis

All statistical analyses were conducted by myself (using SPSS) v23 (296)) under guidance from a statistician (Dr Andrea Venn). Parametric values were described as mean (standard error of the mean (±SEM)) and non-parametric data presented as median (interquartile range (IQR)). To assess variance between the study cohorts, the t-test was used to compares the means of parametric data and Mann-Whitney U-test to compare differences between non-parametric data. The chi-squared test was used for categorical data.

Estimates of the survival function (the probability of achieving full enteral feeding, PN duration and length of hospital stay over time) were used for each comparison; the pre- versus post-ADEPT cohorts and the ADEPT- versus non-ADEPT Hospitals. Survival functions were illustrated using Kaplan-Meier curves. The curve is often used to illustrate the difference in having the outcomes of interest visually. Kaplan-Meier estimate provides non-parametric estimates to survival outcomes (297). Log-rank test was used to assess the significance of any differences.

Cox regression (or proportional hazards regression (HR)) was conducted to examine associations between given survival times and one or more predictor variables. The Cox model, where applicable, was expressed by the HR and 95% CI was also presented

throughout. Variables associated with the exposure of interest were identified by univariate Cox regression analysis, as appropriate. Variables were considered to be important confounders they if changed the HR of interest by > 10% (250).

A p-value of <0.05 was considered significant.

Sensitivity analyses were used to investigate whether missing data have influenced the findings of the study.

3.2.9 Sample size

In accordance with the ADEPT study data power calculation (9) and based on the median number of days to achieve full enteral feeding, 380 infants would be required to show a difference of 3 days in this outcome. With the power of 90% and a 95% significance level, a total of 1080 infants would allow detection of a clinical difference of 8% or more in the incidence of NEC (17% and 25%). A sample size calculation was conducted using the nQuery software.

3.3 Results

From 1st Jan 2007 to 31st December 2015, 72544 babies were admitted to the 12 neonatal units, of whom 22955 were born before a GA of 34^{+6} weeks. A total of 4019 babies had birth weights ≤10th centile, of whom 1435 infants had been diagnosed with abnormal antenatal Doppler results. A total of 350 infants were excluded for the following reasons: had inotropes (n=231), twin-to-twin transfusion (n=51), major congenital anomalies (n=47), and intrauterine transfusion (n=2), rhesus iso-immunisation (n=2), Died on the first 72h (n=17), multi-organ failure (n=0) (Figure 3.2).

3.3.1 Comparison of outcomes between the two eras: pre- and post-ADEPT

3.3.1.1 Baseline characteristics

A total of 1085 infants were included: 659 infants from the pre-ADEPT (from 1st January 2007 to 31st December 2012) and 426 infants from the post-ADEPT cohort (from 1st January 2013 to 31st December 2015. Population characteristics presented in Table 3.2. No significant differences were noted between the two cohorts for: BW (p=0.6), GA (p=0.4), gender (p=0.2), multiple birth (p=0.9), Apgar score at 1 (p=0.1) & at 5 min (p=0.08), need for mechanical ventilation (p=0.2), and mode of delivery (p=0.29).Significant differences were observed in the type of milk in the first feed (p=0.019). Also, there was a higher proportion of infants who had antenatal steroids in the post-ADEPT compared to the pre-ADEPT cohort (p=0.025) as shown in Table 3.2.

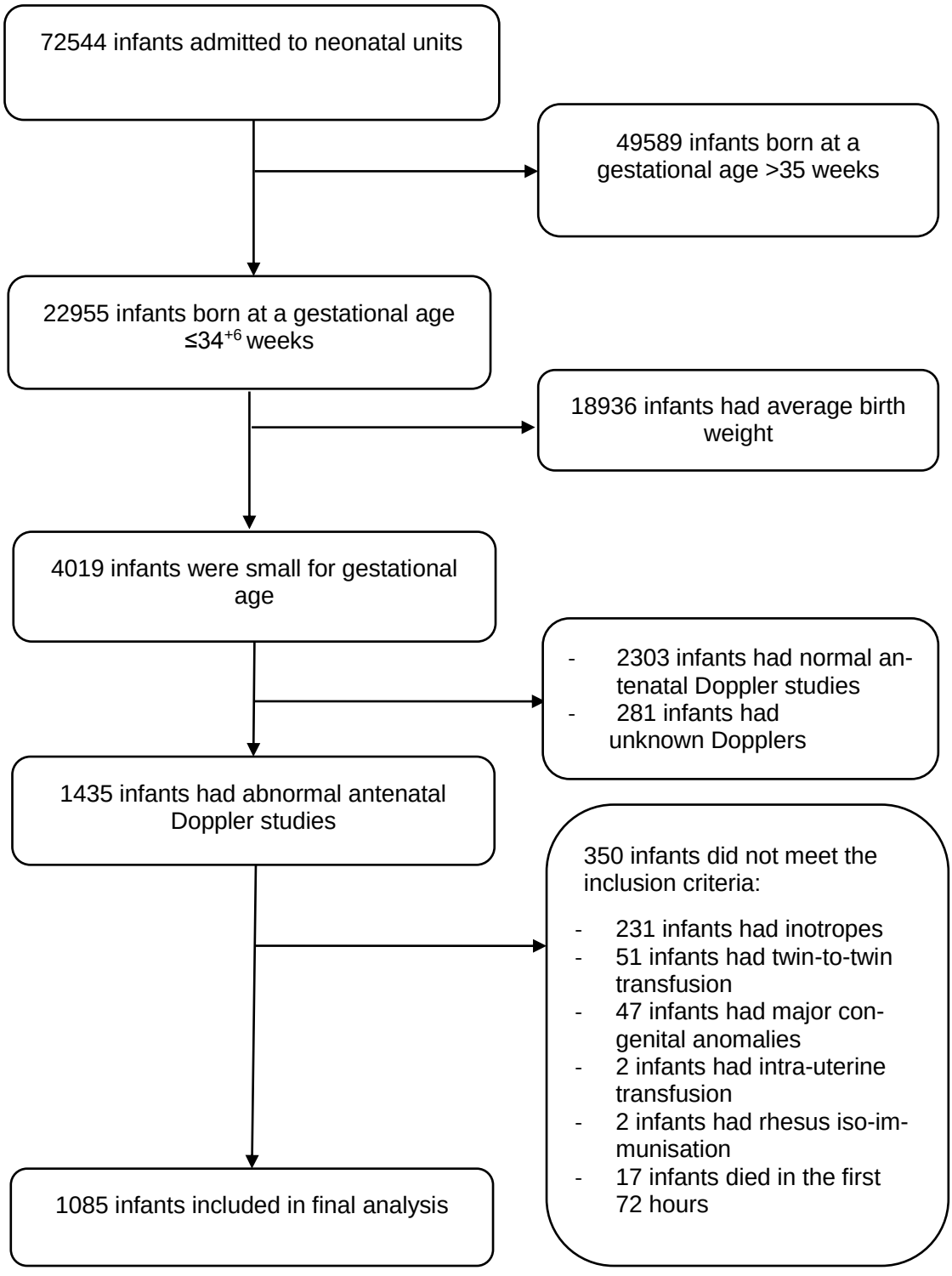

Figure 3.2 Study flow chart

Summary of extracting intra-uterine growth restricted (IUGR) infants with abnormal antenatal Doppler studies from Badger.net database, including the numbers of excluded infants and the reason for exclusion

Table 3.2 Baseline characteristics of the study populations

	All		Pre-ADEPT cohort		Post-ADEPT cohort		Pre- vs post-ADEPT
	N=1085	% or median (IQR)	N=659	% or median (IQR)	N=426	% or median(IQR)	P value
Gestational age (weeks)[a]	1085	31 (±0.1)	659	31.1 (±0.1)	426	31 (±0.1)	0.4*
- **<29**	286	26.4	166	25.2	120	28.2	
- **≥29**	799	73.6	493	74.8	306	71.8	
Birth weight (g) [a]	1085	1047.71 (±10.41)	659	1052.28 (±13.56)	426	1040.65 (±16.25)	0.6¥
- **<600**	82	7.6	54	8.2	28	6.6	
- **600-749**	162	14.9	92	14.0	70	16.4	
- **750-999**	279	25.7	171	25.9	108	25.4	
- **1000-1249**	241	22.2	139	21.1	102	23.9	
- **≥1250**	321	29.6	203	30.8	118	27.7	
Male	577	53.2	341	51.7	236	55.4	0.2*
Multiple pregnancy	231	21.3	140	21.2	90	21.1	0.9*
Apgar score							
- **At 1 min**	1016	7 (5-9)	627	8 (5-9)	394	7 (5-9)	0.1≠
- **At 5 min**	976	9 (8-10)	594	9 (8-10)	386	9 (8-10)	0.08≠
Mechanical ventilation	457	42.1	651	41	183	43	0.2*
Mode of delivery							
- **Caesarean section**	1034	95.3	636	96.5	398	93.4	0.29*
Any antenatal steroids	986	90.9	693	90.0	393	92.3	0.025*
Type of milk given in the first days	1058		640		418		0.019**
- **Exclusive mother's milk**	875	80.6	528	80.1	347	81.5	
- **Complemented mother's milk**	118	10.9	82	12.4	36	8.5	
- **Donor milk**	59	5.4	27	4.1	32	7.5	
- **Donor milk with formula**	3	0.3	1	0.2	2	0.5	
- **Formula milk**	3	0.3	2	0.3	1	0.2	

Values are median (IQR); IQR: (25th–75th percentile), otherwise specified

[a] mean (±SEM)

P values < 0.05 were considered statistically significant

* Analysis using the Chi-Square test; ** analysis using the Fisher's exact test; ¥ analysis using t-test and ≠ analysis using Mann-Whitney U-test.

3.3.1.2 Primary outcomes

3.3.1.2.1 Age of commencement of enteral feeding, and the time required to achieve full enteral feeding

Overall, more than sixty percent (679/1030; 62.6%) of infants commenced enteral feeding within the first three days of life (pre-ADEPT cohort: 382/625 (58%); post-ADEPT: 297/405 (69.7%), p<0.001). There was a shift to earlier initiation of enteral feeding in the post-ADEPT cohort (Figure 3.3 and Figure 3.4). The median (IQR) day of starting enteral feeding: pre-ADEPT cohort: 3 (2-5) days; post-ADEPT cohort: 3 (2-4) days; p < 0.001). Although the medians were not different one from another, the maximum day of starting enteral feeding was greater in the pre-ADEPT cohort compared to the post-ADEPT cohort (pre-ADEPT cohort: 52; post-ADEPT cohort: 34 postnatal days).

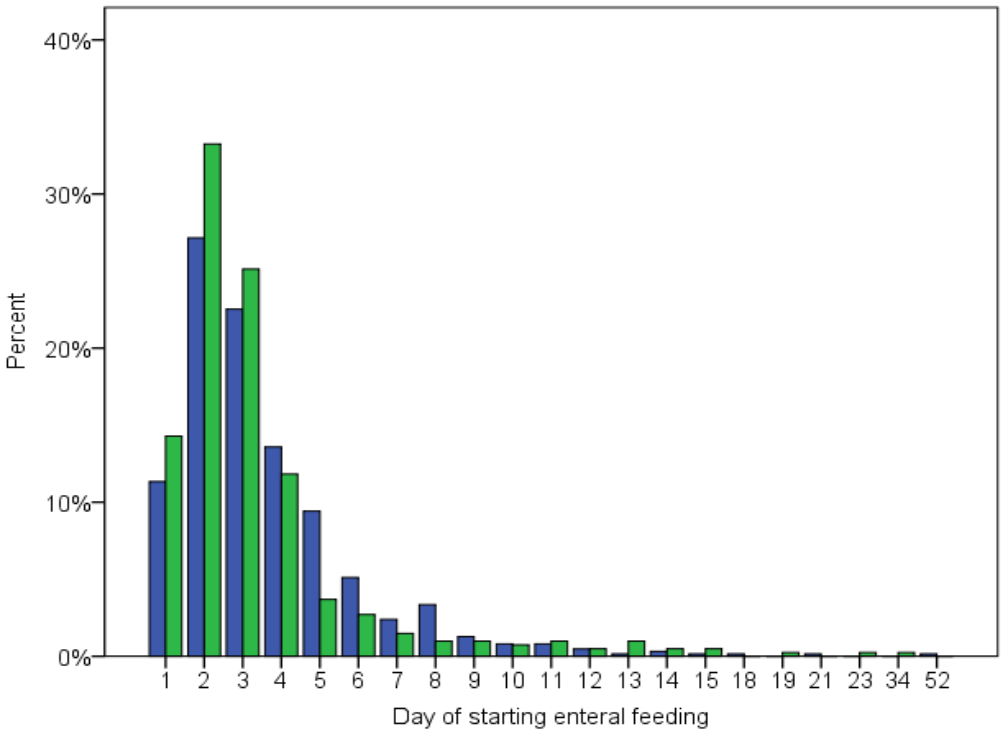

Figure 3.3 Proportion of infants who had enteral feeding presented by postnatal age (days)

Blue bars: pre-ADEPT cohort; Green bars: post-ADEPT cohort

However, there was missing data for 4.9% (53/1085) infants; data on the day of starting enteral feeding were not recorded. Sensitivity analysis was conducted comparing findings from cohorts with and without infants with missing data showed no differences in the p-values ($p<0.001$).

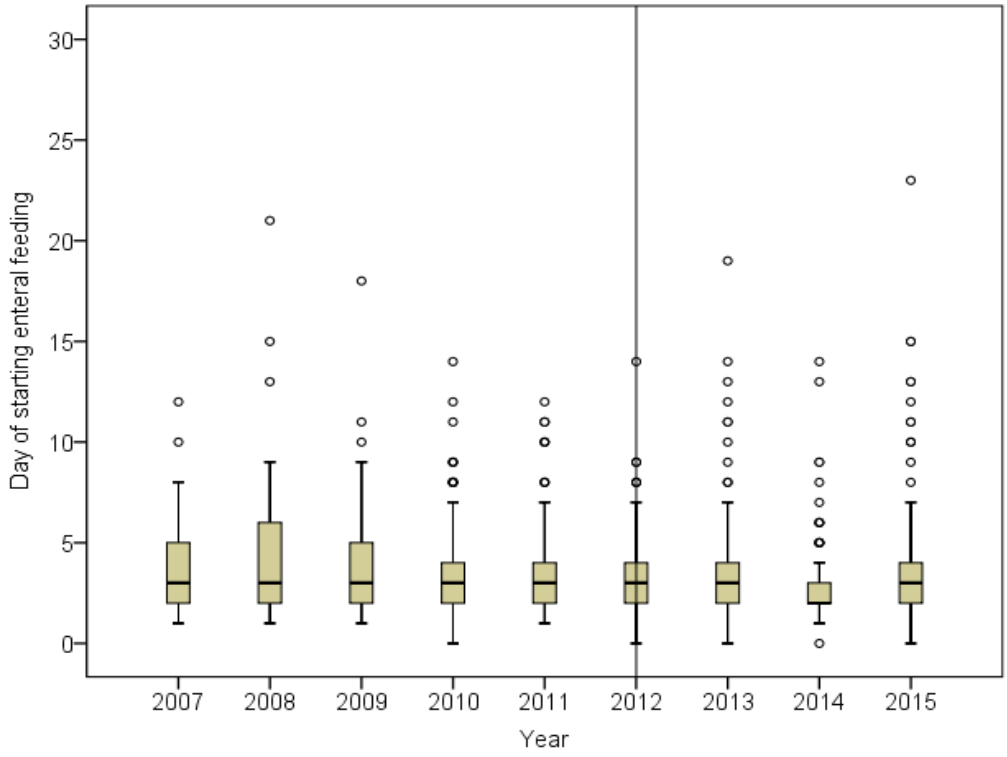

Figure 3.4 Median day of starting enteral feeding by year of birth

Black line: publication of the ADEPT study

Full enteral feeding was achieved in 988/1085 (91.1%) of the study populations (pre-ADEPT cohort: 620/659 (91.4%); post-ADEPT cohort: 386/424 (90.6%)). Approximately two percent of infants died before achieving full feeds (26/1085 (2.4%)) and data for 71/1085 (6.5%) were not reported. No significant difference was seen in the time required to achieve full feeds between the two cohorts at any given time, HR: 1.005 [95% CI: 0.883 to 1.143].

The Kaplan-Meier graph (Figure 3.5) showed almost overlapping curves of the two cohorts indicating that there was no significant difference in the median days required to achieve full

feeds between the two cohorts (pre-ADEPT: 13 [95%CI 12.35 to 13.65] days; post-ADEPT: 13 [95%CI 12.18-13.82] days, p= 0.9).

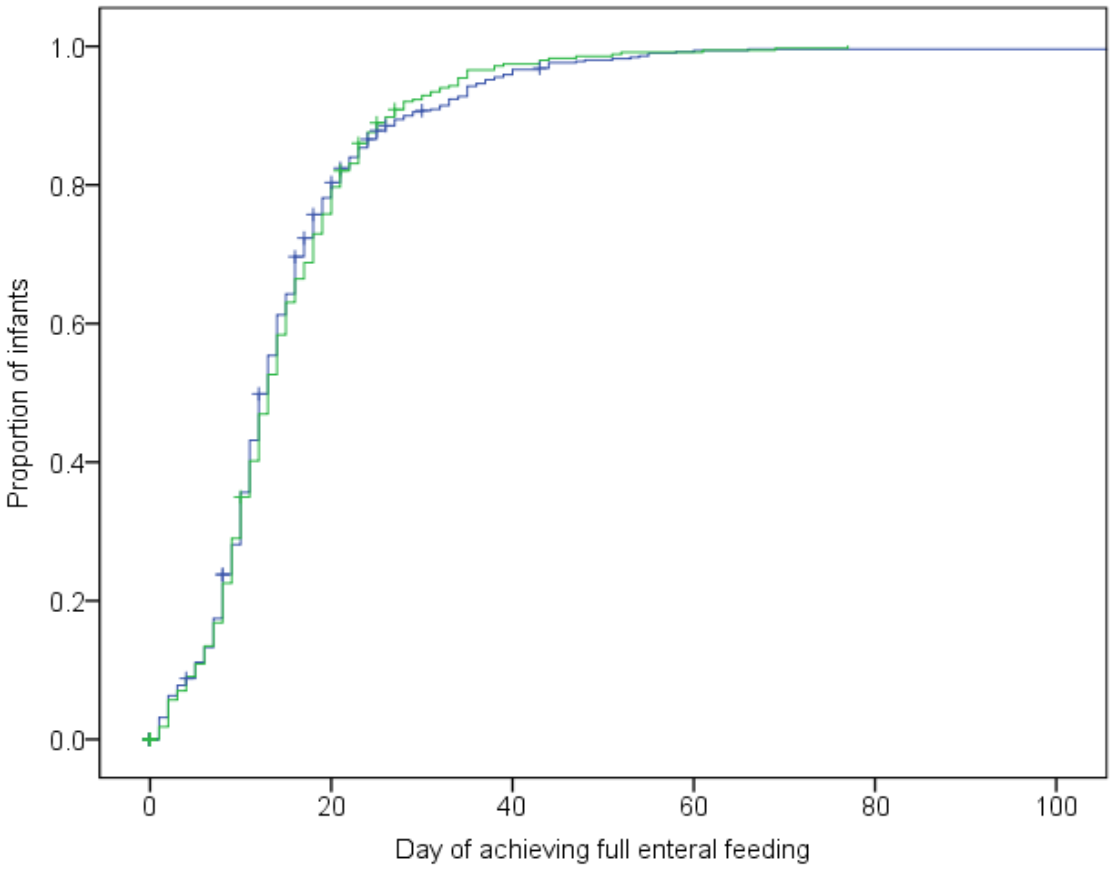

Figure 3.5 Proportion of infants with full enteral feeding established by two cohorts

Log-rank, p= 0.9.
Blue: pre-ADEPT cohort and Green: post-ADEPT cohort

Cox regression to assess factors that may influence the time to achieve full feeds was conducted. The first step compared the time required to achieve full feeds in the pre- versus the post-ADEPT cohorts. The output of the Cox regression analysis of model 1 is presented in Table 3.3 . The unadjusted HR for the time of achieving full feeds in the pre-ADEPT cohort compared to the post-ADEPT cohort was 1.005 (95% CI 0.883 to 1.143). As the 95% CI estimate crosses the line of equivalence (1.0), we may conclude that there was not a statistically significant difference in time to achieve full seeds between the two cohorts.

The second step was undertaken to show if there was any effect of confounders on the HR for the time to achieve full enteral feeding illustrated in Table 3.3. The HR for time to achieve full feeds was adjusted for each potential confounders, and none of them materially altered the magnitude of the HR of time to achieve full feeds. These findings suggest that whether adjusted or not, there is no evidence of changes in time to achieve full enteral feeding in pre-post-ADEPT cohorts.

Table 3.3 Cox regression to detect factors that may influence the time of achieving full feeds (days)

Variable		Estimates			
		Hazard ratio exp (β)	95% CI		P-value
			Lower	Upper	
Unadjusted time of achieving full feeds	Pre-ADEPT vs post-ADEPT	1.005	0.883	1.143	0.94
Adjusted for GA at birth	Pre-ADEPT vs post-ADEPT GA	0.996	0.875	1.133	0.95
Adjusted for BW	Pre-ADEPT vs post-ADEPT BW	0.980	0.861	1.115	0.76
Adjusted for gender	Pre-ADEPT vs post-ADEPT Gender	1.003	0.882	1.142	0.96
Adjusted for multiple pregnancies	Pre-ADEPT vs post-ADEPT Multiple pregnancies	0.999	0.878	1.137	0.99
Adjusted for mode of delivery	Pre-ADEPT vs post-ADEPT Mode of delivery	0.986	0.864	1.126	0.84
Adjusted for Apgar score at 1 min	Pre-ADEPT vs post-ADEPT Apgar score at 1 min	1.091	0.954	1.247	0.21
Adjusted for Apgar score at 5 min	Pre-ADEPT vs post-ADEPT Apgar score at 5 min	1.068	0.932	1.224	0.34
Adjusted for the need for mechanical ventilation	Pre-ADEPT vs post-ADEPT Mechanical ventilation	0.996	0.873	1.136	0.95
Adjusted for exposure to antenatal steroid	Pre-ADEPT vs post-ADEPT Antenatal steroid	1.042	0.914	1.188	0.54
Adjusted for the type of milk given in the first seven days of life	Pre-ADEPT vs post-ADEPT Type of milk	0.991	0.871	1.129	0.90
Adjusted for a day of starting enteral feeding	Pre-ADEPT vs post-ADEPT Enteral feeding	0.955	0.837	1.090	0.50
Adjusted for day of starting PN	Pre-ADEPT vs post-ADEPT PN	1.024	0.898	1.168	0.72

Abbreviations:
Confidence interval: CI; Abnormal Doppler Enteral Prescription Trial: ADEPT; gestational age: GA; birth weight: BW; parenteral nutrition: PN

3.3.1.2.2 Age of commencement of PN and duration of PN

Of the study populations, there was high proportion of infants receiving PN (pre-ADEPT cohort: 567/659 (86.0%); post-ADEPT cohort: 374/426 (87.8%)). Infants in the post-ADEPT study cohort commenced PN significantly earlier than those before the ADEPT study (pre-

ADEPT cohort: 2 (1-2) days; post-ADEPT cohort: 1 (1-2); median (IQR), p=0.003) (Figure 3.6). However, there were missing data for 4.3% (47/1085) infants; data were not recorded in the Badger database. Sensitivity analysis conducted comparing findings from cohorts with and without infants with missing data showed no differences in the p-values. Both were p=0.003.

The Kaplan-Meier graph (Figure 3.7) showed that there was no clear difference in the median duration of PN between the two cohorts (pre-ADEPT cohort: 11 [95%CI: 10.26 to 11.74]; post-ADEPT cohort: 12 [95%CI: 10.90 to 13.10] days, respectively, p=0.5). Therefore, Cox regression to assess factors associated with PN duration cannot be conducted.

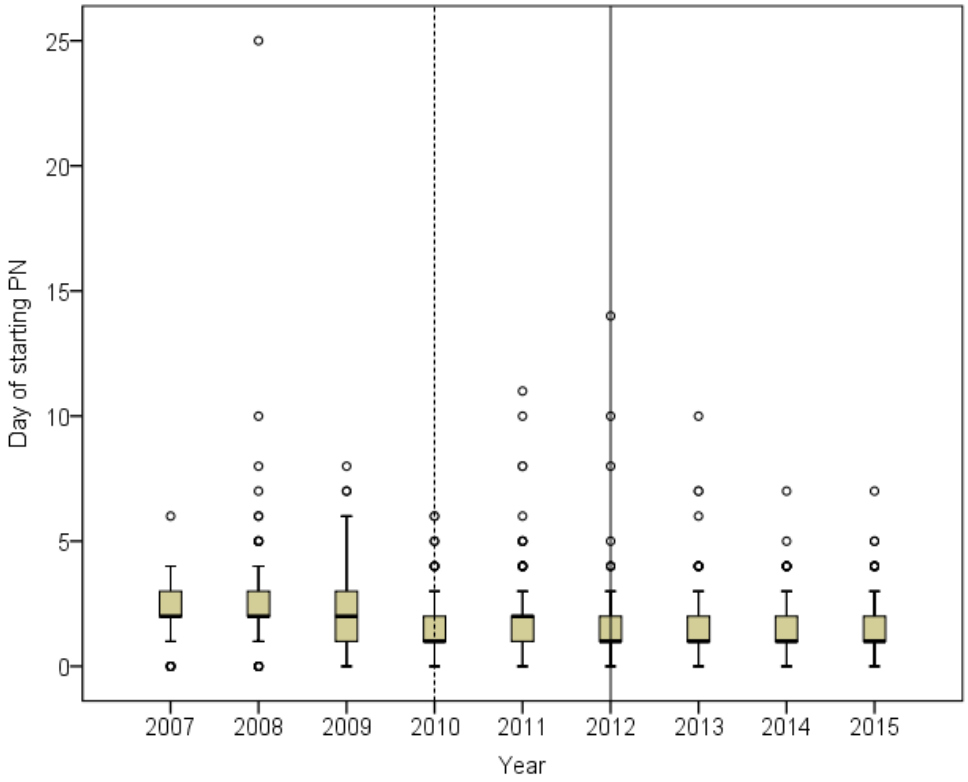

Figure 3.6 Median days of starting PN by year of birth

Dashed line: publication of the NCEPOD report (3); Solid line: publication of the ADEPT study (9)

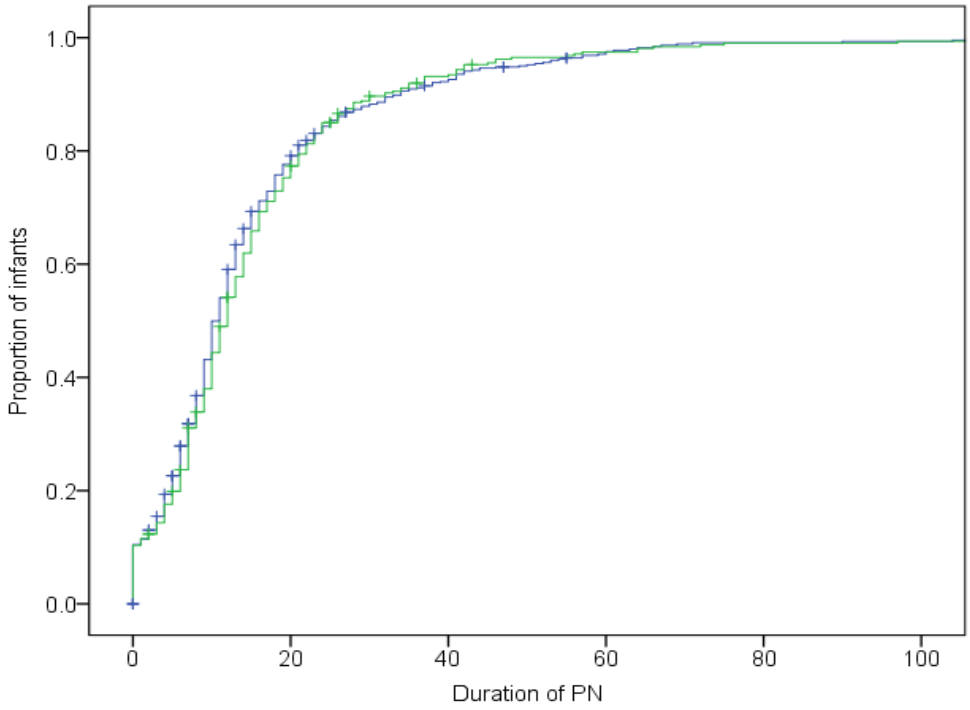

Figure 3.7 Kaplan-Meier survival curves for the PN duration by two cohorts, pre- and post-ADEPT study eras

Log-rank, p= 0.5
Blue: pre-ADEPT cohort; Green: post-ADEPT cohort

3.3.1.2.3 The incidence of NEC

Overall, 230/1085 (21.2%) infants had medical or surgical treated NEC (pre-ADEPT cohort: 143/659 (21.7%); post-ADEPT cohort: 87/426 (20.4%)). There was no statistically significant difference in the risk between the two cohorts (risk ratio (RR): 1.07 [95% CI: 0.85 to 1.36]; p=0.6).

3.3.1.3 Secondary outcome

3.3.1.3.1 Milk feeding

Overall, 993/1085 (91.5%) infants had an initial feed containing mother's breast milk (MBM) (pre-ADEPT cohort: 610/659 (92.6%) infants; post-ADEPT cohort: 383/426 (89.9%) infants, p= 0.047). For some infants, in the first few days, MBM was complemented with either donor breast milk or formula (Table 3.2). Overall, there were some differences in the proportion of infants who had exclusive MBM (pre-ADEPT cohort: 528/659 (80.1%) infants; post-ADEPT

cohort: 347/426 (81.4%) infants). There was a significant difference in the type of milk in the first feed between the two cohorts, p= 0.019. There was a higher proportion of infants who had donor breast milk in the post-ADEPT (27/659, 7.5%) compared to the pre-ADEPT (32/426, 4.1%).

At discharge, 527/1085 (48.6%) infants were on MBM; of whom 370/1085 (34.1%) were exclusively on MBM and 160/1085 (14.7%) had MBM complemented with formula milk, whereas, 395/1085 (36.4%) infants had formula milk, 14/1085 (1.3%) infants died before discharge and for 146/1085 (13.5%) infants no data were recorded. No significant difference in the rate of breast-milk feeding at discharge between the two cohorts (pre-ADEPT cohort: 313/659 (47.5%) infants; post-ADEPT cohort: 214/426 (50.2%) infants, p=0.4).

3.3.1.3.2 The incidence of sepsis

Sepsis was common among the study population (121/1085 (11.2%)); being significantly higher among infants in the pre-ADEPT compared to the post-ADEPT cohort (pre-ADEPT cohort: 93/659 (14.1%); post-ADEPT cohort: 28/426 (6.6%) infants, (RR: 2.1 [95% CI: 1.4 to 3.2]), p<0.0001).

3.3.1.3.3 Cholestatic jaundice

Of the study population, 72/1081 (6.6%) infants had cholestatic jaundice. No significant difference in the rate of cholestasis between the two cohorts was observed (pre-ADEPT cohort: 45/659 (6.8%); post-ADEPT: 27/426 (6.3%), p=0.7.

3.3.1.3.4 Gastrointestinal surgery/perforation

Overall, in the study population, 78/1081 (7.2%) infants had GIT surgery/perforation (pre-ADEPT cohort: 49/655 (7.5%); post-ADEPT cohort: 29/426 (6.8%). No significant difference was detected between the two cohorts, p=0.8.

3.3.1.3.5 Continuous supplemental oxygen

Of the whole study population, 105/1057 (9.7%) infants were on continuous oxygen therapy until 36 weeks postconceptional age. The proportion of infants on continuous supplemental oxygen at 36 weeks postconceptional age was not significantly different between the two cohorts (pre-ADEPT cohort: 59/659 (9.0%); post-ADEPT cohort: 46/426 (10.8%), p=0.4.

There was a continuing need for supplemental oxygen at the time of hospital discharge for one-fifth of the study population, 220/1033 (20.3%). The proportion of infants discharged on oxygen was significantly lower in the pre-ADEPT compared to the post-ADEPT cohort (pre-ADEPT cohort: 120/659 (18.2%); post-ADEPT: 100/426 (23.5%), p=0.044).

3.3.1.3.6 Death before hospital discharge

Approximately 5% (50/1085) of the study population died before hospital discharge. No significant difference in the proportion of infants who died before hospital discharge was observed between the two cohorts (pre-ADEPT cohort: 34/659 (5.2%); post-ADEPT cohort: 16/426 (3.8%), p=0.3.

3.3.1.3.7 Duration of hospital stay

The duration of hospital stay was reported for 790/1085 infants. Over the whole study period, the median (IQR) duration of hospital stay was 42 (26-70) days (Figure 3.8). The median length of hospital stay was not significantly different between the two cohorts (pre-ADEPT cohort: 41 days [95%CI: 38.31 to 43.69]; post-ADEPT cohort: 49 days [95%CI: 43.53 to 54.45], p=0.8). However, there were missing data for 27.1% (790/1085). Sensitivity analysis conducted comparing findings from the two cohorts with and without infants with missing data showed no differences in the p-value (p=0.35).

As can be seen from Figure 3.9, this relationship was complicated with the majority of the pre-ADEPT cohort going home sooner, but after 75 days this pattern reversed with fewer stays over 100 days in the post-ADEPT cohort.

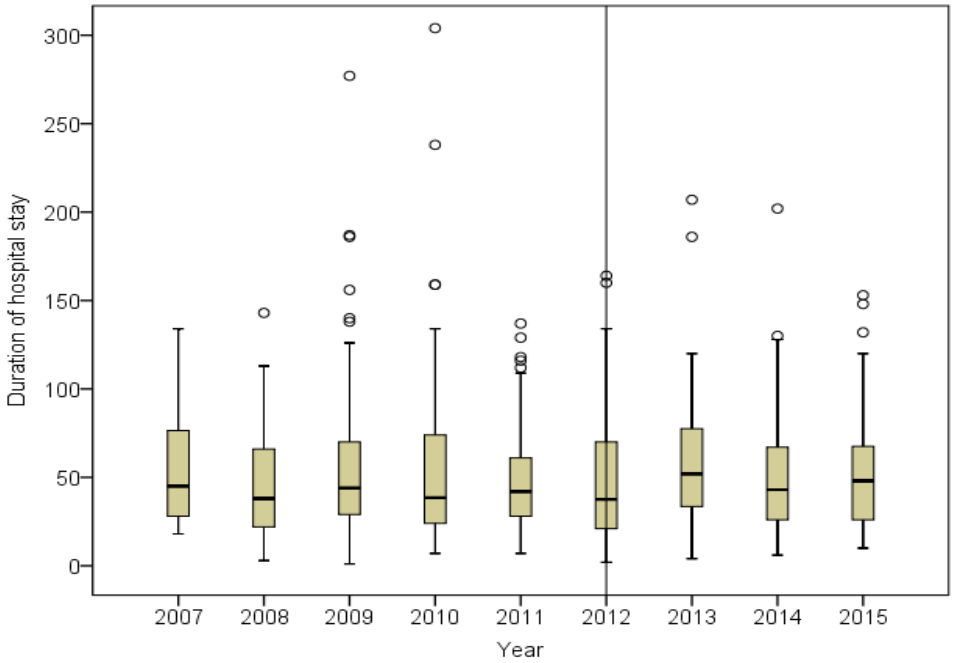

Figure 3.8 Median duration of hospital stay by year of birth

Black line: publication of the ADEPT study

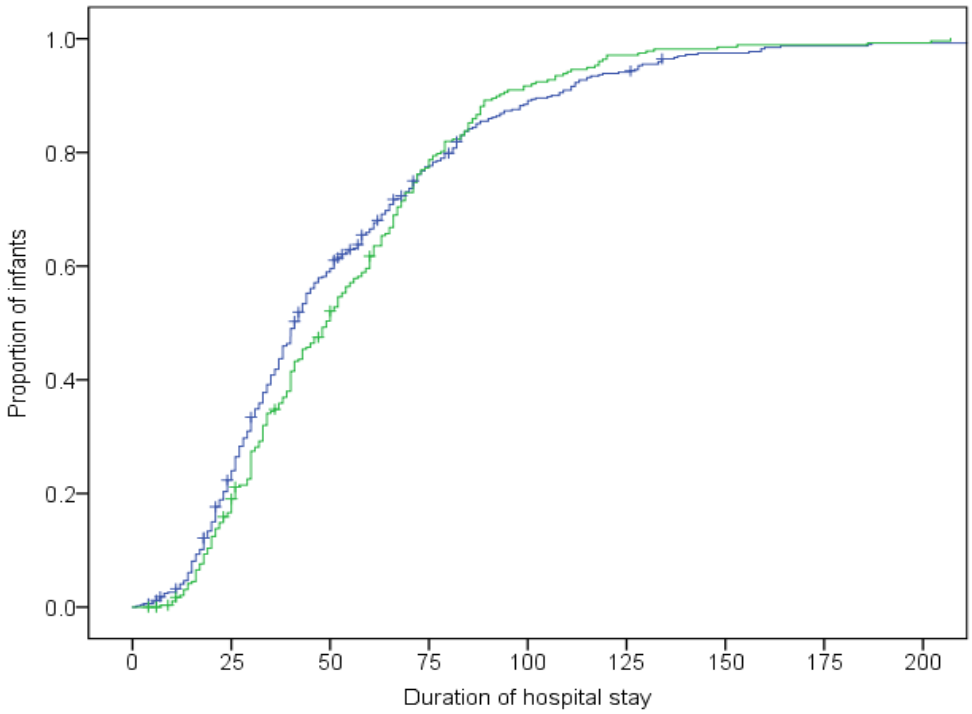

Figure 3.9 Kaplan-Meier survival curves for the length of hospital stay by two epochs, pre- and post-ADEPT study eras

Log-rank, p= 0.8.
Blue: pre-ADEPT study; Green: post-ADEPT study

More than half of the study population (595/790) were discharged before 75 days and 195/790 infants were discharged after that.

The characteristics of infants by the duration of hospital stay groups (<75 or ≥75 days) presented in Table 3.4. In infants discharged before 75 days; post-ADEPT infants had lower BW and GA and were receiving more intensive care, with higher proportion of boys and those receiving antenatal steroids, compared to the pre-ADEPT infants. The median length of hospital stay was shorter in the pre-ADEPT cohort (pre-ADEPT:33 days [95%CI; 30.27 to 35.73]; post-ADEPT: 38 days [95%CI; 34.4 to 41.64], p=0.02).

In infants discharged after 75 days, pre-ADEPT infants had a lower BW, received PN later and for a longer duration. A higher proportion of pre-ADEPT infants had sepsis, compared to post-ADEPT. The difference in the median length of hospital stay between the cohorts was not significantly different (pre-ADEPT: 93 days [95%CI: 84.2 to 101.76]; post-ADEPT: 87 days [95%CI: 84.17 to 89.83], p=0.058.

Since the Kaplan-Meier curves overlapped, which may indicate that the hazard ratio is not constant over time, Cox regression to assess factors associated with the duration of hospital stay cannot be conducted.

Table 3.4 Characteristics of infants by the duration of hospital stay group (<75 or ≥75 days)

	<75 days hospital stay (n=595)			≥75 days hospital stay (n=195)		
Values are numbers (%) or median (IQR)	Pre-ADEPT (n=377)	Post-ADEPT (n=218)	Pre- vs post-ADEPT P value	Pre-ADEPT (n=120)	Post-ADEPT (n=75)	Pre- vs post-ADEPT p-value
Gestational age (weeks)	32.3 (30.6-34.0)	31.6 (30.0-33.4)	0.008 ≠	28.3 (27.5-29.6)	28.6 (28-30)	0.09 ≠
Birth weight (g)	1220 (985-1439)	1160 (895-1362.5)	0.03 ≠	745 (631-838.8)	770 (665-935)	0.04 ≠
Male	186 (49.3)	132 (60.0)	0.008*	62 (51.7)	39 (52.0)	0.9*
Apgar score						
- **At 1 min**	8 (6-9)	8 (5-9)	0.2 ≠	6 (4-8)	6 (5-8)	0.98 ≠
- **At 5 min**	9 (9-10)	9 (8-10)	0.1 ≠	9 (7-9)	9 (7-9)	0.99 ≠
Need for mechanical ventilation	110 (29.2)	72 (33)	0.2*	78 (66.7)	51 (70.8)	0.6*
Mode of delivery						
-Caesarean section	361 (95.8)	207 (95)	0.2*	119 (100)	72 (98.6)	0.2*
Antenatal steroid	329 (87.3)	203 (93.1)	0.02*	112 (93.3)	70 (93.3)	0.5*
Day of starting PN	2 (1-3)	1 (1-2)	0.8 ≠	2 (1-2)	1 (1-2)	0.002 ≠
PN duration	9 (4-13)	9 (5-14)	0.1 ≠	21 (12-38)	17 (11-24)	0.053 ≠
Day of starting enteral feeding	3 (2-4)	2 (2-3)	0.04 ≠	4 (3-6)	3 (2-5)	0.07 ≠
Age of full enteral feeding	10 (7-14)	10.5 (5-17)	0.3 ≠	18 (13-24)	16 (12-22)	0.2 ≠
Type of milk was given in the first days	372	217	0.003*	116	74	0.6*
- **Exclusive mother's milk**	292 (77.5)	182 (83.5)		105 (87.5)	64 (85.3)	
- **Supplemented mother's milk**	61 (16.2)	16 (7.3)		5 (6.2)	6 (8)	
- **Donor milk**	17 (4.5)	18 (8.3)		5 (6.2)	4 (5.3)	
- **Donor milk with formula**	1 (0.3)	1 (0.5)		0 (0)	0 (0)	
- **Formula milk**	1 (0.3)	0		1 (0.8)	0 (0)	
Values are numbers (%) or median (IQR)	Pre-ADEPT (n=377)	Post-ADEPT (n=218)	Pre- vs post-ADEPT	Pre-ADEPT (n=120)	Post-ADEPT (n=75)	Pre- vs post-ADEPT

	<75 days hospital stay (n=595)			≥75 days hospital stay (n=195)		
			P value			p-value
BPD	13 (3.4)	9 (4.1)	0.6*	3 (33.3)	27 (36)	0.5*
NEC	61 (16.2)	33 (15.1)	0.7*	43 (36.1)	22 (29.3)	0.3*
GIT surgery	18 (4.8)	0.2	0.5*	17 (14.3)	10 (13.3)	0.9*
Cholestasis	16 (4.2)	12 (5.5)	0.4*	17 (14.2)	7 (9.3)	0.3*
Sepsis	38 (4.8)	13 (6)	0.08*	31 (26.5)	11 (14.7)	0.053*
PDA	13 (3.4)	13 (12.8)	0.1*	38 (31.9)	18 (24.0)	0.2*
Duration of IC	0 (0-4.5)	2 (0-6)	0.004 ≠	13 (2-33)	11 (2-27)	0.7 ≠

Values are median (IQR); IQR: (25th–75th percentile) or numbers (%), otherwise specified

P values < 0.05 were considered statistically significant

* Analysis using the Chi-Square test and ≠ analysis using Mann-Whitney U-test
Bronchopulmonary dysplasia: BPD; necrotising enterocolitis: NEC; gastrointestinal tract: GIT; patent ductus arteriosus: PDA

3.3.1.3.8 Duration of intensive care

The median (IQR) duration of intensive care (IC) did not significantly change over time (pre-ADEPT cohort: 2 (0-10); post-ADEPT cohort: 3 (0-10) days, p=0.06).

3.3.1.3.9 Duration of high dependency care

There was no significant difference in the median (IQR) duration of high dependency care (HDC) between the two cohorts (pre-ADEPT cohort: 7 (0-15); post-ADEPT cohort: 7 (0-16) days, p=0.5).

3.3.1.3.10 Duration of special care

The difference in median (IQR) duration of special care (SC) between the two cohorts did not reach the significance, p=0.8 (pre-ADEPT cohort: 13 (0-25) days; post-ADEPT cohort: 10 (0-24) days).

3.3.1.3.11 Change in anthropometric measures from birth to discharge

There was no significant difference in BW between the two cohorts. Nonetheless, infants from the post-ADEPT cohort had attained higher weights at discharge compared to the pre-ADEPT cohort; pre-ADEPT cohort: 1827 g (1615-2077); post-ADEPT cohort: 1910 g (1652-2190), median (IQR), p=0.005. The median (IQR) of weight gain was significantly higher for infants from post-ADEPT compared to the pre-ADEPT cohort (pre-ADEPT cohort: 640 g (348-1060); post-ADEPT cohort: 808 g (405-1252), p=0.004). Of note, the duration of hospital stay was not statistically different between the two groups, (p=0.8).

There was significant difference in the median (IQR) head circumference at discharge from hospital between the two groups; pre-ADEPT cohort: 30.9 cm (27.5-32.5); post-ADEPT cohort: 31.5 cm (30-32.8), p<0.0001.

3.3.2 Comparison of outcomes between units who did or did not recruit to ADEPT

The previous part (section 3.3.1) showed some changes in nutrition practices since the ADEPT publication. The current section aimed to show if there were differences in nutrition practices between the ADEPT hospitals (units who recruited patients to the ADEPT) and the Non-ADEPT hospitals (units who did not recruit to ADEPT).

3.3.2.1 Baseline characteristics

Apgar score at 1 min and the type of milk were the only significant difference observed in the perinatal parameters between the ADEPT hospitals compared to the non-ADEPT hospitals, p=0.02. No significant differences were observed between the two groups for: GA (p=0.8), BW (p=0.7), sex (p=0.4), multiple births (p=0.7), Apgar score at 5 min (p=0.9), mechanical ventilation (p=0.2), and mode of delivery (p=0.2) and antenatal steroid exposure (p=0.2) (Table 3.5).

Table 3.5 Baseline characteristics of infants from the ADEPT Hospitals versus the non-ADEPT Hospitals

	ADEPT hospitals		Non-ADEPT Hospitals		ADEPT Hospitals vs non-ADEPT Hospitals
	N=501	median (IQR) or %	N=584	median (IQR) or %	P value
Gestational age (weeks)[a]	501	31 (±0.1)	584	31 (±0.1)	0.9*
- **<29**	125	25	161	27.6	
- **≥29**	375	75	423	72.4	
Birth weight (g)	501	1010 (760-1295)	584	1016 (770-1324)	0.7*
- **<600**	39	7.8	43	7.4	
- **600-749**	72	14.4	90	15.4	
- **750-999**	130	25.9	149	25.5	
- **1000-1249**	122	24.4	119	20.4	
- **≥1250**	138	27.5	183	31.3	
Male	260	51.9	317	54.3	0.4*
Multiple pregnancy	112	22.4	118	20.2	0.2*
Apgar score					
- **At 1 min**	472	7 (5-9)	549	8 (5-9)	0.01≠
- **At 5 min**	443	9 (8-10)	537	9 (8-9)	0.6≠
Need for mechanical ventilation	498	44.5	234	40.1	0.3*
Mode of delivery					
- **Caesarean section**	474	94.6	560	95.9	0.2*
Antenatal steroid	444	88.6	542	92.8	0.2*
Type of milk given in the first days	501		584		0.009*
- **Exclusive mother's milk**	404	80.6	471	80.7	
- **Complemented mother's milk**	47	9.4	71	12.2	
- **Donor milk**	39	7.8	20	3.4	
- **Donor milk with formula**	1	0.2	2	0.3	
- **Formula milk**	1	0.2	2	0.3	

Values are median (IQR); IQR: (25th–75th percentile), otherwise specified

[a] mean (±SEM)

P values < 0.05 were considered statistically significant

* Analysis using the Chi-Square test, ** analysis using the Fisher's exact test and ≠analysis using Mann-Whitney U test

3.3.2.2 Primary outcomes

3.3.2.2.1 Age of commencement of enteral feeding and the time required to achieve full enteral feeding

The median day of starting enteral feeding was identical for infants from the two groups at 3 (2-4) days; median (IQR) p=0.3. Full enteral feeding sustained for 72 h was reported for 988/1085 (91.1%) infants (ADEPT hospitals: 448/501 (89.4%) infants; Non-ADEPT Hospitals: 540/584 (92.5%)). The Kaplan-Meier graph (Figure 3.10) showed almost overlapping curves of the two groups indicating no significant difference in the time required to achieve full feeds between the two groups (ADEPT hospitals: 13 days [95%CI: 12.18 to 13.82]; Non-ADEPT Hospitals: 12 days [95%CI: 11.36 to 12.64], p=0.17).

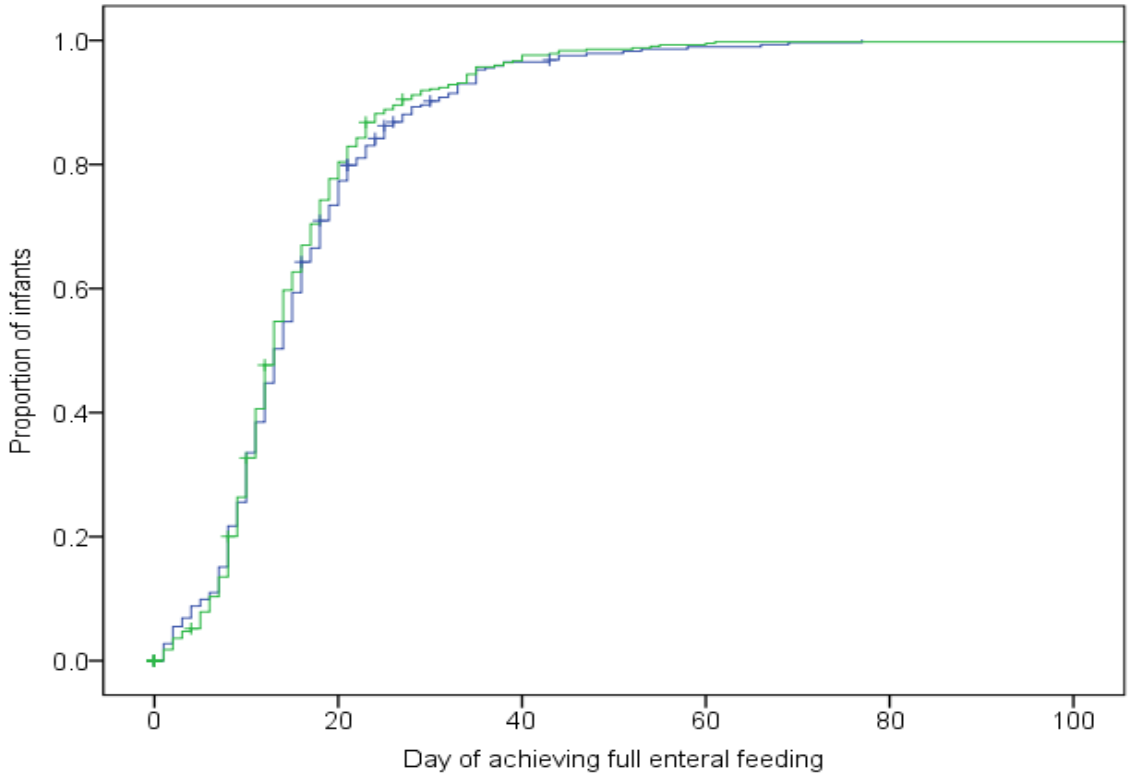

Figure 3.10 Proportion of infants with full enteral feeding established by two groups

Log-rank, p= 0.17
Blue: ADEPT Hospitals; Green: Non-ADEPT Hospitals

3.3.2.2.2 Age of commencement of PN and duration of PN

Eighty-six percent (431/472) of babies from ADEPT Hospitals and ninety percent (510/566) of babies from Non-ADEPT Hospitals received PN. The median (IQR) age of starting PN was identical for the two groups, 2 (1-2) days; p=0.5.

The Kaplan-Meier graph (Figure 3.11) showed no clear difference in the median duration of PN between the two groups (ADEPT Hospitals: 11 [95%CI: 10.09 to 11.91]; Non-ADEPT Hospitals: 10 [95%CI: 9.12-10.88), p=0.3.

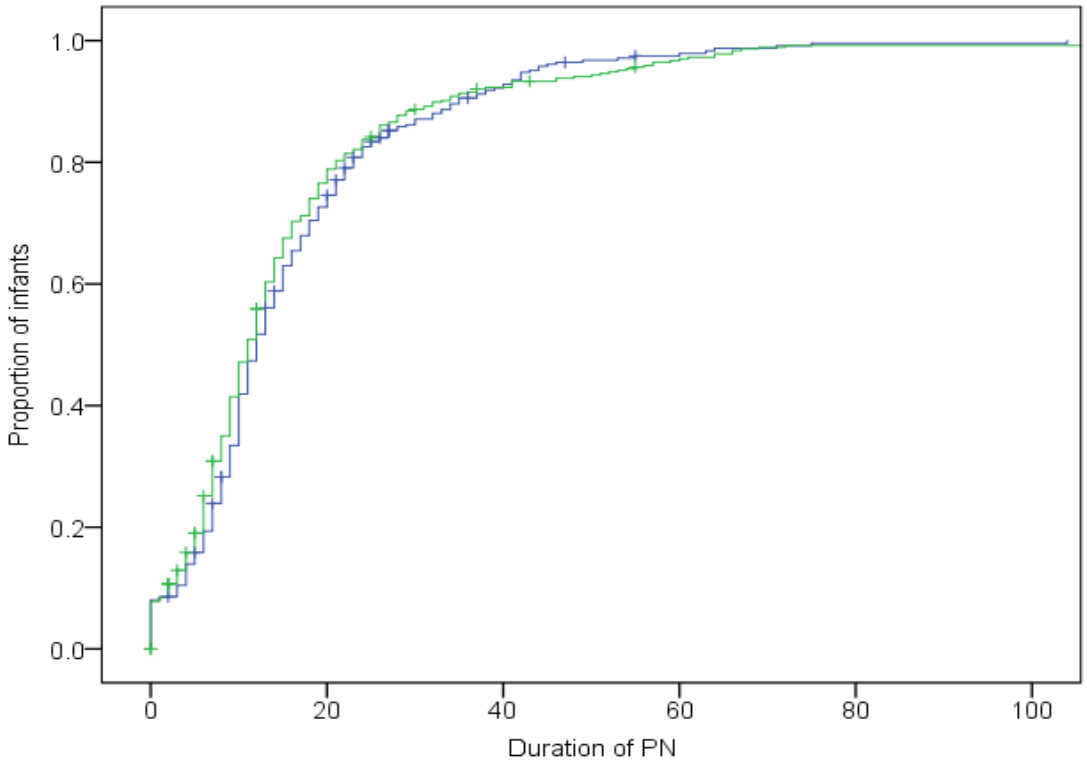

Figure 3.11 Kaplan-Meier survival curves of the length of PN duration by the two groups

Log-rank, p= 0.3.
Blue: ADEPT Hospitals; Green: Non-ADEPT Hospitals

3.3.2.2.3 The incidence of NEC

The-proportion of infants with NEC was not statistically different between the two groups (ADEPT Hospitals: 110/501 (22.0%) infants; Non-ADEPT Hospitals: 120/584 (20.5%) infants, RR: 1.1 [95% CI: 0.84-1.3]; p=0.6).

3.3.2.3 Secondary outcomes

3.3.2.3.1 Milk feeding

Overall, 451/501 (90.0%) infants from the ADEPT Hospitals and 542/584 (92.8%) infants from the Non-ADEPT Hospitals had MBM in the first few days of life, p= 0.06. For some infants, this was complemented with either donor or formula milk (Table 3.5). Overall, 404/501 (80.6%) and 471/584 (80.7%) of infants from the ADEPT Hospitals and the non-ADEPT Hospitals, respectively, received mothers' milk exclusively as a first feed. A higher proportion of infants had donor milk in the ADEPT Hospitals (39/501; 7.8%) compared to the Non-ADEPT Hospitals (20/584; 3.4%).

No significant difference was seen in the proportion of infants who had mothers' breast milk at discharge between the two groups (ADEPT Hospitals: 250/501 (49.9%) infants; Non-ADEPT Hospitals: 277/584 (47.4%) infants, p=0.3).

3.3.2.3.2 The incidence of sepsis

The incidence of sepsis was not significantly different between the two groups (ADEPT Hospitals: 60/501 (12.0%) infants; Non-ADEPT Hospitals: 61/584 (10.4%) infants, (RR: 1.2 [95%CI: 0.82 to 1.6], p=0.4).

3.3.2.3.3 Cholestatic jaundice

No significant difference in the incidence of cholestasis between the two cohorts was observed (ADEPT Hospitals: 35/500 (7.0%) infants; Non-ADEPT Hospitals: 37/581 (6.4%) infants, p=0.7).

3.3.2.3.4 Gastrointestinal surgery/perforation

The proportion of infants who had GIT surgery/intestinal perforation was significantly lower in infants from the ADEPT Hospitals compared to the Non-ADEPT Hospitals (the ADEPT Hospitals: 17/501(3%); the Non-ADEPT Hospitals: 61/580 (10.5%), p<0.001). (.

3.3.2.3.5 Continuous supplemental oxygen at discharge from hospital

There was no difference observed in the proportion of infants on continuous supplemental oxygen at 36 weeks GA between the two groups (ADEPT Hospitals: 48/485 (9.9%); the non-ADEPT Hospitals: 57/572 (10%), p=0.3).

There was no difference in the proportion of infants needing oxygen at discharge from hospital between the two groups (ADEPT Hospitals: 100/472 (21.2%); Non-ADEPT Hospitals: 120/561 (21.4%), p=0.8).

3.3.2.3.6 Death before discharge from hospital

No significant difference was seen in the proportion of infants who died before being discharged from hospital between the two groups (ADEPT Hospitals: 22/501 (4.4%); Non-ADEPT Hospitals: 28/584 (4.8%), p=0.8, (RR: 0.92 [95% CI: 0.53–1.58]).

3.3.2.3.7 Duration of hospital stay

The median length of hospital stay was similar for infants from both groups (ADEPT Hospitals: 44 [95%: 39.7 to 48.3]; Non-ADEPT Hospitals: 43 [95%: 39.7 to 46.3] days, p=0.6. (Figure 3.12).

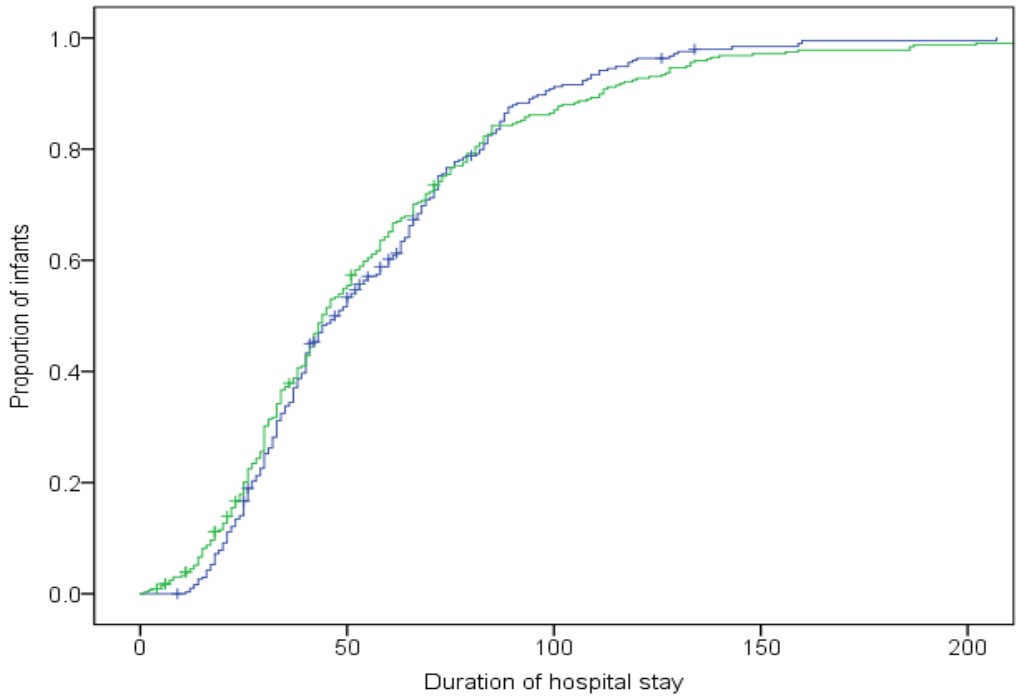

Figure 3.12 Kaplan-Meier survival curves represent the length of hospital stay by units

Log-rank, p= 0.6.
Blue: ADEPT Hospitals; Green: Non-ADEPT Hospitals

3.3.2.3.8 Duration of intensive care

The median (IQR) days of IC was identical in the two groups, 2 (0-10) days, p=0.3.

3.3.2.3.9 Duration of high dependency care

The difference in the median (IQR) duration of HDC was not significantly different between the two groups (ADEPT Hospitals: 7 (0-15); Non-ADEPT Hospitals: 6 (0-16), p=0.9).

3.3.2.3.10 Duration of special care

The differences in the duration of SC between the two groups was not significant, p=0.055 (ADEPT Hospitals: 13 (0-28); Non-ADEPT Hospitals: 10 (0-23): median (IQR).

3.3.2.3.11 Change in anthropometric measures from birth to discharge

The attained weight at discharge did not markedly differ among infants from ADEPT Hospitals and Non-ADEPT Hospitals, the median (IQR) weight was: ADEPT Hospitals: 1850 g (1615-2101); Non-ADEPT Hospitals: 1848 g (1640-2140), p=0.6. Of note, the duration of hospital stay was not statistically different between the two groups, p=0.6. No significant difference was seen in the median (IQR) of weight increment between the two groups (ADEPT Hospitals: 625 g (310-1100); Non-ADEPT Hospitals: 711 g (357-1150), respectively, p=0.7).

When compared to Non-ADEPT Hospitals, the median (IQR) HC at discharge was significantly greater for infants from ADEPT Hospitals (ADEPT Hospitals: 31.4 cm (29.8-32.8); Non-ADEPT Hospitals: 30.9 cm (27.5-32.5), p=0.002).

3.4 Discussion

3.4.1 The outcomes of the two cohorts: the pre- versus the post-ADEPT cohort

3.4.1.1 Summary of the main results

The present study demonstrates that there has been significantly earlier introduction of enteral feeding and PN for IUGR preterm infants in the post-ADEPT compared to pre-ADEPT cohorts from 12 neonatal units in England, Wales and Scotland.

The infants studied comprised a relatively homogeneous sample based on the mean of BW and GA, which were similar for both groups. Earlier initiation of PN and enteral feeding was observed in the post-ADEPT group compared to the pre-ADEPT cohort. From 2007 to 2015, the growth outcomes improved at discharge from hospital, which may partly be due to the changes in PN and enteral feeding practices. However, early enteral feeding was not associated with a shorter time required to attain sufficient enteral feeds to allow for the discontinuation of PN.

Early enteral feeds were not associated with an increased rate of NEC. Lower rates of sepsis were observed in the post-ADEPT cohort compared to the pre-ADEPT cohort. However, other morbidities, such as GIT surgery, cholestasis, BPD and mortality rates, did not change significantly between the two cohorts.

3.4.1.2 Nutrition practices

3.4.1.2.1 Parenteral nutrition and enteral feeding practices

The present study aimed to evaluate the potential changes in the current nutrition practices for both PN and enteral feeding in IUGR preterm infants with abnormal antenatal Dopplers.

Early commencement of PN was observed mainly in IUGR preterm infants from the post-ADEPT cohort. Infants' BW do not explain this recent early initiation of PN use in IUGR preterm infants, nor do GA, gender, mode of delivery or postnatal medical problems. The current study suggests that one important factor is that efforts that have been made to increase the early initiation of PN since the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) (3) and the Paediatric Chief Pharmacist's Group (PCPG) (298) reports were published. These reports highlighted variations in PN practices, particularly for ELBW infants, and it was found that, in one-third of the infants, the first PN provided was inadequate to meet infant's needs. The commencement of PN was delayed in approximately 45% of cases reviewed because the need was unrecognised or was not acted upon (3).

My findings suggest that there may be an increased awareness of the importance of the early commencement of PN to prevent malnutrition in this high-risk group. Similarly, Lapillonne et al. (116) found an improvement in PN practices in NICUs in four European countries: the UK, Italy, Germany and France, when compared to previous studies performed in individual European countries (299) or the US (77, 101).

The earlier commencement of PN observed in the post-ADEPT cohort may also be related to the use of standard PN solutions (300), which are now available and can be provided as a part

of the fluids infants initially receive (301). Adaptations in PN guidelines and practices for preterm neonates have also been established in the past several years (302), offering improved survival and developmental outcomes (303, 304).

In addition to changes in PN use, significant changes in enteral feeding practices since the ADEPT study was published were found in the current study. More post-ADEPT infants had early enteral feeding within the first three days compared to pre-ADEPT infants. Infants in both cohorts had a similar median day of beginning enteral feeding, but overall, there was a significant shift towards early feeding in the post-ADEPT group (Figure 3.4). Early commencement of enteral feeding may reflect changes in clinical practices in response to increased knowledge regarding the importance of early enteral feeding for these high-risk neonates.

Although enteral feeding is commonly delayed for high-risk neonates as attempt to reduce the risk of NEC, little evidence supports this practice (61). Unlike the Viswanathan et al. (61) study (described in Section 1.8.2), some trials relevant to current practices of infants receiving 'modern' perinatal care showed that the early introduction of enteral feeds does not affect the incidence of NEC (9, 89, 139, 140). Although some of these studies were poorly powered to detect the effect of early enteral feeding on the incidence of NEC, the findings were supported by a Cochrane review (64).

Although more infants in the post-ADEPT group received enteral feedings within the first three days of life, there was no significant difference in the median time required to achieve full enteral feeding. This finding is contrary to previous studies (9, 142) which have suggested that early enteral feeding for infants with IUGR and abnormal Dopplers results in earlier achievement of full enteral feeding. Recent literature (9, 89, 142) also shows that infants who were fed <48 h after birth achieved full enteral feeding faster than those who were fed from day six. This inconsistency may be due to differences in the study population. In the previous

studies (9, 84, 140) shorter time to achieve full feeds in relation to early enteral feeding was observed mainly in stable preterm infants born at 29 weeks or more.

The lack of difference in time required to achieve full enteral feeding may be related to what degree the ADEPT study findings influence health professional behaviour.

The current study confirms the well-known problem that the adoption of evidence-based practices (EBP) into routine clinical use is not spontaneous. The time lags in the translation of EBP to routine clinical practice and the widespread application of that evidence in patient care has been previously demonstrated (305). It has been observed that even after publication of high-level evidence in the peer-reviewed scientific literature, the translation of new knowledge to clinical guidelines, and its application in actual patient care, has been frustratingly slow. Barriers that stand in the way of best practice, even when clinical guidelines are based on the best evidence are available.

Numerous individual and organisational factors may impede EBP implementation and uptake, including physician behaviour (306), lack of time, difficulties in developing evidence-based guidelines, lack of continuing education and unsupportive organisational culture individual motivation and culture of specific healthcare practices (307, 308). Central to the successful implementation of research evidence into EBP is changing human behaviour. Any attempt to improve the quality of care for patients by translating research must incorporate a clear understanding of the associated barriers to, and facilitators of, behaviour change (306). Physician behaviour can play an important role in the widespread adoption of early enteral feeding of high-risk infants. For example, they may not agree with the evidence that early feeding does not increase the risk of NEC in preterm infants, have insufficient expectation that management according to the guideline will work, or not be motivated to change practice because of the culture of the intensive care unit is not conducive to change. The lack of difference may also be related to the volume and speed of enteral feeding. It has been observed that prolonged minimal enteral feeding results in a greater need for PN (309).

Furthermore, infants with rapid-feeding advancement often achieve full feedings earlier than infants who had slow advancement feeding (310, 311). The speed of feeding advancement is the theme of a large multi-centre randomised controlled trial; the Speed of Increasing Milk Feeds (SIFT); ClinicalTrials.gov Identifier: NCT01727609. A study of two speeds of a daily increment of milk feeding in very preterm or very low birth weight infants (312). The study has been conducted in the UK, and it began in early 2013 and finished recruitment late 2015. The outcomes include time to achieve full feeding, survival without moderate or severe disabilities at 24 months of corrected age, the incidence of late-onset sepsis and NEC. For the trial, 2804 infants born at <32 weeks of gestation were recruited. The results of SIFT, including time to reach full feeding, have not been published yet.

The present study showed that the total duration of PN was not significantly different between the two cohorts, finding that could be attributed to range of factors. Weaning infants off PN may depend on the severity of the medical complications associated with premature birth, such as hypotension and immature lung function, which may require endotracheal intubation and mechanical ventilation (313). Therefore, most very and extremely preterm infants are dependent on PN in the early weeks of life to help correct in-utero growth restrictions. Infants who may be too ill to receive substantial enteral feeds require prolonged PN. In other words, the duration of PN could be a surrogate marker for feeding tolerance and neonatal morbidity (88). In particular, those born <29 weeks gestation or ELBW are at greater risk for variety of medical complications, including NEC, BPD, and PDA (314). Consistent with the previous observations (314), the current study found no significant difference in infants' medical conditions. Approximately 40% of the study population needed mechanical ventilation, 21% had NEC and 10% needed oxygen support at 36 weeks gestation.

Attainment of feeding milestones has been shown to be inversely related to BW and the presence of the previously mentioned medical complications (315, 316). The type of milk used may also contribute to an earlier achievement of feeding milestones (315, 316). Infants who received breast milk for initial feeds could achieve full enteral feeding more quickly (317).

However, the percentage of infants receiving MBM between the two cohorts did not differ in the current study. Beneficial effects of human milk on the gastrointestinal function, digestion and absorption of nutrients, feeding tolerance and host defence have been previously reported (258, 318).

3.4.1.2.2 Breast milk feeding

Overall, the proportion of infants who had MBM was noticeably high among the study population (pre-ADEPT cohort: 92.6%; post-ADEPT cohort: 89.9%). At hospital discharge, the prevalence of breastfeeding decreased to 47.5% and 50.2% for infants from the pre- and the post-ADEPT cohorts, respectively.

Delayed start of milk expression, infrequent milk expression, early GA, maternal socioeconomic background, mode of delivery, being separated from infants in NICU due to complications related to birth, infant illness and physical immaturity can have negative impacts on milk secretion (319), which in turn will have an effect on the duration of breast milk feeding. Furthermore, Donor milk use may also affect the rate of MBM feeding because of more donor milk use might mean that mothers express less consistently from early on and continue for less time. The use of donor milk was significantly more among the post-ADEPT compared to the pre-ADEPT cohort. The prevalence of breastfeeding was not significantly different between infants from the pre- and the post-ADEPT cohorts; hence, it is likely that the pattern observed during the ADEPT study was a continuation of an existing underlying trend.

Given the documented short and long-term medical and neurodevelopmental advantages of breastfeeding, national (320, 321) and international (157, 322) strategies have been developed to facilitate breastfeeding practices. A progressive increase in the prevalence of breastfeeding has been observed since 1990 (149). Between 2005 and 2010, the UK government and health services across the UK invested in promoting breastfeeding through national, regional and local policies. There has also been a marked increase in engagement with the Baby Friendly Initiative (323) that may have improved rates of breastfeeding.

- Beneficial effects of BM on preterm infant outcome have been previously observed. These infants have lower rates of intestinal morbidity, sepsis (258), NEC (324) and that these infants achieve full feeding more quickly (325).

Unlike previous studies, no difference in the incidence of NEC and/or sepsis was observed in the current study between infants fed exclusively human milk and human milk complemented with formula. This might be partially explained by the provision of donor milk increasing in the post-ADEPT cohort. It has been revealed that the pasteurisation process of donor milk removes bioactive elements (326). Furthermore, donor milk is not superior to formula milk in terms of increased protection against NEC and sepsis (327). It is noteworthy that the significant effect of human milk might be dose-related. In other words, it may be related to the proportion of the total enteral intake of human milk (324, 328).

3.4.1.3 Secondary outcomes

3.4.1.3.1 NEC

In the present study, more than 20% of the study population had medically or surgically treated NEC. Direct comparisons of NEC incidence with other studies are complicated by the differences in case-definitions and population inclusion criteria. The dearth of a consistent case definition adds to the difficulties of determining true disease burden, synthesising the results of clinical studies, and assessing the effectiveness of quality improvement interventions. The present study examined recorded episodes that included all medically and surgically treated NEC, which may have included suspected cases of NEC. This is likely to have led to an overestimation of NEC cases. The difficulty of reliably distinguishing between feeding intolerance and stage I NEC should be acknowledged. Infants with stage I are usually treated conservatively with bowel rest and antibiotics. Therefore, since NEC often affects those with IUGR, especially infants born <29 weeks, which leaves a small possibility for false attribution. The inclusion of medically treated cases may explain the higher incidence of NEC in the current study compared to a recent study by Battersby et al. (329). The investigators

conducted a two-year population cohort study to assess the incidence of NEC in England finding that NEC affects 3.2% of infants <32 weeks GA. Of note, the Battersby et al. (329) study focussed on cases with severe NEC that lead to death, laparotomy or both. The inclusion of cases with severe NEC may have led to underestimating the total burden of the disease (329) and may explain the differences between the two studies.

Feeding practices for this patient group are challenging. Some studies have suggested that early enteral feeds accelerate the maturation of GIT functions without increasing the risk of NEC in SGA infants (132, 330).

Randomised trials have examined the effect of early or delayed introduction of feedings for IUGR infants with AREDF in the UA (9, 89, 139-141). The studies used minimal enteral feeding for their early feeding group and ages of milk introduction that were comparable to my study. The RR of NEC was 1.54 [95%CI: 0.469 to 5.043) in Karagianni et al (140) trial, 1.2 [95%CI: 0.77–1.87] in Leaf et al. (9) trial and no case of suspected or proven NEC was documented in Arnon et al. (89) trial (summary of these studies presented in Section1.8.2). Although these studies were poorly powered to detect NEC, recently, Tewari et al. (142) also assessed the effect of early versus late feeding in preterm IUGR neonates on the risk of NEC. The investigators showed similar findings; RR of NEC in very preterm (RR: 1.58 [95%CI: 0.24 to 10.61], p=0.5) and in the extreme preterm was 2.25 [95%CI: 0.17 to 29.77], p=0.6. Although Tewari et al. (142) trial was powered to assess NEC, the wide 95%CI indicates the uncertainty of their findings.

These findings were supported by a Cochrane systematic review (64), which suggested that early trophic feeding versus enteral fasting for very preterm or VLBW infants did not increase the risk of developing NEC for high-risk infants, including infants with IUGR, RR 1.07 [95%CI: 0.67 to 1.70]. There was no evidence of heterogeneity ($I^2 = 0\%$). Rather, delayed feeding may be associated with prolonged hospital stays and additional time required to achieved full

feeding. It is noteworthy that the review included SGA but did not focus exclusively on IUGR preterm infants with abnormal antenatal Dopplers.

The present study suggests that early feeding does not increase the risk of NEC in preterm infants with IUGR and abnormal antenatal Dopplers and that there is no significant difference in the incidence of NEC between the two cohorts: RR 1.07 [95%CI: 0.85 to 1.36]. The findings are in line with previous studies (9, 89, 139, 140) and is supported by the Cochrane review and meta-analysis (64). However, it is noteworthy that to improve the quantification of NEC prevalence and to assess the nutrition care practices for this high-risk group, a reliable clinical case definition, biomarker, or both are necessary. Recently, Battersby et al. (331) developed a gestational age-specific case definition for NEC. They emphasised that a combination of findings rather than a single clinical or abdominal x-ray finding provided the highest diagnostic accuracy (331).

3.4.1.3.2 Sepsis

The combined strategy of early feeding initiation and the use of exclusive and/or combined breast milk feeding may result in low incidence of neonatal sepsis in the current study population. It is noteworthy that despite the earlier initiation of PN, there was no increase in sepsis in post-ADEPT cohort. Sepsis rates were significantly lower in the post-ADEPT cohort who received PN significantly earlier compared to the pre-ADEPT cohort. That is multifactorial, of course, but is an important result as NICUs feared giving PN would increase sepsis rates.

In literature (332), many factors increase the risk of sepsis in preterm infants, including immaturity, intravascular catheters, mechanical ventilation, delays in establishing enteral feeding and prolonged PN. A significant association between the day of beginning enteral feeding and the incidence of neonatal sepsis was previously observed (333). Apart from the day of beginning PN and enteral feeding, in the current study, there was no significant difference in these risk factors between the cohorts. In the present study, a significant reduction of sepsis from 14.5% in pre-ADET to 6.8% in post-ADEPT was observed. The

reduction in sepsis rates could be related to changing policies and practices used to reduce the incidence of sepsis in NICUs. Infection control practices, such as strict hand washing, the use of disposable gloves and gowns as required, improved antiseptic procedures, closed airway suction systems, careful isolation of infected infants and shortened courses of antibiotic treatment (334, 335) have all been introduced in most centres during the time period of the study. The implementation of these strategies has been associated with decreased nosocomial infection rate and improved quality of care delivered to these vulnerable infants (334, 335).

3.4.1.3.3 Other outcomes

In the present study, further significant changes in clinical practices were observed, including increased use of antenatal steroids, which is known to improve neonatal survival and to reduce short-term morbidities in preterm infants (336).

Notably, despite the increased use of antenatal steroids in the post-ADEPT cohort, a significantly high proportion of infants still required oxygen at discharge. This finding may not be surprising, as there are conflicting findings on the benefits of antenatal steroids for IUGR infants (336, 337). Current evidence is based on observational studies, which have inherent limitations. One large population-based study (338) of 1720 IUGR infants born between 25 and 30 weeks gestation used outcomes reported in the Vermont Oxford Network database. The risks for RDS and neonatal death were all significantly reduced with antenatal steroids. The study also showed a smaller reduction in the rate of RDS among IUGR infants (Odds Ratio (OR): 0.7) compared to infants without IUGR (OR: 0.5) (338). However, the corresponding 95% CI were not reported, which does not allow assessment of margin of error when considering the results from the study.

In contrast, a large prospective cohort (336) of 1771 infants born between 24 and 31 weeks gestation showed that exposure to antenatal corticosteroids did not reduce the rates of RDS nor BPD in SGA infants. Data collected by the Israel Neonatal Network on infants with BW of

≤1500 g born from 1995 to 2012. In the current study, a significantly high proportion of infants still required oxygen at discharge in the post-ADEPT cohort. Once again, the Riskin-Mashiah et al. (336) study included SGA infants and did not focus on IUGR infants.

The completion of antenatal steroid course may have influenced the findings of the current study, as data on antenatal steroid course were not available from the Badger.net downloads. Partial steroid therapy has been found to have a lower protection rate for both SGA and non-SGA infants (336). Hence, the inclusion of the partially treated group may have reduced the estimation of the potential effect of antenatal corticosteroids in the current study.

Overall, no significant difference in the duration of hospital stay was observed between the two cohorts. Nonetheless, for infants discharged before 75 days, a significantly shorter duration of hospital stay was observed in the pre-ADEPT cohort. The prolonged hospital stay for post-ADEPT infants may be explained by the overall clinical condition of the neonates, expressed by low BW & GA and ongoing medical conditions (Table 3.4). It has been observed that the general clinical condition of preterm infants is significantly associated with increased length of hospital stay (339, 340).

The current study suggests that early feeding may not shorten the overall duration of hospital stay, or time of IC, HDC or SC. These findings are consistent with other randomised trials (139, 142). This is not surprising because there were no significant changes between the time required to achieve full feeding and the duration of PN. However, this is different from the Leaf et al. (9) study which showed a significant difference in the duration of HDC between the early and the late feeding groups. This might be due to differences in the neonatal populations. Unlike the current study, only stable preterm infants were eligible to be included in the Leaf et al. study (9). Furthermore, none of these studies (9, 139, 142), including the current study were powered to assess the effect of time to introduce enteral feeding on the duration of IC, HDC, SC and the overall hospital stay.

There are physiological competencies that are generally accepted as required before hospital discharge of a preterm infant. The competencies that are generally recognised for an infant to be considered ready for discharge are (341):

- oral feeding is sufficient to support satisfactory growth
- infant can maintain normal body temperature
- infant has sufficiently mature respiratory control

Not all competencies are achieved at the same postnatal age by all infants (341). The pace of maturation is affected by BW & GA and the degree and chronicity of neonatal medical conditions (342). Infants born earlier in the gestation period with more complicated medical course usually require a longer time to accomplish these physiological competencies (341). In the present study, no significant differences were observed in the neonatal medical conditions between the two cohorts observed, and this may result in a similar length of hospital stay between the two cohorts.

No significant difference in the incidence of GIT perforation/surgery, death or cholestasis was found between the two cohorts. Similar findings were reported previously (9, 139, 140).

3.4.1.3.4 Growth outcomes

Theoretical and practical evidence suggests that early nutrition support may improve growth outcomes for premature infants (106). In this study, changes in nutrition practices were associated with more favourable growth outcomes. Leaf et al. (9) study also showed a significantly higher weight gain for infants from the early feeding group compared to the late feeding group. However, whether the improvement in growth outcomes in the current study resulted from earlier commencement of PN, enteral feeding or unmeasured cohort differences, e.g. improved initial PN prescribed which better meet the needs of preterm infants is, unknown. The significant association between early nutrition support for infants born preterm, however, have been observed and discussed in detail in ChapterTwo.

3.4.2 The outcomes of infants from the ADEPT versus Non-ADEPT hospitals

In this part, few differences in outcomes between the two groups were observed. The infants comprised a relatively homogeneous sample because the mean BW and GA were similar between the two groups. A higher prevalence of donor milk feeding and lower incidence of GIT surgery among infants from the ADEPT hospitals were observed. Furthermore, infants from the ADEPT Hospitals had larger head circumference measurements.

Recently, researchers have described improvements in patient outcomes in hospitals that participate in clinical trials with changes in the hospital environment, which seemingly lead to better care and outcomes (284). However, the current study did not find a significant difference in nutritional care between the two groups. This could be due to the failure of ADEPT study to change health professional behaviour, even within units who recruited to the study.

In the current comparison, differences in some outcomes between the two groups of neonatal units were not found. This may be due to lack of effect or inability to detect the true effect on outcomes for infants from the ADEPT Hospitals versus the Non-ADEPT Hospitals. Clinical practices usually balance the strengths and limitations of all relevant research evidence with the practical realities of healthcare and clinical settings. Most of the available clinical trials described earlier were underpowered to assess very important adverse outcomes that may relate to the early introduction of enteral feeding.

3.4.3 Strengths

The current study has several strengths. To my best knowledge, this is the largest population study evaluating the trends of nutrition practices and outcomes of IUGR preterm infants with abnormal antenatal Dopplers in the UK over nine-year period. This empirical study was conducted using recorded patient-level daily data of a large sample of IUGR infants from different parts of the UK and is likely to be representative of the IUGR population. Whilst

observational studies have limitations, findings of this study have the advantage that they apply to even the extremely small and immature infants; unlike many of the RCTs conducted which usually exclude this high-risk population. Observational population-based data have an important role in informing the design of RCTs by yielding more precise estimates on the effect size of an intervention (343).

Databases such as Badger.net offer a substantial advantage because they provide ready access to local data that is not subject to the interventions or selection bias of other study designs (as described in Section 3.1.2). Data spanning a nine-year period provided as a robust sample as possible.

The national data set consisted of electronic records of a large majority of infant admissions to neonatal-care units in England. The geographical coverage of the databases eliminated issues related to selection bias and questionable generalisability (344).

3.4.4 Limitations

The study has some limitations. These issues may be related to data collection, entry, variability, and quality including data incompleteness.

The internal validity and reproducibility is important in any retrospective study (345), therefore, standardising the detailed nature of data collection is very important.

The overall national data set consisted of electronic records of a large number of infant admissions to approximately 200 neonatal care units in the UK. The geographical coverage of the databases might be limited by concerns related to inconsistencies and omissions in the coding, which could lead to misleading findings. Badger.net uses a national standard coding system and predefined data items to ensure high data entry accuracy. The use of a database to answer a research question may lead to issues as well. Moreover, data extraction is a key issue in using information from a database for research studies (291). However, a

predesigned data collection form, which included categories that clearly defined for the researcher, was used to ensure the validity and accuracy of data collection.

Another limitation may have related to data quality. Despite databases being an attractive source of data in variety of research designs as detailed in Section 3.1.2, they have some limitations. Firstly, data completeness. For example, full enteral feeds were not reported for more than 6% of the study population. This may weaken the association between the variable (e.g. day of beginning enteral feeding) and the outcome (e.g., time required to achieve full feeds and duration of PN). A similar concern has been highlighted in studies that used the Badger.net database or the National Neonatal Research Database (NNRD), which contains data extracted from the Badger.net database (329, 331). Nevertheless, the sensitivity analyses for missing data did not yield differing conclusions for the main outcomes.

Another important consideration when using electronic data for research is data accuracy. However, internal validity is one of the most commonly used methods to assess data accuracy. Badger.net database provides detailed discharge letter production from recorded data during the stay at the neonatal unit (285). Furthermore, data within the Badger database are annually assessed by the National Neonatal Audit Programme (NNAP) to assess and monitor the quality of care provided by the neonatal units, although data entry errors are to some extent inevitable (98). Data were entered into Badger.net database during clinical stays. Prospective data entry helps to eliminate recall bias. However, not all centres have bedside data entry and they may relay or use delayed data entry.

Multiple individuals, including medical and nursing staff, are responsible for data entry into the Badger database, which may ensure the completeness of data entry (97). Also, this allows comparing the same information from different locations within the database. On the other hand, data entry by multiple individuals may cause data inconsistency.

The current study was limited by the focus on medical and surgical treated cases of NEC. This can propagate into biased estimates of the incidence of the disease, the estimation of which

will necessitate either a reliable clinical case-definition or biomarker. It should also be acknowledged that the difficulty in separating food intolerance and spontaneous intestinal perforation from NEC is a concern as these are likely to be false positive case labelled as NEC.

Furthermore, full enteral feeding is defined as the time required to attain a sufficient feed volume to discontinue PN; however, this definition can be inconsistent because the target nutrition level may vary according to local guidelines. This definition could have been confirmed by reviewing nursing charts. The reason for not doing so was that reviewing the nursing charts of patients would have made this study unfeasible with the resources including time available.

I recognise that the inclusion of culture-proven cases of sepsis may be considered a limitation. The potential limitation of the case definition used for sepsis may also be criticised as it is likely to exclude many actual cases. This is because positive cultures are affected by the blood volume inoculated, prenatal antibiotic use, level of bacteraemia and laboratory capabilities. Furthermore, neonatal sepsis is a high-risk disease, infants with risk factors, signs of suspected sepsis or both, receive antibiotics. Both broad-spectrum antibiotics and prolonged treatment with antibiotics may increase antimicrobial resistance rates and cause false negative results from cultures. On the other hand, contamination of blood samples during blood drawing has been suggested to have led to an overestimation of the incidence of sepsis (346).

Another potential limitation of this study was the nature of the study cohort, which included infants born from 1st Jan 2007 to 31st Dec 2015, because in some neonatal units, Badger.net was established after 2007. Therefore, there could have been missing data for some eligible infants, which may have introduced bias. Some of the variations in population coverage could be attributed to differences in the guidelines for the ongoing management of extremely low gestational age neonates. However, the units included were a representative sample.

The most important consideration when using electronic data for research is data quality. To prevent any threats to the internal validity of the study, a sustained assessment of care processes over time, such as annual reports issued by the NNAP, may improve data quality.

3.4.5 Conclusion

The results of this study suggest that the potential benefits of early PN along with early enteral feeding outweigh the unproven risks of NEC in IUGR infants with abnormal antenatal Dopplers. The study findings may provide a platform for planning activities targeted to improve data collection systems further and to standardise neonatal-perinatal terminology based on the most recent definitions, such as the newly developed definition for Neonatal NEC (331). Based on the results of this study, the effect of early initiation of enteral feeding on the long-term growth and development of IUGR infants with abnormal Dopplers should be assessed.

Chapter 4: Evaluation of health service promotion: families'/carers' perceptions about weaning of infants born preterm

4.1 Background and rationale

Weaning as described by WHO "is the process by which a baby slowly gets used to eating family or adult foods and relies less and less on breast milk"(347). It, therefore, encompasses the period from starting weaning foods to the point when their use is established.

The practice of weaning has varied over time and across the UK (149). Although both the recommendations from the WHO (322) and the Departments of Health (DH) UK (348) suggest that weaning should be started at around six months, in 2010, three-quarters of mothers started weaning by the age of five months old (149).

In the UK, commencement of weaning of preterm infants also varies widely and infants often have complementary foods before four months actual age (146, 182). In the early 2000s, 21% of infants studied received first weaning foods before the DH recommendation (146). In another study (349), infants had weaning foods around the age of seven weeks corrected gestational age (CGA: age adjusted by subtracting the number of days or weeks premature from chronological age).

The available evidence-based weaning recommendations (157, 322, 348) apply to full-term infants and may not appropriate for those born preterm, particularly those born before 34 completed weeks of gestation.

The optimal age for commencement of weaning of preterm infants is poorly researched. The decision to commence weaning should be made by taking into account the infant's actual age (from birth) and CGA, nutritional requirements, and developmental maturity (350). Current guidelines for preterm infants recommend that weaning should be commenced safely from

somewhere between five and eight months from the date of birth, but not before three months CGA (151, 160). Many families do not comply with these guidelines and commence weaning earlier than these recommendations (146). One consideration in the application of weaning recommendations is that the populations in weaning studies may not be representative as the burden of morbidity is greater among infants from deprived areas because of increased rates of very preterm births (351).

Families who commence weaning around the recommended time tend to be influenced by formal information sources, such as advice from health professionals or written information (182, 352). Support from health professionals has the potential to influence weaning practices as do cultural values and material resources (353). Early nutrition support resulted in increased knowledge of exclusive breastfeeding and delayed commencement of weaning beyond the first three months of life (206). The UNICEF UK Baby Friendly Initiative standards for maternity, neonatal, health visiting and children's centre services (323) emphasise the importance of educating parents' before their children being discharged from hospital. This general education should include support for carers to make informed decisions regarding the commencement of weaning and enable them to wean as safely as possible (323).

After discharge, community health professionals should be able to offer recommendations and advice to address parents' concerns, including those around nutritional status, growth expectations and determining developmental readiness to start weaning (323). Support provided to parents soon after the discharge of their child from hospital would be expected to improve their skills and capacity to improve children's outcomes such as nutrient intakes and growth (162).

Commencement of weaning is arguably one of the most worrying aspects of parenting of preterm infants (354) and it "...continues to cause more anxiety to mothers, nurses and doctors than almost any other issue in paediatric nutrition" (355). Parental beliefs and understanding are the main determinants of infant feeding behaviour (181) and any

interventions need to take account of their views. Assessing parents'/carers' perceptions, practices and the support provided to them regarding weaning might help to identify gaps in service provision and the improvements possible in weaning practices.

Although the commencement of weaning earlier than recommended in preterm infants has previously been reported (146, 147), little is known about the timing or factors affecting commencement of weaning amongst this population. Furthermore, there has been little-published research into parents'/carers' experiences and satisfaction on the support provided to families on weaning.

Understanding the differences in beliefs and practices is important for the successful delivery of health messages and health services to diverse populations (356). Improvement in quality of care is not, however, provided by health-care providers alone. Individual service users are critical in identifying their own needs with appropriate support from health-care providers (356). This is particularly the case with feeding support for preterm infants.

Up-to-date information observed from a representative population of preterm infants is required to better understand the current attitudes, practices, perceptions and support provided on weaning preterm infants. To explore families' perceptions, attitudes and practices related to weaning, a cross-sectional study design using a questionnaire was conducted.

Questionnaires are commonly used for descriptive research to measure the attitudes and opinions of responders (245). Several types of questionnaires have been described (Figure 4.1) (1). The types of questionnaires differ based on how they are conducted. These types include self-completed questionnaires and interviewer-completed questionnaires. Self-completed questionnaires, which are completed by the participants, include web questionnaires and postal questionnaires. Interviewer-completed questionnaires are a type of questionnaire which is recorded by the researcher based on the participant's verbal response. Telephone questionnaires and face-to-face questionnaires are two commonly used types of Interviewer-completed questionnaires (245). The apparent difference between self- and

interviewer-completed questionnaires is the absence of researcher in the self-completed questionnaire. In other words, the self-completed questionnaire requires the respondent to read and answer the questions independently.

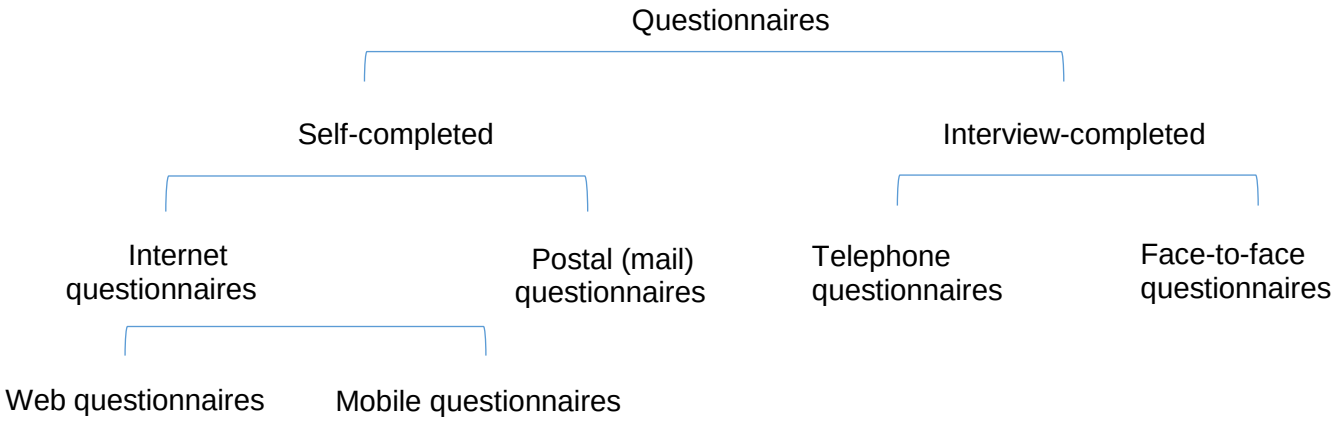

Figure 4.1 Diagram illustrates the different types of questionnaires. Adapted from Saunders et al. (1)

The choice of the questionnaire may be influenced by a variety of factors related to the research question(s) and objectives (357), such as:

- characteristics of the subjects from whom data will be collected
- importance of responses not being influenced by a researcher
- the sample size required for analysis, considering the likely response rate
- types of questions needed to collect the relevant data
- Number of questions needed to collect sufficient data to answer the research question
- resources available for data collection, including the time available to complete data collection, financial implications of data collection and entry and online survey tools, which allow researchers to select an appropriate study design.

4.1.1 Advantages and disadvantages of self-completed questionnaires

Compared to the interview design, self-completed questionnaire is characterised by its ease of administration and reduced costs of administration (358), even if a study sample has a geographically wide distribution (245). Online questionnaires are much less expensive due to

the reduced time and cost of travel required for the interviewer. Bryman (245) highlighted that a large number of online questionnaires could be simultaneously launched and distributed in a shorter time compared to the time required to conduct personal interviews with similar sample size. Self-completed questionnaires also reduce the possibility that researchers might influence participants' responses (245).

Self-completed questionnaires are also more effective than interviews when there are questions that are sensitive or that induce anxiety (245). Moreover, self-completed questionnaires are usually associated with the collection of quantitative data, thus allowing the data to be entered directly onto a spreadsheet in a numerical format and to be analysed quickly (359). Self-completed questionnaires also allow researchers to gather consistent and sufficiently accurate information straightforwardly and conveniently (245).

Closed-ended questions are mainly used to obtain insight into participants' practices, feelings, agreement or discord related to the support provided. Bryman (245) explained that closed questions make it easy to process the answers, they enhance comparability between answers, they are easy for the respondent to complete and they reduce the variability in responses. Nonetheless, closed questions exhibit some disadvantages, such as the risk of loss of spontaneity in a respondent's answer and questionnaires not allowing participants to elaborate on their answers even if they have difficulty answering a question or a preferred option is not available. Also, they may not provide a complete list of options relevant to all participants. Therefore, including some open-ended questions in a questionnaire is recommended (300), and allows the researcher to obtain unique opinions and experiences of each respondent.

Likert-type scales are rating questions often used to measure observations and attitudes (245). Likert scale questions allow participants to report neutral, moderate and extreme attitudes and to provide opportunities for accurate mapping (360). Participants are asked how strongly they agree or disagree with a statement usually on a four-, five-, six-, or seven-point rating scale (1). However, the length of the scale may impact the process by which

respondents map their attitudes to response alternatives (360). Consensus regarding the optimal number of response items on a rating scale has not been attained. Givon et al. (361) argued that reliability might be improved by increasing the points of the scale, but increases beyond seven points become quite minimal for single items. Others (360) suggested that to maximise the reliability and the validity of the rating questions, a 5-point scale is adequate to obtain reliable responses without overlapping in the meaning of the adjacent points.

Intermediate scale lengths are optimal in terms of reliability (362, 363). High reliabilities were reported for five-point scales (364), and this reliability did not change significantly when a five-point rating scale was compared to 6, 7, 8, 9 and 11 items in a scale (365). Furthermore, long rating scales may become too cumbersome, and any additional benefits could be cancelled out by 'respondent fatigue' and reliability decrease (366). The sensitivity of the scales might also be compromised by the fact that respondents tend to interpret the scales in different ways. For example, 'often' to some may mean the same as what others might consider 'sometimes'. This phenomenon could be augmented when the number of potential responses is large.

On the other hand, questionnaires have limitations such respondents ignoring questions that are not considered important or misunderstood. To control this and to reduce the risk of missing data, the questionnaire should not ask too many questions (245). Also, using online or computerised questionnaires enables researchers to make answering questions compulsory.

4.1.2 Hypothesis

The hypothesis in this study was that health carers are meeting the needs and expectations of parents/carers regarding the commencement of weaning of preterm infants and that this has positive influences on weaning practices.

4.1.3 Aim

This study aimed to:

- gain insight into current practice of commencement of weaning of preterm infants
  - to evaluate if health carers are meeting the needs and expectations of carers of infants born preterm
- to determine the current perceptions and practices among parents of preterm infants on:
  i- the appropriate age to commence weaning
  ii- weaning readiness cues
  iii- types of weaning food
- to ascertain:
  i- whether variations in the commencement of weaning is associated with gestation age and body weight at birth
  ii- whether the commencement of weaning differs with socioeconomic characteristics and ethnicity of the parents
  iii- the criteria parents use to determine the appropriate time to commence weaning.

4.2 Methods

4.2.1 Study design

A cross-sectional study was conducted using a questionnaire-based survey. I adapted a previous study protocol designed by Dr Shalini Ojha to suit data collection for the current study.

4.2.2 Setting, sampling and study population

The study took place in outpatient clinics of the Neonatal Service of the Nottingham University Hospitals NHS Trust (NUHs) at both its Queen's Medical Centre and Nottingham City Hospital campuses.

4.2.2.1 Selection of participations and representativeness

Selection of participants in the current study was based on convenience sampling (described in Section 2.5.2.1). All parents of infants in the follow-up clinics were equally likely to be selected in the study. Simple random sampling was used based on a full list of patients in the follow-up clinics of all previously inpatient preterm infants. At the Nottingham University

Hospitals, infants born at ≤30 weeks routinely offered follow-up appointments until two years CGA. The consultant neonatologist decides follow-up for infants born at >31 weeks gestation before discharge and/or at subsequent outpatient clinic appointments. Also all infants born at ≤ 35 weeks gestation who had medical needs in the neonatal period are offered follow-up appointments.

According to the research topic and setting, sampling can follow many different strategies. Bryman (245) suggested taking into account viability issues (in terms of time and respondent availability) when designing the sampling plan. My objective was to find participants who could provide varied insights into weaning preterm infants, families' perception on the support provided on commencement of weaning and to understand the factors that may affect weaning practices. I was interested in how support affected parents differently and why they were practising weaning in a particular way. Therefore, criterion sampling (defined as sampling that involved selecting cases that meet the pre-specified criterion of importance) (245) was used as a sampling strategy in the current study.

The identification and selection of participating parents were based on pre-specified criteria as recommended by Bryman (245). The criteria included their willingness and availability to participate in the survey. Further criteria were based on their preterm infants. All eligible patients in follow-up clinics, who met the inclusion criteria, were approached.

There are weekly outpatient clinics that caters to all socioeconomic classes; the recruitment in this study took place every week. The data were collected between Feb 2016 and Jun 2016.

4.2.3 Inclusion criteria

Caregivers were eligible to participate if they had a child:

- born ≤34^{+6} weeks gestation, and
- who was ≤2 years old at the time of the questionnaire

4.2.4 Exclusion criteria

Caregivers were excluded if they were:

- unable to complete the questionnaire due to language or
- had a child with congenital anomalies or other conditions that were expected to make oral feeding unsafe

4.2.5 Questionnaire development

A detailed structured, paper or web-based questionnaire was designed and conducted using the Bristol Online software available from http://www.survey.bris.ac.uk/ (Appendix 8.7).

To the best of my knowledge, there are three previously published studies-based surveys addressed the commencement of weaning of preterm infants. However, the questions that have been used in the previous studies were not presented (146, 147, 182). Furthermore, to obtain diverse but clear insights of different practices, attitudes and perceptions as well as the support provided for families on commencement of weaning, I decided to develop the questionnaire.

Several methods could have been used to develop a questionnaire (245). The questionnaire design drew on two sources in addition to researchers' creativity (245): (a) previous qualitative data gathered from respondents, such as recorded unstructured/semi-structured interviews; and (b) quote questions from established questionnaires. Therefore, the questionnaire used in the current study was developed based on the structure of previous similar studies (146, 147, 149, 182). These studies have been successful in collecting data on weaning practices and have used a structured interview (146), and questionnaires (147, 149, 182).

When writing the survey questions, I tried to select words carefully that would not confuse the participating parents, as I wanted to encourage them to answer openly and share the experiences that they had about weaning. I also avoided starting the questionnaire with sensitive topics such as respondent’s level of education or the occupation because I wished to obtain responses without missing data so tried to prevent them worrying about me judging them.

The questionnaire was subdivided into four domains containing questions;

- related to weaning advice and practices were stratified into:
    i. questions for families who had previous/current experience of weaning their preterm infant (Families commenced weaning), which were designed to gather information about their actual weaning practices, and
    ii. questions for families who had not yet weaned their babies (Families have not commenced weaning yet), which were designed to gather information about their weaning intention.
- related to experience from weaning previous children
- addressing the history of allergic diseases in a family
- to gather demographic data about participating families

The questionnaire consisted of multiple choice and 5-point scale rating questions. As multiple choice questions with many options are susceptible to bias (1), the order of the choices was changed between each questionnaire to collect the most accurate data from respondents and to reduce the response bias. It has been recommended that a well-designed questionnaire should include reversed items to reduce response bias (367).

As concerns about allergy can influence complementary feeding practices (179), participants were asked if there was family history of allergy/atopy. Allergies were defined as eczema, asthma, hay-fever and an allergy including a food allergy. As there is sometimes confusion between allergy and food intolerance, participants were asked to specify what kind of allergy and which family member had a history of allergy, if any.

Throughout the questionnaire, ‘weaning’ was used according to the WHO definition (described in Section 4.1). Where ‘weaned’ was used, this referred to the time when the child no longer takes any breast milk.

‘Weaned’ is a verb in the past tense. Therefore, some participants might understand it as weaning has been achieved. However, others may read it differently and may not understand the difference between having finished weaning and being in progress. To deal with this I included three choices in the question that is addressing the experience of weaning: ‘yes’, ‘no’,'

‘in progress’. Participants, who chose ‘no’ were defined as families who have not commenced weaning yet and rest were defined as families who commenced weaning.

4.2.6 Piloting

The questionnaire was initially piloted with a diverse group in the Division of Child Health, at the University of Nottingham. The purpose of the questionnaire pilot was to get feedback on the survey that may help to assess respondent comprehension and interpretation of the survey questions, which include overall evaluation on the survey accessibility, contents, effectiveness and errors. A pilot survey also tests the difficulties of the questionnaire and respondent perceptions of the length of the questionnaire. I tried to get feedback from topic experts (who have deep knowledge and expert about the survey theme) and from target population (mothers who had experience of weaning (n=5)). The survey was piloted by two mothers of children around weaning age, a Specialist Neonatal Dietitian, a Dietitian, two neonatologists with experience of weaning, and two researchers. A common theme was that responders felt that the wording for some questions was not easy to understand. Based on the feedback received from the pilot process, the following changes were made on the questionnaire, such as re-wording of questions to aid greater clarity:

- the original question was “Would you mind telling us about the highest educational that you have attained”. This was replaced with “Would you mind telling us about the highest level of education that you have attained”.
- the original statement was “We asking, if you are happy to give us the information about your background, to look at weather cultural orientation may affect weaning practices”. This was replaced with “We asking, if you are happy to give us the information about your background, to look at whether cultural orientation may affect weaning practices”.
- the original statement was “Higher managerial and professionaloccupations” this was replaced with “Higher managerial and professional occupations”.

Following which the amended questionnaire was submitted University of Nottingham Medical School Ethics Committee for ethical approval (described in more detail in Section 4.2.10) and then launched after that.

4.2.7 Process

The researcher attended clinics at both hospitals. All participating parents invited to the study received an information sheet (Appendix 8.8), which summarises the purpose of the study, including how the participant would be involved, what would happen to their confidential information and the researchers' responsibilities. Participating parents/carers had the right to withdraw from the study without prejudice or negative consequence and without giving any reason. They were given time to read the information sheet and to ask questions regarding the study and their participation.

Participating parents who were happy to take part in this survey were asked to complete the questionnaire independently in the clinic. Participants were encouraged to complete the questionnaire before leaving the clinic where the researcher was available to clarify questions where needed. Questionnaires in paper format were made available when the online format could not be used due to technical issues. When questionnaires were completed in paper format, responses were checked for missing or uncompleted answers and data were entered manually into Bristol Online software by the researcher.

4.2.8 Informed consent

To respect participant's autonomy, it is important to permit them to make a 'free, independent and informed choice without coercion' (368). The consent process provided the opportunity for the participants to understand a given research and ask questions and for a researcher to explain the nature of participation, to respect individual autonomy, and to confirm the participant's agreement to participate in the study. All potential participating parents/carers had the basic information to make an informed decision about their involvement in the study. Then,

each participant completed and signed the specific study consent form (Appendix 8.9) and was provided with the questionnaire to complete.

4.2.9 Participants' details

Following informed parental consent, detailed information regarding the child of the participating parent was recorded from the child's medical records. The information including date of birth, birth gestational age (GA), birth weight (BW), sex, birth order, mode of delivery, duration of intensive care (ICU), day of starting enteral feeds, discharge weight, the type and method of feeds at the time of discharge from hospital and any co-existing medical conditions. The information was recorded initially on data collection forms, then anonymised and entered as electronic data and saved on a password-protected computer provided by the University of Nottingham.

4.2.10 Ethical approval

Ethical approval for the study was granted from the Medical School Ethics Committee at the University of Nottingham (Ref: H10112015SoM CHOG PhD: Appendix 8.10). To give the power described in Section 4.2.13, an ethical amendment to permit an increase in the sample size was approved in April 2016 (Appendix 9.10). To have a broad range of opinions of parents'/carers' experience, practice and perception on commencement of weaning, 100 participants were approached.

4.2.11 Confidentiality

Parents'/carers' full name and children's full name, study ID were documented separately from the Case Report File. All Case Report Files were stored in a locked office at the Division of Child Health, Obstetrics and Gynaecology at the Queen's Medical Centre and only the Chief Investigator, the research team and authorised personnel from the relevant regulatory authorities to have access to these files. Electronic data were anonymised and saved on a password-protected laptop, provided by the University of Nottingham.

To fulfil the updated Data Protection Act Policy, I have handled and stored all personal information in accordance with the General Data Protection Regulation (GDPR), 2018.

4.2.12 Data analysis

All statistical analyses were conducted by myself (using SPSS) v23 (309)) under guidance from a statistician (Dr Andrea Venn). Parametric variables were presented as means (± standard errors of the mean (SEM)), whereas non-parametric variables were presented as medians (interquartile ranges (IQR)). Independent t-tests were used where data were continuous and parametric, otherwise, Mann-Whitney U-test was used. Chi-square tests were used when analysing categorical data, otherwise, one-way analysis of variance (ANOVA) test was used for statistical differences between more than two variables.

For each rating question, the percentages of each composite were calculated.

The age of commencement of weaning was considered at both actual, and corrected postnatal age to allow for the degree of prematurity of the infants. As some recommendations have been formulated by actual age (151, 160), CGA also considered being of importance to give an accurate assessment of infants' developmental abilities.

Regression analysis was undertaken to investigate the potential factors that may determine the age of commencement of weaning (dependent variable). The variables were used to predict the age of commencement of weaning were called independent variables. Scatter plots and Person's correlations were used to assess relationships between the variables. Univariate linear regression analysis was performed to detect factors influencing the age of weaning. The univariate analysis included the following predictors: BW, GA, day of starting enteral feeding, duration of ICU stay, gestational age at discharge. Variables found to be significantly associated with age of weaning in the univariate analysis ($p<0.05$) were considered candidate variables for the multiple linear regression.

The variables were then assessed in combination using multiple linear regression analysis.

A p-value of <0.05 was considered statistically significant.

4.2.13 Sample size

To test the study hypothesis, the target sample size was 100 caregivers with their preterm children. A sample size calculation was conducted using the nQuery software. Based on estimates from the infants' feeding survey (149) in which 86% of mothers reported receiving formal advice on commencement of weaning, the study was designed so that we could be 95% certain that between 80 and 92% of all families would have formal advice on commencement of weaning.

4.3 Results

From February 11th to June 9th 2016, at the Nottingham Neonatal Service (Queen's Medical Centre and Nottingham City Hospital sites), 176 families were expected to attend outpatient clinics. One hundred and thirty-nine families attended their appointments, whilst 37 did not (35 families missed their appointments and two families rescheduled to another time outside the study period). Of the 139 families who attended the outpatient clinics, 12 participants were not approached because the study researcher was dealing with other participants at the time. Twenty-seven participants did not wish to participate; 6 participants cited a lack of time to participate, 3 participants did not speak English, one baby was unwell, 13 participants stated that they were not interested and two children were excluded as they had medical conditions that might interfere with feeding. Therefore, 102 participants who attended the clinic participated. Two questionnaires were excluded because the respondents skipped essential questions. Therefore, a hundred questionnaires were completed and included in the final analysis (Figure 4.2).

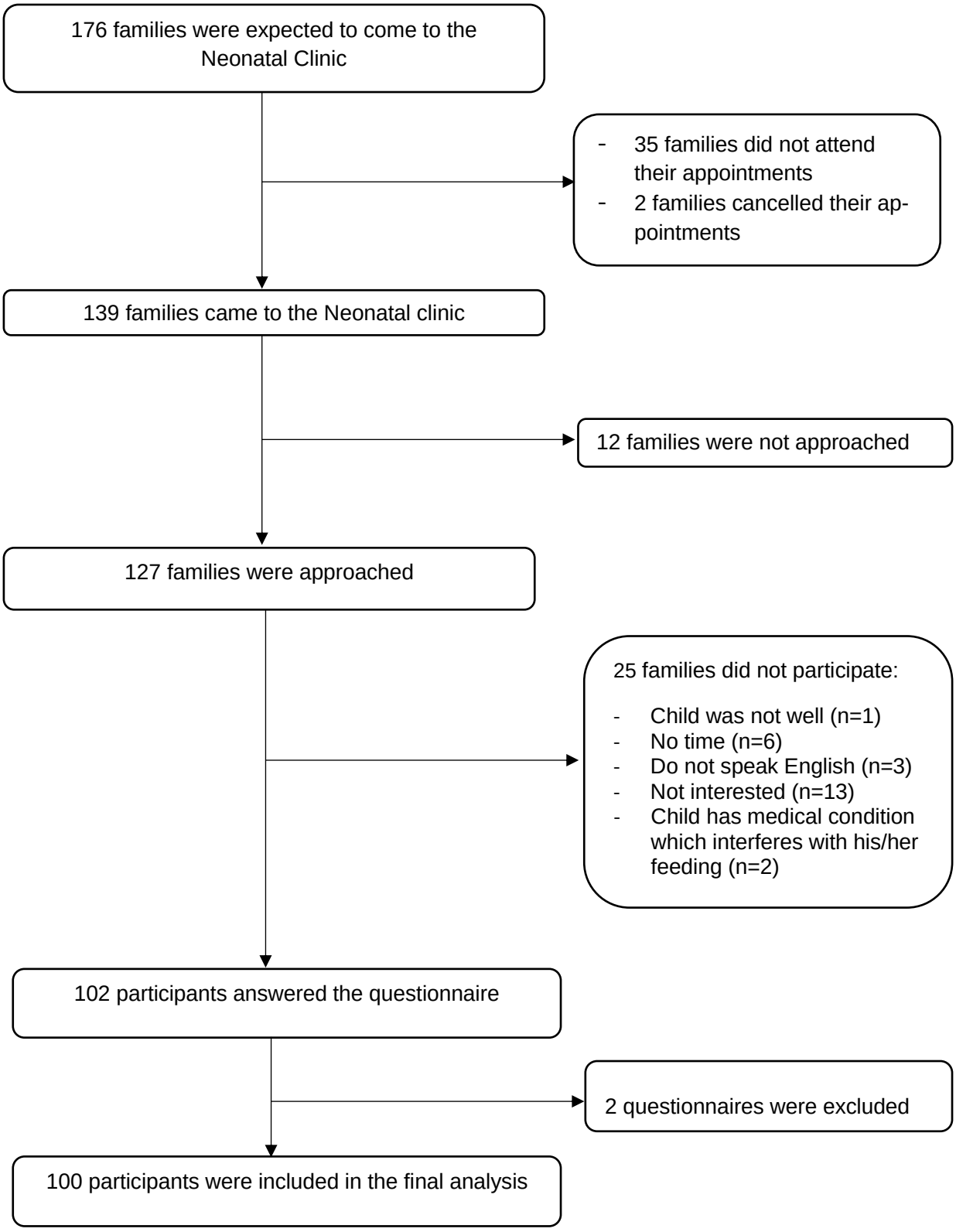

Figure 4.2 Flowchart of study recruitment

4.3.1 Baseline characteristics

At the time the study was conducted, the median (IQR) age of the infants was 43 (19-71) weeks. There was forty female (40%) and 60 male (60%) infants. The median (IQR) GA was 30 (27-31) weeks and the mean (± SEM) BW was 1.3 (± 0.05) kg. There was no significant difference in BW between boys and girls, 1.3 (± 0.06) and 1.3 (± 0.07) kg, respectively, p=0.7. Approximately half (51%) of the children were born between 28 and 31 weeks gestation, 34% born <28 weeks gestation and 15% born between 32 and <37 weeks gestation (Table 4.1).

Table 4.1 Characteristics of preterm infants

Variable	All (n=100)	Families commenced weaning (n=72)	Families have not commenced weaning yet (n=28)
Postnatal age* (weeks)	48 (20-72)	57 (40-80)	16 (10.25-20)
Female sex	40 (40%)	37 (38%)	13 (46%)
Birth GA* (weeks)	30 (27-31)	29 (27-31)	30 (27-32)
BW (kg)	1.3 (0.1)	1.3 (0.6)	1.4 (0.1)
Duration of NIC*	5 (2-17)	4 (2-18)	6 (2.25-14.25)
Mode of delivery:			
Vaginal	46 (46%)	36 (50%)	10 (36%)
C/S	54 (54%)	36 (50%)	18 (64%)
Birth order:			
First	63 (63%)	45 (63%)	18 (64%)
Second	22 (22%)	15 (21%)	7 (25%)
Third	6 (6%)	5 (7%)	1 (4%)
>Third	9 (9%)	6 (8%)	2 (7%)
GA at discharge (weeks)*	36 (35-38)	36 (35-38)	36 (34-37)
Weight at discharge (kg)	2.3 (0.08)	2.3 (0.1)	2.1 (0.1)
Type of milk at discharge			
Breast milk	43 (43%)	27 (37.5%)	16 (57%)
Formula	35 (35%)	27 (37.5%)	8 (29%)
Both	22 (22%)	18 (25%)	4 (14%)

Values are given as mean (± SEM) or n (%), unless otherwise specified; *median (IQR);
Abbreviations:
Birth weight: BW; gestational age: GA; Neonatal Intensive Care: NIC; Caesarean section: C/S

An analysis of the entire set of families who have infants born earlier than 35 weeks who were admitted to the NUHs between Jan 2016 and Dec 2016 showed no significant difference between them and participants in participating parents' age, ethnicity, infants' gender and mode of delivery. Significant differences were observed in infants' birth weight, gestational age

at birth, duration of intensive care, gestational age at discharge from hospital, and the duration of intensive care (Table 4.2).

Table 4.2 Sample characteristics of the study population compared to entire population

Variable	The study population (n=100)	The entire population of preterm infants born between 2014 and 2016 (n=1043)	P-value
Female gender	40 (40%)	400 (42.4%)	0.7
Birth GA* (weeks)	30 (27-31)	31 (27-33)	<0.001
BW (kg)≠	1.3 (0.1)	1.5 (0.2)	0.002
Duration of NIC*	5 (2-17)	0 (0-6)	<0.001
Mode of delivery: **Vaginal**	46 (46%)	(47%)	0.8
Birth order: **First**	63 (63%)	761 (80.9%)	<0.001
GA at discharge (weeks)*	36 (35-38)	34 (33-36)	<0.001
Age group **≤25 years** **26-35 years** **≥ 36 years**	21 (21%) 56 (56%) 23 (23%)	119 (27%) 259 (58%) 67 (15%)	0.1
Ethnic background **British**	74 (74%)	581 (89%)	0.1

Values are given as n (%), unless otherwise specified; *median (IQR); ≠ mean (± SEM) or
Abbreviations:
Birth weight: BW; gestational age: GA; Neonatal Intensive Care: NIC

As observed, the target population corresponds to the entire set of families who have infants born earlier than 35 weeks postconceptional age, which indicates that the study population is representative.

4.3.2 Sociodemographic characteristics of the parents/carers

The study population was predominantly British/Irish with 24% being non-British. The majority (79%) of the participating parents were over 25 years old at the time of the study (Table 4.3).

Table 4.3 Demographics of parents

Parent characteristics	Parents (%)
Ethnic background	
White English/Welsh/Scottish/Northern Irish	74
Black English/Welsh/Scottish/Northern Irish	2
White and Black Caribbean	4
White and Black African	7
White and Black Asia	1
Indian	2
Pakistani	5
Other Backgrounds	5
Respondent highest educational attainment	
School level	28
Further education	64
No answer	8
Occupation	
Higher managerial/professional occupations	39
Lower managerial//intermediate occupations	16
Small employers/lower supervisory and technical occupations	4
Semi-routine/routine occupations	10
Never worked/ student	9
Not specified	22
Age group	
≤25 years	21
26-35 years	56
≥ 36 years	23

n=100

When participating parents were asked to recall their experience about the commencement of weaning and weaning-related events by responding to a questionnaire, they are generally instructed to consider a specific period for their response. This recall period may be the recent past, including the past weeks, or; months or, longer. Since this study included infants <2 years old, the recall time might be perspective for some parents who are approaching weaning age and families' perception and practice of weaning may differ according to infants' age. For this reason, in the analysis, participants were subdivided into 'Families commenced weaning' that included infants who were already weaned or for whom weaning was in progress (72/100), and 'Families have not commenced weaning yet' that included infants who had not yet been weaned (28/100) Figure 4.3.

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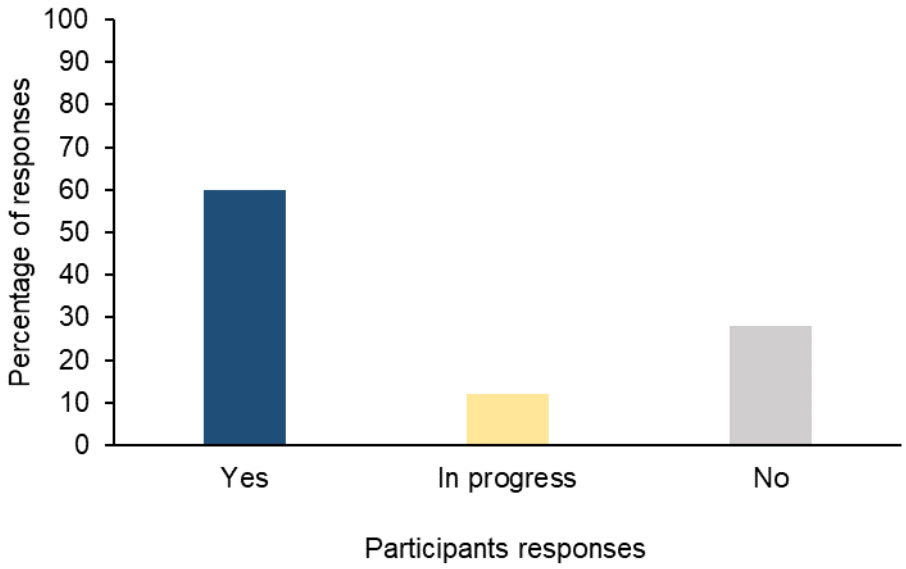


Figure 4.3 "Have you weaned the infant you are bringing to this clinic yet?"

Blue: respondents have already weaned their infants; n= 60; Yellow: respondents were in the process of weaning; n= 12; Grey: respondents have not been weaned yet; n=28

4.3.3 Age of commencement of weaning

The mean (± SEM) actual age of commencement of weaning in the study population was 26 (± 1) weeks, corresponding to CGA of 15 (± 1) weeks (Table 4.4).

Table 4.4 Age of commencement of weaning

	Actual age of commencement of weaning (weeks)	Corrected age of commencement of weaning (weeks)
All participants (n=100)	26 (±1)	15 (±1)
Families commenced weaning (n=72)	26 (±1)	16 (±1)
Families have not commenced weaning yet (n=28)	24 (±1)	13 (±1)

Values are given as mean (±SEM)

Three-quarters of participating parents had not/intended not to start weaning until the age of 20 weeks after birth (Families commenced weaning: 54/72 (75%); Families have not commenced weaning yet 22/28 (77%)). These results show compliance with the few existing general recommendations on commencement of weaning of preterm infants (Bliss (151) and BAPM(160)). DH (157)). However, fewer participating parents weaned/intended to wean after

20 weeks CGA. Overall, 60% of the study population had started/intended to start weaning at >3 months corrected for prematurity (Families commenced weaning: 44/72 (61%); Families have not commenced weaning yet: 16/28 (57%)).

4.3.4 Attitudes of families at the commencement of weaning and sources of information

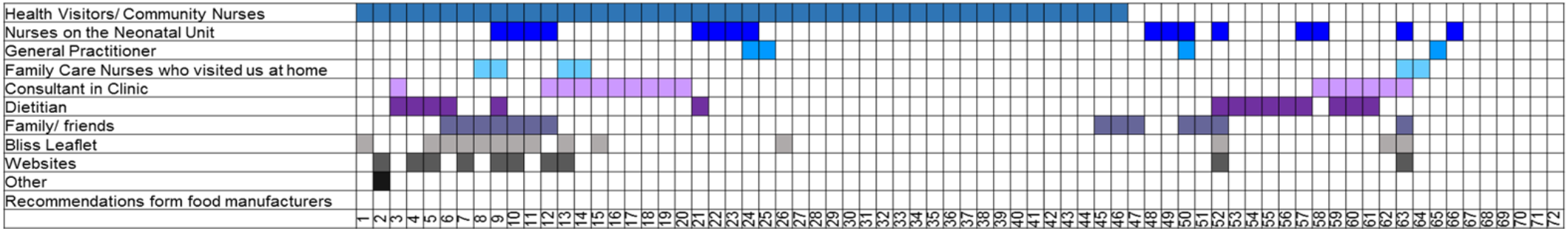
Participants were asked whether they had received information on when to start weaning and what types of food to give. Of the 100 participants, the majority (81%) of the participants recalled having received information on commencement of weaning, of whom 99% (80/81) were from formal information sources.

Participating parents/carers were asked about their source of information. Forty-eight percent of the study population gave more than one answer when asked about their sources of information. Of the families who commenced weaning, 46/72 (64%) had recalled receiving information from health visitors or community nurses. Twenty-two percent (16/72) acted on advice from nurses on the neonatal unit, 6/72 (8%) of families obtained information from family care nurses who visited them at home, 14/72 (19%) from Bliss leaflets, 16/72 (22%) from the consultant in clinic, 15/72 (21%) from dietitian and 4/72 (6%) from a general practitioner. Nine in ten (65/72: 90%) of families who commenced weaning had recalled receiving formal advice from health professionals. Regarding informal sources of information: 14/72 (19%) obtained advice from family or friends, 10/72 (14%) relayed on recommendations available from websites and 1/72 (1%) acted on advice from other sources (Figure 4.4).

Responses to the future expected source of information differed in the families have not commenced weaning yet (n=28). Nevertheless, the highest proportion of information was still obtained from health visitors or community nurses 8/28 (29%). This was followed by family care nurses (who visited them at home after discharge (5/28 (18%)). Fourteen percent (4/28 (14%)) of families were planning to act on advice from nurses on the neonatal unit, 4/28 (14%) from Bliss leaflets, 4/28 (14%) from consultants in clinic, 1/28 (4%) from a dietitian, and 1/28

(4%) on advice from a general practitioner. Approximately five in ten (15/28: 54%) of families have not commenced weaning yet had recalled receiving formal advice from health professionals. Regarding informal sources of information: 1/28 (4%) reported expecting to rely on advice from family or friends, 1/28 (4%) from other sources, but no participating parent reported expecting to rely on recommendation available at websites (Figure 4.4).

A



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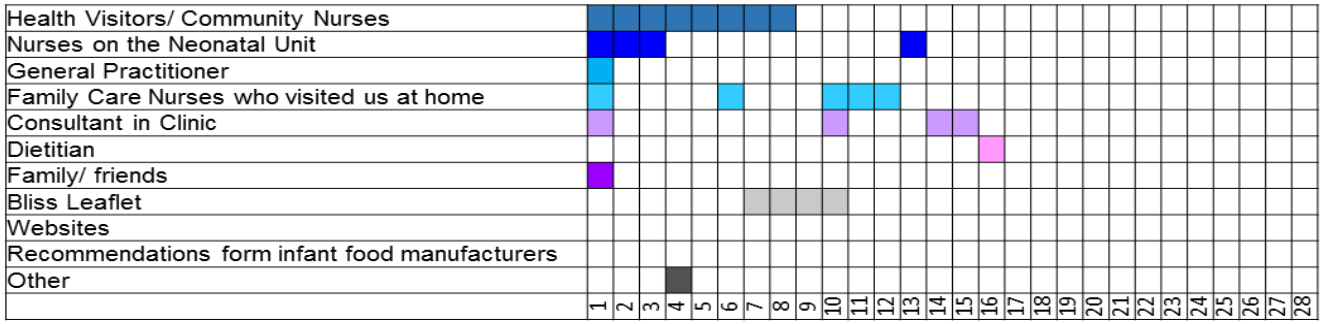

Figure 4.4 The sources of information on weaning as recalled by the participating parents, showing overlapped information sources per participating parent.

A) Families who commenced weaning (n=72); Families who have not commenced weaning yet (n=28)

Each column represents a participating parent; each row represents the sources of information on weaning. Therefore, each cell represents the sources of information on weaning. Participating parents who had not recall receiving information on weaning were 6 from families who commenced weaning (A) and 13 from families who have not commenced weaning yet (B)
Other sources of information included: families who commenced weaning “Just knowing the time was right then asked health visitor"; families who have not commenced weaning yet “other leaflets”

4.3.5 The effects of support provided for families regarding weaning on infant feeding practices

4.3.5.1 The timing of commencement of weaning

Participating parents who received advice on commencement of weaning (n=81) started/intended to start weaning at a mean (±SEM) age of 26 (±1) weeks, while participants from the group, which had not received advice (n=19), started/intended to start weaning at a mean (±SEM) age of (23 (±1) weeks; mean difference of 3 weeks later [95% CI: 0 to 6], p=0.026) (Figure 4.5).

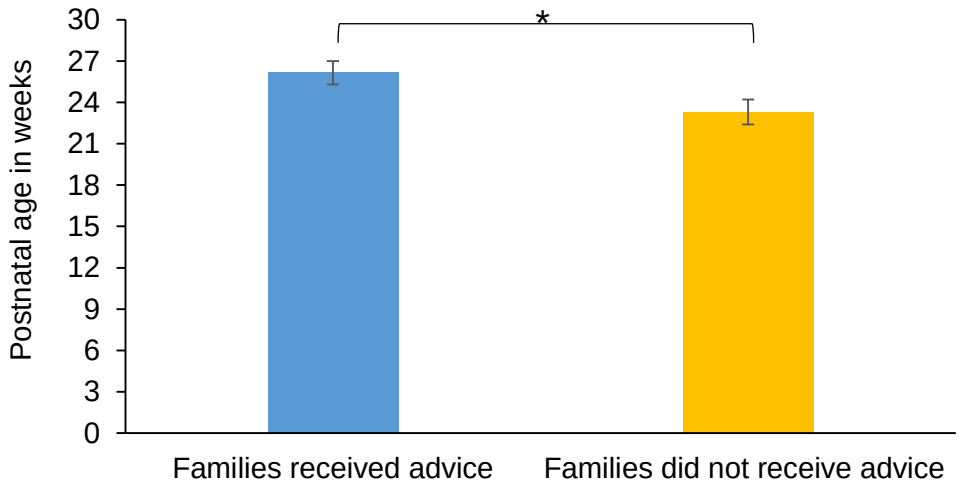

Figure 4.5 Effect of the support provided to families on commencement of weaning on the actual weaning age
Values: mean (±SEM); Blue bar: weaning age for infants from families who received advice (n= 81); Yellow bar: weaning age for infants from families who did not receive advice (n=19). * p<0.05 (independent t-test)

For families who commenced weaning, there was a trend to start weaning at older actual age when parents recalled receiving advice (families who commenced weaning: recalled receiving advice (n= 66): 27 (±1); did not recall receiving advice (n=6): 21 (±3) weeks of age, p=0.09). For families who did not commence weaning, there were no differences between the intended actual age of commencement of weaning between those who recalled or did not recall

receiving advice (Families have not commenced weaning yet: recalled receiving advice (n= 15): 24 (±1); did not recall receiving advice (n= 13): 24 (±1) weeks, p=0.7).

When the CGA was considered, the difference in age of commencement of weaning remained when assessed for infants from families recalled receiving advice compared to families who did not recall receiving advice. The mean (±SEM) CGA at weaning (Parents who recalled receiving advice: 16 (± 1) weeks; parents who did not recall receiving advice: 12 (± 2) weeks; mean difference two weeks [95% CI: 0.1 to 8], p=0.04) (Figure 4.6).

For families who commenced weaning, 66 participating parents recalled receiving advice and reported weaning their infants at a mean (±SEM) of 16 (±1) weeks CGA; for the six who did not recalled receiving advice weaning age was 11 (±6) weeks CGA (p=0.5). For families who have not commenced weaning yet, there were no differences between the intended CGA to commence weaning between those who recalled or did not recall receiving advice. Fifteen participating parents recalled receiving advice and reported weaning their infants at a mean (±SEM) of 13 (±4) weeks CGA; the thirteen who did not recalled receiving advice weaning age was 13 (±4) weeks CG (p=0.7).

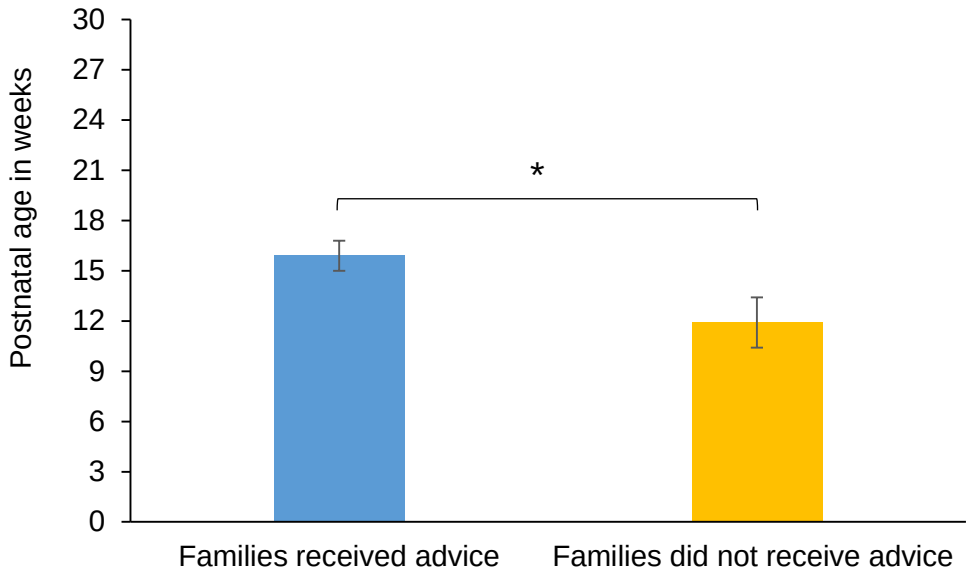

Figure 4.6 Effect of the support provided to families regarding weaning on the corrected age at weaning

Values: mean (±SEM), Blue bar: weaning age for infants from families who received advice (n=81); Yellow bar: weaning age for infants from families who did not receive advice (n=19). * p<0.05 (independent t-test)

The sources of advice on weaning were classified as face-to-face advice and/or paper or website information to explore to what extent the source of information may influence weaning practices. The current study did not show any difference in age of commencement of weaning between participants who received only face-to-face advice, face to face and/or paper/website advice and participants who did not receive advice, p=0.2. The mean (±SEM) actual age of commencement of weaning was (face-to-face advice: 26 (± 8); paper/website information: 26 (± 8); not advised 23 (± 4) weeks).

When the data were analysed by CGA, the difference between groups based on the source of information did not reach significance (face-to-face advice: 16 (± 1); paper or website information: 15 (± 2); did not receive advice: 12 (± 2) weeks CGA, p= 0.2).

4.3.5.2 Dietary practices and first foods

A high proportion of children received homemade foods 85/100 (85%); either exclusively homemade (48%) or in a mixed diet with some ready-made foods, (37%). The remaining 15%

of the children received exclusively ready-made foods. There was no association between receiving any advice on the type of first foods provided for infants, p=0.1. No association was observed between receiving any advice on the type of first foods provided for infants from families commenced weaning, p= 0.7 or foods intended to be provided for infants from families have not commenced weaning yet, p= 0.7.

The majority of the participating parents offered mashed or pureed food (96%), whilst only 7% had given finger food (Families commenced weaning, mashed or pureed food:70/72 (97%); finger food: 5/72 (7%)). Families who have not commenced weaning yetwere intending to use: mashed or pureed food: 24/28 (86%); finger food: 7/28 (25%).

The study population were exposed to a broad range of food types as first food at the time of commencing weaning (Figure 4.7). In families who commenced weaning, baby rice was the most common type of food provided as a first food 56/72(78%), followed by vegetables 41/72(57%), fruits 33/72(46%), dairy products 5/72(7%), meat 3/72(3%) and 7/72 (7%) of participating parents provided other foods. Only one infant had cornmeal as a first food.

For families who have not commenced weaning, baby rice still the most common type of first food to start with 22/28(79%), followed by vegetables 13/28(46%), fruits 7/28(25%), dairy products 2/28(7%), cornmeal 1/28(4%) and 6/28 (21%) of participating parents intended to provide other foods. No one intended to introduce meat as a first food.

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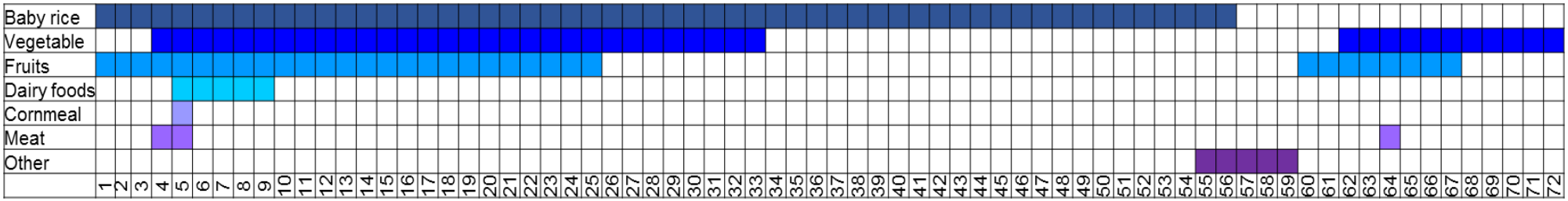

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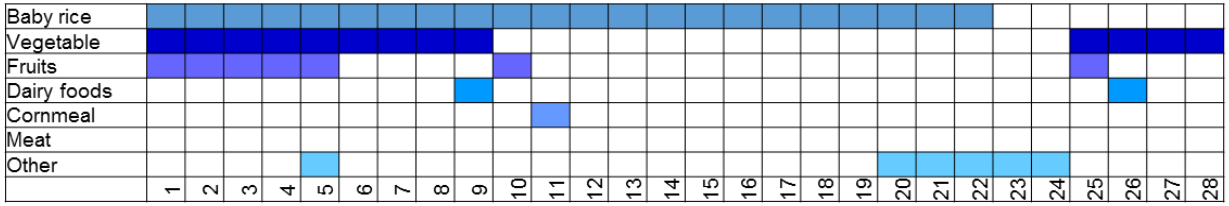

Figure 4.7 First foods that participating parents introduced or intended to introduce at the time of weaning;

Each column represents a participating parent; each row represents first weaning foods parents intended to provide to their infants. Therefore, each cell represents a food type provided by a participating parent.
Foods type listed “Other include baby rice with milk or rusks (A) not sure or rusks (B).

4.3.6 Recognition of appropriate readiness cues from a child

Despite a lack of robust research evidence on commencement of weaning of preterm infants, the BAPM (160) has published a joint consensus statement that aims to assist health professionals giving advice. The statement highlights that there are developmental signs of readiness for the commencement of weaning that should be considered in preterm infants. These include the infant's actual age, skills and developmental readiness (160). In this study, participating parents were asked about the factors which had the greatest influence on their decision on when to start weaning/intended to start weaning their children. Factors listed on the questionnaire were their child's

- age,
- ability to stay in the sitting position and control his/her head,
- coordinating their eyes, hand and mouth and bringing objects to mouth to chew, and
- showing interest in others' food.

The majority of the participants agreed on the importance of these factors. The most influential reason was the perception that their child was able to stay in a sitting position with 96% of the participants indicating that this was moderately to very important factor. Also, 92% of participating parents rated their child's interest in others' food, as a moderately to very important factor in deciding when to start weaning. Of note, no significant difference in perceptions regarding readiness cues between parents from families who commenced weaning and families who have not commenced weaning yet. .

Participating parents in this explorative study was also asked what other key factors they considered when deciding to commence weaning. Across 17 respondents, the factors cited were:

- advice from health professionals (5/17; 29%).
- their perception that their children were ‘‘not satisfied on only milk’’, “not satisfied by milk’’, “milk doesn't seem to satisfy him completely” or ‘hunger’’ (4/17; 23%)
- ‘‘we weaned due to reflux’’ or “reflux” (2/17; 12%)
- ‘‘to gain weight’’ or “need to increase weight gain” (2/17; 12%)

- “corrected age” or “prematurity” (2/17; 12%), and
- ‘‘ability to chew’’ (1/17; 6%)
- “able to take a spoon in their mouth… flat tongued” (1/17; 6%)

The perceptions of participating parents regarding the readiness cues presented in Table 4.5 presents.

Table 4.5 The perceptions of participating parents regarding readiness cues as determinant factors to decide when to commence weaning

The difference in perceptions between families who commenced weaning and families who have not commenced weaning yet was assessed using Mann-Whitney Test

	Families commenced weaning (n=72)					Families who have not commenced weaning yet (n=28)					P-value
Readiness cues	**Very important**	**Important**	**Moderately important**	**Not very important**	**Not important at all**	**Very important**	**Important**	**Moderately important**	**Not very important**	**Not important at all**	
Child's age	44 %	32%	13%	8%	3%	43%	28%	29%	0%	0%	0.8
Staying in sitting position and controls his/her head	65%	21%	10%	4%	0%	61%	28%	7%	0%	4%	0.5
"Coordinating their eyes, hand and mouth and bringing objects to mouth to chew"	44%	24%	14%	14%	4%	25%	46%	18%	11%	0%	0.1
"Showing interest in others' food"	41%	32%	19%	7%	1%	25%	50%	18%	7%	0%	0.4

4.3.7 Participants' satisfaction in the support given on weaning

Within the families who commenced weaning, the majority of parents were satisfied when they were asked about the support that they have had on the commencement of weaning (Table 4.6). More than two-thirds of the participating parents agreed that they were given enough information about how to commence weaning (Strongly agree: 22/72 (931%); Agree: 24/72 (33%)). Twenty-two percent (16/72) of participants were not sure, and only 10/72 (14%) thought that they had not been given enough information. Similarly, three-quarters of the participants agreed that it was easy for them to find the answer when they had any questions about the commencement of weaning (Strongly agree: 19/72 (26%); Agree: 35/72 (49%)), whilst 13/72 (18%) were unsure. Only 5/72 (7%) felt that it was difficult for them to find answers when they had questions. Although 21/72 (29%) of participating parents were confident and felt that they did not need further support, 25/72 (35%) were uncertain and 26/72 (36%) agreed that they would like to have had more support. More than half of the participating parents 43/72 (60%) felt that they knew what food should be given, 15/72 (21%) were not sure what food items to start with, and 14/72 (19%) were uncertain. More than half of the participating parents 41/72 (57%) were confident about when their infant was ready to commence weaning, while 17/72 (24%) found it difficult to decide when their child was/will be ready to commence weaning and 14/72 (19%) found it neutral. These findings suggest that a large minority of participating parents may need more support about the commencement of weaning to increase their confidence.

Overall in families who commenced weaning, 55/72 (76%) agreed with the statement "Do you think that you have been given enough advice about your child's nutrition during his/her weaning?", whereas 17/72 (24) did not agree with this statement.

Families who have not commenced weaning yet had similar perceptions about the support provided on weaning as presented in Table 4.6. More than half of the participants felt that they had been given or were expecting to be given enough information about how to commence

weaning (Strongly agree: 14%; Agree: 39%), although 15% were unsure and 32% thought that they were not given enough information. Of families who have not commenced weaning yet, more than one-third (9/28 (32%)) of participating parents who did not recall receiving information have infants were older than three months.

Almost two third of the participating parents felt that it was/will be easy for them to find the answer when they had any questions about the commencement of weaning (Strongly agree: 14%; Agree: 54%). However, more than two-thirds of the participating parents (70%) thought that they would like to have more support on commencement of weaning. In families who have not commenced weaning yet, 40% of participating parents disagreed with the statement ‘‘I was unsure about what food items to use for weaning my child’’, 42% agreed with the statement and 18% were not sure. Thirty-two percent of the participants were confident about the proper time to start weaning, 29% were uncertain and 39% felt that it will be difficult to decide when their children were going to be ready to start weaning.

Of note, no significant difference in perceptions regarding support provided on commencement of weaning between families who commenced weaning and families who have not commenced weaning yet.

Overall, approximately nine in ten (88%) participating parents think it is important to do research to establish the best way to support the commencement of weaning of preterm infants and 84% of participating parents felt they would be likely to participate in a research study to establish the best way to support the commencement of weaning of preterm infants.

Table 4.6 The perceptions of the participating parents who completed the questionnaires on the support provided on commencement of weaning
The differences in perceptions between parents who had already weaned and parents who had not yet weaned were assessed using Mann-Whitney Test

	Families who commenced weaning (n=72)					Families who have not commenced weaning yet(n=28)					P-value
	Strongly agree	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	**Strongly agree**	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**	
"I think I have been given/ will be given enough information about how to wean my preterm child"	31%	33%	22%	10%	4%	14%	39%	15%	25%	7%	0.5
"When I have questions about weaning, it is/will be easy to find the answers"	26%	49%	18%	6%	1%	14%	54%	14%	18%	0%	0.7
"I feel that I would have liked more support during weaning my preterm child"	7%	31%	33%	18%	11%	27%	43 %	30%	0%	0%	0.7
"I am unsure about what foods I will start with"	6%	15%	22%	40%	17%	14%	28%	18%	29%	11%	0.9
"I feel unsure about when my child will be ready for weaning"	8%	15%	21%	38%	18%	14%	25%	29%	25%	7%	0.9

4.3.8 Factors which may influence the age of commencement of weaning

4.3.8.1 Gender

On average, there was no significant difference in the mean (±SEM) age of weaning between boys and girls (Boys: 25 (±1) weeks; girls: 27 (±1) weeks). Mean difference of weaning age was -2 weeks [95% CI: -4 to 1], did not reach statistical significance either when data were analysed using actual age; p=0.3 or CGA; mean difference was -1 week [95% CI: -5 to 2], p=0.4.

Subgroup analysis showed no significant difference in the age of commencement of weaning in relation to children's gender (Families who commenced weaning: Boys (26 (±1)); Girls (28 (±2) weeks, mean (±SEM); p=0.13). Similarly, in those who had not yet weaned their infants the mean intended age of commencement of weaning was similar (Families who have not commenced weaning yet: Boys 24 (±1); Girls: 25 (±1) weeks, mean (±SEM); p=0.2).

4.3.8.2 Type of milk at discharge home from the neonatal hospital

There was high prevalence of breastfeeding at discharge among the study population (65%) (mother's breast milk (43%); mixed milk feeding (22%)) and 35% of the children were discharged on formula milk alone. The mean (±SEM) actual age of commencement of weaning was not significantly different between infants who had mother's milk and/or formula milk at discharge from hospital (mother's milk: 27 (±1) weeks; formula milk: 26 (±2) weeks; mixed milk feeding: 27 (±2) weeks, p= 0.9).

Similarly, when CGA was considered, there was non-significant difference in age of commencement of weaning (mother's breast milk: 17 (±1); formula milk: 16 (±2); mixed milk feeding: 14 (±2) weeks, p= 0.3)).

Within groups' analysis showed no difference in actual age of commencement of weaning based on the type of milk at discharge to home (Families who commenced weaning (n=72):

p=0.9; families who have not commenced weaning yet (n=28): p= 0.9). No difference in CGA of commencement of weaning based on the type of milk at discharge to home (Families who commenced weaning (n=72): p=0.6; Families who have not commenced weaning yet(n=28): p=0.8).

4.3.8.3 Mode of delivery

There were no associations between mode of delivery and actual age (vaginal delivery (n= 46): 26 (±1); Caesarean section (n= 54): 26 (± 1) weeks, p= 0.9) or CGA of commencement of weaning (Vaginal delivery (n= 46): 14 (±1); Caesarean section (n= 52): 15 (± 1) weeks, p= 0.6).

No difference was observed in actual age of commencement of weaning either in children from families who commenced weaning (n=72; p=0.9) or families who have not commenced weaning yet (n=28; p=0.9). No difference was observed in CGA of commencement of weaning either in children from families who commenced weaning (n=72; p=0.5) or families who have not commenced weaning yet (n=28; p=0.5).

4.3.8.4 Participants' age

Only 21/100 (21%) of participating parents were from a young age group (aged ≤25 years), 56/100 (56%) were aged between 26 and 35 years, and 23/100 (23%) were 36 years of age and over. The mean (±SEM) actual age of commencement of weaning was not significantly different between the different age groups (Participant age, ≤25 years: 26 (± 2); 26 - 35 years: 26 (± 1); ≥36 years: 28 (± 2) weeks, p=0.5). Similarly, the CGA of commencement of weaning was not significantly differing (Participant age, ≤25 years: 16 (± 2); 26 - 35 years: 15 (± 1); ≥36 years: 17 (± 2) weeks, p=0.6).

None of these comparisons significantly differed for infants from families who commenced weaning or families who have not commenced weaning yet.

4.3.8.5 Socioeconomic status

There was no difference in the mean (±SEM) age of weaning between participants from the different socio-economic background (School level: 26 (±1); further education: 25 (±1); Not specified: 27 (±4); p= 0.8). Similarly, there was no difference observed when the data were analysed using CGA at weaning (p=0.6). There were no differences when participating parent educational level was considered for families who commenced weaning (p=0.3) and families who did not commence weaning yet (p=0.4) separately.

Weaning age was not different between participants with different occupations; higher managerial/professional occupations: 25 weeks (±1), lower managerial and professional occupations/intermediate occupations: 24 weeks (±1), small employers/lower supervisory and technical occupations: 19 weeks (±2), semi-routine/routine occupations: 28 weeks (±3), never worked/ student: 28 weeks (±3), not specified 28 weeks (±2). p=0.67. The difference did not reach significance even when CGA was considered, p= 0.11.

4.3.8.6 Participants' ethnicity

Within families who had commenced weaning, the mean (±SEM) age of commencement of weaning was not different when participating parent ethnicity was considered (British background (52/72): 26 weeks (±1); non-British background (20/72): 28 weeks (±2), p=0.2).

Within families who have not commenced weaning yet, the mean (±SEM) age of commencement of weaning was not different when participating parent ethnicity was considered (British background (20/28): 24 weeks (±1); non-British background (8/28): 24 weeks (±1), p=0.6).

4.3.8.7 Internet use

Approximately eight in ten (83%) of the participants use the internet on daily basis (of these, 56% felt that they use the internet all of the time and 27% felt they use it most of the time). Overall mean (±SEM) age of commencement of weaning was significantly lower, 25 (± 1)

weeks when participating parents commonly use internet on daily basis compared to when carers less commonly use the internet 30 (± 3) weeks, p=0.02. Although there was a trend to a similar effect of internet use on CGA of commencement of weaning, this did not reach statistical significance (p=0.08).

This result is significant at the p = 0.03 in families who commenced weaning, but not for families who have not commenced weaning yet.

4.3.9 Regression analysis

Scatterplots were performed with the corrected age of commencement of weaning and the potential confounders showed roughly linear relationships (Figure 4.8 - Figure 4.12). There were weak positive correlations with birth GA, birth weight and negative relationship with the duration of ICU. There was no significant association between age at weaning and age of starting enteral feeding, or age at discharge.

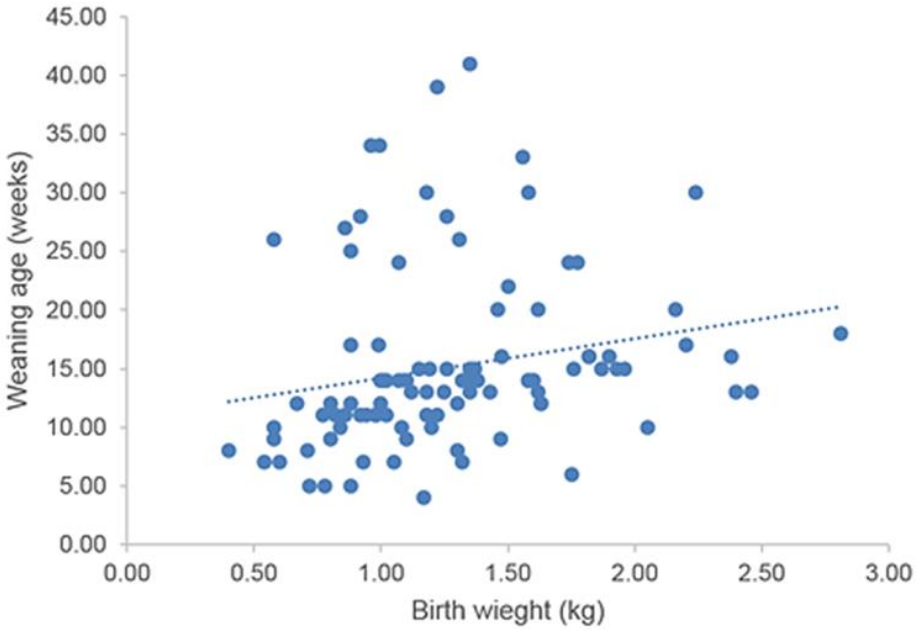

Figure 4.8 The association between age at weaning (weeks) and birth weight (kg)

Pearson correlation coefficient (r) = 0.2, p= 0.049
Each symbol represents an individual infant. Dotted line represents the linear fit of data

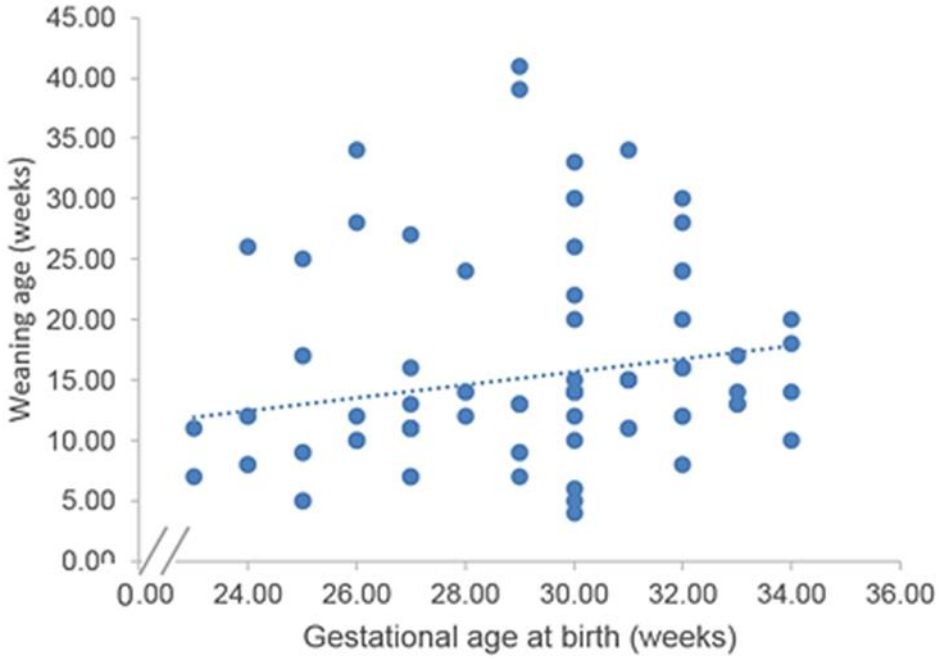

Figure 4.9 The association between age at weaning (weeks) and gestational age at birth (weeks)

Pearson correlation coefficient (r) = 0.3, p < 0.
Each symbol represent an individual infant. Dotted line represents the linear fit of data

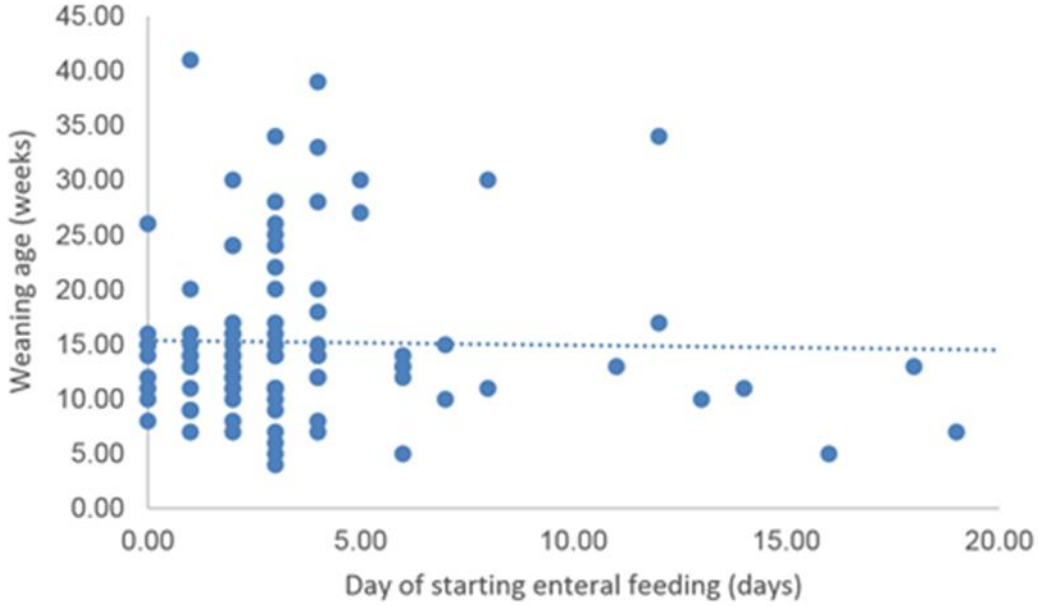

Figure 4.10 The association between age at weaning (weeks) and age of starting enteral feeding (days)

Pearson correlation coefficient (r) = -0.04, p = 0.7
Each symbol represent an individual infant. Dotted line represents the linear fit of data

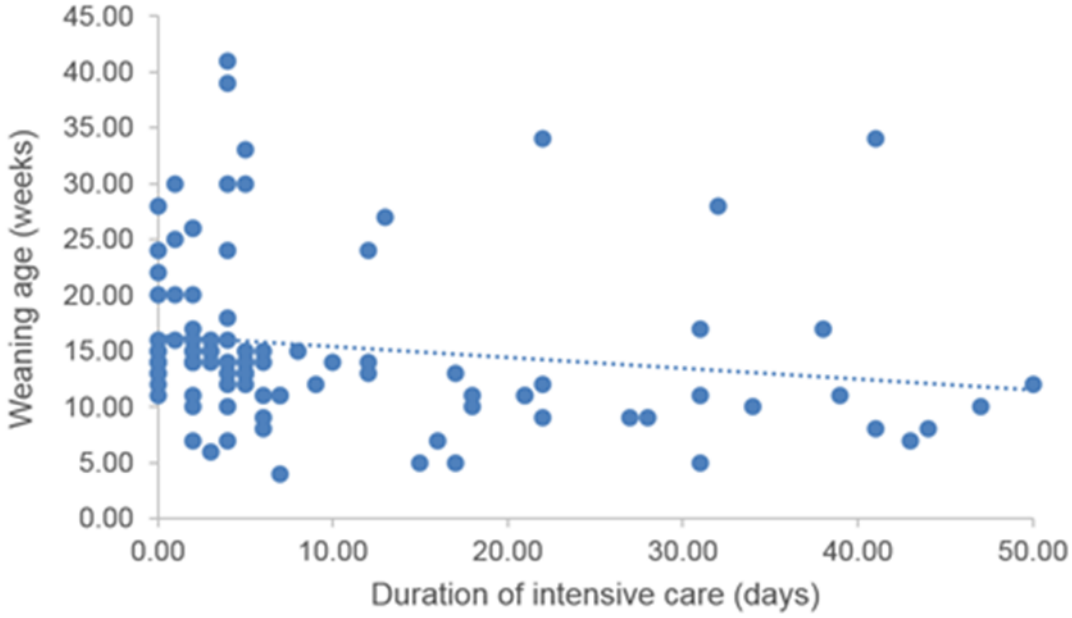

Figure 4.11 The association between age at weaning (weeks) and duration of intensive care (days)

Pearson correlation coefficient (r) = -0.2, p = 0.04
Each symbol represent an individual infant. Dotted line represents the linear fit of data

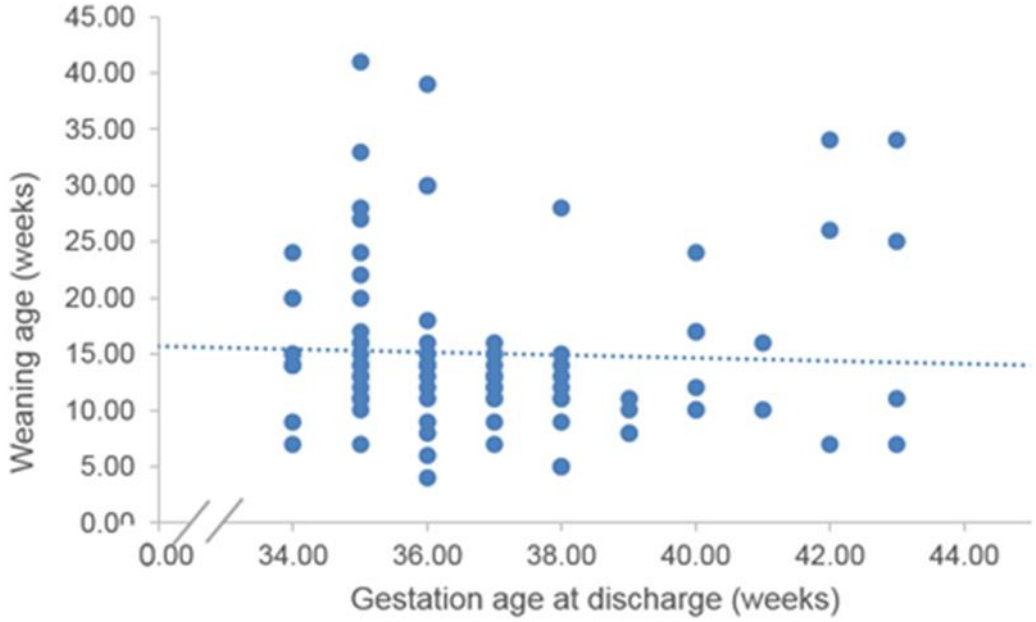

Figure 4.12 The association between age at weaning (weeks) and corrected age at discharge (weeks)

Pearson correlation coefficient (r) = -0.2, p = 0.06
Each symbol represent an individual infant. Dotted line represents the linear fit of data

Univariate analysis included GA at birth, BW, day of life on starting enteral feeding, duration of ICU stay during neonatal life and age at discharge and illustrated in Table 4.7.

Table 4.7 Univariate analysis to determine which variables were associated with age of commencement of weaning

Variables	B	95%CI		P-value
		Lower	Upper	
BW (kg)	3.2	0.01	6.43	0.049
GA at birth (weeks)	0.6	-0.03	1.06	0.06
Age of starting enteral feeding (days)	-0.1	-0.41	0.29	0.7
Duration of ICU stay (days)	-0.1	-0.19	-0.002	0.04
GA at discharge (weeks)	-0.03	-0.63	0.57	0.09

Abbreviations:
Birth weight: BW; gestational age: GA; intensive care unit: ICU; values for the regression equation for predicting the dependent variable from the independent variable: B; confidence interval; CI

Multivariate analysis (Table 4.8) indicated that none of these variables could explain the variation in the weaning age when adjusted for each other.

Table 4.8 Multiple regression analysis for weaning age

Age at weaning as dependent variable and duration of ICU stay, the day of starting enteral feeding and GA at discharge as independent variables
Final Model (multivariate analysis performed using corrected weaning age)

Variables	B	95%CI		P-value
		Lower	Upper	
BW (kg)	1.869	-3.118	6.855	0.46
GA at birth (weeks)	0.05	-0.883	0.982	0.92
Duration of IC (days)	-0.059	-0.184	0.066	0.35

Abbreviations:
Intensive care: IC; gestational age: GA at discharge; values for the regression equation for predicting the dependent variable from the independent variable: B; confidence interval; CI

4.4 Discussion

This study was designed to evaluate the support provided to families on weaning, along with the attitudes, experiences and behaviours of the participants. Therefore, a survey questionnaire methodology was chosen for the study.

4.4.1 Summary of main results

The study included participating parents of infants who had significantly lower birth weight and gestational age than the target population. Infants with low birth weight and low gestational age at birth are at high-risk of malnutrition during childhood. Therefore, the finding could be generalised to the entire population of infants born ≤ 35 weeks gestation.

Three-quarters of participating parents did not/intended not to start weaning until the age of 20 weeks after birth. There was a delay in the commencement of weaning in infants from families who had recalled receiving advice on weaning in adherence with the available recommendations (151, 160). There was a significant association between age of commencement of weaning and BW & GA and duration of ICU stay. Frequent use of the internet was significantly associated with earlier commencement of weaning.

Finally, most parents were satisfied when they were asked about the advice provided on commencement of weaning although a large minority were not. Most infants were offered either non-wheat cereals, pureed vegetables and/or fruit as their first weaning foods. The novelty of the current study was to build on these findings by including assessment of the association between the support provided to families and their perceptions and practices around commencement of weaning of preterm infants.

4.4.2 Parenting practice and attitudes towards the infant diet and support provided regarding the commencement of weaning

Weaning began on average (±SEM) at 26 (±1) weeks from birth, corresponding to 15 (±1) weeks CGA. Therefore, infants included in this study received weaning foods seven weeks later than infants included in the study of Norris et al.(146) and about 2 weeks later than infants included in the Fanaro et al. (147) study. The other studies (146, 147) included infants with average GA of 34 and 32 weeks gestation where the average birth GA of the current study population was 30 weeks which might explain the difference in age of commencement of weaning. The current study, and others (146, 147), showed that infants born with a higher

grade of prematurely were weaned significantly earlier than infants born nearer to term. In the current study, approximately two-thirds of those infants in both weaned and not weaned group were born to first-time parents. First-time parents may feel ill-prepared to initiate feeding of a full-term infant, and feeding a preterm infant is even more complex and nuanced. The behaviour of parents in relation to commencement of weaning may be influenced by providing advice and support for infants' feeding. More than three-quarters of caregivers received advice on commencement of-weaning and which food to start with. The proportion of families who recalled receiving advice from a health professional was markedly higher in the current study compared to the proportion reported in the national infant feeding survey (86%) (149). This proportion represents an increase since 2005. Seventy-one percent recalled receiving advice on when to commence weaning and 68% on the types of food to be given (149).

Nineteen percent of the study population recalled that they had not received advice on commencement of weaning. Of whom, more than two-thirds were from families who have not commenced weaning yet. The current study has also shown that there was large proportion of infants from families who have not commenced weaning yet (32%) did not approach weaning age when studied.

Unlike a study by Norris et al.(146), who reported that no mother received advice on the commencement of weaning whilst in the neonatal unit, we found, in total, 20/100 of the participants have received advice from nurses on the neonatal unit. This proportion might be even more, as 11/100 of the respondents were fathers, and fathers may not have been aware of the advice that mothers had received. Fathers may face some challenges during their time on the neonatal unit, including problems with information sharing (369). Although family-centred care in NICU should include the active engagement of both parents in the daily care for infants born preterm, mothers tend to be present more often on NICUs than fathers (369). Moreover, organisational, cultural and interpersonal barriers may restrict the active engagement of fathers in neonatal unit (369).

Likewise in the Infant Feeding Survey (149), formal advice is a major source of information about infants feeding in the first year of life. In the current study, the most common sources of information were from health visitors, nurses on the neonatal unit, the consultants, and dietitian in the outpatient clinics. Health visitors were the principal source of information/advice, which concurs with previous reports (146, 149). In the UK, every family is assigned a health visitor when they have a new baby. Health visitors are qualified and registered nurses or midwives who have additional training and qualifications as a specialist community public health nurses. Their additional training enables them to provide a universal health visiting service and assess the health needs of individuals and families. Health visitors are the main professional support for the family once an infant discharged home unless he/she still needs to see a specialist (370). The proportion of caregivers who received advice from health professionals, including health visitors, was higher in the current study compared to the study by Savage et al. (352) in which 31/98 of families reported that their weaning practice was based on advice from the health visitor or doctor. This may reflect the Health Visiting Programme (371), which commenced in 2011. This programme is aiming to provide a universal health visiting service to families.

Although the commencement of weaning tended to be influenced by formal information from written information sources (149), and leaflets are intended to be used as a teaching aid when health professionals are giving advice, they were not very commonly used as a source of information in the current study. Overall, twenty percent of the study population obtained information from Bliss leaflet. A similar proportion was reported previously (372) where 23.5% of mothers cited written material as a source of information. The possible explanations of these findings are that the leaflet may not be convincing, difficult to understand, or people may need help to find, understand and act on written information (373). Furthermore, parents may prefer the use of the internet as a source of information. The current study showed that 83% of carers commonly use the internet on a daily basis. In recent years, the ubiquitous availability of the internet has heralded it as an accessible source of health information (374),

and there has been a four-fold increase in the proportion of mothers relying on information from the internet between 2005 and 2010 (149).

Although there was a high proportion of participating parents who recalled receiving advice on weaning, more than thirty percent of the study population still felt that it is difficult to decide when to start weaning. The current study, and others (149, 352), showed that recommendations from health professionals have an impact on weaning practices. However, there are some conflicting influences on the decision about when to start weaning including written guidelines and signs from a baby (149). Furthermore, most of these families who found commencement of weaning difficult were from families who have not commenced weaning yet. The postnatal age of infants from families ranges between 2 and 20 weeks actual age. It has been observed that premature birth has a psychosocial impact on parents. This impact varies depending on medical condition, postnatal age and developmental outcome of the infant. In the first few months of an infant's life, symptoms of anxiety and obsessive-compulsive behaviour, including difficulties in concentration and decision making are prominent amongest parents (375), which may affect post-discharge feeding practice (376).

4.4.3 First foods

The current study showed that home-prepared foods were the most commonly used first foods (86%). The proportion of infants receiving home-made food was markedly higher compared to findings from the infant feeding survey (149), which showed that there was only 11% of infants received home-made foods as first weaning foods.

A wide array of marketing techniques exist such as advertising, sales promotions, cross promotions using celebrities websites, packaging, labelling, e-mails and text messages (377). Such commercial marketing techniques did not seem to have an impact on the parents' decision and practices of commencement of weaning; none of the participating parents relied on recommendations from infant food manufacturers. These findings suggest that in addition to advice provided on infants' nutrition, parents realise that home-made foods can be

nutritious and allow them to retain control over which ingredients are used in the preparation (148). Shop-bought foods generally have higher sugar levels than home-made foods (378). Furthermore, parents may choose to make baby food for variety of reasons, such as freshness, increased variety and texture, cost, and lower amounts of salt, additives and preservatives (148).

It is essential to teach a child about eating and accepting a variety of foods at this stage of life. The DH recommends that the introduction of weaning foods should be gradual, introducing first cereals, vegetables and fruits, followed by protein-rich foods (159). Typical current feeding practices amongst the study population included the use of cereal, vegetables, and fruits but very little meat. Likewise, other studies (146, 147), that showed baby rice was the most popular choice. Baby rice may be considered a suitable first food for a variety of reasons including its easy availability, its lack of a strong taste making it less likely to be rejected and its hypo-allergenic nature. These reasons may explain the high proportion of parents offering baby rice as a first food during the commencement of weaning. However, except iron-fortified baby rice, early weaning based on baby rice might not be a good source of the nutrients that preterm infants need, such as protein (166), long-chain polyunsaturated fatty acids (167), iron (168), and calcium (379).

4.4.4 Factors affecting age of commencement of weaning

4.4.4.1 Birth weight and gestational age

The study showed that low BW was associated with the later commencement of weaning and this finding agrees with other studies (146, 147). Fewtrell et al. (171) analysed data from two prospective randomised trials and concluded that BW is a strong predictor of earlier commencement of weaning. The fact that higher BW was associated with earlier commencement of weaning could be due to social and/or biological factors. Parents may be interpreting the larger size of their infant as indicator to start weaning and/or the heavier baby may genuinely require and demand foods other than breast or formula milk (181).

In contrast to earlier findings, in the United Kingdom (146) and Italian cohorts (147), no evidence of an association between birth GA and age of commencement of weaning was detected in the current study. In previous studies (146, 147), infants born with greater prematurity received solids significantly later considering their actual age, but significantly earlier when weaning age was corrected for prematurity. This finding could be explained by the fact that carers of preterm infants may consider actual age as opposed to corrected age, which consequently influences the age at which they introduce solids. Although there is no previous study concerning parent use of actual versus corrected age, primary care providers use actual age for most routine childcare follow-ups. Therefore, this may affect both assessments and recommendations for care, including the age of commencement of weaning (380).

4.4.4.2 Gender

Male gender has been shown to be associated with an earlier commencement of weaning (146, 147, 274). The gender of the infant was not significantly associated with the age of commencement of weaning in this dataset. Once again, evaluation of the impact of infant gender on the age of commencement of weaning might be complicated by other factors such as the degree of prematurity.

4.4.4.3 Type of milk at discharge

In accordance with a published Italian cohort (147), the type of milk feeding had no significant effect on the age of commencement of weaning in the current study. However, some other studies that included preterm (146) and full-term infants (352) showed a significant correlation between the type of milk fed and age of commencement of weaning. These studies found that formula-fed infants were started weaning earlier than both human milk- and combined milk-feeders. This might be confounded by the fact that infants receiving formula milk are usually heavier than infants fed exclusive breast milk, and heavier infants usually wean earlier (171). Nonetheless, evaluation of the impact of the type of milk on the age of commencement of

weaning is complicated by the fact that studies may use different definitions, especially for 'human milk-fed' infants. This term is used to describe infants who received human milk initially or infants who received human milk exclusively. In this dataset, no difference was found in the age of commencement of weaning between those infants fed breast milk, a combination of human milk and infant formula or infant formula alone at discharge from hospital. This could be because the current study was not powered to assess this association.

Socioeconomic status found to be an important factor that may influence weaning practices (149), it is noteworthy that there is no single best indicator of SES, The Office of National Statistics suggested categories that could be used for all official surveys and statistics (381). These categories were used in the current study; however, it should be acknowledged that some of these categories were ambiguous and may not have been understood by some participating parents. This may have an impact on the information obtained from this question as they may not measure what they intended to measure.

4.4.4.4 Participants' age

Unlike previous studies (146, 147, 183), the current study showed no association between parental age and age of commencement of weaning. Participants' education may partially explain these findings. In the current study, participants were generally not well educated with 91% (19/21) of young-age, 41% (23/56) of mothers aged between 26 and 35 years and 30% (7/23) of older participants reported school level as their highest education level attained. Only 9/56 (16%) of participants aged between 26 and 35 years and 6/23 (39%) of older participants reported a postgraduate degree. Furthermore, the current study was not powered to examine the association of participants' age and infants' age of commencement of weaning, which may partially explain the results.

More educated women tend to delay motherhood to later ages, particularly for those of higher socioeconomic status (382). They tend to be more confident and have the emotional maturity and life experience (383) that translates well to motherhood. They are more likely to

breastfeed and breastfeeding continues for longer and delayed introduction of solids into their infants' diets has been reported previously in this group (149).

4.4.4.5 Duration of intensive care (IC) stay during neonatal life and gestational age at discharge

The duration of IC and GA at discharge was inversely associated with age of commencement of weaning. The association disappeared while adjusting for birth weight and GA. The association could be explained by the fact that lower GA at birth is associated with prolonged duration of NICU stay and later discharge from hospital (342). Infants born very or extremely premature, particularly those who have lung diseases such as bronchopulmonary dysplasia (BPD), often experience difficult transition from gavage to oral feedings that may delay discharge. Early introduction and advancement of enteral feeds may be associated with earlier attainment of full enteral feeding and decreased the length of IC (9). In contrast, long-standing needs for endotracheal and nasogastric tubes and/or nasal prongs causes abnormal tactile stimulation of perioral and intraoral tissue (315). Therefore, sicker premature infants may have delayed attainment of oro-motor skills and transitioning to oral feeding and, consequently, prolonged hospital stay (315).

Furthermore, premature birth and prolonged hospital stay are family stressors that may be associated with risk of neglect (384), failure to thrive (65), and adverse developmental outcomes (385). Demographic factors, including poor socioeconomic status, young maternal age, inadequate perinatal care, and lack of family support may increase these risks (354). Hence, these may affect the weaning practices and confound individual interpretation of some items in the current study.

4.4.5 Parents' satisfaction with support provided on weaning

Responses regarding the advice provided to parents on weaning were generally positive although a large minority of participating parents may need more support about weaning to increase their confidence. The perceptions about the advice and support provided on weaning

were not significantly different between parents' who had already weaned and those who were approaching weaning their infants.

Generally, a high proportion (81%) of participating parents recalled receiving formal advice on weaning. However, this was slightly less than what has been previously reported in the infant feeding survey, 86% (149). The difference may be attributed to the fact that 28% of children in the current study had not yet been weaned, and of these, only 32% of infants were older than three months and approaching weaning age. Furthermore, there was a low representation of preterm infants in the survey (149) where the majority of babies were born at term (93%), only 4% were born at 35-36 weeks gestation and 3% ≤ 34 weeks (149). Moreover, guidelines on commencement of weaning full-term infants are fully detailed and giving advice would not present difficulties.

The responses were positive for the majority of items included in the satisfaction questions and ranged from strongly agree to agree. Participating parents had recalled receiving information from multiple providers; hence, multiple interactions and opinions appeared to influence their overall perception and practice. This may have caused some of the differences in weaning practices observed in the current study. Although more than three quarters recalled receiving advice at the time of the survey conducted, just above 50% felt that they were confident on which food to start weaning. This uncertainty is likely to be the case as there are no evidence-based recommendations on commencement of weaning of preterm infants and different opinions and thoughts are likely to be received by parents (386).

Within families who have not commenced weaning yet, approximately half of the participating parents felt that they were unsupported and they needed more information on weaning their infants. It is noteworthy that were only 32% of infants were studied from families who have not commenced weaning yet were older than three months, in other words, there was a high proportion of infants who were yet not approaching weaning age.

4.4.6 Strengths

The current study has a number of strengths. Firstly, it is the first study to examine the impact of consumer health awareness and source of information on commencement of weaning of preterm infants. Other studies have examined the weaning practices in preterm infants, but none to my knowledge has specifically studied the impact of support provided to families regarding the commencement of weaning. Secondly, the data collected covered many aspects of child and family characteristics, allowing the examination of multiple elements that could affect the timing of commencement of weaning. Finally, using a questionnaire with closed type questions permitted the responses to be used quantitatively.

4.4.7 Limitations

Limitations of this study include the disadvantages of using a questionnaire, as previously described in the literature (245). The first of these was the missing data: some participants failed to answer all the questions. The second was missing participants: some caregivers did not complete the questionnaire. Therefore, results obtained using this method might lead to the risk of bias. Participants who do not complete/answer the questionnaire may have different responses from those who do (245). The third was recall time: the longer the recall, the less accurate and reliable the information became (245). Nonetheless, the average postnatal age of commencement of weaning in the current study was 48 weeks (12 months) and the recommendation was to commence weaning between 5 to 8 months, it was felt that this had to be balanced against the ability of participating parents to recall these events accurately. Furthermore, weaning is a social event in which parental anxieties about infant feeding might be manifest as controlling feeding practices. This might be perceived as an emotional event that might be remembered better than less emotional information. The fourth potential limitation was there no data were collected on why parents commence weaning before the recommended age and which source of information had the most influential effect on their decisions. Although the questionnaire was designed to keep the questions as simple and

straightforward as possible, the researcher had no control over how the participating parents interpreted the questions. Furthermore, closed-end questions limit researchers from collecting additional data to explore a new proposition or hypothesis.

Although I tried to find a range of different people who are representative of my target group population to pre-test the questionnaire, one limitation of the piloting is that the people who pre-tested the questionnaire had high levels of education and may have understood questions in the questionnaire differently.

Another drawback of the study is that respondents may have understood the questions differently because the meaning of some questions that seemed clear to the creator were not clear enough for the respondents and this may have affected the results randomly. For example, some respondent asked for clarification on some questions such as:

- "Please tell us at what age (actual) you introduced solid food into his/her diet?"
- "Please could you tell us if there is a history of atopy/allergy in your family"
- questions addressing level of education
- questions addressing participant's occupation.

Therefore, some of these questions were excluded from the analysis, because they may not accurately reflect his or her opinion or situation.

In addition, due to the nature of observational study designs, the current study could only confirm possible associations but could not determine cause-and-effect relationships.

Finally, this study was single site; therefore, this may not represent practice across the UK.

4.4.8 Conclusion

In spite of the lack of evidence-based guidelines, the provision of support for families on commencement of weaning appears adequate and the majority of parents were satisfied. There was a trend towards the later commencement of weaning among the study population compared to previous studies. A further study using in-depth interviews with families of preterm infants would provide richer contextual data to support and explain these survey

findings further. Some areas for improvement have been identified including support for parents to make informed decisions regarding the commencement of weaning considering CGA, ensuring that written materials intended for families who have preterm infants are provided, and ensuring that parents begin with nutritionally balanced foods.

Chapter 5:

5.1 Part 1. The effect of nutrition education of family members on weaning and nutrition in later infancy for infants born preterm

The work described in this part has been published (387).

5.1.1 Background and rationale

Inadequate nutrition is estimated to be associated with 45% of all child deaths (322). The first two years of life are considered to be a 'critical period', because inadequate nutrition during this period may be associated with increased morbidity and mortality (322). According to the World Health Organisation (WHO) recommendations, during this period infants should receive nutritionally adequate and safe weaning foods while breastfeeding continues for up to two years of life or beyond (322).

With increasing recognition of the importance of post-discharge feeding and commencing weaning as a crucial dietary event (164), the debate has focused on the optimum time and method of commencement of weaning to preterm infants (171). Inappropriate weaning practices, such as early or delayed commencement of weaning, poor quality and insufficient quantities of food, could introduce further problems into the already fragile nutritional status of preterm infants. Commencement of weaning after the age of six months may unintentionally reduce nutrient intake and expose the infant to further deficiencies (388). Delayed commencement of weaning is a major risk of iron deficiency (ID) and iron deficiency anaemia (IDA) for infants (168, 219); especially preterm infants who require additional iron to compensate for increased consumption for rapid growth and relatively low stores at birth (212). At the other end of the spectrum, early commencement of weaning could be unsafe in developmentally immature infants due to lack of head control, truncal instability (389) and underdeveloped oro-motor (390) function. Early commencement of weaning may also be

associated with increased risk of childhood obesity and potentially long-term detrimental effects from nutritional programming (144).

As discussed in Chapter Four, families feel unsupported and experience anxiety due to a variety of factors such as inadequate knowledge and understanding of the physiological needs of the infant, social pressures, controversial cultural patterns and lack of information about healthy diet (181). Families need information about best practices and support while commencing weaning (147). Such intervention should be specifically tailored to the needs of preterm infants to enable families in making an appropriate decision about what weaning foods to introduce and when (391). Promoting optimal weaning practices is a global health priority (322). Families and infants in difficult circumstances, such as premature birth, infants with low socioeconomic status and adolescent motherhood may require special, practical support to use the most appropriate feeding option.

Nutrition education to mothers about practices of commencing weaning is one of the most commonly used interventions to improve infants' feeding during weaning. Nutrition education involves encouragement of practitioners' adoption of beliefs and perceptions and the need for awareness of cultural encapsulation and cultural sensitivity (392). Education that provides relevant information to families could induce changes in behaviour and may influence nutritional practices, thereby improving nutrition, growth and long-term metabolic health outcomes in children (393). Although variety of strategies, such as group training sessions and individual counselling, were used previously to disseminate nutrition education to carers, all suggest that the intervention improved carers' knowledge and food selection, as well as children's physical growth (195, 394).

In this review, the term "*nutrition education" is* defined as "any education about the commencement of weaning (392). This included any form of support involving education provided to families in determining the *best timing* and *method* of commencing weaning and improving the nutrition of their infant and education to delay weaning.

The importance of nutrition education to improve infant nutrition has been highlighted previously (181, 198, 395). The double threat of childhood malnutrition and its potential long-term effects on health has driven attention to effective, nutrition-specific packages of care, which improve the nutritional status of children in all parts of the world (396). Previous systematic reviews evaluating the impact of nutrition education demonstrated improvements in infant nutrition and anthropometric measurements (185, 191, 393). However, these reviews did not differentiate between preterm and full-term infants. The reviews concentrated on populations in low- and middle-income countries and included non-randomised studies as well as studies that included children older than 12 months of age. The review in this chapter collated the current evidence using Cochrane metanalytic methodology to determine whether the use of nutrition education interventions on commencement of weaning optimises growth and nutrition in preterm infants.

5.1.1.1 What is a Cochrane systematic review?

Cochrane reviews are systematic reviews carried out by members of the Cochrane Collaboration, an international non-profit organisation (397). Cochrane systematic reviews of RCTs are considered to be the highest level of evidence for assessing intervention efficacy and effectiveness (398), as they are regarded as the most likely to inform with the lowest risk of bias (397). On the other hand, by focusing exclusively on RCTs, a large number of the published literature might be excluded.

Cochrane reviews appraising, synthesising research-based evidence, presenting the available evidence in an accessible format and determining research gaps (418). Cochrane reviews also help people make well-informed decisions related to a specific health-related issue by preparing and promoting the accessibility of the systematic reviews of the effects of healthcare interventions (397).

Due to the nature of the research question in the current chapter and the desire to produce ‘gold standard’ evidence-based research and to highlight research gaps, a Cochrane systematic review was carried out.

5.1.1.2 The role of Cochrane systematic reviews in evidence-based medicine

Evidence-based medicine defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” (399). Therefore, good evidence-based practice is a combination of the healthcare clinical expertise with the best available external evidence, to provide optimal treatment for each patient based on their circumstances.

Cochrane reviews are internationally recognised as the highest standard in evidence-based health care because the reviews have specific advantages (397), including:

- using explicit methods that minimise the risk of bias
- drawing reliable and accurate conclusions
- easily providing required information to healthcare providers, researchers and policymakers
- helping reduce the time delay from research discoveries to implementation
- improving the generalisability and consistency of findings
- identifying research gaps and helping generate new hypotheses
- Cochrane reviews are updated regularly, ensuring that treatment decisions can be based on the most up-to-date and reliable evidence.

5.1.1.3 The process of conducting Cochrane reviews

Undertaking a Cochrane systematic review follows a rigorous step-wise process. By using an explicit and systematic methodology, poorly designed studies with a high risk of bias can be identified and the consistency of results across studies can be compared. Cochrane methodology allows for systematic interpretation of the data and an evaluation of the validity of the results and the implications for practice and future research. Given the virtue of the scientific methodology, recommendations originating from Cochrane systematic reviews are

usually more reliable and accurate than the potentially biased individual views of ‘experts’ carrying out traditional narrative reviews that are not conducted without a rigorous approach. Six fundamental steps should be followed when conducting the systematic review, including: define the question, review the literature, examine the studies to select relevant studies, extract data and assess the quality of studies, complete the summary of finding a table and interpret the results (400).

The step-wise process of Cochrane reviews are:

1. The foremost step in conducting a Cochrane review is defining the review question, title registration and preparing a review protocol.

   Defining the review question is the most important element of a review/meta-analysis that has been undertaken at the protocol stage (415). The review question should stipulate the types of population, types of interventions/comparisons and the types of outcomes that are of interest - the acronym PICO (Participants, intervention, and outcome). Then the titles for Cochrane Intervention reviews should be agreed by and registered with Cochrane Review Groups, who then administer the editorial process of publishing protocols and reviews. Title registration reduces the potential for review duplication. Followed by preparing a review protocol should include detailed methods to be used in the review. This step is important to prevent duplication of effort, reduce the impact of reviewers’ bias, promote transparency of methods and process and allows peer review of planned methods.

2. Reviewing the literature and examining the studies to select relevant studies.

A thorough, objective and reproducible search of a range of sources should be undertaken to identify as many relevant studies as possible. This distinguishes Cochrane reviews from traditional narrative reviews. This also helps minimise the risk of bias and therefore helps produce reliable findings (401). Of note, duplicate publications may introduce substantial biases if studies are unintentionally included more than once in a meta-analysis (402).

Duplicate publications may come in various forms, such as identical manuscripts and reports describing different numbers of participants and different outcomes (403). Useful criteria could be used to identify duplicate publication (404), which include:

i. author names; often, duplicate reports have authors in common, but this is not always the case
ii. location and setting, particularly if institutions, such as hospitals, are reported
iii. specific details of the interventions, such as the type of intervention and its frequency
iv. sample size and baseline criteria of a study population
v. date and duration of the study. This can also clarify whether a different number of participants is due to different periods of recruitment.

3. Assessing the quality of studies

Interpretation of the findings in a systematic review depends mainly on the validity of results from included studies; that may lead to either an under- or over-estimation of the effect size of a given intervention. Bias is defined as a systematic error, or deviation from the truth, in results or conclusions. Many tools and scales have been proposed to assess the quality of RCTs included in a review. Many of these tools included assessment of the reporting and methodological quality of studies, but they did not focus on methodological faults which may introduce bias.

Cochrane handbook (400) recommends a specific tool for assessing the risk of bias in each included study. This tool is a domain-based evaluation. The tool includes critical assessments are made separately for each domain accompanied with support for the judgement for each entry in a 'Risk of bias' table, where each entry addresses a specific feature of the trial. The domains in a standard 'Risk of bias' table include:

i- selection bias: method of generation of the randomisation sequence and method of treatment allocation concealment (considered to be adequate if the assignment could not be foreseen)
ii- performance bias: blinding of participants, outcomes and clinicians' assessors
iii- attrition bias: withdrawals from a study (including attrition and exclusions from analysis) and whether the analysis was on an intention-to-treat
iv- reporting bias: selective reporting
v- other biases: concerns about other biases not addressed in the other domains of the tool.

5.1.2 Hypothesis

Given the potential benefits of nutrition education on weaning (191, 393) and based on data from previous studies (146, 147, 171), the question arises: is nutrition education effective in preventing malnutrition and improving outcomes of preterm infants?

On the basis of the survey studydescribed in Chapter 4, I hypothesised that there is insufficient evidence to support the implementation of nutrition education on weaning in the standard care of preterm infants.

5.1.3 Aims

This review aimed to assess the potential effects of family nutrition educational interventions (provided as nutritional counselling, face-to-face sessions, and audio-visual packages) targeted at improving weaning practices, including determination of the best time and method of commencement of weaning. The review also looked at nutrition education with an emphasis on the importance of breastfeeding duration, frequency of feeding and composition of food. This review also aimed to evaluate nutrition education to improve the nutrition, growth, and development of infants compared with conventional management.

5.1.4 Methods

The methods of the review followed the standard methods recommended in the Cochrane Handbook for Systematic Reviews of Intervention and the policies of the Cochrane Neonatal Review Group (400, 405)).

5.1.4.1.1 Define the question

The title for this Cochrane systematic review was registered with the Cochrane Neonatal Group. The review protocol was written by Dr Zenab Elfzzani (ZE) and Dr Shalini Ojha (SO) and reviewed by Dr Jon Dorling (JD) and published in the Cochrane Library in Jun 2016 (405). Publication of a protocol before completing a systematic review reduces the impact of

reviewers' biases, reduces the potential for duplication, and promotes transparency of methods (406).

5.1.4.2 Criteria for considering studies for this review

5.1.4.2.1 Types of studies

All trials using random or quasi-random participant allocation were considered. Cluster randomised trials in which baseline characteristics and outcome measurements were similar (i.e. not statistically significantly different) between clusters in both groups, were also considered. Non-randomised trials, such as controlled before-and-after studies, were excluded. The review was not limited to any region or socio-economic category and studies published in any language were considered.

5.1.4.2.2 Participants

Participants included carers of preterm infants (<37 weeks postconceptional age) up to the age of 1 year corrected gestational age (CGA).

5.1.4.2.3 Interventions

The studies planned to be included were trials comparing any nutrition education intervention for families of preterm infants with conventional management for the commencement of weaning up to one year of age. In this review, nutrition education includes one or more of the following, nutritional counselling, face-to-face sessions, audio-visual packages, support groups, and additional input from health visitors or other allied professionals, i.e. this included any other form of support involving education provided to families in determining the best time and method of commencement of weaning and improving the nutrition of their infant.

Any nutrition educational strategies, such as dissemination of booklets on child feeding guidance, demonstrations of preparing enhanced recipes, methods of training session delivery and duration of education were included in this review.

Conventional management was defined as standard clinical support and appointments that families usually receive without a nutrition education focus.

5.1.4.2.4 Types of outcome measures

The systematic review process was designed to record the outcomes that were likely to reproduce the domains targeted by nutrition education intervention.

The primary outcomes included:

- growth rates (weight gain, linear growth, and head growth) in the first two years CGA; weight, height/length or head circumference z-scores
- neurodevelopmental scores in children aged 12 months or older, measured using validated assessment tools such as the Bayley Scale Index (407). These scores were considered abnormal if the Bayley Mental Developmental Index (MDI) was < 70, Psychomotor Developmental Index (PDI) was < 70, or if there was visual or hearing impairment. Neurological examinations were considered abnormal if the motor and sensory functions were impaired

The secondary outcomes included:

- duration of exclusive breastfeeding
- adherence to weaning advice
- cognitive ability at five, six or seven years of age, using validated tools such as the Wechsler Intelligence Scale for Children (408) and school examinations (231)
- long-term growth: weight, height, skinfold thickness or body mass index assessed at five, six or seven years of age
- serum ferritin (< 12 µg/L) and haemoglobin (Hb) levels (< 110 g/L) in children aged six months or older of CGA (409)
- parental stress when the child is aged six months or older corrected for prematurity, measured using validated assessment tools such as the Parenting Stress Index (PSI) (410)
- infant quality of life when the child is aged six months or older corrected for prematurity, measured using the Infant and Toddler Quality of Life Questionnaire (ITQOL) (411)
- death between one and five years of age

5.1.4.3 Search methods for identification of studies

The criteria and standard methods of Cochrane and Cochrane Neonatal Review Group (The Cochrane Neonatal Group search strategy for specialised register) were used.

The Trials Search Coordinator for Cochrane Neonatal Review Group (CNRG) helped the reviewers in searching for relevant studies. The range of assistance include the following:

- providing relevant studies from the CNRG's Specialised Register
- designing search strategies for the main bibliographic databases
- running these searches in databases available to the CNRG
- saving search results and sending them to reviewers

Both published and unpublished works were eligible for inclusion. A comprehensive search was conducted; both electronic and manual searches were performed. The search was carried out in August 2015 and updated in August 2016. Also, the following bibliographic databases were searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library)
- MEDLINE (1966 to 2016)
- EMBASE (1980 to 2016)
- CINAHL (1982 to 2016)
- PsycINFO (1978 to 2016)

Relevant studies were identified using the terms: Weaning OR Wean* Weaning OR (Feed* NEAR complementary) AND (Family] OR Parent OR mother OR father OR parent* OR famil* OR carer OR caregiver) AND (program* OR education* OR training OR intervention*). The full search strategies, using standard search filter for neonatal population, for database-specific limiters for randomised controlled trials presented in Appendix 8.12.

Clinical trials registries for ongoing or recently completed trials (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), the World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), and the ISRCTN Registry were also searched.

In an effort to identify all relevant studies, the following additional searches were performed: the reference lists of all included studies and previous reviews and the proceedings of the Paediatric Academic Societies' annual meetings (1993 to 2016), the European Society for Paediatric Research (1995 to 2016, the Royal College of Paediatrics and Child Health (2000 to 2016) and the Perinatal Society of Australia and New Zealand (2000 to 2016). Trials reported as abstracts were also eligible for inclusion if there is sufficient information to meet the inclusion criteria. Authors were contacted to inquire about relevant information unavailable from the report.

5.1.4.4 Data collection and analysis

5.1.4.4.1 Selection of studies

The principal review author (ZE) independently screened the title and abstract of studies and potentially relevant reports identified from the above searches and excluded all studies that did not refer to randomised controlled trials (RCTs) or a cluster RCTs. Studies that did not consider educational interventions on weaning were also excluded. Two reviewers (ZE and SO) independently assessed the full articles for potentially relevant trials. They examined each study for eligibility and identified multiple reporting of the same study by comparing reports using author names, study location and intervention details as described in the *Cochrane Handbook* (400). The reviewers resolved disagreements through discussion.

5.1.5 Results

5.1.5.1 Results of the search

The original search (June 2015) identified 1165 publications, and an updated search (August 2016) identified a further 638 titles (Figure 5.1). After duplicates were excluded, screening of the titles (1774) and abstracts (14) and after exclusion of clearly irrelevant titles, five articles using nutrition education on weaning in preterm infants for potential inclusion were retrieved. Of these, four studies were excluded after reviewing full reports for the reasons stated below (Characteristics of excluded studies), and one was an ongoing trial awaiting classification

(Characteristics of ongoing studies). Although further details were requested from the study investigator, no response was received. Therefore, there were no eligible studies.

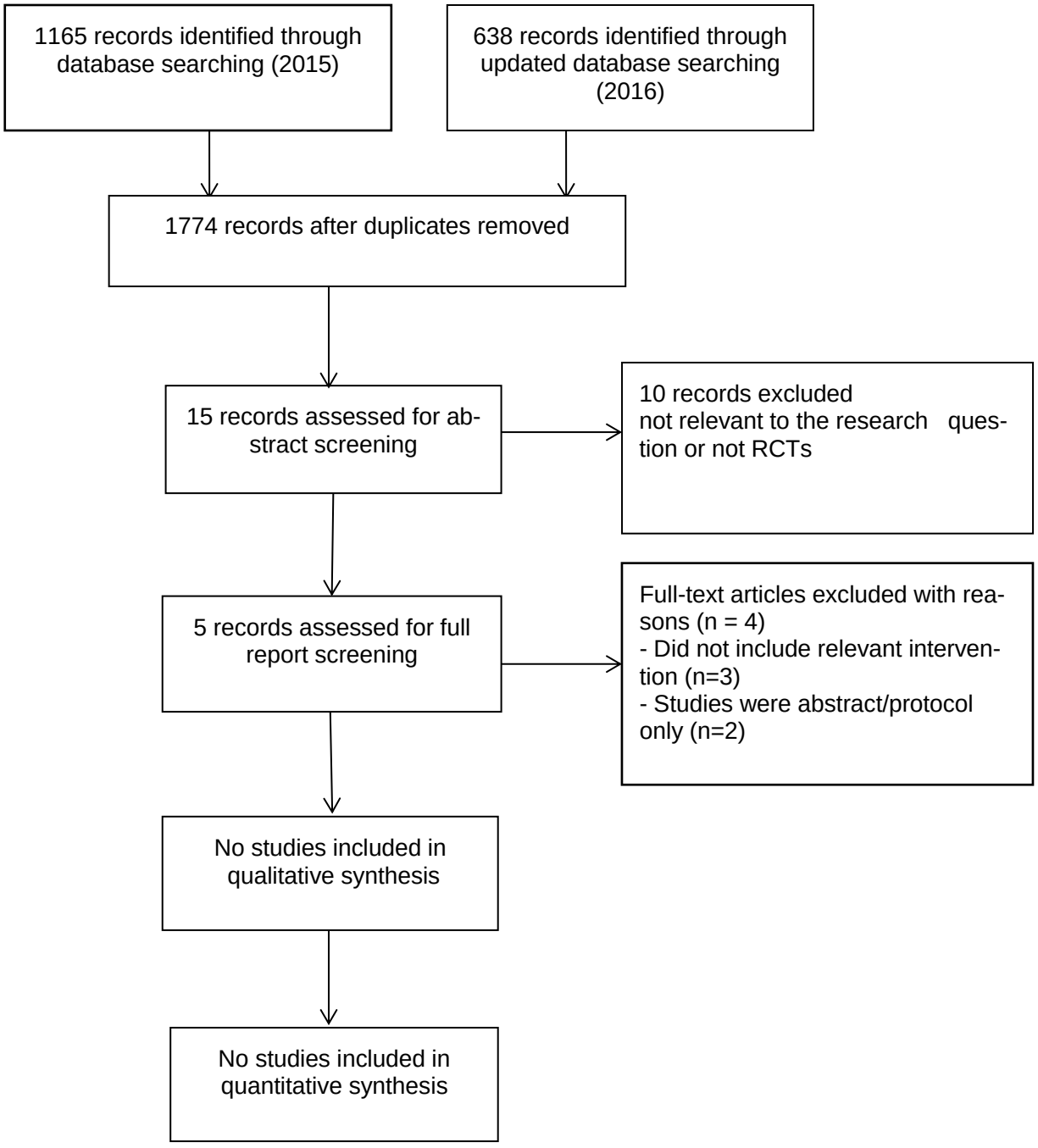

Figure 5.1 PRISMA flow chart summarising the process of identifying and screening studies for inclusion

Preferred Reporting Items for Systematic reviews and Meta-analysis: PRISMA

5.1.5.1.1 Included studies

There were no eligible studies, which meet the inclusion criteria of this review.

5.1.5.1.2 Ongoing studies

One ongoing study by Jeng (412) appeared to meet the inclusion criteria. The study investigator was contacted, but there was no response. However, as no data were available for this trial, it will be reconsidered in future updates of this review. Further details of this study can be found in Characteristics of ongoing studies table.

Table 5.1 Characteristics of ongoing studies

Study name	**A family-centred intervention programme for preterm infants: Effects and their biosocial pathways**
Methods	RCT Blindness: single (Outcomes Assessor) Duration of the study: The start date was May 2012 and the estimated completion date was December 2016 Setting: Three medical centres in northern and southern Taiwan
Participants	N=250 participants Parents and their preterm infants Inclusion: Birth body weight < 1500 grams, gestational age < 37 weeks, parents of Taiwanese nationality, married or together at delivery, the northern family residing in greater Taipei and southern family residing in greater Tainan, Kaohsiung or Chiayi. Exclusion: Severe neonatal and perinatal diseases (e.g. seizures, hydrocephalus, meningitis, grade III-IV IVH and grade II NEC), congenital or chromosome abnormality, mother < 18 years or mental retardation or history of maternal substance abuse at any time (smoking, alcohol, and drugs).
Interventions	Randomised to family-centred intervention programme/conventional management Intervention group: An in-hospital intervention, after-discharge intervention and neonatal follow-up. The in-hospital intervention will include modulation of the NICU, education in child developmental skills, feeding support, massage, interactional activities and parent support and education. The post-discharge intervention will involve clinic visits and home visits with specific care in modulation of home environment, teaching of child developmental skills, feeding support, teaching of interactional activities and parent support and education The intervention started at birth up to 7 days of life
Outcomes	Primary outcomes: change of medical and growth from baseline; change of neurophysiological functions from baseline. Secondary outcomes: Parenting Stress Index; Infants Quality of life
Contact information	Suh-Fang Jeng, Professor
Notes	- Final data collection date for primary outcome measure planned to be in December 2016 - The National Taiwan University Hospital funded the study - ClinicalTrials.gov Identifier: NCT01807533

Abbreviations:
Randomised controlled trial: RCT; Interventricular haemorrhage: IVH; necrotising enterocolitis: NEC; neonatal intensive care unit: NICU

5.1.5.1.3 Excluded studies

Four studies were excluded. Three studies were excluded following consideration of the full papers, and one study was excluded after details were obtained from the study investigator, which aided judging ineligibility. Studies were excluded when interventions were not related to nutrition education. The excluded studies are listed in the Characteristics of excluded studies table.

Table 5.2 Characteristics of excluded studies

Study ID	Reason for exclusion
Hoffenkamp 2015	A multicentre RCT is evaluating hospital-based video interaction guidance for parents of premature infants. The intervention aimed to facilitate parental bonding: i.e. the intervention was not related to nutrition education
Kim 2016	RCT investigating the effect of early intervention combined home visiting and group intervention in very low birth weight infants after discharge from NICU on neurodevelopmental outcome. The intervention focused on infant behaviour; no data on complementary feeding was included as described by the study's investigator.
Marriott 2003	Nutrition education was provided to both intervention and control groups
Wu 2014	RCT assessed the effects of early-improved mother-infant interaction and infant emotional regulation on cognitive and behavioural outcomes. The study groups received family-centred care. The interventions were focused on infants' neurodevelopment rather than nutrition education: i.e. the intervention was not within the scope of this review

Abbreviations:
Randomised controlled trial: RCT; neonatal intensive care unit: NICU

5.1.5.2 Risk of bias in included studies

No eligible trials were identified.

5.1.5.3 Effects of interventions

No eligible trials were identified.

5.1.6 Discussion

5.1.6.1 Summary of main results

This systematic review aimed at measuring the potential effects of family nutrition education, targeted at improving weaning practices of infants born preterm. Also, it aimed to evaluate the

effect of nutrition education to improve growth, development and nutrition status of infants compared with conventional management. Currently, no RCTs were addressing the impact of nutrition education of families to support weaning in preterm infants. However, this review found one trial comparing two different weaning strategies for preterm infants (162) (described in Section 1.10.2).

An ongoing study (412) was evaluated for potential inclusion, but the data was not yet available. There was lack of evidence to determine whether nutrition education intervention can improve growth development and nutrition status of preterm infants.

5.1.6.2 Overall completeness and applicability of evidence

The current review highlighted the scarcity of RCT data related to the nutrition education of families who had preterm infants.

The lack of RCTs evaluating the efficacy of nutrition education on weaning practices is likely to be due to the lack of evidence-based guidelines that provide the ideal strategy of commencement of weaning of preterm infants. No major organisation, including WHO (152), the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (155) or the American Academy of Paediatrics (AAP) (157) provides evidence-based recommendations concerning the optimal time of commencing weaning in preterm infants. Hence, most practices of weaning preterm infants are based on studies of full-term infants. To the best of my knowledge, one published recommendation on commencing weaning of preterm infants is the 2007 joint consensus statement from UK and Irish speech and language therapists and paediatric dietitians based on a literature review and the Delphi questionnaire. The statement was updated in 2011 (160). The statement indicates that weaning can be safely commenced in preterm infants between 5 and 8 months after birth, considering readiness cues from the infants.

Although no eligible studies were found to answer the main question of this review, there were two RCTs which may shed some light on the optimal weaning strategy in preterm infants (162,

170). Marriott et al. (162) (described in Section 1.10.2) randomly assigned preterm infants to receive weaning foods after 13 weeks after birth if the infant weighed at least 3.5 kg, or after 17 weeks after birth if weighing at least 5.0 kg. Of note, the corrected age of weaning was not reported. The authors reported that the commencement of weaning in both groups was subject to families' perception of an infant being ready to accept weaning foods. However, data to support the statement were not presented. The study did not show any significant difference in the mean weight, length or head circumference between the two groups at any measurement point. The study also did not show differences in the SDs of weight, length or head circumference between the two groups at any assessment point. However, infants in the intervention group had a significantly greater mean rate of length growth per week than babies in the control group, but there was no significant difference in mean length at 12 months CGA between the two groups. This may be because infants in the intervention group were shorter at the entry to the study but this cannot be judged as infant length measurements at baseline were not reported.

In addition, further information from another study is available (170) (described in Section 1.10.2). This study was published after the searches for this review and did not meet the eligibility criteria for inclusion because the educational intervention was delivered to both groups. The study showed no evidence of improved growth or neurodevelopment. The findings of this RCT support the results in Marriott et al. (162) study with respect to weight, length and head circumference outcome measures. On the other hand, higher serum haemoglobin level in infants who were randomised to receive weaning foods at 13 weeks was reported by Marriott et al. (162), although Gupta et al. (170) showed no differences in iron status between the two groups. This conflicting result may be due to the differences in the intervention. In the Marriott et al. (162) study, intervention started from discharge from the hospital, wherein the Gupta et al. (170) intervention started at four months CGA. The age at which serum iron was assessed was also different between the two studies; it was assessed at six months CGA in the Marriott et al. (162) study, but in the Gupta et al. (170) study, serum

iron was evaluated at 12 months CGA. In Marriott et al. (162) study, infants in the intervention group received nutrient dense foods with higher iron and zinc contents supplemented with preterm formula. Whereas, in the Gupta et al. (170) study, parents of the included infants were given a set of guidelines based on WHO recommendations and iron supplementation was given as a standard for both groups.

Furthermore, in the Gupta et al. (170), early (at 4 months CGA) commencement of weaning was associated with a higher rate of hospital admissions compared to infants commenced weaning later at six months CGA. These conflicting results may be due to the different healthcare settings where the studies were conducted; the Marriott et al. (162) trial being conducted in the UK, whereas the Gupta et al. (170) study was conducted in India. Furthermore, the intervention examined in the Gupta et al. (170) study was the timing of commencing weaning.

5.1.6.3 Potential bias in the review process

Two independent reviewers conducted the literature search. We are confident that, through a comprehensive electronic database search and manual search of relevant journals without restrictions on language or the status of the publication, all relevant published studies were identified. Nonetheless, there is always a possibility that some additional studies (published or unpublished) may have been missed when conducting the systematic review. If this was the case, it could have potentially introduced bias into the review.

There were no studies to perform funnel plot to explore any possible publication bias.

5.1.6.4 Agreements and disagreements with other studies or reviews

To my knowledge, the effects of nutrition education for family members to support weaning to preterm infants have not been systematically reviewed before.

A secondary analysis of data (171) was conducted to evaluate the effect of the commencement of weaning at ≤ 12 weeks or > 12 weeks on growth outcomes of preterm

infants, from two studies: one on post-discharge formula versus full-term formula (published), and other study was unpublished. The investigators had narratively described that the data did not show any difference in weight gain, length gain and head circumference gain between 12 weeks and 9 months CGA, or between 12 weeks and 18 months CGA. However, no data were reported.

5.1.6.5 Limitations

Although the review results were limited by the lack of evidence, this finding informs that there is a lack of RCTs that address the impact of nutritional education on weaning preterm infants.

Although much effort was applied to ensure that the literature search was as thorough as possible, we searched databases that serve as the most comprehensive source of reports of controlled trials; Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL and PsycINFO, but it is possible that relevant studies were not identified.

5.1.6.6 Conclusion

5.1.6.6.1 Implications for clinical practice

The effectiveness of nutrition education on the weaning of preterm infants remains unclear because of the lack of RCTs.

Furthermore, the available two RCTs (162, 170) provided conflicting evidence in determining the ideal weaning strategies in infants born preterm.

5.1.6.6.2 Implications for research

There has been an increase in preterm birth rates over the past 20 years (10), yet commencement of weaning of preterm infants, a group most susceptible to post-discharge growth restriction, has not been investigated in the form of rigorous RCTs. Therefore, more clinical trials are needed to determine the ideal weaning strategy for preterm infants, with respect of the time to commence weaning and the type of weaning foods with respect of

energy, protein and nutrient contents. These trials should also look at long-term growth, neurodevelopment, and metabolic outcomes.

The lack of RCTs evaluating the efficacy of nutrition education interventions for the commencement of weaning preterm infants suggests that more high-quality research in this area is needed. The Family-Centred Intervention Programme study (463) (described in Section 5.1.5.1.2) aims to improve parent-infant relationships and includes after-discharge interventions to modulate the home environment, feeding support, parent support and education to enhance infants' neurodevelopment. This study was registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01807533) is currently ongoing, with results not available at the time of the review.

As there were no relevant studies identified in preterm infants, the same research approach was undertaken in term infants. It was hoped that this would identify evidence that could be extrapolated to preterm infants. This follows in the next section.

5.2 Part 2. The effect of education of family members to support weaning to solids and nutrition in later infancy in infants born at term

5.2.1 Background and rationale

Undernutrition and overweight can be prevented with many of the same approaches. The UNICEF (413) suggested that double duty actions could have the potential to minimise the burden of malnutrition which includes actions to optimise early nutrition and promotion of appropriate early nutrition and commencement of weaning in infants.

Generally, full-term and preterm infants with low birth weight show rapid catch up growth and have more central fat distribution during childhood than other children of average birth weight (144, 163). Therefore, early interventions that target family eating environments and feeding

practices could be an effective approach to prevent obesity. Providing parents with evidence-based advice and recommendations may improve parental knowledge and feeding practice.

As seen in the systematic review (in Part One of this Chapter), there is a lack of evidence to conclude that nutrition education improves weaning practices and outcomes for preterm infants. Nonetheless, whilst searching for RCTs addressing nutrition education, which targeted preterm infants, it was apparent that there have been some RCTs targeting full-term infants.

5.2.2 Hypothesis

Based on findings from previous reviews (185, 191, 393), the question arises: is nutrition education during the first year of life compared to control, effective in preventing malnutrition and improving outcomes of full-term infants?

On the basis of the systematic review described in Part One of this chapter, I hypothesised that there is evidence to support the implementation of nutrition education on weaning practices in the standard care of full-term infants.

5.2.3 Aims

This review aimed to assess the effects of family nutrition educational interventions on the growth, development and nutritional status of full-term infants, compared with conventional management. It was hoped that the data from term infants could be extrapolated to preterm infants.

5.2.4 Methods

The methods of the review followed the standard methods recommended in the *Cochrane Handbook* (400, 414). The review protocol was written by ZE and SO and reviewed by JD and published in the Cochrane Library in Jun 2016 (414).

5.2.4.1 Criteria for considering studies for this review

The inclusion and exclusion criteria were as described in Section 5.1.4.2.1 with different gestational age criteria.

5.2.4.1.1 Types of participants

Parents and families of full-term infants (≥ 37 weeks postconceptional age) and up to the age of 1 year were enrolled.

5.2.4.1.2 Types of interventions

The included studies were trials that compared any nutrition education intervention for improving the weaning practices of parents or carers of full-term infants with conventional management. Where the intervention continued beyond one year, the data after the first year of life were not reproduced. The educational interventions were described in Section 5.1.4.2.3.

5.2.4.1.3 Types of outcome measures

The systematic review process was designed to assess growth and neurodevelopment of full-term infant. The review also assessed the rate of exclusive breastfeeding, compliance with weaning advice, cognitive ability, long-term growth, infants' quality of life, and incidence of ID and IDA, as described previously in Section 5.1.4.2.4.

5.2.4.1.4 Data extraction and management

Two review authors independently extracted data from the full-text articles of included studies, using a standard data collection form, as described in the *Cochrane Handbook* (400). The form used to extract the following data from each study:

- administrative details: study ID, study investigator(s) and contact details
- trail details: design, duration of the study, country and location of a study, informed consent, ethical approval and complements of follow-up
- details of participants: total number, gestational age, sex, socio-economic & ethnic group, diagnosis, and status

- details of intervention: type of education message, number, duration and technique of education sessions, and any additional interventions
- details of outcomes: time of outcome was reported, reporting method, effect size.

Study investigator was contacted when the reviewers were unable to extract the information that they seek from available reports.

The extracted data were independently entered by ZE using the Review Manager software (415) and checked with SO. Review Manager 5.3 (415) used to prepare and maintain the review, to carry out a meta-analysis of the data and to present the findings graphically.

The reviewers compared the information and resolved any discrepancies through discussion with the third reviewer.

Review Manager 5.3 software was used for data analysis (415). Meta-analysis was approached using the statistical methods; inverse variance for continuous variables and Mantel–Haenszel for categorical variables. These methods are typically used in meta-analysis to summarise the effect from independent measurement (studies). Inverse variance method calculates the weighted mean of the effect size using the inverse variance of the individual study as weights and Mantel–Haenszel calculate method calculates risk ratio as an effect measures (416).

To simplify the comparison between trials, variables that could be reported using different descriptive statistics, such as growth outcomes, were reported as means (standard error (SE)). These measures were transformed to means (standard deviation (SD)) using the Review manager calculator.

Regarding the direction of graphs, where possible, data were entered in such way that the area to the right of the line of no effect indicated a favourable outcome for nutrition education intervention.

Where needed, SDs were imputed for change from baseline using correlation coefficient calculated from a study reported in considerable detail: i.e. a study that presents mean and SD for change as well as for baseline and final measurements. For data reported as absolute values, such as weight and length measures, the correlation coefficient was calculated using data from the Bhandari et al. (394) study. For data reported as WAZ and LAZ scores, the correlation coefficient was calculated using data from the Olaya et al. (417) study.

5.2.4.1.5 Assessment of risk of bias in included studies

The Cochrane Neonatal Group criteria and standard methods were used to assess the methodological quality of the included trials. Details of this method were presented in Section 5.1.1.3 (418).

Appendix 8.13 describes each of these biases and introduces the corresponding domains assessed in the Cochrane risk of bias tool. The trials, therefore, were categorised as:

- low risk
- high risk
- uncertain risk

5.2.4.1.6 Unit of analysis issues

The unit of analysis was the participating infant in individually RCTs. The participating health organisation was the unit of analysis in cluster RCTs. In cluster RCTs, we analysed the results at the same level as the allocation. We planned to use summary measure of effect from an analysis that adequately accounted for the cluster design. If this was not available, we planned to analyse them using an estimate of the ICC derived from the trial (if possible), or from another source as described in the *Cochrane Handbook* (400).

Where cluster RCTs were appropriately analysed with ICCs and relevant data were documented in the paper, synthesis with other studies was possible using the generic inverse variance (GIV) technique. GIV is a method of aggregating two or more random variables to

minimise the variance of the weighted average, which adjusted measures of the effects of cluster RCT were combined with the results of non-cluster trials.

Where a trial included more than two treatment groups, if the additional treatment groups were not relevant, the data were not reproduced.

ITT analyses were conducted.

5.2.4.1.7 Data synthesis

The choice of whether to use a fixed-effect or random-effects model was based on the extent to which studies were homogeneous, based on their PICOS characteristics. The random-effects method is intended primarily for heterogeneity that cannot be explained. This model considers differences between studies, even if there is no statistically significant heterogeneity. However, the weakness of the random-effects model is that it puts added weight onto small studies that are often the most biased. These studies can inflate or deflate the effect size, depending on the direction of the effect (416). Therefore, a fixed-effect model was used in Review Manager 5.3 (415). A fixed-effect model provides a result that might be viewed as a 'typical intervention effect' from the studies included in the meta-analysis. The defining feature of the model is that all studies in the analysis share a common effect size and to calculate CI for a model the assumption is made that the true effect of an intervention is fixed across studies. This assumption implies that there is no statistical heterogeneity (416).

5.2.4.1.8 Quality of evidence

The quality of evidence for the main comparison at the outcome level was assessed by using the Grading of Recommendations Assessment, Development and Evaluation approach (GRADEpro), the software used to create Summary of findings' (SoF) tables (419, 420). SoF table presents information about the quality of evidence, the size of the effect of the interventions investigated, and the sum of available data on all important outcomes for a given

comparison (420). This methodological approach considers evidence from RCTs as high-quality that may be downgraded based on consideration of any of these five areas:

- design (risk of bias)
- consistency across studies
- the directness of the evidence
- precision of estimates
- presence of publication bias

The GRADEpro results in an assessment of the quality of a body of evidence in one of four grades (420) presented in Appendix 8.14. The review author independently assessed the quality of the evidence found for outcomes identified as critical or important for clinical decision-making:

- growth rates
- neurodevelopmental scores
- duration of exclusive breastfeeding
- adherence to weaning advice
- cognitive ability at five, six or seven years of age
- long-term growth
- serum ferritin and Hb levels
- parental stress
- infant quality of life

5.2.5 Results

5.2.5.1 Description of studies

5.2.5.2 Results of the search

The original search (June 2015) identified 1165 publications, and an updated search (August 2016) identified a further 452. Two additional records were identified through other sources (Figure 5.2). Duplicates were removed, resulting in 1774 records for initial screening. Of these reports, 97 titles were potentially relevant studies. Forty-six studies were excluded after reviewing the abstract and 51 studies after reviewing full reports for the reasons stated in Appendix 8.15 Characteristics of excluded studies. There were four trials awaiting

classification (Characteristics studies awaiting classification) and nine trials included (Characteristics of included studies).

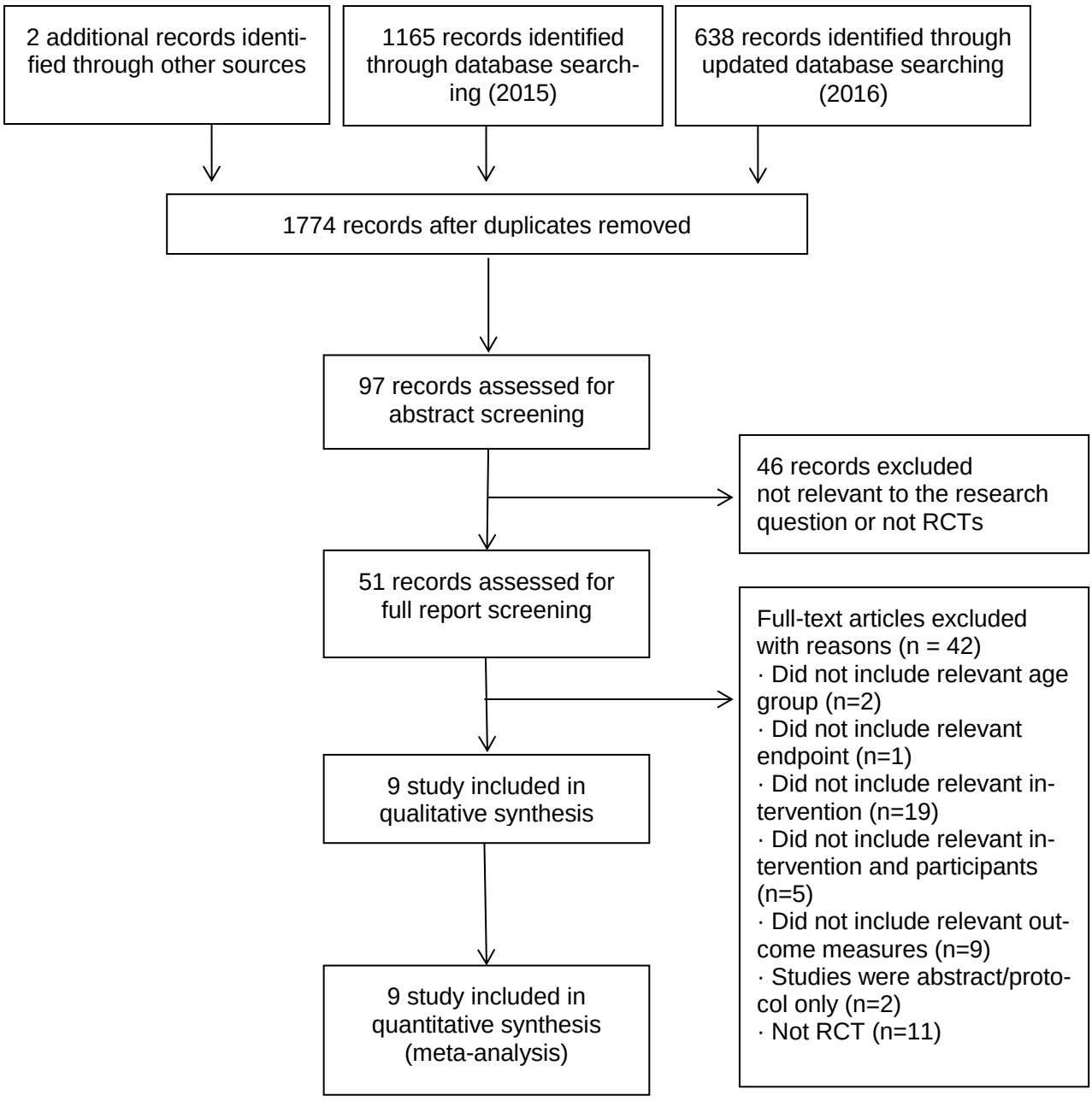

Figure 5.2 PRISMA flow chart summarising the process of identifying and screening studies for inclusion

Preferred Reporting Items for Systematic reviews and Meta-analysis: PRISMA

5.2.5.3 Included studies

Nine studies were included in the review (Bhandari 2001 (394); Bhandari 2004 (421); Bortolini 2012 (422); Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Vazir 2013 (196); Zhang 2013 (195)), as shown in Characteristics of included studies table.

Table 5.3 Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Bhandari 2001 (394)	Allocation: RCT Duration: intervention started from the age of 4 months and delivered over the first year of life Setting: the urban slum of Nehru Place, South Delhi, India Period: not stated Process evaluation to assess implementation: not stated	N=418 infants Age: the average age of the intervention group was 16.2 weeks (±0.5); the average age of the control group was 16.1 weeks (±0.4); mean (±SD) Gender: 56.7% in the intervention group and 58.1% in the control group were girls Inclusion criteria: infants under four months of age Exclusion criteria: planning for emigrating during the study, infants with major congenital malformations	Intervention group: carers received 30–45 min of counselling monthly by trained nutritionists. In addition to twice-weekly visits for morbidity ascertainment. N=104 Control group: carers were only contacted at 6, 9 and 12 months of age for anthropometry and dietary recalls. N=106	Weight gain from 6 to12 months and length gain at from 6 to12 months	There were four arms; three were intervention groups; for this review, only data from one intervention group was included (nutritional counselling group) whereas the other intervention groups, i.e. food supplementation group and visitation group were not included.

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Bhandari 2004 (421)	Allocation: a cluster randomised controlled trial Duration: intervention started from birth and delivered or the first two years of life Setting: the state of Haryana in India Period: October 1999 to June 2000 Process evaluation to assess implementation was reported	N=1025 infants Age: infants were enrolled from birth Gender: 47.8% in the intervention and 46.5% in the control groups were girls Inclusion criteria: full-term infants and residents and informed written consent was obtained Exclusion criteria: N/A	Intervention: A mother and child card listing the feeding recommendations was given to all mothers antenatal or at the first home visit. Carers received counselling with monthly home visits were performed for new births until age 12 months. The intervention messages included starting weaning at six months of age, providing specific foods while continuing to breastfeed. The frequencies and amounts of food to be fed at different ages was also included. Ways to encourage children to eat more, hand washing before a meal, and continuing feeding during illness. N=552 Control: routine services were provided. According to national policy, caregivers were advised to initiate CF at 4–6 months. Also, they have been advised on the types of foods to be fed, and the frequency of feeding. However, their focus was on family planning and immunisation. N=473	Weight gain from 6 to 12 months, length gain at from 6 to 12 months, the prevalence of exclusive breastfeeding at six months	The intervention was up to age of 2 years, so we used data for up to 12 months of age, i.e. we have included the relevant outcome measures just in the first year of life Some information were provided in another publication from the same research group (Bhandari 2003) Exclusive breastfeeding defined as “defined exclusive breastfeeding as maternal milk being the only food source, with no other liquids or food given except medicines, minerals, and vitamins.”

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Bortolini 2012 (422)	Allocation: RCT Duration: intervention started from birth and delivered or the first years of life Setting: Hospital Centenário, state of Rio Grande do Sul, Brazil Period: October 2001 to June 2002 Process evaluation to assess implementation: not stated	N=500 infants Age: from birth Gender: 42.9% in the intervention and 44.5% in the control groups were girls Inclusion criteria: full-term infants with birth weight ≥ 2,500g Exclusion criteria: infants with haemoglobin <110g/L at the age of 6 months	Intervention group: mothers received counselling during home visits monthly up to 6 months and then at 8, 10, and 12 months. Dietary recommendations were given prioritised exclusive breastfeeding up to six months; commencement of weaning at age of six months and CF with fruit snacks and meals made from cereals or roots, meat, pulses, greens, vegetables. N=200 Control group: families were visited at 6 and 12 months to collect anthropometric, dietary and socio-demographic data. Also, data on infants' health status were collected during these visits. N=300	Prevalence exclusive breastfeeding at six months and prevalence of anaemia at age of 12 months	Some information were provided in another publication from the same research group (424). Google translation was used to translate the article from Portuguese to English. Exclusive breastfeeding defined as "exclusive breastfeeding, defined as breastfeeding as the only food offered to the child, with no infusions or water."

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Olaya 2013 (417)	Allocation: RCT Duration: intervention started from the age of 6 months Setting Bogota, Colombia Period: not stated Process evaluation to assess implementation: not stated	N= 85 infants Age: 6 months of age Gender: 50% were girls in both intervention and control groups* Inclusion criteria: full-term infants with birth weight >2.500g and were exclusively breastfed for ≥ 4 months Exclusion criteria: if haemoglobin, at baseline, was <110g/L (22 of the eligible infants)	Intervention group: mothers had face-to-face sessions with individual nutrition counselling and detailed verbal and written guidance. This counselling prioritised the importance of continuing breastfeeding alongside weaning food, the importance of including red meat as a source of iron, and the importance of fruit and vegetables as part of an infant's diet. N=42 Control group: received advice on breastfeeding and general recommendations on suitable weaning foods including meat, food hygiene, and food preparation; no specific advice was given on the frequency or amount of foods that should be offered. N=43	Prevalence of anaemia at 12 months, prevalence of ID at 12 months Z scores at 12 months, including; WAZ, LAZ, HCZ, MUACZ, WLZ Change in z scores from 6 to 12 months, including; WAZ, LAZ, HCZ, MUACZ, WLZ	The numbers incurring ID were derived from percentages

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Penny 2005 (192)	Allocation: a cluster randomised controlled trial Duration: the intervention started from birth Setting: Trujillo, Peru Period: August 1999 to February 2000 Process evaluation to assess implementation was reported	N= 377 infants Age: the average age of the intervention group was 0.15 days (±0.06); the average age of the control group was 0.15 days (±0.05), mean (±SD) Gender: 46% in the intervention and 52% in the control groups were girls Inclusion criteria: infants aged 10 days or younger Exclusion criteria: congenital anomalies or chronic conditions	Intervention: demonstrations of the preparation of weaning food accompanied by group sessions for carers. Also, flip charts and single-page recipe fliers were provided. N=187 Control: not stated. N=190	Z scores at 12 months of age, including WAZ and LAZ months Z scores at 15 months of age, including WAZ and LAZ Z scores at 18 months of age, including WAZ and, LAZ Change in WAZ and LAZ scores from 12 to 18 months	WAZ and LAZ at 12 and 15 months were presented graphically, so these measures were calculated from the graphs provided. An email was sent to the investigator to check the accuracy of these calculations WAZ and LAZ were reported as mean (SE), data were transformed to means (SD) using the Revman calculator

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Roy 2007 (194)	Allocation: a cluster randomised controlled trial Duration: the intervention started at the age of 6 to 9 months and continued for six months Setting: Community Nutrition Centres, Bangladesh Period: June 2001 to July 2002. Process evaluation to assess implementation was reported	N= 605 infants Age: children aged 6 to 9 months Gender: 50.2 % in the intervention and 42.9% in the control groups were girls Inclusion criteria: infants aged between 6 and nine months at the baseline with normal nutrition or mild malnutrition Exclusion criteria: children with severe illnesses or handicaps affecting development, feeding, or activity	Intervention: mothers received nutrition education messages, which address child growth, feeding practices, disease control, and childcare. Also, they were provided with communication materials, such as flip charts. The intervention continued for six months, during which mothers received nutrition education messages once a week for the first three months and then once every two weeks for the next three months. N=306 Control: mothers received regular care. N=305	Z-scores at 12 months, including; WAZ, LAZ, MUACZ, WLZ Z-scores at 18 months, including; WAZ, LAZ, MUACZ, WLZ Changes in z-scores from 12 to 18 months, including WAZ, LAZ, MUACZ, WLZ.	

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Shi 2009 (423)	Allocation: a cluster randomised controlled trial Duration: the intervention started at age of 2 to 4 months Setting: Maternal and Child Health Hospital in Laishui, China Period: April to September 2006 Process evaluation to assess implementation: not stated	N= 599 infants Age: the mean (±SD) age at baseline was 2.7 (±0.5) months in the intervention and 2.8 (±0.6) months in the control group Gender: 51.7% in the intervention and 46.9% in the control groups were girls Inclusion criteria: Full-term infants (>37 weeks), single tone, Exclusion criteria: congenital anomalies	Intervention components were: (1) training sessions on food selection, preparation and hygiene, childhood nutrition, growth, and responsive feeding style; (2) demonstrations of preparing enhanced CF recipes, using locally available, affordable, acceptable and nutrient-dense foods, (3) booklets which contained infant feeding guidance and methods of preparing the recommended recipes, and (4) home visits every three months to identify possible feeding problems and provide individual counselling. N=294 Control group: received a standard package of child health care from the township hospitals, which include breastfeeding counselling. This group did not receive anything other than standard counselling on CF. N=305	Weight change from 6 to 12 months, length change from 6 to 12 months	The standard deviation for changes in anthropometric measures from baseline were imputed from data provided in the paper and correlation coefficient calculated from Bhandari 2001

Study ID	Methods	Participants	Interventions	Outcomes	Notes
Vazir 2013 (196)	Allocation: a cluster randomised controlled trial Duration: intervention started from age of 3 months and continued to age of 15 months Setting: Andhra Pradesh, India Period: not stated Process evaluation to assess implementation: not stated	N= 600 infants Age: 3 months Gender: 49.2% in the intervention and 51.7% in the control groups were girls Inclusion: Sets of three villages that matched on population size, maternal literacy and birth rate Exclusion: sets of village strata, which are sharing geographical boundaries	Intervention: mothers received 11 nutrition education messages on breastfeeding and CFs plus ICDS through twice to four times a month home-visits over 12 months. The messages suggested three meals a day should be given with the rationale to motivate adherence. The researchers used flip charts, other visual material, demonstrations and counselling sessions. N=201 Control: received routine Integrated Child Development Services (ICDS), which include home-visit counselling on breastfeeding and CF, monthly growth monitoring, and non-formal preschool education for children. These services consist mainly of centre-based supplemental food provided to 1–6-year-olds. N= 202	Change in weight at age of 12 months, change in length, WAZ, and LAZ at 12, Motor development scores at age of 15 months and Mental development scores at age of 15 months	The intervention was up to 15 months of age, so data in the first year of age were used, i.e. anthropometric measures just until the age of 12 months were included There were three arms; two were intervention groups; for this review, only one intervention group was included. Whereas the second intervention group in which families received responsive weaning and developmental stimulation messages was not included
Zhang 2013 (195)	Same as Shi 2009	Same as Shi 2009	Same as Shi 2009	Z scores at 12 months, include; WAZ, LAZ, WLZ Changes in z scores from 6 to 12 months, include; WAZ, LAZ, WLZ	This study is an extended follow up of the participants of the Shi 2010 study The intervention was extended up to the age of 18 months, therefore, we included data up to the age of 1 year

Abbreviations:
Randomised controlled trial: RCT; weight for age z score: WAZ; length for age z score: LAZ; head circumference z score: HCZ; mid-upper arm circumference z score: MUACZ; and weight for length z sore: WLZ; Routine Integrated Child Development Services: ICDS; iron deficiency: ID
* Proportion of each gender was shown for infants with outcome data at 12 months of age

5.2.5.3.1 Trial design

Five studies were described as cluster RCTs, and further four studies were parallel RCTs. Studies were from South Asia (n=4), China (n=2), Brazil (n=1), Colombia (n=1) and Peru (n=1). Seven studies compared two groups of participants, and two studies had four arms (Table 5.3).

5.2.5.3.2 Participants

The included studies involved 4209 participants. Many of these studies recruited more than 300 participants each; only one study recruited fewer than 100 participants. The largest study randomised 1025 participants (Bhandari 2004 (421)), while the smallest study recruited 85 participants (Olaya 2013 (417)).

In the majority of the included studies, the nutrition education intervention started between two and four months of age (Bhandari 2001 (394); Shi 2010 (423); Vazir 2013 (196); Zhang 2013 (195)) three studies started the education intervention at 10 days of age or even younger (Bhandari 2004 (421); Bortolini 2012 (422); Penny 2005 (192)), one study started the intervention at 6 months (Olaya 2013 (417)) and one started between 6 and 9 months of age (Roy 2007 (194)).

Data were available for gender split in all studies. The groups were almost equally split.

5.2.5.3.3 Intervention

The duration of the intervention varied. In most of the studies, the intervention lasted up to 1 year of age (Bhandari 2001 (394); Bortolini 2012 (422); Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Vazir 2013 (196)). The intervention continued extended up to 18 months (Zhang 2013 (195)) and, to two years (Bhandari 2004 (421)).

We identified five studies that investigated the effect of face-to-face education on weaning. Three of these studies involved counselling sessions, demonstrations and home visits (Bhandari 2004 (421); Shi 2010 (423); Zhang 2013 (195)), one study compared the effect of counselling sessions

accompanied with home visits versus conventional management (Bortolini 2012 (422)), and one study involved a comparison between nutrition counselling sessions and conventional management (Bhandari 2001 (394)). Four studies compared face-to-face education accompanied by written guidance versus conventional management. Two of these studies involved counselling sessions accompanied by written guidance and demonstrations (Penny 2005 (192); Roy 2007 (194)). One study compared counselling sessions and written guidance versus standard care (Olaya 2013 (417)), and one study involved counselling sessions accompanied by written guidelines and home visits.

5.2.5.3.4 Outcomes

Not all outcomes were reported in each study. Growth rates (weight gain, linear growth) were reported in four studies; however, these measures were variably reported as change or absolute values. WAZ and LAZ at 12 months age were commonly reported outcomes (Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); (Zhang 2013 (195)). In the Penny 2005 (192) study, the scores were presented graphically.

Only one study reported head circumference for age z-scores (HCZ) at the age of 12 months (Olaya 2013 (417)).

Most of the included studies measured breastfeeding outcomes (Bhandari 2001 (394); Bhandari 2004 (421); Bortolini 2012 (422); Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Vazir 2013 (196); Zhang 2013 (195)). However, only two studies reported the proportion of children who were exclusively breastfed until six months of age (Bhandari 2004 (421); Bortolini 2012 (422)). Penny 2005 (192) also reported the prevalence of breastfeeding at three and four months of age and used the WHO definition of exclusive breastfeeding. Bhandari 2004 (421) and Bortolini 2012 (422) defined breastfeeding as the only food offered to the child, with no infusions or water.

Two studies reported the prevalence of anaemia (Bortolini 2012 (422); Olaya 2013 (417) and one study reported the prevalence of ID (Olaya 2013 (417)).

Neurodevelopmental scores, compliance with advice regarding the timing of weaning; cognitive ability in children at five, six or seven years of age; long-term growth; parental stress; infant quality of life; the prevalence of atopic conditions in childhood; prevalence of food neophobia or 'picky/fussy eating' and death before one and five years of age were not reported in any study.

5.2.5.4 Studies awaiting classification

Four studies appeared to meet the inclusion criteria (Characteristics studies awaiting classification table). Of these, two studies were presented as protocols, and, therefore, no data could be used in our analyses (Kimani-Murage 2013 (425); Kulwa 2014 (426)). Although outcomes stated in the published protocol are within the scope of the review, recently the study by Kimani-Murage et al. was identified as in press (427), but the results included in the report are not within the scope of this review. A further two studies met the inclusion criteria (Paul 2011 (428); Saleem 2014 (429)) but did not report any outcomes listed in this review. The reviewers sought but did not obtain further data from the trial investigators. Hence, the studies will be reconsidered in future updates of this review.

Table 5.4 Characteristics studies awaiting classification

Study ID	**Kimani-Murage 2013 (425)**
Methods	A cluster randomised controlled trial
Participants	N = 780 pregnant women and their respective children
Interventions	Intervention: includes personalised, home-based counselling of mothers on maternal, infant and young child nutrition, distribution of educational materials, and home-based counselling by community health workers on usual care (for example, antenatal care, delivery with skilled attendants, immunisation) Control: includes distribution of educational materials (usual care) and home-based counselling by CHWs on usual care (for example, antenatal care, delivery with skilled attendants, immunisation)
Outcomes	Exclusive breastfeeding for six months, WAZ, HAZ and WHZ
Contact information	Email: ekimani@aphrc.org
Notes	Information including changes in anthropometric measurements, the proportion of infants on exclusive breastfeeding, and compliance with advice regarding the timing of weaning, were requested, no response

Study ID	Paul 2010 (428)
Methods	RCT with 2*2 design Dyads were randomised into one of four treatment cells to receive both, one, or no interventions ;(“Soothe/Sleep”) and/or (“Introduction of Solids”), no interventions
Participants	N=160 Inclusion criteria: singleton with a gestational age of 34 weeks or more without morbidities that would affect sleeping or feeding. Mothers of these infants were required to be primiparous and English speaking with intent to breastfeed after hospital discharge and intent to follow-up with a University-affiliated primary care provider Exclusion criteria: if either the infant or mother had an extended hospital stay of 7 days or more after childbirth, mothers had a major pre-existing condition or morbidity that would affect postpartum care or study participation (e.g., cancer, multiple sclerosis, lupus)
Interventions	Intervention: parents in nutrition education (Introduction of Solids) group taught about hunger and satiety cues, the timing for the introduction of solid foods, and how to overcome infants’ initial rejection of healthy foods through repeated exposure. The intervention delivered at two nurse home visits Control: participants did not receive specific advice. Questions about general infant care and breastfeeding were answered
Outcomes	Conditional weight gain scores are the standardised residuals from the linear regression of the weight-for-age z-scores between two time points, weight-for-length percentile, exclusive breastfeeding duration
Contact information	Email: ipual@psu.edu
Notes	Although in the inclusion criteria, researchers aimed at recruiting babies were born at 34 weeks gestation and older, but in the baseline criteria, gestational age was around 39 weeks Further information including changes in anthropometric measurements, the proportion of infants on exclusive breastfeeding, and compliance with advice regarding the timing of weaning, were requested, no response.

Study ID	Saleem 2014 (429)
Methods	A cluster randomised study
Participants	Full-term infants N=212 infants Inclusion criteria: aged 10-20 weeks, who were either exclusively breastfeed or partially breastfed but had not started weaning or had recently started complementary food (less than one week) Exclusion criteria: infants found below 5th percentile on weight for age at baseline, history of two or more hospital admissions for more than 7 days each, serious congenital anomalies (cleft palate, congenital heart disease, neural tube defect) or other chronic conditions impairing feeding (e.g. cerebral palsy), acute illness requiring urgent hospitalisation, infants from families of very low socioeconomic status where adequate calorie-provision is constrained (assessed by a questionnaire on household possessions of items such as mobile phone, bicycle or other vehicle, TV)

Interventions	Intervention: there were four visits, at a 10-week interval. Baseline visit covered the importance and the duration of breastfeeding, the importance of commencement of weaning at six months, the importance of hand washing and general hygiene. The second visit covers breastfeeding promotion, selection of initial weaning foods and education on age-related weaning. The third visit covers the previously mentioned teaching sessions plus advice on prompting protein-based and iron-rich foods. The duration of each teaching session 15-20 minutes Control: families received advice about breastfeeding according to the national guidelines
Outcomes	Weight, length, and MUAZ at 10, 20 and 30 weeks from baseline
Contact information	Email : anita.zaidi@aku.edu
Notes	Clarification and further information were requested to calculate changes in anthropometric measures from the authors, no response received
Study ID	**Kulwa (426)**
Methods	A cluster randomised controlled trial
Participants	N= 297 infants Inclusion criteria: including breastfeeding infants aged six months; parents (or caregivers) resident in the sampled village and without plans to move away during the intervention period. Exclusion criteria: including infants with congenital or chronic abnormalities that interfere with their feeding or physical growth measurements, oedema, severely ill or had clinical complications necessitating hospitalisation
Interventions	Intervention: participants received a nutrition education package in addition to the routine health education. The education package include 1) education and counselling of mothers, 2) training community-based nutrition counsellors and monthly home visits, 3) sensitisation meetings with health staff and family members, and 4) supervision of community-based nutrition counsellors Control: participants will receive routine health education offered monthly by health staff at health facilities
Outcomes	LAZ and changes in WLZ scores at age of 12 and 15 months
Contact information	Kulwa K: kissakulwa@yahoo.com,
Notes	The investigator was contacted, no further information were provided

5.2.5.5 Excluded studies

Forty-two studies were excluded (Appendix 8.15). Eleven studies were not randomised (Brown 1992 (430); Guldan 2000 (199); Guptill 1993 (431); Jimenez 2016 (432); Kapil 1995 (433); Lakkam 2014 (434); Navarro 2013 (435); Ruel 1992 (436); Tang 2014 (437); Fahmida 2015 (438); Palwala 2009 (439) and three studies were excluded since they involved children between 6 to 24 months old at baseline and, therefore, did not meet our inclusion criteria. Nineteen

studies were excluded since the intervention (was nutrition education accompanied by food supplements), nine studies were excluded because the outcome measures were not relevant.

5.2.5.6 Risk of bias in included studies

The reviewers' judgments about each risk of bias item for the included studies presented in risk of bias table (Appendix 8.16).

5.2.5.6.1 Allocation

5.2.5.6.1.1 Sequence generation

All included studies were described as RCTs. However, only four studies reported the process of the allocation sequence generation (Bhandari 2004 (421); Olaya 2013 (417); Penny 2005 (192); Vazir 2013 (196)). Therefore, five studies were classified as being at unclear risk of bias (Bhandari 2001(394); Bortolini 2012 (422); Roy 2007 (194); Shi 2010 (423); Zhang 2013 (195)). Although two studies (Shi 2010 (423); Zhang 2013 (195)) stated that block randomisation was performed, the methods were not described. Therefore, the risk of bias was unclear. Four studies were judged to be at low risk of bias for this domain. Different sequence generation processes were used for each study: Bhandari 2004 (421) used table of random numbers; Penny 2005 (192) used coin tossing; Olaya 2013 (417) used block randomisation; Vazir 2013 (196) used computer random number generator.

5.2.5.6.1.2 Allocation concealment

Four studies described either central allocation or sealed opaque envelopes as a mechanism to conceal allocation after randomisation (Bhandari 2004 (421); Olaya 2013 (417); Penny 2005 (192); Vazir 2013 (196)). Therefore, these studies were at low risk of allocation bias. The remaining five studies were judged to have an unclear risk of bias due to insufficient information (Bhandari 2001 (394); Bortolini 2012 (422); Roy 2007 (194); Shi 2010 (423); Zhang 2013 (195)).

5.2.5.6.2 Blinding

For blinding of participants and personnel, the reviewers agreed to judge the risk of performance bias as low for seven studies because it was not possible to blind the intervention (Bhandari 2001 (394); Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Zhang 2013 (195)). Furthermore, the outcome measures were objective and unlikely to be affected by the lack of blinding.

Two studies (Bhandari 2004 (421); Bortolini 2012 (422)) included subjective outcome measureswere judged to have high risk of bias because of the inadequate blinding, e.g. prevalence of exclusive breastfeeding,

For blinding of outcome assessment (detection bias), the risk of bias was low for eight studies (Bhandari 2001 (394); Bhandari 2004 (421); Olaya 2013 (417); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Vazir 2013 (196); Zhang 2013 (195)). Further trial (Bortolini 2012 (422)) did not describe the method of assessor blinding, but the outcome was objective. Therefore, the risk of bias was considered unclear.

5.2.5.6.3 Incomplete outcome data

Only one study (Roy 2007 (194)) was at low risk of attrition bias since the proportion of incomplete outcome data for the review's primary outcome was low (< 10%). Six studies were at high risk of bias due to high losses in follow-up (Bhandari 2004 (421); Bortolini 2012 (422); Olaya 2013 (417); Shi 2010 (423); Vazir 2013 (196); Zhang 2013 (195)). For the remaining studies (Bhandari 2001 (394); Penny 2005 (192)), the reviewers were unable to judge attrition bias because, in total, the attrition rate was < 10%; with > 10% in one group.

5.2.5.6.4 Selective reporting

The inadequate reporting of studies made it difficult to reach a decision regarding selective reporting. Reviewers were unable to retrieve the protocols for most of studies included (Bhandari 2001 (394); Bhandari 2004 (421); Penny 2005 (192); Roy 2007 (194); Shi 2010 (423); Vazir

2013 (196); Zhang 2013 (195)) and thus considered these studies to have unclear risk of bias. The remaining two studies were considered to be at high risk of reporting bias: one study was retrospectively registered (Olaya 2013 (417)) and in the other study some pre-specified outcomes within the study protocol were not presented in the published report (Bortolini 2012 (422)).

5.2.5.6.5 Other potential sources of bias

In four studies (Bhandari 2004 (421); Penny 2005 (192); Roy 2007 (194); Vazir 2013 (196)), no evidence of other potential sources of bias was found Risk of bias due to other potential sources of bias was high in five studies: there was imbalanced baseline characteristics between the intervention and control groups (Penny 2005 (192); Bhandari 2001 (394)) and three studies were commercially supported (Olaya 2013 (417); Shi 2010 (423); Zhang 2013 (195)).

5.2.5.7 Effects of interventions (Nutritional education versus conventional management)

5.2.5.7.1 Primary outcomes

5.2.5.7.1.1 Weight gain during the first two years of life

Meta-analysis for this outcome was conducted on four studies (196, 394, 421, 423) (2246 infants) that assessed the effect of nutrition education on body weight during the first two years of life. Bhandari 2004 (421) reported weight gain, and data for Vazir 2013 (196) study were obtained from the authors. In the Bhandari 2001 (394) and Shi 2010 (423) studies, the SDs for changes in weight from baseline was imputed (as discussed in Section 5.2.4.1.4). Using fixed-effect model, the MD was 0.03 kg [95% CI: -0.02 to 0.08], p=0.2. As there was a moderate level of heterogeneity (I^2 = 64%), random-effect model was also generated, which produced MD of 0.02 kg [95% CI: -0.06 to 0.11], p = 0.6. Point estimates from both the fixed- and random-effect models suggest slightly improved weight outcomes. Nonetheless, CIs and p values from both models suggest that there was no evidence of the effect of nutrition education on weight gain from 6 to 12 months.

One of the main contributors to heterogeneity was the study by Bhandari 2001 (394), an individual RCT, which had methodological limitations. Removing this study reduced the heterogeneity (I^2 = 0%) and, therefore, fixed-effect model was used. The fixed-effect model produced MD of 0.06kg [95% CI: 0.01 to 0.11], p = 0.03 (Figure 5.3).

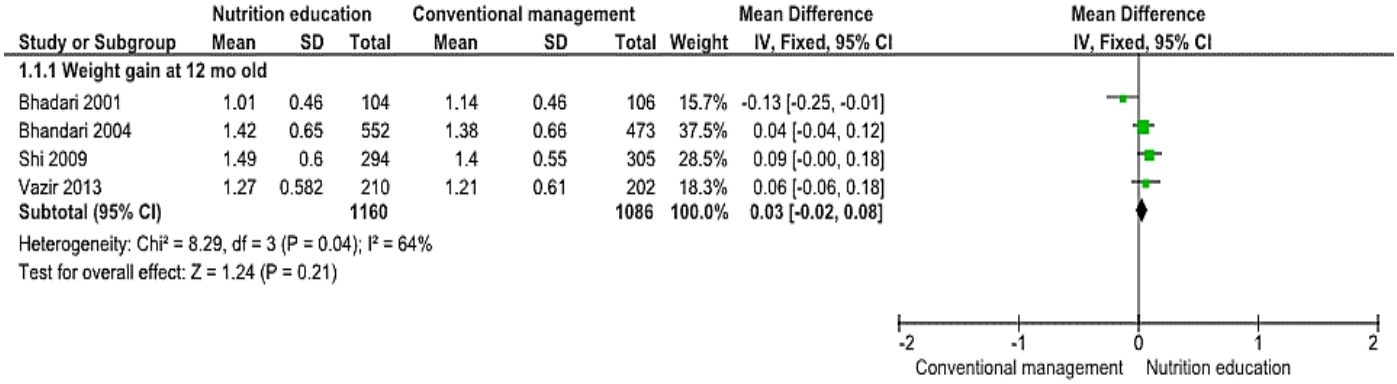

Figure 5.3 Forest plot of the intervention effect on weight gain (kg) from 6 to 12 months of life

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.2 Length gain during the first two years of life

Four studies (196, 394, 421, 423) (2246 infants) were included in the meta-analysis for the effect of nutrition education on length gain. Again, Bhandari 2004 (421) reported length gain, but for the Vazir 2013 (196) study data were obtained from the authors. For the Bhandari 2001 (394) and Shi 2010 (423) studies, we imputed the SDs of mean change. Using fixed-effect model, the MD was 0.20 cm [95% CI: 0.08 to 0.32], p = 0.0007. As there was a moderate level of heterogeneity (I^2 = 64%), random-effect model was also conducted, which produced MD of 0.16 cm [95% CI: -0.05 to 0.36], p = 0.1.

One of the main contributors to the heterogeneity was the study by Bhandari 2001 (394), an individual RCT, which had methodological limitations. Removing this study reduced the

heterogeneity (I^2 = 0%) and, therefore, fixed-effect model was used. The fixed-effect model produced MD of 0.27cm [95% CI: 0.14 to 0.39], p < 0.001 (Figure 5.4).

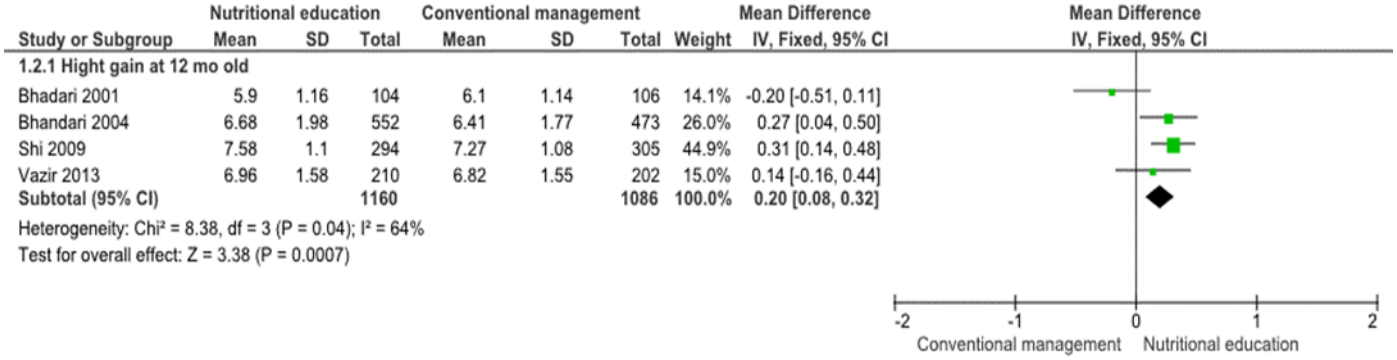

Figure 5.4 Forest plot of the intervention effect on length gain (cm) during the first two years

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.3 Weight-for-age z-scores in the first two years of life

Four studies (192, 194, 195, 417) (1672 infants) reported WAZ scores in the first two years of life that were included in the meta-analysis (Figure 5.5).

5.2.5.7.3.1 WAZ scores at the age of 12 months

The meta-analysis of WAZ scores at 12 months included four studies (1672 infants) (192, 194, 195, 417) (Figure 5.5). Using fixed-effect model, the MD was 0.11 [95% CI: 0.02 to 0.20], p = 0.02. There was evidence of high level of heterogeneity (I^2 = 79%). Hence, random-effects model was generated, which produced MD of 0.04 [95% CI: -0.20 to 0.28], p = 0.7. Point estimates from the random-effects model suggest no evidence of improved WAZ scores related to nutrition education.

A second analysis of this outcome was conducted by excluding the Olaya 2013 (417) study, a small, individual RCT study with a high risk of bias. There was moderate heterogeneity (I^2 = 68%) and, therefore, random-effects model was used. The random-effects model produced MD of 0.14

[95% CI: -0.05 to 0.33], p = 0.1. The second analysis indicated that there was no evidence that the intervention affected WAZ scores at 12 months of age.

5.2.5.7.3.2 WAZ scores at the age of 15 months

One study (192) (377 infants) reported WAZ scores at the age of 15 months (377 infants). Fixed-effect model was used, producing MD of 0.32 [95% CI: -0.03 to 0.67], p = 0.07 (Figure 5.5)

Trials were insufficient to allow firm conclusions to be drawn.

5.2.5.7.3.3 WAZ scores at the age of 18 months

Two studies (192, 194) were included in the meta-analysis (988 infants) (Figure 5.5). The fixed-effect model produced MD of 0.41 [95% CI: 0.31 to 0.51], p < 0.001. As there was moderate heterogeneity (I^2 = 64%), random-effects model was used, producing MD of 0.39 [95% CI: 0.22 to 0.57], p < 0.001. Point estimates from both the fixed- and random-effects models suggest there were improved WAZ scores at the age of 18 months related to nutrition education.

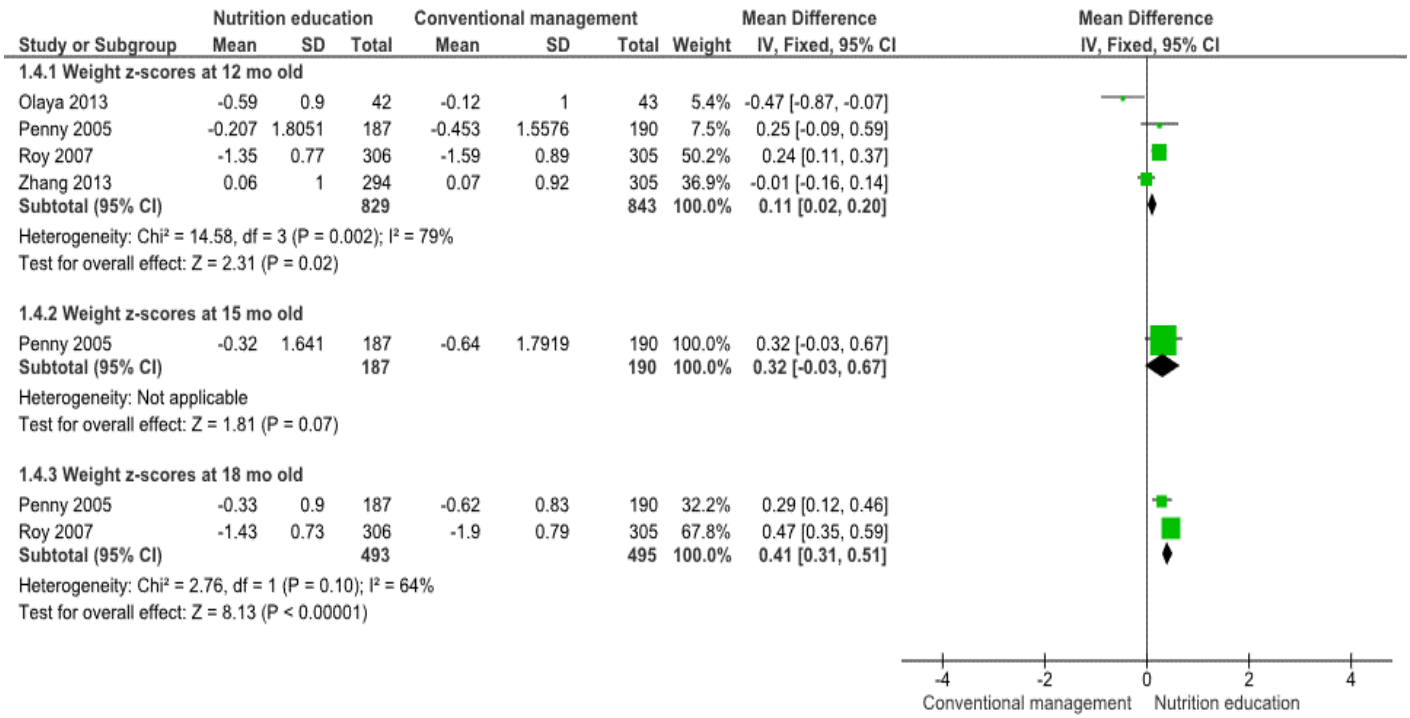

Figure 5.5 Forest plot of the intervention effect on weight z-scores in the first two years of life

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.4 Length-for-age z-scores in the first two years of life

Four studies (192, 194, 195, 417) (1672 infants) were included in the meta-analysis for LAZ scores in the first two years of life (Figure 5.6).

5.2.5.7.4.1 LAZ score at the age of 12 months

The meta-analysis of LAZ scores at 12 months included four studies (192, 194, 195, 417) (1672 infants). There was evidence of low level of heterogeneity (I^2 = 36%). A fixed-effect model produced MD of 0.16 [95% CI: 0.06 to 0.26], p = 0.001. Pooled estimate from the included studies showed that this intervention had a significant positive impact on LAZ scores related to nutrition education (Figure 5.6).

5.2.5.7.4.2 LAZ scores at the age of 15 months

One study (192) reported LAZ scores (377 infants). Fixed-effect model was used, producing MD of 0.36 [95% CI: -0.0003 to 0.72], p = 0.05 (Figure 5.6).

The impact of the intervention on LAZ scores was not significant, but there were insufficient trials to allow firm conclusions to be drawn.

5.2.5.7.4.3 LAZ scores at the age of 18 months

Two studies (192, 194) were included in the meta-analysis (988 infants). There was low level of evidence of heterogeneity (I^2 = 21%), so fixed-effect model was used. The fixed-effect model produced aMD of 0.31 [95% CI: 0.20 to 0.42], p < 0.001. Point estimates suggested that there was evidence of improved LAZ scores at the age of 18 months related to nutrition education (Figure 5.6).

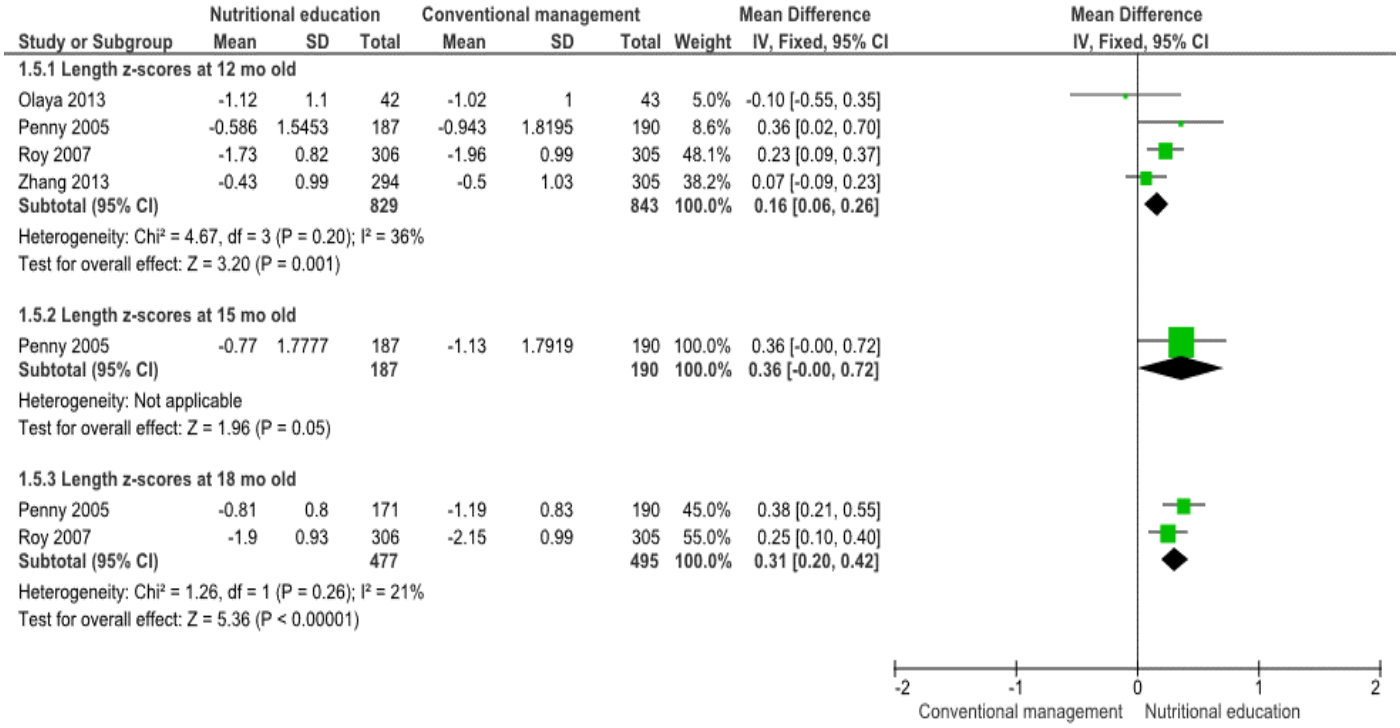

Figure 5.6 Forest plot of the intervention effect on length z-scores in the first two years of life

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.5 Weight-for-length z-scores in the first two years of life

Three studies (194, 195, 417) (1672 infants) reported weight-for-length z-scores (WLZ) comparisons between the experimental groups during the first two years of life (Figure 5.7).

Meta-analysis of WLZ scores at the age of 12 months included three studies (1295 infants). Using fixed-effect model, the MD was 0.01 [95% CI: -0.1 to 0.12], p = 0.85. There was evidence of high level of heterogeneity (I^2 = 82%). As there was heterogeneity, random-effects model was generated, which produced MD of -0.09 [95% CI: -0.39 to 0.20], p = 0.5. CIs from both models showed no evidence of improved WLZ scores at the age of 12 months.

Meta-analysis for WLZ at the age of 18 months included two studies (192, 194) (988 infants), MD of 0.33 [95% CI: 0.22 to 0.44], p < 0.001. As there was heterogeneity (I^2 = 92%), random-effects model was also conducted, which produced MD of 0.30 [95% CI: -0.09 to 0.69], p = 0.1. Neither

the point estimates nor CIs indicated the possibility that there was evidence of improved WLZ scores at the age of 18 months (Figure 5.7).

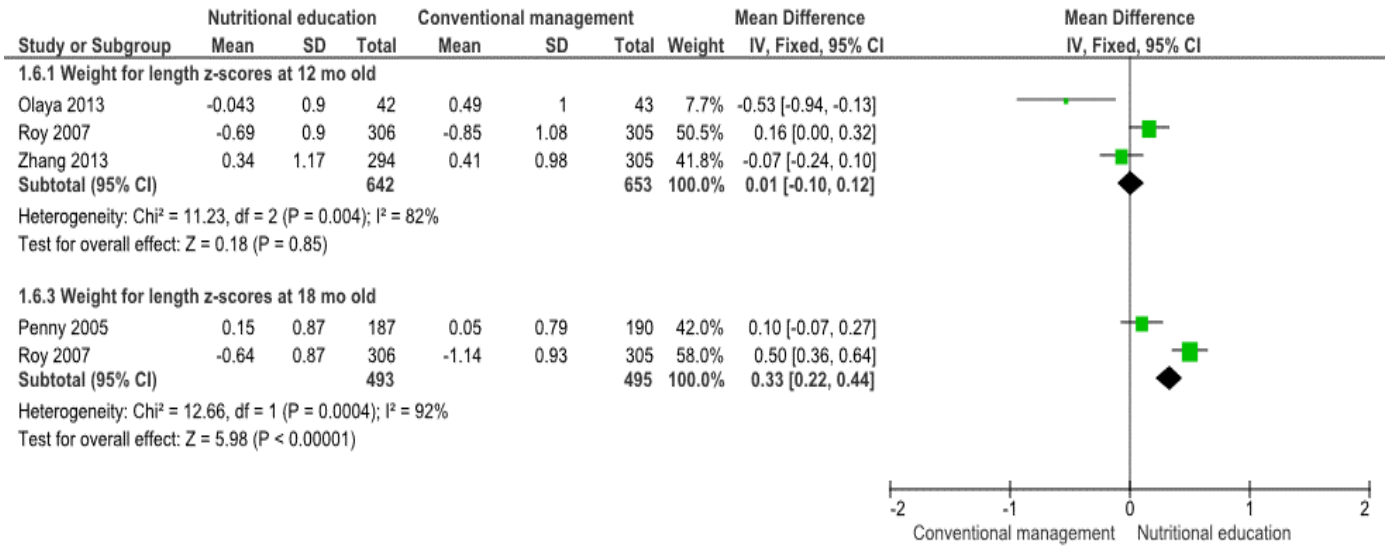

Figure 5.7 Forest plot of the intervention effect on weight for length z-scores in the first two years of life

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.6 Change in weight-for-age z-scores during the first year of life

Data on change in WAZ scores from 6 to 12 months related to nutrition education obtained from four studies (196, 394, 421, 423) (1473 infants). Meta-analysis using fixed-effect model indicated that there was no evidence that the intervention affected the change of WAZ scores. The fixed-effect model produced MD of 0.06 [95% CI: -0.02, 0.14], p = 0.15. There was evidence of moderate heterogeneity (I^2 = 64%), so random-effects model was also used; the MD was 0.06 [95% CI: -0.09 to 0.20], p = 0.4 (Figure 5.8).

None of the trials reported data on change in WAZ at the age of 15 months, 18 months or two years.

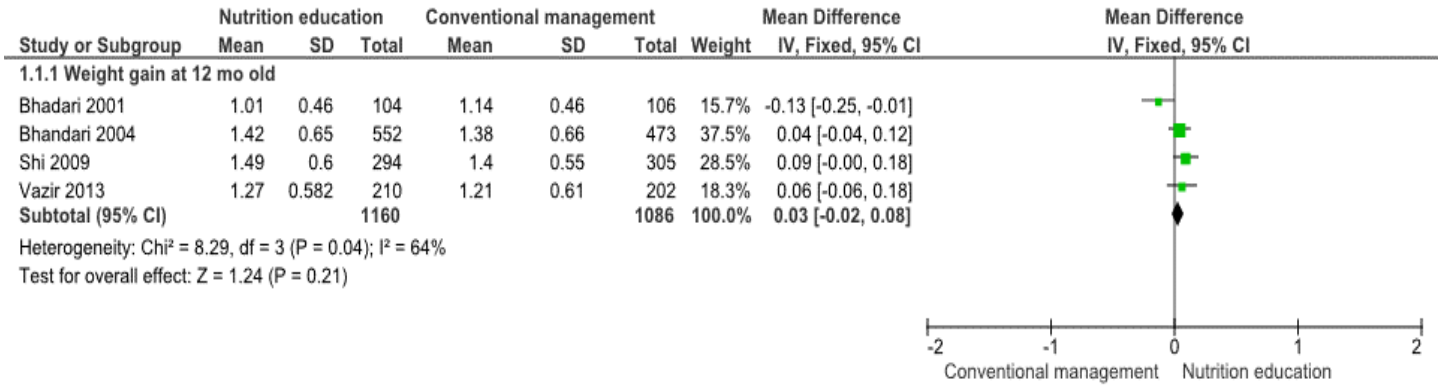

Figure 5.8 Forest plot of the intervention effect on changes in weight z-scores from 6 to 12 months

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.7 Change in length-for-age z-scores during the first two years of life

Data on change in LAZ scores from 6 to 12 months related to nutrition education obtained from four studies (192, 195, 196, 417) (1473 infants). There was no heterogeneity (I^2 = 0%) and, therefore, fixed-effect model was used, producing MD of 0.20 [95% CI: 0.12, 0.27], p < 0.001 (Figure 5.9).

None of the trials reported data on change in LAZ at the age of 15 months, 18 months or age two years.

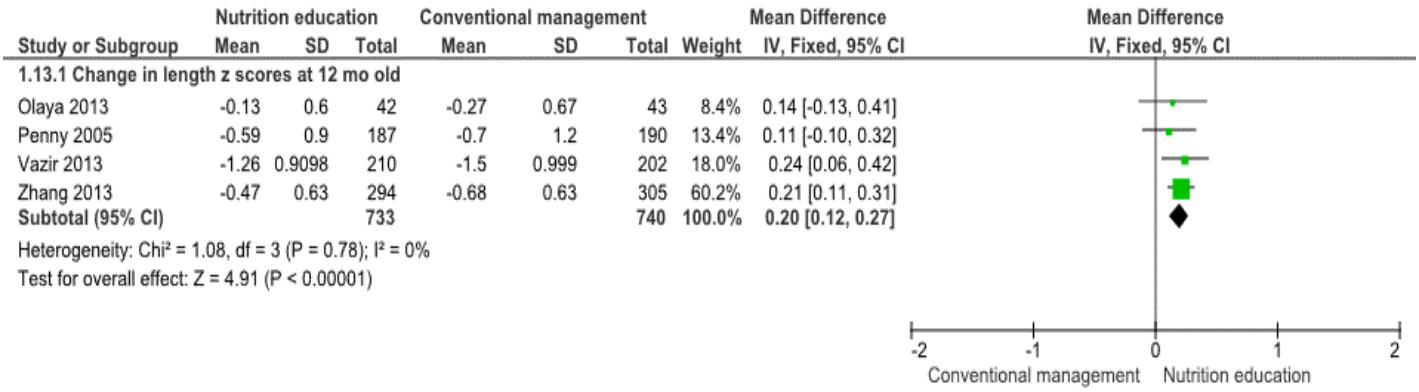

Figure 5.9 Forest plot of the intervention effect on changes in length z-scores from 6 to 12 months

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi²: Chi-square; df: degrees of freedom; P: p-value; I²: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.8 Head circumference z-scores in the first two years of life

Analysis of HCZ scores related to nutrition education included one study (417) (85 infants). Using

fixed-effect model, the MD was -0.15 [95% CI: -0.53, 0.23], p = 0.4 (Figure 5.10).

There were insufficient trials to draw a firm conclusion.

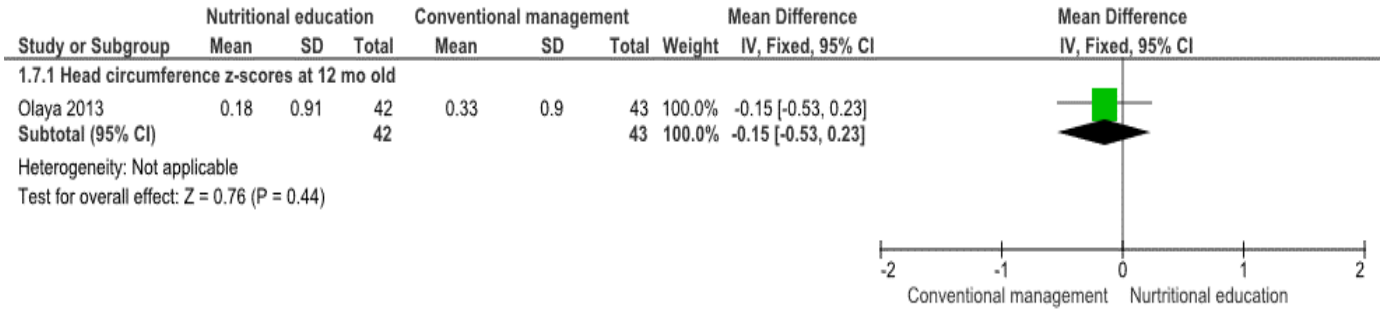

Figure 5.10 Forest plot of the intervention effect on head circumference zscore in the first two years of life

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi²: Chi-square; df: degrees of freedom; P: p-value; I²: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.8.1 Change in head circumference z-scores during the first two years of life

One study (417) (85 infants) reported no evidence of change in HCZ scores from 6 to 12 months related to nutrition education. However, the analysis showed a tendency to improved head growth from the intervention. The MD was 0.12 [95% CI: −0.07, 0.3], p=0.2 (Figure 5.11).

There were insufficient trials to draw firm conclusions.

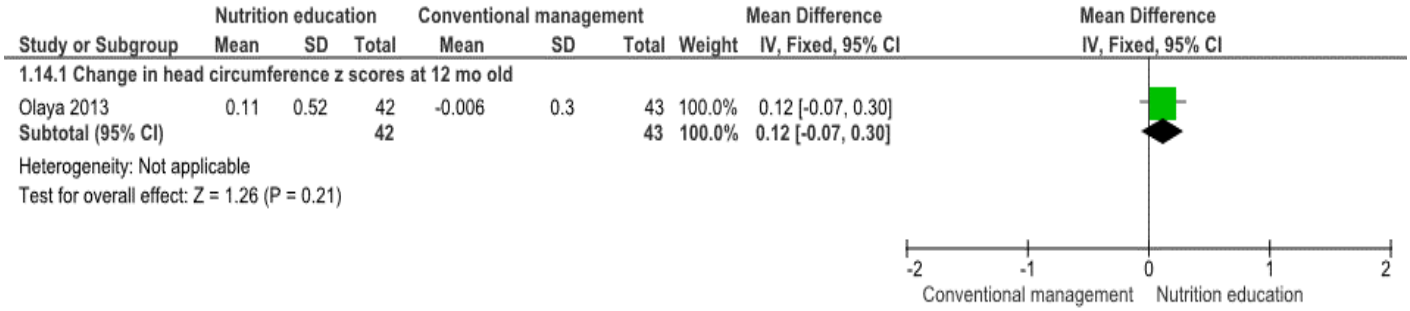

Figure 5.11 Forest plot of the intervention effect on changes in head circumference z-score from 6 to 12 months

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; IV: inverse variance; Fixed: analysis model; CI: confidence interval

5.2.5.7.9 Secondary outcomes

5.2.5.7.9.1 Prevalence of exclusive breastfeeding for six months

Olaya 2013 (417) compared the number of breastfeeds per day; time per breastfeed and the number of breastfeeds per night. Shi 2010 (423) and Zhang 2013 (195) compared breastfeeding rate and frequency. Vazir 2013 (196) and Roy 2007 (194) compared the frequency of breast milk feeds between the intervention groups. Penny 2005 (192) reported exclusive breastfeeding for three and four months and the proportion of infants who received breastfeeding for more than six months of life. Only two trials Bhandari 2004 (421) and Bortolini 2012 (422) provided data for the meta-analysis (1525 infants) for the prevalence of exclusive breastfeeding at the age of 6 months.

There was substantial heterogeneity (I^2 = 94%), which could be due to the quality of the included studies (Figure 5.12). Also, there were differences in the type of interventions regarding messages that emphasised breastfeeding. The intervention in Bhandari 2004 (421) study included antenatal feeding education, and starting weaning at six months of age, with meal frequencies and amounts to be fed at different ages while continuing to breastfeed. In the Bortolini 2012 (422) study, dietary recommendations were given that prioritised exclusive breastfeeding up to 6 months and commencing weaning at the age of 6 months.

Both studies showed a clear difference between the intervention and control groups and the analysis also showed a statistically significant difference, RR 6.64 [95% CI: 4.62, 9.54], P < 0.001. As there was high heterogeneity, random-effects model was also conducted, which produced RR of 5.1 [95% CI: 1.42 to 4.21], P = 0.03.

Results indicate higher rates of breastfeeding with the intervention. However, this outcome needs to be considered with caution, given that the high heterogeneity and that there were insufficient trials to allow firm conclusions to be drawn.

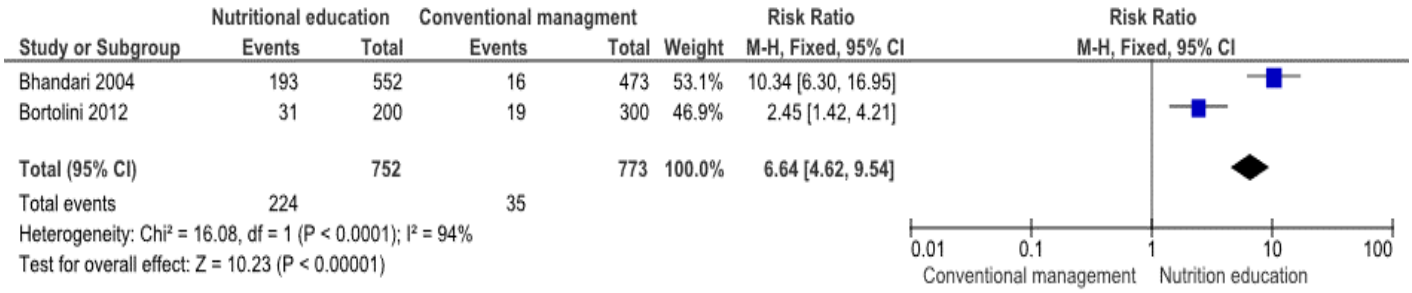

Figure 5.12 Forest plot of the intervention effect on exclusive breastfeeding for 6 months of age

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; M-H: Mantel-Haenzel; Fixed: analysis model; CI: confidence interval

5.2.5.7.9.2 Prevalence of iron deficiency at the age of 12 months

One study reported analysable data on this outcome Olaya 2013 (417). The proportion of children who had ID was higher in the control group (10/28; 37.1%) than in the intervention group (8/29; 29%). Nonetheless, results were not statistically significant, producing RR of 0.79 [95% CI: 0.39, 1.6], P = 0.5 (Figure 5.13).

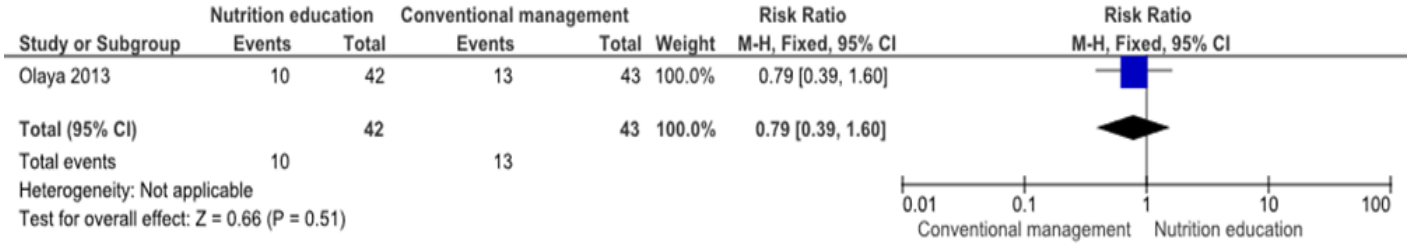

Figure 5.13 Forest plot of the intervention effect on prevalence of iron deficiency at 12 months of age

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; M-H: Mantel-Haenzel; Fixed: analysis model; CI: confidence interval

5.2.5.7.9.3 Prevalence of iron deficiency anaemia at the age of 12 months

Two studies reported the proportion of children who had IDA (Olaya 2013 (417); Bortolini 2012 (422)). Bortolini 2012 (422) showed that there was no significant effect of the intervention on the prevalence of anaemia, but there was a non-significant higher proportion of infants diagnosed with anaemia among infants from the intervention group (105/158; 66.5%) compared to the control group (131/213; 61.8%). However, Olaya 2013 (417) showed a lower proportion of infants with anaemia from the intervention group (0/36; 0%) when compared with controls (4/37; 11%). A pooled estimate for both studies shows no significant effect, producing RR of 1.16 [95% CI: 0.96, 1.39], P= 0.1. Moderate heterogeneity was observed between the two studies (I^2 = 62%) (Figure 5.14). Hence, random-effect model was also conducted, which produced RR of 0.58 [95% CI: 0.07 to 5.09], P = 0.6.

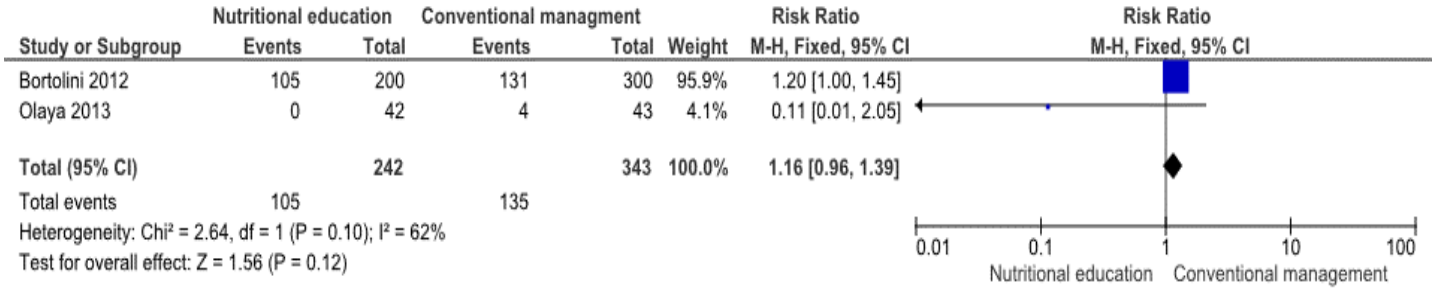

Figure 5.14 Forest plot of the intervention effect on prevalence of Anaemia at 12 months of age

Green box: the effect estimate of each study. The horizontal line: the confidence interval. The vertical line: the line of no effect. The black diamond: Average effect size
Chi^2: Chi-square; df: degrees of freedom; P: p-value; I^2: a statistical measurement of heterogeneity; Weigh: weight assigned to study in the analysis; M-H: Mantel-Haenzel; Fixed: analysis model; CI: confidence interval

5.2.5.7.10 Other outcomes

The following outcomes were not reported in the included studies:

- adherence with advice regarding the timing of weaning
- long-term growth: weight, height, skinfold thickness or body mass index at five, six or seven years of age
- cognitive ability in children at five, six or seven years of age
- parental stress
- infant quality of life when the child is aged six months of age or older
- prevalence of atopic conditions
- prevalence of food neophobia or 'picky/fussy eating' and
- death before one and five years of age.

5.2.5.8 Quality of the evidence

Evidence shows statistically significant (very low to moderate) heterogeneity for the primary outcome (growth outcomes) high heterogeneity for three important secondary outcomes (duration of exclusive breastfeeding, ID and IDA).

The SoF table with judgments according to GRADE is presented in Appendix 8.17.

The GRADE was rated as moderate for LAZ scores at the age of 12 months and 18 months. The GRADE was rated as low for length gain at 12 months; WAZ scores at 12 months, 15 months

and 18 months; LAZ scores at 15 months; HCZ scores at 12 months; change in LAZ scores at 12 months; change in LAZ scores at 12 months; MDI scores at 15 months; and PDI scores at 15 m. The GRADE was rated as very low for weight gain at 12 months; WAZ scores at 12 months; WLZ scores at 12 months and 18 months; change in WAZ scores at 12 months; exclusive breastfeeding at six months; ID at 12 months; and IDA at 12 months. The quality of evidence was downgraded because of methodological limitations in the included trials (including uncertainty about allocation concealment and blinding) and imprecision of effect size estimates.

The risk of bias in the included review has been summarised in are presented in “Risk of bias” graph (Figure 5.15) and “Risk of bias” summary (Figure 5.16) below.

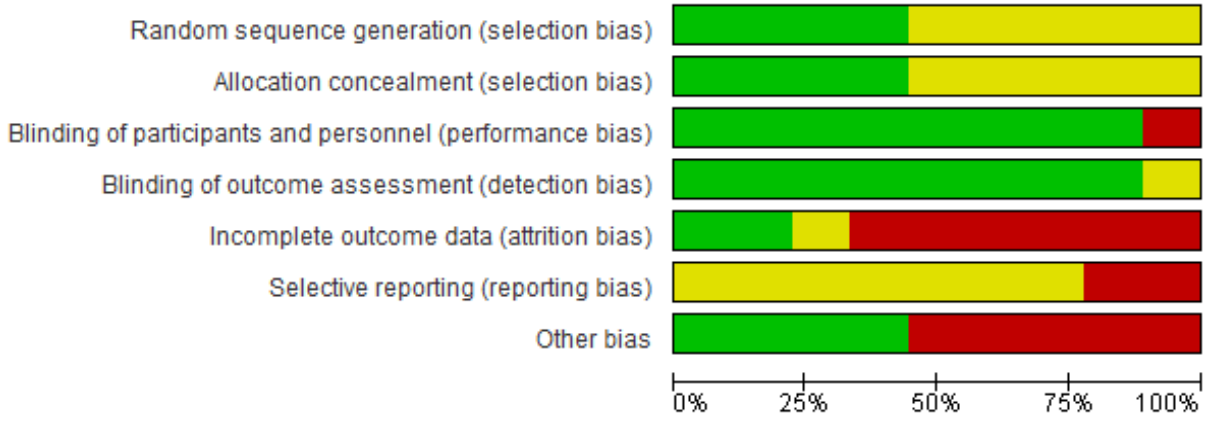

Figure 5.15 Risk of bias graph

Reviewers’ judgements about each risk of bias item presented as percentages across all included studies Each bar presents a risk of bias item with all judgements; green, low risk; red, high risk; yellow, unclear risk of bias

5.2.5.9 Potential bias in the review process

Two reviewers, independently, conducted data selection and extraction. We double-checked the data extracted. We are confident that, through a comprehensive electronic database search and manual search of relevant journals without restriction on language and the status of the publication, all relevant published studies should be identified. Nonetheless, there is always the possibility that some additional studies (published and unpublished) may have been missed when conducting the systematic review. If this was the case, it could have potentially introduced

bias into the review. There were insufficient studies to perform a funnel plot to explore any possible publication or reporting bias.

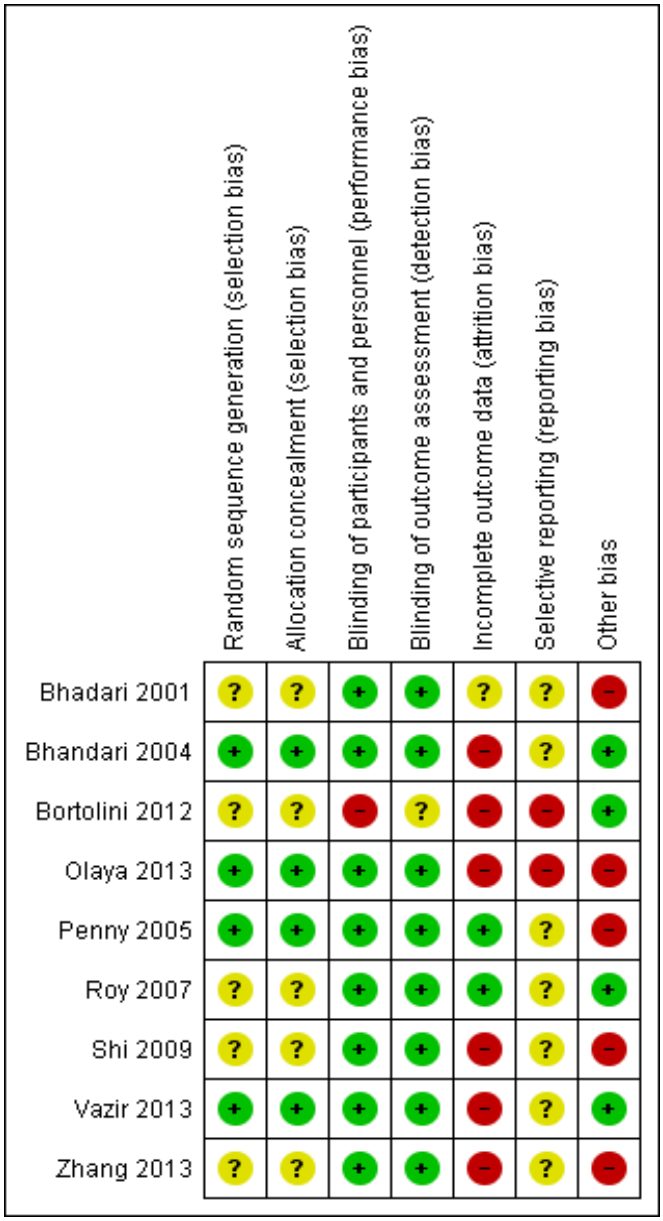

Figure 5.16 Risk of bias summary

Reviewers' judgments about each risk of bias item for the included study
The included study was analysed for bias across all domains with each of the judgements as; green ball, low risk; red ball, high risk; yellow ball, unclear

5.2.6 Discussion

This systematic review aimed at measuring the effects of family nutrition education, targeted at improving weaning practices of full-term infants. Both the included studies and studies waiting for classification share the objective of evaluating nutrition education delivered to families of full-term infants, targeted at improving infants' nutrition, growth and development.

5.2.6.1 Summary of main results

This review included nine RCTs that considered the effects of nutrition education intervention on growth, neurodevelopment and nutrition status of full-term infants. Although studies from countries of all income bands were sought, all of the detected trials were undertaken in low- and middle-income countries and, therefore, the results are relevant to prevent undernutrition in full-term infants but are not necessarily applicable to high-income countries and preventing obesity. The included studies involving a total of 4209 infants with sample sizes varied between 85 and 1025 infants. Ages of starting the intervention ranged from birth to 6-9 months after birth and continued to 1 year of life. Different forms of nutrition education were used; counselling sessions, demonstrations and home visits.

Most of the included studies were not blinded because of the nature of the intervention. However, some of the outcomes included in this review such as growth measures and iron status are unlikely to be affected by the lack of blinding. The overall quality of evidence ranged from very low to moderate across almost all the outcomes of interest for this review.

5.2.6.1.1 Impact of nutrition education intervention on growth

All the included studies, except Bortolini 2012 (422), reported growth in the first two years of life. The intervention targeted at improving weaning practices in the first year of life improves weight and height in the first two years of life. Meta-analyses showed improvement in length gain at 12 months, WLZ scores at 18 months, WAZ scores at 18 months and LAZ scores at 12 and 18 months.

The increased attained length related to the intervention ranged from a MD of 0.32 cm [95% CI: 0.03 to 0.61] (421) to 0.66 cm [95% CI: 0.03 to 1.29] (423). The increase in attained weight varied from 0.04 kg [95% CI: 0.06 to 0.15] (421) to 0.22 kg [95% CI: 0.003, 0.45] (423).

The diversity in outcomes in relation to the intervention could be explained by many reasons, such as the age of children at enrolment, including children with failure to thrive (FTT), social and economic contexts, differences in intervention strategies, methodological aspects of the included studies and possible publication bias.

Variations in the age of infants at enrolment were observed between the included studies. Some studies started the intervention in the newborn period (192, 421), and some between two and four months (195, 196, 394, 423), whereas others started the intervention at the later age of 6 months (417) or between 6 to 9 months (194). The differences in the age of infants at enrolment may lead to various results in intervention effectiveness.

Children with FTT may have long-term impaired growth outcomes. The study in India (394) enrolled 23% of infants who were stunted (HAZ score ≤ -2) and 1% of infants were wasted (WLZ score ≤ -2). In the Bangladesh study (194), mildly malnourished infants were enrolled at the beginning of the intervention so that baseline nutrition status could have influenced the intervention effects. Early nutrition deficits have been linked to long-term impaired growth outcomes (440).

Infants exposed to high levels of infection are susceptible to gut damage and growth faltering (441). Nutrition interventions by themselves may not result in improved growth if the target population suffer from frequent infections, both symptomatic (442) and asymptomatic (441). UNICEF WASH (Water, Sanitation, and Hygiene) and nutrition teams jointly assessed the relations between sanitation and stunting, using UNICEF data to identify factors associated with stunting among children during the first two years of life. Both unimproved latrines and untreated drinking water were associated with an increased probability of stunting in Indonesia compared with improved conditions (443).

Socioeconomic status of families studied may have the potential to affect the efficacy of the intervention. The caregiver may know the recommended feeding practices, but this knowledge may not translate into good practice. Financial constraints may limit the ability to include adequate amounts of nutrient-dense weaning foods. RCTs were conducted in areas where various nutritious foods are available to almost all families, particularly those who have ready access to professional health service showed a positive effect of nutrition education on growth outcomes (192, 195). Similar findings were observed in a non-randomised community-based education programme in China (199). However, a study carried out in poor communities in India (421) where the population could not afford animal-source foods, showed that infants were predominantly fed cereal-based weaning foods with low consumption of animal-source foods, even after the intervention. Animal products are energy dense and an excellent source of high-quality and readily digested protein and essential fatty acids. These foods are also containing multiple micronutrients and in a highly bioavailable form (444). Of note, when education included key messages that encouraged caregivers to include animal-source foods in children's meals, the intervention had a positive impact on growth outcomes (192).

Nutrition education interventions varied between the studies. Differences were observed in the intervention strategies and intensities. Some studies provided group training (192, 195, 421, 423) or individual counselling (417) along with community mobilisation through educating influential community leaders and key family members (194, 421). Some investigators formulated meal recipes (192, 421). All studies, except Bhandari 2001 (394) and Bortolini 2012 (422), provided visual materials to families in the intervention group. Some interventions also included recipe preparation demonstrations (192, 194-196, 421, 423).

The goal of nutrition education research is to elucidate aspects that enable people to improve diet-related behaviours and cognitions coupled with better health outcomes (392). Some components of the interventions are designed to have a greater impact than others on nutrition-related health outcomes. The components may have the greatest impact were cooking skills workshops and group education sessions. Other contributing elements included visual materials

that provided healthy recipes and nutrition tips. There is little evidence demonstrating the exclusive effect of training groups on nutrition-related health outcomes. Nonetheless, a qualitative study reported that cooking classes improved nutrition knowledge and cooking skills (445).

5.2.6.1.2 Impact of nutrition education on the prevalence of exclusive breastfeeding

This systematic review of the limited evidence suggests that it may be possible to increase the prevalence of exclusive breastfeeding at the age of 6 months with the intervention. Bhandari 2004 (421) showed a higher rate of exclusive breastfeeding than the Bortolini 2012 study (422). Differences in the rate of exclusive breastfeeding could be partially explained by the fact that the rate of breastfeeding at baseline might be low. Bortolini 2012 (422) report that approximately one-third of the infants studied were exclusively breastfed at the age of <1 month, but no information were reported by Bhandari 2004 (421). Although similar definitions of exclusive breastfeeding were used in the two studies, the comparison between the studies could be problematic; because the investigators used varied methods, therefore, it would difficult to compare accurately.

Breastfeeding counselling is considered an effective way to increase the rate of exclusive breastfeeding at the age of 6 months (446, 447). However, in low- and middle-income countries, the effect of nutrition education on the duration of breastfeeding might be limited by several factors, including the promotion of manufactured breastmilk substitutes and economic factors. The low prevalence of breastfeeding may be compounded in countries where the International Code of Marketing Breast-milk Substitutes (448) or other similar legislation which regulates the promotion of formula has not been implemented and infant formula is widely available as part of existing public health or nutrition programmes (449).

Economic status could be a factor that may affect the rate of exclusive breastfeeding. Studies in Uganda and South Africa (450, 451) showed that women with their own source of income are

more likely to stop breastfeeding early. In the current review, 38% in the Bhandari 2004 (421) study and 26.8% in the Bortolini 2012 study (422) of mothers were working outside the home.

Another factor that could explain the low prevalence of exclusive breastfeeding at the age of six months in the Bhandari 2004 study (421) is that dietary intake was assessed for 85.9% of mothers. The investigators used dietary recall based on seven days of 24-hour dietary recall (421), whereas Bortolini 2012 (422) performed an assessment of dietary intakes in which dietary intake was assessed for 63.4% of the mothers and the recall was based on a single 24-hour recall. Once again, a single 24-hour dietary recall may have limited the results (452).

5.2.6.1.3 Impact of nutrition education intervention on iron status and the prevalence of anaemia

One study reported the impact of nutrition education on the prevalence of ID (417) and two studies (417, 422) reported the impact of the intervention on the prevalence of anaemia.

Data from 585 infants included in two RCTs did not demonstrate a clear or consistent benefit of nutrition education for preventing anaemia (Hb concentration <11 g/dl). There was some variability between the studies as indicated by the incidence of anaemia in response to the intervention. Olaya 2013 (417) showed higher rates of anaemia among infants from the control group. However, there is a potential concern because of the high risk of bias in this small RCT and the planned sample size was not achieved.

On the other hand, in the Bortolini 2012 study (422) a higher incidence of anaemia in the intervention group was observed. This might be partially explained by the higher proportion of infants who were exclusively breastfed after the age of six months and more infants had cow's milk after six months in the intervention group when compared to the control group. Furthermore, in this study (432), dietary intake was assessed based on a single 24-hour dietary recall, which may have limited the results. It is recognised that a given individual's dietary intake includes a wide range of variation. Therefore, to obtain more reliable data, it would be necessary to conduct more than one dietary recall per person (452).

Both studies (417, 422) were conducted in low-income countries where high prevalence of anaemia was reported. Iron stores of infants are usually lower if maternal reserves are deficient because the fetus has a limited capacity to acquire iron (453). Infants born with birth weight over 2.5 kg to anaemic mothers had twice the likelihood of low haemoglobin when compared with infants of a similar weight to non-anaemic mothers (454). The Olaya 2013 study (417) excluded infants had anaemia who were treated with iron supplements. However, the investigators did not provide information regarding the serum ferritin levels of the included infants at baseline.

It was not possible to produce a conclusion for the effect of nutrition education on iron status or the prevalence of anaemia in children because the included studies were few with low methodological quality and high risk of bias and there were differences in the constructs used by other studies to measure this outcome.

5.2.6.2 Overall completeness and applicability of evidence

All the included trials were conducted in low- and middle-income countries. We identified some studies that were conducted in several high-income countries (5.2.5.5), but their results could not be included in our review because these studies had ineligible inclusion criteria and outcomes. Therefore, the results drawn from this review are relevant to prevent undernutrition in full-term infants in such countries. Furthermore, four studies are retained as further information may allow them to be included in the future. As intended to update the review future, hopefully including data from these four studies once published or provided by the investigators. The results of the interventions were mixed. Although meta-analyses indicate that nutrition education improves rates of growth, the typical effect size was small. When comparing across studies, it appears that educational interventions are likely to have an impact on growth.

Weight and length gain at age 12 months were improved when nutrition education was accompanied by encouraging the child to eat (196, 421, 423). Also, improvement in growth outcomes was observed when the intervention's implementation process was assessed. The interventions with the greatest impact on both weight and length z-scores were the trials in Peru

(192) and Bangladesh (194). The trials emphasised consumption of nutrient-rich foods, including animal-source foods, by the infants. In Pure (192), animal-source foods are available and affordable. Three other included trials in China (195, 423) and India (196) have also shown the potential to improve growth outcomes as a result of nutrition education that emphasises food diversity and consumption of animal-source foods. However, the impact on growth was quite small. Also, it is possible that the evaluation process can lead to improved outcomes as well. Three studies (192, 194, 421) reported the pathway through which an effective nutrition intervention operated and showed a significant effect of the intervention on growth outcomes more than other studies (195, 394). The evaluation process can lead to successful behaviour changes of caregivers and the nutritional status of infants (455). Intervention implementation positively influenced participant exposure, participant exposure positively influenced participant key message recall, and participant key message recall positively influenced initial key participant behaviours of caregivers (455). Furthermore, implementation of training is one of the pathways used to help explain how the nutrition counselling component works to achieve success and demonstrate positive and significant changes in the intervention for caregivers (455).

Furthermore, these intervention packages prompted the home preparation of weaning food mixture, which included egg, meat or fish. The results of these studies support the conclusion that to improve growth outcome, infants and young children need nutrient-dense weaning foods, especially at 6 to 12 months. The potential for improved growth outcomes appears to be greater with interventions that use nutrition educational messages (overall effect size 0.06 for weight and 0.27 for length), excluding the Indian study (394) which was considered as an outlier. In other words, the analysis was restricted to studies at low risk of bias. The average effect sizes are in the small to moderate range, which is in agreement with estimates from the earlier review of programmatic efforts to improve growth in 6 to 12-month-old infants in developing countries. The review was completed between 1970 and 1997; in that review, the effect size was generally

0.10–0.50 (456). More details were discussed in the Agreements and disagreements with other studies or reviews section (5.2.6.3).

The review has highlighted the lack of evidence from RCTs considering the effectiveness of nutrition education on neurodevelopment, duration of exclusive breastfeeding and the prevalence of ID and IDA in full-term infants. It does, however, show an increased rate of exclusive breastfeeding relation to the intervention.

None of the included studies that investigated the effects of this intervention reported data on the other secondary outcomes considered in this review including long-term growth outcomes, parent and infant quality of life, the risk of atopy, food neophobia.

5.2.6.3 Agreements and disagreements with other studies or reviews

The equivocal findings of the nutrition education interventions on weaning are, in part, like previous reviews. An early review conducted by Caulfield et al. (456) evaluated programmatic efforts, including nutrition education, weaning practices, and supplementation to improve dietary intake and growth in 6 to 12 months old infants in low- and middle-income countries. The reviewers included the results of five trials and 16 programmes conducted in 14 countries. The trials were able to improve infants' growth by 0.04 to 0.46 SD. Programmes changed infants' growth by –0.08 to 0.87 SD. The authors measured programmatic efforts, in which food supplementation was included. Therefore, it is difficult to ascertain that the improvements shown in the Caulfield review (456) were because of nutrition education or due to food supplementation.

Dewey and Adu-Afarwuah (185) reviewed various education strategies on weaning and concluded that the interventions had modest effect on weight (MD: 0.28 SD; range -0.06 to 0.96) and linear growth (MD: 0.20 SD; range 0.04 to 0.64). However, the provided pooled effect estimates were presented without showing a formal meta-analysis.

In the same year, another review published in the Lancet Maternal and Child Undernutrition Series (457) addressed weaning promotion in children 6 to 24 months of age. The review

demonstrated that nutrition education in food-secure countries had a significant effect on length (standard mean difference (SMD): 0.35 cm [95% CI: 0.08 to 0.62], four studies), and HAZ (SMD: 0.22 [95%CI: 0.01 to 0.43], four studies). The review also showed a significant effect on weight gain (SMD: 0.40 kg [95% CI: 0.02 to 0.78], four studies), but no effects were observed for WAZ (SMD: 0.12 [95% CI: –0.02 to 0.26], four studies). Studies of nutrition education in food-insecure countries also showed significant effects on HAZ (SMD: 0.25 [95% CI: 0.09 to 0.42], one study), and WAZ (SMD: 0.26 [95% CI: 0.12 to 0.41], two studies).

Imdad et al. (191) performed a systematic review and meta-analysis to evaluate the effectiveness of two commonly used strategies of weaning: timely provision of food supplements (± nutrition education) and education about practices of weaning on children's growth. Among children 6 to 24 months of age, weight gain was SMD: 0.30kg [95% CI: 0.05 to 0.54] and length gain was SMD: 0.21cm [95% CI: 0.01 to 0.41].

Lassi et al. (393) reviewed the literature for RCTs and non-RCTs, which addressed the effect of nutrition education intervention, for at least six months, on children younger than two years. The review included ten studies that assessed the effect of nutrition education. Studies of nutrition education in food-secure countries showed a significant increase in height (SMD: 0.35 [95% CI: 0.08 to 0.62], four studies), and HAZ (0.22 [95%CI: 0.01 to 0.43], four studies), but there was no evidence of intervention effect on stunting (RR 0.70 [95% CI: 0.49 to 1.01], four studies). A significant effect was observed on weight gain (SMD: 0.40, [95% CI: 0.02 to 0.78], four studies), but not on WAZ (0.12 [95% CI: –0.02 to 0.26], four studies). Studies of nutrition education in food-insecure countries showed significant effects on HAZ (SMD 0.25 [95% CI: 0.09 to 0.42], one study), stunting (RR 0.68 [95% CI: 0.60 to 0.76], one study), and WAZ (SMD 0.26 [95% CI: 0.12 to 0.41], two studies).

Recently, Panjwani and Heidkamp (458) conducted a systematic review and meta-analysis of RCTs and controlled before-and-after studies to assess the impact of nutrition education on LAZ and WLZ. Studies with a sample size of <50 children per arm, a cross-sectional design or those

that reported extreme estimates without adequate justification were excluded. Among children aged 6 to 23 months, nutrition education in food-secure countries was associated with a significant impact on linear growth populations (SMD: 0.11cm [95% CI: 0.01 to 0.22], five studies) but not in food-insecure settings (SMD: -0.01cm [95% CI: -0.10 to 0.08], four studies). When pooled analysis included both food-secure and insecure populations, the impact of nutrition education on LAZ did not persist (SMD: 0.06 cm [95% CI: -0.02 to 0.14], nine studies). The review did not show a significant effect of nutrition education on WLZ (SMD: 0.09 kg [95% CI: -0.04 to 0.21]). Overall estimates of length gain were significant for the nutrition education studies (MD: 0.37 [95% CI: 0.10, 0.64]). It is noteworthy that the authors have limited the definition of nutrition education to approaches delivered through the health system or community health workers. There was no limit for the duration of the intervention. Furthermore, the outcomes reported in the included studies were not consistent. Z-score values were calculated with different references: The Centres for Disease Control (CDC: USA) National Centre for Health Statistics (NCHS) growth reference and the WHO 2006 growth standard.

In summary, the previous mentioned systematic reviews have evaluated the impact of nutrition education and demonstrated improvements in growth outcomes. However, these reviews concentrated on populations in low- and middle-income countries only, included non-randomised studies and studies that included children older than 12 months of age. The present review collated the current evidence from RCTs that address the impact of nutrition educational interventions to support families during the weaning process to optimise growth and nutrition in full-term infants during the first year of life in all parts of the world.

5.2.6.4 Limitations

Although much effort was applied to ensure that the literature search was as thorough as possible, it is unavoidable that some relevant studies might be missed. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and PsycINFO, but it is possible that relevant studies were not identified. Searches that are sensitive enough to

detect case series generally lack specificity, making it likely that some studies are not identified. Some studies identified in the review were identified after scrutinising reference lists.

Publication bias occurs when studies with statistically significant or clinically favourable results are more likely to be accepted and published than studies with non-significant or unfavourable results. The published studies may not represent all clinical trials that have been done. Furthermore, the investigators may tend to show the favourable results. Among the nine studies included, four studies reported the impacts of nutrition education on WAZ and LAZ scores (192) and changes in the z-scores (194, 195, 417). Only one study reported weight and length increments (421) and three reported absolute weight and length measurements (196, 394, 423). One study did not report growth data at all (422). It is reassuring, however, that both positive and negative effects on either weight or length were presented.

Assessment of potential reporting bias using funnel plotting was intended, but this was not possible as only nine studies were included in the review.

ITT analysis is recommended to be used to estimate the unbiased effect of an intervention in RCTs (459). Therefore, ITT analysis was applied when missing or unclear data were provided by the study author.

Additional information from the studies investigators were requested and, when no data was provided, the SD of the mean of change in weight and length measurements were imputed in accordance with the Cochrane Handbook. However, some methods were not robust (400).

There were limitations in the studies included in this systematic review. Some of them were open-label, which may affect the quality of a study and introduce bias for some outcome measures such as duration of exclusive breastfeeding.

Another limitation in this review is that the different types and methods used to deliver nutrition education varied across the included studies. Moreover, studies started at different time points after birth and had different weaning recommendations. Studies were conducted in many

different countries (India, Bangladesh, Peru, China, Colombia, and Brazil). However, these factors also represent strength of this review. Even with a substantial mixture of trial design and inclusion of infants from three different continents, there was little evidence of heterogeneity in some outcomes, which should be generalisable for a wide population of children.

Many outcome measures specified in this review were not reported, including adverse effects. Thus, the results of these studies should be interpreted with caution.

5.2.6.5 Conclusion

5.2.6.5.1 Implications for clinical practice

Results of this review indicate that evidence currently supports the use of nutrition education with the potential to improve weaning practices and thereby to improve growth of infants and young children born at term. Nonetheless, there was considerable heterogeneity in growth response to intervention packages, which may be related to potential benefit and response to improve nutrition.

Several approaches can be used to improve weaning practices. There is no single ‘best’ approach yet demonstrated that it could be employed universally. Also, opportunities and constraints vary greatly in different countries. Also, the evidence base for weaning interventions is still relatively limited, and many unanswered questions require further research.

The clinical implications of the evidence available to date including nutrition education interventions should start early in the postnatal period, in large part, because a considerable proportion of stunting may occur during the first year of life. Also, nutrition education is likely to have a greater effect on growth outcomes if it is considered as a part of package of interventions that take into account the multiple causes of stunting. This means that attention should be given to prevent and control prenatal and postnatal infections and subclinical conditions that restrict growth and to care for women and children. This is particularly relevant for some nations, such as those in South Asia. Approximately 40% of the global burden of stunting in South Asia. Poor

hygiene and sanitation are common problems, which increase the prevalence of child stunting (460).

Introducing solids before sufficient development of the neuro-muscular co-ordination or before the gut and kidneys have matured can make weaning food unsafe and increase the risk of infections and development of allergies. This review demonstrates that nutrition education delivered to families may help families to determine the optimal time of commencement of weaning, reduce undernutrition and improve growth outcomes of full-term infants. This would probably be the same for preterm infants who are at greater risk of delayed neurodevelopment and more vulnerable to nutrition deficit during the first two years of life than full-term infants. Furthermore, the commencement of weaning with appropriate choice of food groups could make a significant contribution to energy and other nutrients needs for both, full-term and preterm infants.

The UNICEF (437) suggested that double duty actions could have the potential to minimise the burden of malnutrition, which includes actions to optimise early nutrition and promotion of appropriate nutritional support and commencement of weaning in infants. These actions may have the potential to reduce the risks or burden of undernutrition, and overweight and obesity. The current systematic review demonstrates that nutrition education delivered to families of infants (during the first 12 months of age) can reduce undernutrition as shown by improvement in somatic growth in the first two years of the life of preterm and term infants. Nevertheless, there is a lack of evidence to support that such educational interventions would also ameliorate the risks of childhood overweight and obesity among young children.

There is extensive scientific evidence to support the consensus that exclusive breastfeeding is the best way to feed an infant for the first six months of an infant's life. The present review of limited evidence also suggests that it may be possible to increase the prevalence of exclusive breastfeeding in full-term infants. This finding would possibly be the same for preterm infants;

however, the result should be interpreted with caution due to the small number of studies included with high heterogeneity.

5.2.6.5.2 Implications for research

Effective intervention strategies learned from the current review include the following:

- the intervention should be culturally sensitive, approachable and integrated with local resources. When developing the intervention strategy, researchers should obtain a good understanding of how local families prepare weaning foods, whether regional foods are adequate to meet nutrient requirements, what are the most important difficulties in CF, and whether the intervention approaches are acceptable, affordable and appropriate for local people
- effective interpersonal communication using an intervention targeted at changing carers' feeding behaviours
- the intervention should target major carers (mothers of young children), as well as the other family members and community members. Involvement other family members will create a supportive environment to facilitate behaviour change and maintenance
- although some data on growth and development during the first two years of age outcomes are available, continuing follow-up and additional data for randomised children have been justified, as subtler differences may become obvious in later childhood.
- Data from high-income countries are needed to inform strategies to prevent obesity.

Chapter 6: Conclusion

6.1 Overview

Premature birth is one of the most significant issues of perinatal medicine and creates a substantial global burden due to high mortality and morbidity in this population. Of particular concern is that preterm infants have an increased risk of suboptimal nutrition and growth at hospital discharge that may continue through the first year of life.

Adequate nutritional support during the first year of life is associated with improved growth and neurodevelopment of infants born preterm. Hence, appropriate early postnatal nutritional support has been introduced in many neonatal units. Post-discharge feeding strategies to enhance growth are also being used more frequently.

This thesis describes the flowing research:

- daily delivered enteral and parenteral fluids, including non-nutrient fluids, were recorded to assess changes in nutrition support in homogenous groups of preterm infants admitted to the neonatal unit at Nottingham University Hospitals NHS Trust (NUHs) through three epochs; 2007, 2012 and 2014
- to assess nutritional practice in comparison to the international guidelines using routinely collected data recorded daily in the medical records of babies
- A national database was used to identify a high-risk group of preterm infants. Parenteral nutrition (PN) and enteral feeding practices, including the day of starting nutrition therapy, duration of PN and time to achieve full feeds, were assessed and compared between two cohorts. To evaluate whether the Abnormal Doppler Enteral Prescription Trial (ADEPT) has changed nutrition practices
- a survey of parents was conducted at the NUHs to gather information on the weaning practices, the support provided to families on weaning and to ascertain factors which may affect weaning practices of children born preterm
- a critical appraisal of the evidence using Cochrane metanalytic methodology of randomised controlled trials (RCTs) addressing the effect of nutrition education on weaning in preventing malnutrition and improving growth in children under two years of age.

This PhD thesis focused specifically on the nutritional support of preterm infants during early postnatal as well as during post-discharge periods. A previous study (70) assessing nutritional intakes in relation to recommendations showed that most infants remained below recommended intakes for protein and energy during a hospital stay. The rationale of undertaking an observational study (Chapter 2) was to assess early postnatal protein and energy intakes in preterm infants in relation to two available international recommendations (106, 107). This study will inform strategies for future nutrition protocols and further research.

The parenteral and enteral protein and energy intakes in relation to the recommendation in a sample of preterm infants admitted to the neonatal unit in NUHs were assessed in three different epochs. The study showed a trend toward improved nutrition practices during the first two weeks of life of infants born between 2007 and 2014 (Chapter 2).

To assess the nutrition support provided in relation to the available recommendations in neonatal units of different care levels further data analysis from units across the UK Trent Perinatal and Central Newborn networks was undertaken. Overall, nutritional intakes in the study population were close to the recommendation for infants from some Neonatal Intensive Care Units (NICUs), although protein and energy intakes were below the recommended range for infants from Special Care and Local Neonatal Units (Chapter 2).

The study described in Chapter 3 identified intra-uterine growth restricted (IUGR) infants with absent or reversed end-diastolic flow velocity (AREDF) in the umbilical artery from Badger database. The specific aim of the study was to evaluate changes in nutrition practices before and after the publication of the ADEPT results (9). The study showed an earlier commencing of PN and enteral feeding. The study also showed that infants who have earlier PN and enteral feeding attained a higher weight gain at hospital discharge compared to the comparison group of infants. The study found an impact of the trial on clinical practice but not on clinical outcomes.

Nutrient requirements of preterm infants in neonatal units are still being defined because the current guidelines are based on low- to moderate-quality evidence. There remains a great need

for further strategies to provide an effective nutrition support for this population. Similarly, post-discharge nutritional support needs to be considered because catch-up growth is not always achieved and this may have health consequences. Recently, findings are emerging that postnatal growth outcomes can affect diseases known to have origins in fetal life; especially obesity, cardiovascular diseases, and diabetes. Understanding the differences in beliefs and practices relating to infant feeding support is important for the successful delivery of health messages and health services to diverse populations. However, less attention has been focused on post-discharge nutrition support, in particular, parents'/carers' experiences on weaning infants born preterm.

The following study focused specifically on the weaning practices and perceptions of parents on weaning preterm infants (Chapter 4). This study aimed to explore parents'/carers' experiences and satisfaction. The findings of the survey of families' practices and perception on the support provided on weaning revealed that a large minority of participating parents feel unsupported and many parents were satisfied with the support provided on weaning. This support was associated with a significantly later commenecement of weaning that complies with the few available recommendations.

Nutrition education interventions have been reported to improve nutrient intakes and growth among infants and young children. A review of previous studies showed modest effects on growth and nutrition status (191). However, in this review improving caregiver nutrition knowledge was combined with food supplementation to produce an impact on growth and nutrition of children born at term. An approach that includes nutrition education delivered to families of preterm infants is likely to provide an effective way of addressing suboptimal weaning, which in turn would lead to improved young children growth and nutrition.

Chapter 6, to the best of my knowledge, is the first systematic review on the education of family members during the first year of life for weaning preterm and full-term infants. The review addressed the effect of nutrition education on growth and development of preterm infants

(Chapter 5; Part One). There were no RCTs that looked at the impact of nutrition education of family members to support weaning. . Further review was therefore undertaken including full-term infants bringing data from 9 studies in 5 countries (Chapter 5; Part Two). The most commonly applied nutrition education packages ware counselling, demonstrations, home visits and written guidance. Nutrition education improved growth outcomes in the first two years of the life of full-term infants.

6.2 Strengths of this programme of research

A strength of this PhD programme of research was the multiple research methods that were employed to investigate the nutritional support of preterm infants during the first year of life.

The use of secondary data (Chapter 2 and 3) has potential errors that can affect the accuracy of the data including sampling errors, errors that invalidate the data and errors that require data reformulation. To avoid this form of bias, a clearly defined target group was identified (1) for selecting study populations was used to outline the type of study population specifically (244). Similar to primary data, problems with accuracy can result from many factors, such as data entry mistakes or reporting errors (294). However, the inter-observer reliability of data was high (Chapter 2).

The main strength of the observational study using the national database (Badger.net) was the large sample size. The key strength of the use of data extracted from Badger.net database is its creation through extractions from electronic patient records (EPRs), and in the last few years there is a noticeable improvement in data quality in the database that covers all admissions to neonatal units as previously reported in National Neonatal Audit Programme (NNAP). A succinct reporting of important details regarding the validity of the data (by the provider) and a careful investigation of all relevant documents (by the user) can alleviate errors that reduce reliability (1).

The survey study provided data on the content of clinical support provided to families on weaning in Nottingham University Hospitals. In the local population, the burden of mortality and morbidity

is greater among babies born to mothers from deprived areas because of increased rates of very preterm births (351). I believe this is the first study (Chapter 4) providing such information which is representative of the current UK population of preterm children and it provides information to better understand the contemporary attitudes, practices and perceptions about the commencement of weaning of infants born preterm. The strength of this study was that both online and paper format of the questionnaire were used to ensure that responses were not limited to internet users and included views of parents from different socioeconomic groups.

The Cochrane reviews sought to draw together relevant high-quality research evidence from an international perspective that could be related to nutrition education on weaning in preterm and full-term infants. To the best of my knowledge, the review in Part One (Chapter 5) is the first review assessing the effect of nutrition education on weaning of infants born preterm. The review have shown a clear lack of clinical trials addressing nutrition education for parents of infants born preterm. Similarly, the review in Part Two (Chapter 5), to best of my knowledge, is the first systematic review to include RCTs assessing the effect of nutrition education for parents during the first year of life in full-term infants.

6.3 Limitations of this programme of research

As is the case with most, if not all research studies, this PhD thesis had some limitations.

There are limitations to the early postnatal nutrition study (chapter 2). The nutrient composition of breast milk was not analysed but rather estimated from literature values. Furthermore, the study did not differentiate between enteral feeds that consisted of colostrum or transitional breast milk, which may contain different amounts of energy and protein. However, the values we used for protein, and energy composition of milk are virtually identical to those reported in a systematic review by Gidrewicz and Fenton (461).

The secondary analysis results presented in Chapter Three are also limited to the participating centres in the UK and the analysis was limited to the data that was available in Badger.net

database. As data are not recorded specifically for research purposes and entered by various health professionals, data quality may vary over time and between units. However, the NNAP provide regular updates on data assessment with respect to data completeness.

As in common with descriptive approaches, this study depended on parents' responses, making it possible that distortion of the data could have occurred from recall bias. The generalisability of the survey study was limited to those carers that responded. Nonetheless, the current study included parents from different socioeconomic groups.

Undertaking systematic review may be limited as a result of selection of studies, choice of relevant outcome, methods of analysis, interpretation of heterogeneity, and generalisation and application of results. Furthermore, reviews may be limited by the potential risk of reporting bias. However, using explicit, systematic methods documented in advance with a protocol minimise the limitations.

6.4 Clinical implications for nutritional support

The current recommended nutrition support in preterm infants is to initiate PN and enteral feeding from birth, with progressive increase in nutrient delivered during hospital stay. The nutritional support is based upon infants' characteristics. However, nutrition support practices such as early initiation of PN and enteral feeding vary between neonatal units providing the same and different levels of care.

The current locally used nutrition guideline results in energy and protein intakes that were close to the latest recommendations for some units, although for infants from SCUs and LNUs, protein and energy intakes were below the recommended range. The findings of the current study may help to improve nutrition management decision making by providing relevant, accurate and timely information. These findings also highlight that further improvements in nutrition plans for preterm infants are needed. Nutrition intake should be reviewed daily to ensure that nutrients provided are in keeping with the guidelines.

This thesis demonstrated that there is a trend toward the early introduction of enteral feeding for IUGR infants with abnormal antenatal Dopplers. Provision of early enteral feeding offers enhanced infant growth at hospital discharge.

The findings of the survey of families' practices and perception on the support provided on weaning revealed that a large minority of participating parents feel unsupported. Those parents were at higher risk of inappropriate feeding practices, such as starting weaning at an earlier age than parents who recalled receiving advice on weaning. The potential for early commencement of weaning is even more likely if there is insufficient evidence to inform clinical care professionals and families of this specific population. Whilst it is a positive finding that some infants are receiving weaning foods as recommended, many families feel that they were unsupported.

At the time of completing the findings of the Cochrane systematic review of the effectiveness of nutrition education on weaning of preterm infants remained unclear the paucity of RCT. On the other hand, the review addressing nutrition education delivered to families of full-term infants demonstrated that the intervention during the first year of life could reduce undernutrition as shown by improvement in growth measurements in the first two years of life. However, caution should be applied in extrapolating the results to preterm infants as this group are at higher risk of feeding and nutritional problems.

6.5 Implications for research and future work

The nutritional support improved significantly in neonatal units in NUHs from 2007 to 2014. Overall, PN was initiated more promptly during the first week after birth and was delivered at higher quantities. Nonetheless, many preterm infants did not achieve the recommended energy and protein intakes. Studies have shown that a significant weight gain improvement was observed with a higher quantity of protein and energy intakes. It may be more realistic to focus on future research interventions on maintenance and quality of life rather than aiming to improve nutrition support for this population. Additional research is required to evaluate body composition and focus on specific organs would help to define the growth of the individual tissues in response

to different amounts of amino acids/protein and total energy. Furthermore, it would be useful to investigate whether increasing protein intake during the first two weeks of life will improve longer-term outcomes should be an area for future research.

The findings of this thesis also contribute to the validation of using the routinely collected general practice Badger.net database to explore the incidence of NEC in IUGR infants with abnormal antenatal Dopplers and to assess the nutritional support in this high-risk population in the UK. The lack of variation of outcomes between the two cohorts despite the wide variation observed in the nutrition practices, together with the finding that most of the infants received exclusive human milk, highlights the uncertainties of optimal preventive feeding strategies; therefore, further research is required. It would be useful to investigate the effect of early initiation of enteral feeding on the long-term growth and development of IUGR infants with abnormal Dopplers should be assessed.

Probing of responses was not possible in the questionnaire and a follow-up interview study will add further clarity to the survey responses and key findings. Furthermore, the current study has determined parents' views on the support provided on weaning, but it might be helpful for future studies to assess the current approaches and views consultant neonatologist on weaning.

This thesis identified gaps in the evidence and areas of uncertainty in post-discharge nutritional support and highlighted that more clinical trials are needed to define the ideal weaning approach for preterm infants including the time to commence weaning and the type of foods to introduce from the perspective of micro- and macro-nutrient contents.

The finding of the systematic review suggests that nutrition education on weaning in infancy is an effective tool for reducing the risks of malnutrition during the first two years of life in full-term infants from low- and middle-income countries. Optimising early nutrition during infancy may have double duty actions; it has the potential to reduce the risks of undernutrition, overweight and obesity.

To date, there has been a lack of RCTs addressing nutrition education interventions on growth, development and nutritional status of infants born preterm. Further robust RCTs in this area are, therefore, warranted. Before that, further research is needed to optimise weaning strategies for preterm infants regarding the age to commence weaning, the type of foods to start with respect of nutrient contents. A systematic review addressing the effect on early weaning before four months of age for prevention of postnatal growth restriction in preterm infants is underway and may answer the question for the timing of weaning.

The beneficial effect of nutrition education to decrease undernutrition in full-term infants from low- and middle-income countries has been demonstrated. A systematic review addressing the effect on nutrition education on obesity is underway and will answer the question of the beneficial effect of nutrition education to reduce obesity in infants from high-income countries. A review to assess the effects of nutrition education interventions on behavioural outcomes and changes in knowledge of families is also needed.

6.6 Final remarks

This study highlighted the importance of adopting nutritional support goals and the importance of periodically evaluating the success in achieving them. Initiation of early nutritional support results in improved nutrition and growth outcomes of preterm infants. The findings in this study could in part help to expand the current knowledge and highlight the implications of a new body of research evidence for early postnatal and post-discharge nutrition support clinical practice, guidelines and future research.

Chapter 7: References

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Chapter 8: Appendices

Appendix 8.1 Nutrient content of solutions (Chapter 3)

	preparation	in 100ml			
		Energy(kcal)	Protein(g)	Fat(g)	Carbohydrate(g)
Glucose solutions	5% glucose	20	0	0	5
	10% glucose	40	0	0	10
	12.5% glucose	50	0	0	12.5
	15% glucose	60	0	0	15
	20% glucose	80	0	0	20
PN solutions	Starter PN	74	3.5	0	15
	Preterm PN (aqueous)	74	3.5	0	15
	Term PN (aqueous)	70	2.5	0	15
	Peripheral PN	52	2	0	11
	Intralipid 2	160	0	16	0
	Intralipid 3	171	0	17.1	0
Enteral feeds	EBM - Early Preterm (<14d)	70	1.8	4	7
	EBM + Nutriprem BMF	86	2.5	4	9.8
	Nutriprem 1	80	2.6	3.9	8.4

Appendix 8.2 Current recommendations of advisable nutrients for preterm infants

(Chapter 3)

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day7
Protein (g/kg)	Tsang et al. (2005)*	2	225	2.50	2.75	3	3.25	3.5
	Koletzko at al. (2014)	2	2.75	3.5	3.5	3.5	3.5	3.5
Calories (kcal/kg)	Tsang et* al. (2005)	55	67.5	80	92.5	105	117.5	130
	Koletzko at al. (2014)	60	80	90	105	105	105	105

*Adapted from (106, 107) by Professor Helen Budge and Mrs Chris Jarvis

Appendix 8.3 Neonatal parenteral nutrition (PN) Guidelines of Nottingham Neonatal Service (Chapter 3)

Nutritional Composition of Standard Regimens used in three different yeas; 2007, 2012 and 2014

Year	Nutrients	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
2007	Protein (g/kg)	-	-	2.5	2.5	2.5	2.5	2.5
	Energy (kcal/kg)	40	40	75	75	85	85	85
2012	Protein (g/kg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5
	Energy (kcal/kg)	74	74	78	78	87	87	87
2014	Protein (g/kg)	3.5	3.5	3.5	3.5	3.5	3.5	3.5
	Energy (kcal/kg)	74	74	94	94	104	104	104

Appendix 8.4 Ethics approval letter 1 (Chapter 4)

The Uni
Notti

Faculty of Medi
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24th April 2015

Dr Zenab Effzzani
PhD Student
Division of Child Health, Obstetrics & Gynaecology
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QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Dr Effzzani

Ethics Reference No: M16042015 SoM CHOG BADGER – please always quote
Study Title: Exploring the current management of infants diagnosed with AREDFV, using neonatal database (BADGER)
Chief Researcher/Academic Supervisor: Professor Helen Budge, Co-Director of Clinical Academic Training Programme, Dr Jon Dorling, Clinical Associate Professor in Neonatology, Academic Child Health, School of Medicine.
Lead Researcher/Student: Dr Zenab Effzzani, PhD Student, Child Health, Obstetrics & Gynaecology, School of Medicine
Duration of Study: 01/04/2015-31/03/2016 12 mths **No of Subjects:** n/a dataset study

Thank you for submitting the above application which has been reviewed by the Committee and the following documents were received:

FMHS Research Ethics Application Form dated 09/03/2015
Study Protocol version 1.0, dated 09.03.2015

These have been reviewed and are satisfactory and this interesting study is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. Please can you confirm whether you need any permission from gatekeepers to access both the NEC (Badger) data base and the ADEPT trial data. If so please can you submit copies of these permissions when they are available for our records please.

2. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

3. You must notify the Chair of any serious or unexpected event.

4. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

5. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr Clodagh Dugdale
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 8.5 Ethics approval letter 2 (Chapter 4)

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
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19th January 2016

Dr Zenab Effzzani
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Dear Dr Effzzani

Ethics Reference No: M16042015 SoM CHOG BADGER – please always quote
Study Title: Exploring the current management of infants diagnosed with AREDFV, using neonatal database (BADGER)
Chief Researcher/Academic Supervisor: Professor Helen Budge, Co-Director of Clinical Academic Training Programme, Dr Jon Dorling, Clinical Associate Professor in Neonatology, Academic Child Health, School of Medicine.
Lead Researcher/Student: Dr Zenab Effzzani, PhD Student, Child Health, Obstetrics & Gynaecology, School of Medicine
Duration of Study: 01/04/2015-31/03/2016 12 mths
No of Subjects: n/a dataset study

Thank you for notifying the committee of amendment no 1: 05 January 2016 as follows:

To change one of the two practice and outcomes time periods from 2010 -2014 to 2010-2015 in order to the see the impact of the ADEPT (Abnormal Doppler Enteral Prescription Trial) study on feeding practices of small for gestational age preterm infants.

And the following revised documents were received:

- Protocol version 1.0, 09/03/2015

These have been reviewed and are satisfactory and the study amendment no 1: 05 January 2015 is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).
2. You must notify the Chair of any serious or unexpected event.
3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.
4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

pp Lamiaggatini

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 8.6 Ethics approval letter 3 (Chapter 4)

North of Scotland Research Ethics Service
Summerfield House
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Telephone: 01224 558458
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NHS Grampian

29 April 2016

Dr Jon Dorling
Neonatal Unit
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Derby Road
NOTTINGHAM
NG7 2UH

Dear Dr Dorling

Study title: **Exploring the current management for infants diagnosed with AREDFV, using the national neonatal database (BADGER)**
REC reference: **16/NS/0040**
Protocol number: **16034**
IRAS project ID: **195953**

Thank you for e-submitting your response. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 30 March 2016.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
IRAS Checklist XML: Checklist 29042016		29 April 2016
Protocol - Exploring the current management for infants diagnosed with AREDFV, using the national neonatal database (BADGER)	1.1	6 April 2016
Letter to Individual Units re Badger Adept Comparison	1.0	19 April 2016

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper		26 February 2016
IRAS Checklist XML: Checklist 29042016		29 April 2016
Ethics approval letter	1	24 April 2015
Ethics approval letter extension	1	19 January 2016
Letter to Individual Units re Badger Adept Comparison	1.0	19 April 2016
Protocol - Exploring the current management for infants diagnosed with AREDFV, using the national neonatal database (BADGER)	1.1	06 April 2016
REC Application Form: REC Form 17032016	195953/939393/1/243	17 March 2016
Summary CV for Chief Investigator (CI): Dorling Jan 16 short CV	1	11 January 2016
Summary CV for Student: Zenab CV	1	18 March 2016

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

16/NS/0040 Please quote this number on all correspondence

Yours sincerely

Carol Irvine

Carol Irvine
Senior Ethics Co-ordinator

Copy to: Miss Angela Shone
Dr Maria Koufali, Nottingham University Hospitals NHS Trust

Appendix 8.7 The questionnaire (chapter 5)

Weaning preterm children onto solid foods

Thank you for agreeing to take part in this survey.

In this survey, we would like to ask you about the service provided during weaning your baby onto solid foods.

This will help us understand what parents think about weaning their infant, whether appropriate information was available, and helpful, and what other support parents would like to see.

The information from the survey will be used to inform us about how the Nottingham Neonatal Service might be better able to support parents in the future.

One of the neonatal team will be happy to answer any further questions you have about weaning your baby in the clinic.

Introducing your baby to solid foods is a really important part of his/her development and can be a pleasurable time for both you and your baby.

Many babies who were born preterm wean easily, but not much is known about how to help them. The information we have to guide parents with weaning has been brought together by experts in nutrition and in child development. This is provided to families by BLISS, the premature baby charity.

We will keep your answers completely anonymous. When we have finished the survey, we may share our findings with other health professionals so that Neonatal Services can provide the best possible information for parents in the future. You will not be identified in any way from the information you have given us.

You have brought your baby to the neonatal clinic. We would like to ask you some questions about her/his feeding (11% complete).

1. How old is your child? (in months or weeks since they were born)

2. How many weeks of gestation were they when she/he were born?
   - o <28 weeks
   - o 28 to <32 weeks
   - o 32 to <37 weeks

3. Do you mind telling us your relation to this child:
   - o Mother
   - o Father
   - o Grandmother
   - o Grandfather
   - o Foster carer
   - o Guardian
   - o Family friend
   - o Prefer not to answer
   - o Others
   - o

3. a. If you selected Other, please specify:

About the child you have brought to this clinic (16% complete)

4. Have you been given any advice about when to wean your child?

- Yes
- No
- Do not know

4.a Please tell us where this advice came from? (tick all that apply)

- Consult in clinic
- Nurses on the neonatal unit
- Health visitors/ Community nurses
- General Practitioner
- Dietitian
- Recommendations from infant food manufacturers
- Family/ Friend
- Family Care Nurses who visited us at home
- Bliss leaflet
- Web sites
- Do not remember
- Other

4.a.i. If you selected Other, please specify:

5. Have you weaned the infant you are bringing to this clinic yet?

- Yes
- No
- In progress

Further questions for parents/carers of children who have already been weaned (22% complete)

6. Please tell us at what age (actual) you introduced solid food into his/her diet? Required

- 2 Months
- 3months
- 4months
- 5 months
- 6 months
- Other

If you selected Other, please specify

How important were the following factors in deciding **when** to introduce solid foods?

	Very important	Important	Moderately important	Not very important	Not important at all
Your child age	○	○	○	○	○
Able to stay in the sitting position and control his/her head	○	○	○	○	○
Coordinating their eyes, hands and mouth and bring objects up to the mouth to chew	○	○	○	○	○
Showing interest in others' food	○	○	○	○	○

8. Were there any other things you considered when deciding (Optional)?

9. How easy was it to tell:

	Very easy	Rather easy	OK	Difficult	very difficult
When your baby was ready to wean	○	○	○	○	○

10. What food items were you advised to start with? (27% complete).

- Baby rice
- Vegetable
- Fruits
- Dairy foods
- Cornmeal
- Meat
- Other

10.a. If you selected Other, please specify:

11. How did you first offer the food to your infant?

- Puréed /Mashed
- Finger food
- Other

11.a. If you selected Other, please specify:

12. Was this food:

- Home-made
- Manufactured baby food
- Both

13. Do you think that you were given enough advice about **your child's nutrition** during his/her weaning?

- Yes
- No

14. Did you experience any concerns or worries during weaning your child that was not resolved?

- Yes
- No

14.a If yes, please specify

For each statement, please choose the option that best describes how much you agree (33% complete) .

	Strongly agre	Agree	Neutral	Disagree	Strongly disagree
I think I was given enough information about how to wean my preterm child.	○	○	○	○	○
When I had question about weaning, I was easily able to find the answers.	○	○	○	○	○
I would like to have more support during weaning my preterm child.	○	○	○	○	○
I was unsure about which food items to use for weaning my child.	○	○	○	○	○
I found it difficult to decide when my child was ready to wean.	○	○	○	○	○

Here are couple of questions which may help us to understand how food allergy or intolerance may influence weaning conception (55% complete)

16. Please could you tell us if there is a history of atopy/allergy in your family

- o Yes
- o No
- o Do not know

16.a If you selected Yes, please specify (by type of relative) who has a history of atopy/allergy:

17. Considering a family history of allergy, please select the response below that best describes your level of concern during weaning your child.

	Extremely concerned	Moderately concerned	Somewhat concerned	Slightly concerned	Not at all concerned
To what extent does your family history of allergy concern you?	○	○	○	○	○

History of weaning (66% complete)

18. Have you weaned a child previously?

- o Yes
- No

18.a. Please tell us how many children have you weaned in the past.

- o 1
- o 2
- o 3
- o Other

18.a..i If you selected Other, please specify:

19. Do you think it is easy to tell:

	Very easy	Rather easy	OK	Difficult	very difficult
When your baby is ready to wean	○	○	○	○	○

20. What food items have you been advised to/ or will you start with?

- o Baby rice
- o Vegetables
- o Fruits
- o Dairy foods
- o Cornmeal
- o Meat
- o Other

20.a. If you selected Other, please specify:

21. How will you offer these foods to your child?

- Puréed /Mashed
- Finger food
- Other

21.a. If you selected Other, please specify:

22. Please tell us how likely would you be interested to participate?

	Extremely likely	Likely	Natural	Unlikely	Extremely unlikely
Do you think it is important to do research to establish the best way to support the weaning of preterm children?	○	○	○	○	○

Please give us some further information to help us understand your responses

23. Would you mind telling us which age group you are in?

- ○ <20 y
- ○ 20-25 y
- ○ 26-30 y
- ○ 31-35 y
- ○ 41-45 y
- ○ 46-50 y
- ○ >50 y
- ○ Prefer not to answer

We asking, if you are happy to give us the information about your background, to look at whether cultural orientation may affect weaning practices (83% complete).

24. Would you mind telling us your background

- White English/Welsh/Scottish/ Northern Irish
- Black English/Welsh/Scottish/ Northern Irish
- White Irish
- White and Black Caribbean
- White and Black African
- White and Black Asian
- Indian
- Pakistani
- Bangladeshi
- Chinese
- Other
- Prefer not to answer

24.a If you selected Other, please specify:

25. How would you describe the background of your baby?

- White English/Welsh/Scottish/Northern Irish
- Black English/Welsh/Scottish/ Northern Irish
- White Irish
- White and Black Caribbean
- White and Black African
- White and Black Asian
- Indian
- Pakistani
- Bangladeshi
- Chinese
- Other
- Prefer not to answer

25.a If you selected Other, please

Thinking of Socio-economic status we asking, but you do not have to answer, to look at the relation between Socio-economic status and weaning practice and perception (94% complete)

26. Would you mind telling us about the highest educational qualification that you have attained

- Primary School
- Secondary School
- Tertiary education
- Prefer not to answer
- Bachelor or equivalent
- Master or equivalent
- Doctorate or equivalent

Finally, we would like to thank you for taking part in our survey. The information you have provided should help to support parents in the future and plan research for future generations.

Thank you

Appendix 8.8 Participant Information Sheet (Chapter 5)

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

Evaluation in health service promotion:
Families'/Carers' perceptions about weaning of preterm infants
Weaning to solid food in preterm infants study (WSIP)
The WSIP Study Leaflet

Researchers:

Dr Zenab Elfzzani, Dr Shalini Ojha, Dr Jon Dorling, Prof Michael Symonds,

Prof Helen Budge

Introducing your baby to solid foods is a really important part of his/her development and can be a pleasurable time for both you and your baby.

As a parent/carer of a premature baby you are the most important judge of the support we provide for weaning your baby. Asking for your opinions about this support will help us understand your ideas about the service provided and will subsequently help to improve the quality of service provided by the Nottingham Neonatal Team.

What is WSIP study?

The current advice for weaning are based on clinical experience, and we would like to know if the advice worked for you and your baby. In this survey, we would like to know what you think about our support so that we can improve the quality of the Nottingham Neonatal Service.

The WISP study wants to find the answer to the following questions:

- What do you, as a parent/ carer, think about weaning your preterm baby?
- What information and support did you get for weaning?
- How was your baby affected by the advice we gave?

To better understand your opinions about and evaluate your experience of weaning in preterm babies, we would like to collect some information from you, such as:

- When did/will you start weaning your baby?
- Did you have/do you have enough support and information during weaning your baby?
- What factors may have affected/will affect your decision when to wean your baby?

All information collected will be confidential and you and your baby will not be identified.

How will the evaluation work?

The researchers will talk to you and ask you to fill in a questionnaire. As part of the study we would like to look at your baby's medical notes. If you agree we will collect data about the clinical characteristics, such as birth weight and gestational age, duration of intensive care, day of starting enteral feeds during hospitalization and mode of feeding. This will help us understand factors associated with weaning.

How I will be involved?

In this evaluation, you are being invited to share your experience of weaning your preterm baby. If you are happy to take part, you will be asked to complete an online/paper questionnaire.

What are the possible benefits of taking part in the study?

There are no direct benefits for you or your baby from taking part in this study, but the information which you will provide might be able to support parents in the future.

What if I do not want to continue in the study?

Your and your baby's participation in the study is voluntary and you are free to withdraw at any time, without giving a reason and without your or your baby's legal rights or medical care being affected. However, if you withdraw them, then the information collected up to that point cannot be erased and this information may still be included in the findings.

What will happen to the results of the study?

The results of the study will be published in medical journals and in a thesis submitted to the University of Nottingham for examination for a research degree (PhD) so that others can see them. You or your child will not be identified in any way.

Contact details:

If you want further information, contact Dr Zenab Elfzzani by email by telephone (0115 8230790) (zenab.elfzzani@nottingham.ac.uk)

Other members of the Research Team:

Prof Helen Budge Tel: 0115 8230611

Dr Jon Dorling Tel: 0115 8230611

Dr Shalini Ojha Tel: 0115 8230619

Appendix 8.9 Study consent form (Chapter 5)

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Evaluation in health service promotion: Families'/Carers' perceptions about weaning of preterm infants
(Weaning to solid food in preterm infants Study)
(WSIP)
PARENT CONSENT FORM
(29/09/2015)

Researchers: Dr Zenab Elfzzani, Dr Shalini Ojha, Dr Jon Dorling, Prof Michael Symonds, Prof Helen Budge

Name of Participant:

Participant Study Number:

Please initial box

1.	I confirm that I have read and understand the information sheet dated 29/09/2015 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my child's participation is voluntary and that I am free to withdraw them at any time without giving any reason, and without my child's medical care or our legal rights being affected. I understand that should I withdraw then some of the information collected so far cannot be erased and that this information may still be used anonymously in the analysis and reporting of the study.	☐
3.	I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the University of Nottingham and from regulatory authorities where it is relevant to my child taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my child's participation in this study. I understand that my child's personal details will be kept confidential.	☐
4.	I understand that participation in this study will not require any additional procedures or any additional samples being taken from my child.	☐
5.	I agree for my child (named above) to take part in the above study.	☐

Name of Person giving consent	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 8.10 Ethics approval letter 1 (Chapter 5)

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

20th January 2016

Zenab Elfzzani
PhD Student
Division of Child Health, Obstetrics & Gynaecology
School of Medicine
E Floor, East Block
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Zenab

Ethics Reference No: H10112015 SoM CHOG PhD - please always quote
Study Title: Evaluation in health service promotion: Families'/Carers' perceptions about weaning of preterm infants (WISP) Study.
Chief Researcher/Academic Supervisors: Professor Helen Budge, Academic Child Health, School of Medicine
Other Key Researchers: Dr Jon Dorling, Dr Shalini Ojha, Professor Michael Symonds, Academic Child Health, School of Medicine.
Lead Researcher/student: Zenab Elfzzani, PhD Student, Academic Child Health, School of Medicine.
Duration of Study: 01/11/2015-31/10/2016 12 mths **No of Subjects:** 50 (18+ yrs)

Thank you for your letter dated 6th January 2016 responding to the comments made by the Committee and the following revised documents were received:

Weaning to solid food in preterm infants (WSIP) Study:

- WSIP Study: Table of FHMS Ethics Committee and changes made on Study comments
- WSIP Study protocol, version 2, 9/12/2015
- Participant Information Sheet version 1.2, 09/12/2015
- Letter from Ian Brown, Health Audit Officer, Acute Medical Directorate & Childrens Hospital/NNU Clinical Quality, Risk and Safety Team Nottingham University Hospitals Trust confirming project approval no 15-813C dated 10th December 2015.

These have been reviewed and are satisfactory and the study is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 8.11 Ethics approval letter 2 (chapter 5)

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
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Direct line/e-mail
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27th April 2016

Zenab Elfzzani
PhD Student
Division of Child Health, Obstetrics & Gynaecology
School of Medicine
E Floor, East Block
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Zenab

Ethics Reference No: H10112015 SoM CHOG PhD - please always quote
Study Title: Evaluation in health service promotion: Families'/Carers' perceptions about weaning of preterm infants (WISP) Study.
Chief Researcher/Academic Supervisors: Professor Helen Budge, Academic Child Health, School of Medicine
Other Key Researchers: Dr Jon Dorling, Dr Shalini Ojha, Professor Michael Symonds, Academic Child Health, School of Medicine.
Lead Researcher/student: Zenab Elfzzani, PhD Student, Academic Child Health, School of Medicine.
Duration of Study: 01/11/2015-31/10/2016 12 mths **No of Subjects:** 100 (18+yrs)

Thank you for notifying the Committee of amendment no 1: 19 April 2016 as follows:

Increase no of participants to 100 in order to have a more precise overview of the current practices provided by Nottingham Neonatal Service.

and the following documents were received:

- WSIP Protocol Draft v1.2 19/4/2016

These have been reviewed and are satisfactory and the study amendment no 1: 19/4/2016 is approved.

Approval is given on the understanding that the conditions set out below are followed:

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be

performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 8.12 Search terms (Chapter 6)

Cochrane library search terms

(Weaning OR Wean* OR (Feed* NEAR/6 complementary) OR (Food NEAR/6 complementary) OR (Feed* NEAR/6 supplementary) OR (Food NEAR/6 supplementary)) AND (Family OR Parent OR mther OR father OR parent* OR famil* OR carer OR caregiver) AND (program* OR education* OR training OR intervention*) AND (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW).

PubMed search terms

(Weaning OR Wean* Weaning[MeSH] OR (Feed* NEAR complementary) OR (Food NEAR complementary) OR (Feed* NEAR supplementary) OR (Food NEAR supplementary)) AND (Family[MeSH] OR Parent[MeSH] OR mther OR father OR parent* OR famil* OR carer OR caregiver) AND (program* OR education* OR training OR intervention*) AND ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])).

Embase search terms

(Weaning OR Wean* OR (Feed* NEAR complementary) OR (Food NEAR complementary) OR (Feed* NEAR supplementary) OR (Food NEAR supplementary)) AND (Family OR Parent OR mther OR father OR parent* OR famil* OR carer OR caregiver) AND (program* OR education* OR training OR intervention*) AND (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).

CINAHL search terms

(Weaning OR Wean* OR (complementary feeding) OR (complementary food) OR (supplementary feeding) OR (supplementary food)) AND (Family OR Parent OR mther OR father OR parent* OR famil* OR carer OR caregiver) AND (program* OR education* OR training OR intervention*) AND (infant, newborn OR newborn OR neonate OR neonatal OR

premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Clinical trials database search terms

ClinicalTrials.gov terms: (weaning AND education AND infant) OR (feeding AND education AND infant)

Controlled-Trials.com terms: (feeding AND education AND infant) OR (weaning AND education AND infant)

WHO terms: (weaning AND neonate) OR (weaning AND infant)

Appendix 8.13 "Risk of bias" tool (Chapter 6)

Potential sources of bias in RCTs and domains in the Cochrane Collaboration's Risk of Bias tool which address these domains (Adapted from: Assessing risk of bias in included studies (418)

Type of bias	Description	Relevant domains in the Cochrane "Risk of bias" tool
Selection bias	Systematic differences between baseline characteristics in the comparator groups	- Sequence generation (was the sequence allocation adequately generated? e.g. random number generator, minimization, coin tossing) - Allocation concealment (could the assignment have been foreseen? e.g. central allocation, sequentially numbered
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	- Blinding of participants and personnel (were measures taken to prevent participants, key study personnel and outcome assessors having knowledge of which intervention was allocated or no blinding or incomplete blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding - Other potential threats to validity
Detection bias	Systematic differences between the comparator groups in how outcomes are assessed	- Blinding of outcome assessment (were measures taken to ensure blinding of outcome assessment, and unlikely that the blinding could have been broken or no blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding - Other potential threats to validity
Attrition bias	Systematic differences between the comparator groups in withdrawals from a study A study was considered to be at high risk if loss of follow-up is >10%	- Incomplete outcome data (were incomplete outcome data addressed adequately? e.g. missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups)
Reporting bias	Systematic differences between reported and unreported findings	- Selective outcome reporting (were the study protocol is available and expected and pre-specified primary and secondary outcomes addressed?)

Appendix 8.14 Quality of evidence grades (Chapter 6)

The GRADEpro results in an assessment of the quality of evidence in one of four grades, adopted from (420)

Grade	Definition
High	Reviewers are very confident that the true effect lies close to that of the estimate of the effect
Moderate	Reviewers are moderately confident in the effect estimate, when the true effect is close to the estimated effect, but there is a possibility that it is substantially different
Low	Reviewers confidence in the effect estimate is limited, because the true effect may be substantially different from the estimate of the effect
Very Low	Reviewers have very little confidence in the effect estimate, because the true effect is likely to be substantially different from the estimate of effect

Appendix 8.15 Characteristics of excluded studies (Chapter 6)

Study ID	Reason for exclusion
Cupples 2010	RCT, in which a tailored peer-mentoring intervention programme was conducted throughout pregnancy and the first year of life. The intervention was conducted by a mentor, a non-professional peer, who delivered health-related information, including general child care and diet
Cofie 2012	RCT involved mothers and grandmothers of young children 6 to 24 m of age
de Oliveira 2012	RCT involved timing of introduction of complementary feeding in preventing the introduction of non-breast milk and CFs in the first 6 m
Louzada 2012	RCT in mothers of infants born at term assessed the impact of dietary counselling on food consumption, nutritional status, and anthropometric data at 12 to 16 m, 3 to 4 years, and 7 to 8 years and lipid profiles at 3 to 4 years and 7 to 8 years old. The outcomes reported are irrelevant to this review
Daniels 2013	RCT in healthy infants born at term. Infants were assessed at age of 2 years (ranged between 21 to 27 m). The study evaluated the effect of nutritional counselling on the risk of childhood obesity
Navarro 2013	A cluster controlled trial, but not randomised
Krebs 2013	RCT examined the effect of complementary feeding regimens that provided food supplements on iron status in infants born at term.
Lakkam 2014	Secondary analysis of data from an observational study of supplementary feeding
Negash 2014	RCT in mothers of infants ages 6-23 m. There was a co-intervention; nutrition education with food supplements, just given to the intervention group
Newman 2014	A cluster randomised controlled trial to examine the effect of daily portions of study food and educational messages to enhance complementary feeding on infant growth
Tang 2014	A secondary data analysis of a RCT that examined the effect of fortified cereal–based compared with meat-based CFs on zinc homeostasis and iron status in exclusively breastfed infants
Yousafzai 2014	A community-based cluster-randomised. Children were randomised to receive routine health and nutrition services (controls) or nutrition education and multiple micronutrient powders (intervention)
Fahmida 2015	A quasi-experimental study in infants aged between 9 and 16 m
Fildes 2015	Multicentre, RCT in healthy term infants aged between 4 and 6 m enrolled into the intervention group who received a variety of single vegetables as first foods, i.e. food supplements vs. control who received usual care. This study investigated the impact of advising parents on weaning on their child's subsequent acceptance of a novel vegetable
Skau 2015	A cluster randomised controlled trial involved children 6–18 m of age. The trial investigated he effect nutrition education about diet diversity improvement needs to be conducted promotes behaviour change, i.e. irrelevant population and outcome measures
Tariku 2015	RCT in infants aged 6-18 m at baseline. This study examined the effectiveness education compared to the traditional method and a control group in prompting appropriate feeding practices of the mothers on intake of infants and children
Gross 2016	RCT involved pregnant women in the third trimester to assess the prevalence of exclusive breast feeding at age of 3 m
Horodynski	RCT conducted to promote the development of healthy infant eating, opportunities for mothers to develop and practice skills, and a discussion of strategies to overcome

Study ID	Reason for exclusion
Guptill 1983	Not an RCT. The study investigated the effect using face-to-face nutrition education methods and food supplementation on mothers' knowledge, trial, and adoption a specific home prepared weaning food "eko ilera"
Ruel 1992	Not ann RCT. Mothers from two groups received the same intervention
Brown 1992	Non-randomised, prospective, controlled study in families of breastfed children. Participants ranged in age from 4 to 14 m at baseline
Cohen 1995	RCT involving exclusively breastfed infants aged 4 to 6 m. The study aimed to determine the appropriate time of weaning using exclusive breastfeeding to 6 m vs. introduction of CFs at 4 m of age. Commercially prepared baby foods were used in addition to nutrition education
Kapil 1995	Observational study examined feeding practices in children aged 0-35 m
Dewey 1998	RCT. The intervention involving the timing of introduction CFs with exclusive breastfeeding to 6 m vs. introduction CFs at 4 m of age with ad libitum breastfeeding or introduction CFs at 16 weeks, with the maintenance of pre-intervention breastfeeding frequency. i.e. the intervention is not nutrition education
Guldan 2000	A cluster controlled trial, but not randomised, assessed the effect of nutrition education of pregnant women and neonates on children growth
Santos 2001	RCT in infants aged up to 18 m. The study assessed the impact of the nutrition-counselling component on child growth
Makrides 2002	RCT in healthy infants born at term. The study investigated the effect of nutritional education with food supplementation vs no intervention on infant's haemoglobin, ferritin, plasma iron, transferrin, and transferrin DHA status and plasma cholesterol concentrations
Mursi 2003	RCT in infants born at term who were provided with food supplements
Roy 2005	RCT in children aged 6-24 m. Both intervention and control groups received nutritional education
Krebs 2006	RCT conducted to assess the feasibility and effects of consuming either meat or iron-fortified infant cereal as the first CFs
Koehler 2007	RCT involved mothers of infants born at term to assess the effects of nutritional counselling for the infant diet focused on complementary feeding and total diet by the use of dietary scores, i.e. irrelevant outcomes
Aboud 2008	RCT in infants aged between 12 and 24 m. Both intervention and control groups received sessions on nutrition relevant to complementary feeding
Palwala 2009	Not RCT conducted to develop and implement a need-based, situation-specific education program for mothers to improve complementary feeding practices, with emphasis on the quantity and nutritional quality of CFs
Watt 2009	RCT to assess the effect of monthly home visits from trained volunteers on improving infant feeding practices and growth at age 12 m. Data were collected at baseline when children were aged 10 weeks i.e. it is eligible study but it did not report outcomes specific for this review
Horodynski	RCT conducted to promote the development of healthy infant eating, opportunities for mothers to develop and practice skills, and a discussion of strategies to overcome challenges and problem-solving techniques. Both intervention and control groups received a nutritional education
Jimenez	Single group assignment trial to assess effectiveness study of maternal nutrition/hygiene education program combined with infant egg supplementation

Appendix 8.16 Risk of bias in the included studies (Chapter 6)

Study ID	Bias	Reviewers' judgment	Support for judgment
Bhandari 2001	Random sequence generation (selection bias)	Unclear risk	No information provided Comment: unable to judge whether sequence generation was adequate
	Allocation concealment (selection bias)	Unclear risk	"Children were stratified by weight for height status (≤80% and >80% of the National Centre for Health Statistics median for that age) and randomly assigned to one of the four study groups" Comment: unable to judge whether allocation concealment was adequate
	Blinding of participants and personnel (performance bias)	Low risk	Although no information was provided on blinding o participants, the outcome specified to be of interest in this review are unlikely to be affected by lack of blinding
	Blinding of outcome assessment (detection bias)	Low risk	Although no information was provided on blinding outcome assessor, the outcome measures relevant to this review are unlikely to be affected by lack of blinding
	Incomplete outcome data (attrition bias)	Unclear risk	In total the attrition rate was 9.5%, and, at 12 m follow-up, outcomes are reported for 97 (93.2%) infants in the intervention group and 93 (87.7%) in the control group
	Selective reporting (reporting bias)	Unclear risk	The protocol of the study was not available to us, so we could not judge whether selective reporting happened
	Other bias	High risk	At baseline (4 m of age) there were some differences between the two groups in energy intake and in the socio-demographic characteristics (fathers' education)

Study ID	Bias	Reviewers' judgment	Support for judgment
Bhandari 2004	Random sequence generation (selection bias)	Low risk	"generated 4 single-digit random numbers using a random numbers table; the first listed community in a pair was allocated to the intervention group if the random number was 0–4 and the second if it was 5–9"
	Allocation concealment (selection bias)	Low risk	"A statistician, not involved with the study has done the randomisation" i.e. there was central allocation using random number tables
	Blinding of participants and personnel (performance bias)	Low risk	"Mothers and infants were visited at home by workers who were not involved in the delivery of the intervention". Furthermore, some outcome measures relevant to this review are objective, hence they are unlikely to be affected by incomplete blinding
	Blinding of outcome assessment (detection bias)	Low risk	"Mothers and infants were visited at home by workers who were not involved in the delivery of the intervention"
	Incomplete outcome data (attrition bias)	High risk	The attrition rate was >10% and it was higher among the intervention group. At 6 m follow-up, the attrition rate was 15.2% and 12.9% from the intervention and the control group. At 18 m follow-up, the attrition rate was 21.2% in the intervention group and 16.7% from the control group
	Selective reporting (reporting bias)	Unclear risk	All predefined outcomes state in the paper were reported, but, the study protocol was not available to us, so we could not judge whether selective reporting happened
	Other bias	Low risk	Study appeared free of other bias

Study ID	Bias	Reviewers' judgment	Support for judgment
Bortolini 2012	Random sequence generation (selection bias)	Unclear risk	Quoted from earlier report for the same research group Vitolo 2005:"Each five mothers who accepted to participate in the sample, two were drawn to belong to the intervention group, and the other three allocated to the control group, and thus, consecutively, until the estimated sample number was reached. Block randomisation was used to avoid or lessen possible imbalances at some point in the randomisation process" Comment: unable to judge whether sequence generation was adequate, method is not clear
	Allocation concealment (selection bias)	Unclear risk	No information provided
	Blinding of participants and personnel (Prevalence of anaemia)	Low risk	Although blinding of intervention might be not possible, prevalence of anaemia at age of 12 m is objective, it is unlikely to be affected by incomplete blinding
	Blinding of participants and personnel (Prevalence of exclusive breast feeding)	High risk	Exclusive breast feeding at 6 m of age may be affected by reporting bias which can be affected by the fact that such an intervention cannot be blinded
	Blinding of outcome assessment (detection bias)	Unclear risk	"Interviewers who were not involved in the intervention process and who were blind to which group children belonged to conducted home visits at 6 and 12 m in order to collect data on the study variables". On the other hand, in Vitolo 2005, it says that they were not blinded Comment: unable to judge whether blinding of assessor was adequate or not, method is not clear and reported differently in two reports of the same study
	Incomplete outcome data (attrition bias)	High risk	Loss of follow up for both outcomes; anaemia at 1 year of age and exclusive breast feeding at 6 m was >10%
	Selective reporting (reporting bias)	High risk	The protocol for the study was available to us, but some outcomes, such as; effectiveness of a nutrition advice programme in occurrence of diarrhoea, respiratory problems, dental caries, and hospitalisation, were not reported
	Other bias	Low risk	This study appears free of other bias

Study ID	Bias	Reviewers' judgment	Support for judgment
Olaya 2013	Random sequence generation (selection bias)	Low risk	" Randomisation assignments were prepared by using randomised blocks of permuted length by a member of the team who had contact with study subjects"
	Allocation concealment (selection bias)	Low risk	"stored in sealed opaque envelopes"
	Blinding of participants and personnel (performance bias)	Low risk	Although blinding of intervention was not possible, the outcome measures relevant to this review are objective, and they are unlikely to be affected by incomplete blinding Laboratory measurements were blinded
	Blinding of outcome assessment (detection bias)	Low risk	Anthropometric and laboratory measures are objective, hence, they are unlikely to be affected by incomplete blinding
	Incomplete outcome data (attrition bias)	High risk	Loss to follow-up for anthropometric measures at 12 m of age was 10.6% in total; 9.5% from the intervention group and 11.6% from the control, but attrition for haemoglobin measurements at 12 m was 14.1% in total; 14.3% from the intervention and 14% from the control group and for serum ferritin was 31% in total; 19% from the intervention group and 14% from the control group
	Selective reporting (reporting bias)	High risk	Retrospectively registered in the ISRCTN registry (ISRCTN57733004). Some predefined outcomes, such as; iron and zinc status, anthropometric parameters, and mothers' opinions are reported, whereas others, such as; motor development, energy and nutrient intakes, and serum retinol were not reported in this paper
	Other bias	High risk	There was commercial support for the study At baseline (6 m of age) there were significant differences in WAZ, WHZ, MUACZ scores in control group compared to the intervention group

Study ID	Bias	Reviewers' judgment	Support for judgment
Penny 2005	Random sequence generation (selection bias)	Low risk	"the investigator (MP) tossing a coin in the presence of the local health authorities"
	Allocation concealment (selection bias)	Low risk	"Randomisation was done before formative research to avoid it acting as an intervention" The investigators used coin flipping as the means of randomisation. Comment: if faithfully flip the coin for each participant this would effectively conceal each upcoming allocation
	Blinding of participants and personnel (performance bias)	Low risk	"Families were not told whether they were in the intervention or control group" Comments: the relevant outcome measures are objective, therefore, they are unlikely to be affected by incomplete blinding of participants
	Blinding of outcome assessment (detection bias)	Low risk	"Data were collected by project field workers who were not involved in the delivery of the intervention" Comments: the relevant outcome measures are objective, therefore, they are unlikely to be affected by incomplete blinding of personnel
	Incomplete outcome data (attrition bias)	Unclear risk	Researchers took into account the anticipated (low) loss to follow-up, they increased the sample size by 25%, however, the attrition rate was 10%; it was higher among the control group (12%) in comparison to the intervention group (9%)
	Selective reporting (reporting bias)	Unclear risk	Trial registration not reported in the published paper
	Other bias	High risk	Socioeconomic differences between families in the intervention and control groups e.g. more educated mother in the intervention group (52%) in comparison to the control group (36%)

Study ID	Bias	Reviewers' judgment	Support for judgment
Roy 2007	Random sequence generation (selection bias)	Unclear risk	No information were provided
	Allocation concealment (selection bias)	Unclear risk	No information were provided
	Blinding of participants and personnel (performance bias)	Low risk	Although blinding of intervention was not possible, the relevant outcome measures are unlikely to be affected by incomplete blinding of participants
	Blinding of outcome assessment (detection bias)	Low risk	Although blinding of intervention might be not possible, the relevant outcome measures are unlikely to be affected by incomplete blinding of personnel
	Incomplete outcome data (attrition bias)	Low risk	The attrition rate in total low (5.7%). It was higher in the control group (7.5%) compared to the intervention group (3.9%)
	Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us, therefore, we could not judge whether there were any differences from the protocol
	Other bias	Low risk	This trial appeared free of other bias

Study ID	Bias	Reviewers' judgment	Support for judgment
Shi 2009	Random sequence generation (selection bias)	Unclear risk	"The paired townships were listed alphabetically in blocks of two and assigned randomly to be intervention or control sites", however, the method of randomisation was not clear
	Allocation concealment (selection bias)	Unclear risk	The townships were listed alphabetically, but the method of randomisation was not described in sufficient detail Comment: whether there was allocation concealment or not could not be judged
	Blinding of participants and personnel (performance bias)	Low risk	Although blinding of intervention might be not possible, the outcome measures are objective, hence, they are unlikely to be affected by the lack of blinding
	Blinding of outcome assessment (detection bias)	Low risk	Although blinding of intervention might be not possible, the outcome measures are objective, therefore they are unlikely to be affected by the lack of blinding
	Incomplete outcome data (attrition bias)	High risk	The attrition rate was 18.2% in total (12.9% of the infants from the intervention group and 23.3% of the infants in the control group)
	Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us, therefore we cannot judge whether there were any deviations from the protocol
	Other bias	High risk	The study is commercially funded, creating potential conflicts of interest At baseline there were some differences in parental occupation between the two groups

Study ID	Bias	Reviewers' judgment	Support for judgment
Vazir 2013	Random sequence generation (selection bias)	Low risk	"The random allocation using a random number generator (facilitated through a tailor-made syntax programme in the Statistical Package for the Social Sciences (SPSS)"
	Allocation concealment (selection bias)	Low risk	"allocation was undertaken by a researcher who was not familiar with the villages or their characteristics" Comment: the process of randomisation described would have allowed for allocation concealment
	Blinding of participants and personnel (performance bias)	Low risk	Not possible to blind intervention, however, the outcome measures are objective and are unlikely to be affected by the lack of blinding
	Blinding of outcome assessment (detection bias)	Low risk	"The assessment teams were blinded to the intervention and had no interaction with the village women" Comment: the outcomes relevant to this review are objective, they are unlikely to be affected
	Incomplete outcome data (attrition bias)	High risk	At 12 m, total attrition rate was 17.5%. Losses to follow up was 16.8% in the control group, and 18.1% in the intervention groups
	Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us, therefore, we cannot judge whether there were any deviations from the protocol
	Other bias	Low risk	The trial appears free of other risks of bias

Study ID	Bias	Reviewers' judgment	Support for judgment
Zhang 2013	Random sequence generation (selection bias)	Unclear risk	"The paired townships were listed alphabetically in blocks of two and assigned randomly to be intervention or control sites", but the method of randomisation is not reported
	Allocation concealment (selection bias)	Unclear risk	The townships were listed alphabetically, but whether there was allocation concealment or not cannot be judged as the method of randomisation is not described in sufficient details
	Blinding of participants and personnel (performance bias)	Low risk	Not possible to blind families and staff, however, the outcome measures are objective, therefore, they are unlikely to be affected by the lack of blinding
	Blinding of outcome assessment (detection bias)	Low risk	Not possible to blind families and staff, however, the outcome measures are objective, therefore, they are unlikely to be affected by the lack of blinding
	Incomplete outcome data (attrition bias)	High risk	At 12 m, the attrition rate was 18.2% in total (12.9% of the infants from the intervention group and 23.3% of the infants in the control group)
	Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us, therefore we cannot judge whether there were any deviations from the protocol
	Other bias	High risk	The study was commercially funded creating potential conflicts of interest At baseline there were some differences in parental social class

Appendix 8.17 Summary of findings (SoF) table: Nutrition education of families on weaning v control (Chapter 6)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with conventional management	Risk with nutritional education			
Weight gain (kg) at 12 months old	The mean weight gain (kg) at 12 months old ranged from **1.1 to 1.4** kg	The mean weight gain (kg) at 12 months old in the intervention group was 0.03 kg higher (0.02 lower to 0.08 higher)	-	2246 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
Height gain (cm) at 12 months old	The mean height gain (cm) at 12 months old ranged from **6.1 to 7.3** cm	The mean height gain (cm) at 12 months old in the intervention group was 0.2 cm higher (0.08 higher to 0.32 higher)	-	2246 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
Weight z-scores at 12 months old	The mean weight z-scores at 12 months old ranged from **-1.6 to 0.1**	The mean weight z-scores at 12 months old in the intervention group was 0.11 higher (0.02 higher to 0.2 higher)	-	1672 (4 RCTs)	⊕⊕◯◯ LOW [d,e]
Weight z-scores at 15 months old	The mean weight z-scores at 15 months old was **-0.6**	The mean weight z-scores at 15 months old in the intervention group was 0.32 higher (1.06 lower to 1.7 higher)	-	377 (1 RCT)	⊕⊕◯◯ LOW [f,g,h]
Weight z-scores at 18 months old	The mean weight z-scores at 18 months old ranged from **-1.9 to -0.6**	The mean weight z-scores at 18 months old in the intervention group was 0.41 higher (0.31 higher to 0.51 higher)	-	988 (2 RCTs)	⊕⊕◯◯ LOW [b,i]
Length z-scores at 12 months old	The mean length z-scores during the first 2 years - Length z-scores at 12 months old ranged from **-1.96 to -0.5**	The mean length z-scores at 12 months old in the intervention group was 0.16 higher (0.06 higher to 0.26 higher)	-	1672 (4 RCTs)	⊕⊕⊕◯ MODERATE [d]
Length z-scores at 15 months old	The mean length z-scores at 15 months old was **-1.1**	The mean length z-scores at 15 months old in the intervention group was 0.36 higher (0 to 0.72 higher)	-	377 (1 RCT)	⊕⊕◯◯ LOW [f,g,h]
Length z-scores at 18 months old	The mean length z-scores at 18 months old ranged from **-2.2 to -1.2**	The mean length z-scores at 18 months old in the intervention group was 0.31 higher (0.2 higher to 0.42 higher)	-	972 (2 RCTs)	⊕⊕⊕◯ MODERATE [i]
Weight for length z-scores at 12 months old	The mean weight for length z-scores at 12 months old ranged from **-0.9 to 0.5**	The mean weight for length z-scores at 12 months old in the intervention group was 0.01 higher (0.1 lower to 0.12 higher)	-	1295 (3 RCTs)	⊕◯◯◯ VERY LOW [a,c,j]
Weight for length z-scores at 18 months old	The mean weight for length z-scores at 18 months old ranged from **-1.1 to 0.1**	The mean weight for length z-scores at 18 months old in the intervention group was 0.33 higher (0.22 higher to 0.44 higher)	-	988 (2 RCTs)	⊕◯◯◯ VERY LOW [d,k]
Head circumference z-scores at 12 months old	The mean head circumference z-scores at 12 months old was **0.3**	The mean head circumference z-scores at 12 months old in the intervention group was 0.15 lower (0.53 lower to 0.23 higher)	-	85 (1 RCT)	⊕⊕◯◯ LOW [g,h,j]
Mid upper arm circumference z-scores at 12 months old	The mean mid upper arm circumference z-scores at 12 months old was **1**	The mean mid upper arm circumference z-scores at 12 months old in the intervention group was 0.42 lower (0.8 lower to 0.04 lower)	-	85 (1 RCT)	⊕⊕◯◯ LOW [g,h,j]
Weight for length z-scores at 18 months old	The mean weight for length z-scores at 18 months old ranged from **-1.1 to 0.1**	The mean weight for length z-scores at 18 months old in the intervention group was 0.33 higher (0.22 higher to 0.44 higher)	-	988 (2 RCTs)	⊕◯◯◯ VERY LOW [d,k]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with conventional management	Risk with Nutritional education			
Head circumference z-scores at 12 months old	The mean head circumference z-scores at 12 months old was **0.3**	The mean head circumference z-scores at 12 months old in the intervention group was 0.15 lower (0.53 lower to 0.23 higher)	-	85 (1 RCT)	⊕⊕◯◯ LOW [g,h,i]
Mid upper arm circumference z-scores at 12 months old	The mean mid upper arm circumference z-scores at 12 months old was **1**	The mean mid upper arm circumference z-scores at 12 months old in the intervention group was 0.42 lower (0.8 lower to 0.04 lower)	-	85 (1 RCT)	⊕⊕◯◯ LOW [g,h,i]
Change in weight z-scores at 12 months old	The mean change in weight z scores at 12 months old ranged from **-1.3 to 0.02**	The mean change in weight z scores at 12 months old in the intervention group was 0.06 higher (0.02 lower to 0.14 higher)	-	1473 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
Change in length z-scores at 12 months old	The mean change in length z scores 12 months old ranged from **-1.5 to -0.3**	The mean change in length z scores at 12 months old in the intervention group was 0.2 higher (0.12 higher to 0.27 higher)	-	1473 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
Change in head circumference z-scores at 12 months old	The mean change in head circumference z scores at 12 months old was **-0.01**	The mean change in head circumference z scores at 12 months old in the intervention group was 0.12 higher (0.07 lower to 0.3 higher)	-	85 (1 RCT)	⊕⊕◯◯ LOW [g,h,i]
Exclusive breast feeding for 6 months	**Low**		**RR 6.40** (4.84 to 8.23)	1525 (2 RCTs)	⊕◯◯◯ VERY LOW [d,h,m]
	3 per 100	**19 per 100** (15 to 25)			
	High				
	6 per 100	**38 per 100** (29 to 49)			
Prevalence of Anaemia at 12 months old	**Low**		**RR 1.17** (0.96 to 1.39)	585 (2 RCTs)	⊕◯◯◯ VERY LOW [a,h,n]
	9 per 100	**11 per 100** (9 to 13)			
	High				
	44 per 100	**51 per 100** (42 to 61)			
Prevalence of iron deficiency at 12 months old	30 per 100	**24 per 100** (11 to 45)	**RR 0.79** (0.36 to 1.49)	85 (1 RCT)	⊕◯◯◯ VERY LOW [g,h,i]

Explanations

a. Some concern with random sequence generation, allocation concealment, high losses to follow-up reporting the outcomes and other sources of bias (see RoB table)

b. Downgraded for inconsistency owing to moderate heterogeneity: I^2=64%

c. Downgraded owing to imprecision, because of a wide confidence interval for the estimated effect and it crosses the threshold of clinical relevance

d. Some concern with random sequence generation, allocation concealment, high losses to follow-up and reporting the outcomes

e. Downgraded for inconsistency owing to high heterogeneity: I^2=79%

f. Some concern with reporting the outcomes and other sources of bias (see RoB table)

g. N/A as there was only one study included

h. Downgraded owing to imprecision, because a small number of participants and wide confidence interval

i. Some concern with random sequence generation, allocation concealment, reporting the outcome and other sources of bias (see RoB table)

j. The level of statistical heterogeneity between study results was substantial (I^2=82%)

k. Downgraded for inconsistency owing to high heterogeneity: I^2=92%

l. Some concern with high losses to follow-up, reporting the outcomes and other sources of bias

m. Downgraded for inconsistency owing to high heterogeneity: I^2=95%

n. Downgraded for inconsistency owing to high heterogeneity: I^2=67%