GROWTH & DEVELOPMENT IN VERY PRETERM INFANTS: THE INFLUENCE OF INFANT, MATERNAL AND MEDICAL FACTORS

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PREFACE

The work described in this thesis was carried out at the Department of Psychology, University of Hertfordshire, Hatfield, under the direction of Professor Dieter Wolke.

The work presented here has primarily been carried out by me, and I have endeavoured to acknowledge the contribution of other members of the research team and to reference appropriately any ideas or findings that are not my own.

This dissertation has not been submitted, either in whole or in part, for any other degree, diploma or qualification at this or any other University.

Publications

Preliminary results of this study were published at the following conference proceeding:

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The research presented in this thesis comprises part of a comprehensive longitudinal study entitled "GAIN" (Growth & Attachment in At-Risk Infants). Naturally a project of this magnitude involves input from many different individuals over a period of time, and I would like to acknowledge the assistance I have received during the past few years.

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In addition, I would like to thank Karine Edme and Laura Goldner who assisted Tina Gutbrod in carrying out the 18-month assessments on the infants in the Study. I appreciate also the contributions of Anne Hagues, who assisted in the coding of the strain gauge data, and my father, who meticulously proofread this thesis on more than one occasion.

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ABSTRACT

It is generally acknowledged that infants born very preterm are at a high risk of developmental delay. It has been suggested that the first few months of life ex-utero might constitute a "sensitive period" during which growth rate could influence later outcome measures including cognitive development. This study investigated the early growth of a sample of 90 infants born very preterm and the developmental status (at 18 months of age) of 81 of those infants (mean gestational age 29.4 weeks; mean birth weight 1283g). Two main issues were addressed. One concerned the relative contribution of various early infant, maternal and medical factors to rate of growth up to 3-months corrected age. The other issue was the extent to which these early factors, as well as early growth rate, were predictive of developmental status at 18 months of age (again corrected for gestation), using the Mental Development Index of the Bayley Scales.

Analyses revealed that there were few significant predictors of early growth among the variables that were examined. Infants who had required more intensive medical care during the neonatal period showed a slower growth rate than the more robust infants. Breast-fed infants grew slower from birth to term, but thereafter grew significantly better, resulting in no discernable difference over the whole 5-7 month period. None of the infant behavioural, maternal or social variables examined appeared to be related to early growth. Infants who were born lighter-for-gestation grew faster than the infants who were heavier for gestational age.

At the 18-month follow-up assessment this very preterm sample performed poorly overall in comparison to published norms for full term infants. When regression analyses were performed, weight at 3-months of age was found to be predictive of developmental status at 18-months (even when concurrent weight was taken into account), whereas actually being born growth retarded was not found to be a risk factor for poorer developmental outcome. This supports the concept of a "sensitive period" during the first few months of life, when growth rate may influence developmental outcome. Other significant predictors of developmental outcome were gender, early brain scan and mean parental height.

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OVERVIEW OF THESIS

The research presented in this thesis comprises part of a larger, comprehensive study entitled "GAIN" (Growth & Attachment in At-Risk Infants) (Wolke, Gutbrod, Rust), which was a prospective, longitudinal, observational study of very preterm infants from birth onwards. The overall purpose of the GAIN study was to examine medical, infant and maternal factors, together with mother-infant interactions, and relate these to subsequent physical growth, developmental progress and attachment outcome.

There has been a considerable volume of research published that has revealed that very preterm infants are at a higher risk of developmental delay than infants born at or around term (e.g. Hack & Fanaroff, 1999; Tessier et al; 1997, Wolke, 1998). Furthermore, preterm infants who are born with intrauterine growth retardation have been shown to have an even greater risk of later cognitive delay compared to the infants born at a weight appropriate for gestational age (Martikainen, 1992; Smedler et al, 1992; Sung et al, 1993). However, it has been proposed that the first few months of life might constitute a "sensitive period" during which rate of growth might influence later outcome measures, including cognitive performance (Skuse et al, 1994). For example, a particularly slow rate of growth during these early months of life (i.e. failure to thrive) might be associated with a poorer developmental outcome for these very preterm infants who are already considered to be "at risk" of developmental problems. Conversely, if such a "sensitive period" exists, rapid early catch-up growth in infants born small-for-gestational age might be expected to ameliorate the effects of a poor intrauterine environment. Some research has previously been conducted on the relationship between poor early growth (i.e. failure to thrive) and developmental outcome with normal term infants, but no prospective study has yet reported on an exclusively very preterm sample in order to investigate whether (a) there is an association between the two issues (i.e. growth and development) and (b), if there is such an association, the direction of causality. That is to say, it is unclear whether differences in growth rates are the cause of the observed variation in developmental outcome, or rather that infants whose developmental potential has already been compromised tend to grow worse than their neurologically intact peers.

This thesis reports on some of the data obtained at the first four assessment points in the GAIN study: i) during hospitalisation; ii) at "term" (i.e. when the infant should have been born; iii) at three months of age; and iv) at 18 months (both corrected for gestation). The two main foci of this thesis were, firstly, to examine the factors associated with individual growth rate during the first few months of life and, secondly, to establish whether, and if so how, early growth is related to developmental status at 18 months corrected age.

Initially the intention of the thesis was solely to explore the extent to which various early infant, maternal and medical factors contributed to growth rate during the first few months of life. However, because of the nature of the study and the time taken to analyse and report on the large volume of data from the first few months of life, the 18-month follow-up data also became available. The decision was therefore made to include some of the information available from this later assessment, and thereby to test the hypothesis that the first few months of life might constitute a "window of opportunity" during which growth rate might influence later developmental outcome. Both as a consequence of this change from the original thesis plan and for ease of reading, there are two separate Results & Discussion Sections, the first pertaining to the assessments that took place between birth and 3-months, and the second pertaining to the 18-month assessment..

The thesis is thus divided into five Sections:

The first Section, (the Literature Review), is divided into three chapters and commences with background information on definitions of terms used in the thesis, and the causes of premature birth/intrauterine growth retardation. This is followed by a description of research in the areas of very preterm birth, intrauterine growth retardation and nutrition particularly relating to early growth (including catch-up growth/failure to thrive) and later developmental outcome. Chapter two examines infant factors, i.e. oral-motor function and infant temperament/behaviour regulation, and their relationship with early growth rates and developmental outcome.

As we will see, despite the considerable volume of research that has been carried out to date, it remains very difficult to make predictions regarding the developmental course of individual children born very preterm. Chapter 3 comprises a brief summary of the Literature Review, together with the stated aims of the study and the a priori hypotheses that were tested and reported.

The second Section (the Method) is also divided into three chapters. The first gives detailed information on the study design, recruitment criteria and sample characteristics. In the second chapter the procedures and instruments used in the first phase of the study (i.e. birth - 3 months) are described. The instruments are described chronologically, i.e. in the order in which they were used, and the frequency data and psychometric evaluations on each of the variables are presented. In the third and final chapter in this section the instruments and procedures used at the follow-up assessment at 18 months are described.

The third Section (Birth - 3 Months corrected age) addresses the issue of which, and to what extent, early variables are related to growth rate during the first few months of life, and comprises three chapters. The first brief chapter introduces the concepts of growth and weight status. In the second chapter the relationship between a variety of independent variables (divided into four categories - medical, nutritional, infant behavioural and maternal/social) and growth rates are presented. Subsequently the regression analyses that were performed in order to build prediction models for growth outcomes are reported. The third and final chapter in this section comprises the Discussion of the findings presented in the previous Results chapter, their clinical significance and their relation to previous research.

The fourth Section (18-Month Assessment) concerns the follow-up assessment at 18 months of age (corrected for gestation). It comprises two chapters: in the first, the results are presented, i.e. the developmental assessment using the Mental Developmental Index of the Bayley Scales and significant prediction models for developmental outcome at 18-months are proposed. Subsequently the anthropometric measurements of the subjects at the 18-month assessment are presented. The second chapter consists of the Discussion relating to the previous results chapter.

The fifth and final section provides a discussion of the main findings, together with the implications for future research and clinical management of very preterm infants.

SECTION I. LITERATURE REVIEW

Chapter 1: Very Preterm Birth, Intrauterine Growth Retardation, Infant Nutrition and Growth in the Early Months of Life

1.0 Introduction

This first chapter covers the issues of very preterm birth and intrauterine growth retardation, including the long-term consequences of these conditions. It continues with a review of research on infant nutrition, including the particular needs of very preterm infants, and the influence of early nutrition on growth and later developmental outcome. At the end of the chapter the concept of catch-up growth and, in contrast, "failure to thrive", and the possible evidence for a relationship between growth parameters and developmental outcome is examined.

1.1. Background Information

Rapid and on-going advances in medical expertise and technology have resulted in ever-increasing numbers of smaller and more immature infants surviving the neonatal period (Stevenson et al, 1998; Wolke, 1998). As a rule, the more premature the infant, the poorer the outcome, but many factors may influence both the initial survival and longer term outcome for these infants, in addition to the principal ones of birth weight and gestation (e.g. gender, birth weight status, quality of perinatal care, early nutrition etc).

Neonates can be classified according to gestational age at birth, and/or by birth weight, and there are universally recognised categories within each of these classifications (see Table 1 below).

Table 1: Classifications of prematurity and birth weight

Term	Definition
Term	Born 37-42 completed weeks gestation
Pre-term/premature	Born before 37 completed weeks gestation
Very pre-term/premature	Born before 32 completed weeks gestation
Extremely pre-term/premature	Born before 28 completed weeks gestation
Low birth weight (LBW)	Birth weight below 2500g
Very low birth weight (VLBW)	Birth weight below 1500g
Extremely low birth weight (ELBW)	Birth weight below 1000g

There is usually a high correlation between gestational age and birth weight, although this correlation is not perfect. Birth weight is governed by two principal factors - gestational age and intrauterine growth rate (i.e. period of growth and rate of growth). Sub-optimal growth in-utero is known as intrauterine growth retardation (IUGR) and infants born with IUGR are often referred to as "small-for-gestational age".

As shown in Table 1, "term" birth is defined as being born between 37 and 42 weeks gestational age. Birth before that time may be spontaneous in onset or clinically induced. Spontaneous onset of preterm labour may be due to acute maternal infection (e.g. of the urinary tract) but is most commonly of unknown aetiology. Clinically induced preterm birth is usually due to either maternal illness (e.g. pre-eclampsia) or fetal distress (e.g. due to placental insufficiency).

1.2. Long-term Consequences of Very Preterm Birth

There has been a large volume of research into the long-term prognosis for infants born very preterm. Much of this research indicates that, as a group, they are at an increased risk of a variety of problems in the areas of cognitive development, motor performance, social and behavioural problems, compared to their term peers (e.g. Tessier et al, 1997; Schothorst et al, 1996; Elder et al, 1998; Whitfield et al, 1997; Wolke, 1998; Hack & Fanaroff, 1999; Hille et al, 2001; Johnson et al, 2003).

One of the difficulties inherent to the investigation of outcome for these at-risk infants is the technological progress in neonatal intensive care units that has taken place over the past two decades. This means that children currently being assessed at school age did not receive the same neonatal care as those being born now (Vohr & Msall, 1997). A positive consequence of this progress is that the infants currently being born at any given gestation are likely to have a better long-term prognosis than those born at a similar gestation a few years ago. However, because the lower limit of survival has gradually been extended, the number of very low birth weight infants who are later found to have problems has remained relatively stable (Campbell, 1997).

Due to the plasticity of the infant brain (i.e. its ability to compensate for injury) normal developmental progress may occur despite early evidence of damage (e.g. abnormal ultrasound scans of the brain). Recovery from such neurological insult may occur at any time during the first year of life among very low birth weight infants. For example problems such as hypertonicity, asymmetry, jerkiness and tremors, which are present up to 6 months of age, may resolve by 12 months. Conversely symptoms of cerebral palsy may not be obvious during the first year of life, but gradually become apparent from 12-18 months of age. As a general rule of thumb the risk of long-term morbidity increases with degree of prematurity and with decreasing birth weight (Hack & Fanaroff, 1999; Johnson et al, 1993). However, despite the advances in the care of these at-risk infants it has so far proved frustratingly difficult to predict outcome for individuals based on early medical variables, with infants of similar gestational age and birth weight, who have apparently very similar neonatal experiences, developing very differently (Bennett & Scott, 1997). Whereas major motor or sensory handicaps in very preterm children are usually recognised quite early, the more subtle deficits may not become apparent until the child reaches school age. Up to 50% of very low birth weight children may exhibit these more subtle deficits, and it has been suggested that such apparently minor impairments can nonetheless significantly impede academic and social progress (Bennett & Scott, 1997).

Research findings will be reviewed in terms of the long term consequences of the types of problems that infants born very preterm face as they mature, which can be grouped into four main areas: cognitive development, social/behavioural performance, motor development and general health. The focus of my study in terms of outcome is specifically on cognitive development and the prediction of this from the early months of life and as a consequence more attention is paid to this topic than the others. However, as they leave infancy and progress through childhood, individuals born very preterm often exhibit a combination of deficits, and this can make accurate assessment of specific areas of functioning difficult. For instance, a young child with cerebral palsy may actually be cognitively normal, but this is difficult to establish due to the types of assessment instruments available. Furthermore, as already mentioned, to date it has appeared that individuals with what are apparently very similar early medical histories go on to present with very different deficits as they grow older. The mechanisms that determine outcome of individuals is not clear, which in turn makes any prediction of outcome very difficult except in cases where neurological damage has patently been catastrophic.

1.2.1. Cognitive Outcome

Most research in this field is unanimous in finding that children born very preterm tend to have lower cognitive scores than those born at term, and the suggestion has been made that the relationship between birth weight and IQ is approximately linear (Lagercrantz, 1997).
When considering the results of research into cognitive outcome among very preterm children, it is very important to note that many follow-up studies exclude those subjects who have severe motor or sensory disabilities, because it is not possible to assess accurately the cognitive function of these individuals. Furthermore, as with other longitudinal studies, the prospective studies of very preterm term infants do suffer from subject "drop-out". As reported by Wolke

et al (1995), "drop-outs" tend to have had lower cognitive development scores at previous assessments, and have mothers who were less educated. In addition, for many of the developmental tests used, same-age control infants actually perform better than the test norms, and therefore the difference between very preterm infants and "normal" is actually somewhat greater than it appears unless matched controls are used. Each of the foregoing points would indicate that the published outcome findings are likely to paint a more positive picture for this group of infants than is actually justified, and therefore results should be interpreted cautiously unless it is clear that these issues have been taken into account.

There are a variety of developmental tests available for use both with pre-school and school-age children, but the Bayley Scales are currently the most commonly reported test used during the pre-school years. In general all such tests should be interpreted with caution for individual cases as their predictive values are poor (Vohr & Msall, 1997). There is, however, a recognised tendency for low to stay low, i.e. the subjects who score particularly badly as infants are also likely to score badly at school-age (Largo et al, 1990; Liaw et al, 1993). Early testing does, therefore, have value as a surveillance tool to identify those individuals who are likely to exhibit difficulties in childhood.

It has been suggested that, although outcome studies often show a *statistically significant* difference between very low birth weight and normal children in terms of IQ, the mean differences between the groups may not actually be clinically relevant (Hack et al, 1992; Hoy et al, 1992). However, other studies have reported larger IQ differences (Zelkowitz et al, 1996; Pharoah et al, 1994; Levy-Shiff et al, 1994; Smith et al, 1990; Anderson et al, 2003). For example, among very preterm infants without major neurological impairment, and when same-age controls were used, it has been reported that there was a 7-10 point difference in mean IQ scores between groups (Wolke, 1994; Gross et al, 1992; Breslau, 1995). Despite common belief, these mean differences are not found to reduce over time (Breslau, 1995; Wolke 1997b; Botting, 1997). In fact, multiple problems may only become apparent at school age because of greater demands on the individual e.g. spatial, verbal and phonological processing skills etc. Children with persistent IQ deficits from infancy (often in conjunction with neurological and neurosensory problems) are often found to have multiple cognitive deficits including language, speech, reading and maths (Wolke, 1997). Interestingly, there is little evidence that very low birth weight children are more likely to have specific learning disorders in isolation (e.g. reading difficulties) (Breslau 1995). There is, however, growing evidence that they are at an increased risk of having a central deficit in processing different stimuli simultaneously, e.g. as is needed in visual motor integration or logical reasoning (Saigal et al, 1991; Wolke et al, 1994).

As mentioned, speech and language disorders are recognised as being more prevalent in children born very preterm (Bennett & Scott, 1997). These problems persist beyond the pre-school years, with these at-risk children having significantly poorer reading and spelling skills at 8 years of age. For example, one study found that three times as many children born at a very low birth weight were in the bottom 10% of the class at these skills than controls (Marlow et al, 1993). One of the other principal subjects for school-age children is mathematics, which incorporates a variety of skills including non-verbal reasoning and problem solving. Again children born at a very low birth weight have been shown to perform poorly compared to age-matched controls at 8 years of age (Marlow et al, 1993), with three times as many children born at a very low birth weight in the bottom 10% of their class than controls. A more recent study of children born very preterm during the 1990's, who were followed up at eight years of age, showed that this type of at-risk group continue to perform significantly worse on reading, spelling and arithmetic, in addition to have a significantly lower full-scale IQ (Anderson, 2003).

It has been suggested that approximately 45% of children born very pre-term require special educational support due to the types of problems mentioned above, although sometimes this can be provided within a mainstream school. It has also been reported that 20% of children born very preterm have an IQ between 70-85, and a further 9% have an IQ below 70 (Campbell, 1997).

In a British study reported by Marlow et al (1993) of 72 children born very preterm, 20% had a major impairment requiring special schooling and only 40% of the total sample were free of educational problems at 8 years of age. The children in this study showed no specific pattern of deficits, with their problems changing as they matured. Motor performance at 6 years appeared to be the best predictor of school performance two years later, with those who performed poorly on motor function at 6 carrying a 33% risk of later learning difficulties. Another British study (Johnson et al, 1993) reporting on a cohort of very preterm infants assessed at four years of age reported that 23% exhibited severe disability, and just 35% of children were seemingly unimpaired. A later follow-up in mid-teens showed that one sixth of the sample had severe disabilities and were attending special schools. Of those in mainstream education, children born very preterm continued to perform worse than a control group in all areas of learning (Johnson et al, 2003). Large epidemiological studies in Holland and Germany have produced similar results: 19-22% of very low birth weight children were in special education at 8-9 years, with a further 22-26% being educated below their chronological age. Less than half of all the very low birth weight children (40-45%) were in an age-appropriate class in a mainstream school (Wolke, 1997; Hille et al, 1994). Both of these studies reported that the best predictors of schooling problems included cognitive deficits from an early age, early language delay, and neuro-sensory and behaviour problems during the pre-school period.

Interestingly, even among children within the normal range of IQ, those born at a very low birth weight are more likely to be underachieving at school. Lloyd (1984) compared a group of very low birth weight children with their similar IQ siblings and found that 28% of those born at a very low birth weight under-performed at school, compared with just 3% of the normal birth weight siblings. This finding may be due to the types of social and behavioural problems that these children often exhibit, which may be independent of actual intelligence level but can nonetheless affect their performance at school.

In conclusion then, the deficits manifested by school-age children born very preterm appear to be particularly in areas of language, memory, attention, motor co-ordination, perceptual-motor skills, non-verbal reasoning and problem solving (Campbell, 1997). Two particular risk factors for educational difficulties that have been identified among children born very preterm are male gender and low socio-economic status. However, as already stated, however, it is currently very difficult to predict which children born very preterm are going to present at school age with problems that necessitate special educational support. One of the main aims of this study is to identify specific early risk factors that predict developmental outcome at 18-months of age, in the knowledge that those children who are severely developmentally delayed at that age are very likely to remain so at school-age.

1.2.2. Social/Behavioural Performance

It has been reported that over 20% of children born very preterm exhibit behavioural problems (Hack et al, 1989; 1996). The types of problems in the area of social and behavioural functioning found among children born very preterm are varied, and in some cases there is evidence that behavioural problems are related to neurological and cognitive dysfunction (Gillberg & Gillberg, 1989; Shaffer et al, 1985). It has been suggested that the difference in the incidence of social and behavioural problems between children of very low birth weight and age-matched controls is considerably reduced if IQ is controlled for. That is, some very low birth weight children may have behaviour problems because of a lower IQ, which restricts their ability to behave appropriately (McCormick et al, 1990).

In a 4-centre study, Hille et al (2001) reported very similar social and behavioural problems associated with very preterm birth in four different countries (Holland, Germany, US and Canada), which the authors suggest point to biological causes. Hille et al reported that the functional areas in which the children born very preterm differed most from controls were: (a) social, i.e. they acted younger than their chronological age and were not popular with peers; (b) thought processing, i.e. hearing or seeing things and repeating acts in an abnormal fashion; and (c) attention, i.e. problems with concentration and impulsivity. Interestingly, in the US cohort in particular, there was a strong association between early abnormal ultrasound of the brain and ADD (Attention Deficit Disorder) at 6 years of age, which again points to an organic basis for this disorder. Other authors, however, have suggested that the behavioural problems that are manifested in many very low birth weight children, as with the normal population, may be associated with Socio-Economic Status and the home environment (McCormick et al, 1990).

The incidence of social or behavioural problems among children born very preterm, particularly delinquent behaviour and aggression, appear to be higher in boys than girls (Schothorst et al 1996). In a study published by Ross et al (1990) children who were born very preterm were found to be less socially competent generally, and the behavioural problems apparent in the boys in particular were associated with other factors (e.g. lower IQ, and lower socio-economic status). Hoy et al (1992), too, found that children born at a very low birth weight were less socially competent, but in addition found that they were also more withdrawn. It has also been reported that there is a higher incidence of emotional problems among these children (Marlow et al, 1993).

Interestingly, it would appear that children born very preterm differ from their term peers in the patterns of co-morbidity as shown by deficits in the various functional areas. For example, in one study of very preterm children, attentional problems were related to poor social abilities, and social difficulties were also related to impaired school competence (Schothorst et al 1996).

A further long-term problem for a proportion of children born very preterm is the failure to achieve normal physical growth, this being a particular risk for those born small for gestation or who had severe neonatal medical complications (Campbell, 1997). Recently Wood et al (2003) reported that the extremely preterm infants participating in the EPICure study had a mean weight, head circumference and height more than one standard deviation below the norm at 30 months of age, despite being a normal size for gestation at birth. Similar results were reported by Cooke et al (2003) who followed up 280 children born very preterm at seven years of age. The index children were significantly smaller than the control group children in terms of weight, height and head circumference. This small stature in relation to peers may also affect social relationships as children grow older.

1.2.3. Physical/Motor Development

In addition to the increased risk of cognitive impairment and behavioural difficulties, a significant minority of children born very preterm will be found to suffer from a major handicapping disorder. The most commonly occurring one of these is cerebral palsy, followed by blindness (or severe visual impairment) and deafness. Campbell (1997) reported major handicapping conditions occurring in approximately 20% of infants born below 1000g, and 15% of those born 1000-1500g.

For children born very preterm, but without major motor or sensory impairment, the area of function in which they tend to show most delay compared to controls at age 15 months, is gross motor function (Schendel et al, 1997). Some studies have also suggested that poor performance on motor testing at this early age has been associated with a significantly increased risk of school-related problems later on (Lindahl et al, 1988; Drillen et al, 1988).

1.2.4. Health Outcome

Finally, in addition to the heightened risk of cognitive deficits, behavioural difficulties and physical/motor problems that children born very preterm are exposed to, they are also at an increased risk of medical health problems. Many of these children require re-admission to hospital, particularly during the first year of life (De Elder et al, 1999). In particular respiratory problems are common (including asthma), as are recurrent ear infections and gastrointestinal problems (feeding difficulties and food intolerances). There is an increased incidence of failure to thrive (FTT) among children born very preterm, which may be at least in part due to the gastrointestinal problems that are encountered. Often these medical problems result in increased absence from school, which in turn exacerbates learning difficulties, and also restricts activity compared to same-age peers (which may adversely effect social relationships). The study by Johnson et al (2003) that followed up a cohort of individuals born very preterm showed that even in their mid-teens these children had a much higher incidence of health problems than the control group children.

1.2.5. Summary of Long-term Consequences of Very Preterm Birth

As the foregoing sub-sections have shown, children born very preterm are at risk of long-term problems in a multitude of areas. In addition to the cognitive deficits that are frequently seen and which are the focus of this study, various motor, social and health problems have also been mentioned briefly, in order to give a fuller picture of the range of difficulties facing these individuals as they grow up.

1.3. Intrauterine Growth Retardation

There are various definitions of Intrauterine Growth Retardation (IUGR) or Small-for-Gestational Age (SGA) that can be used for research purposes. The first type of definition uses percentiles as cut-off criteria, with sex specific norms that take into account females being lighter. Generally the 10^{th}, 5^{th}, 3^{rd}, or even 2^{nd} percentile for the gestation at which the baby is born is used as the cut-off criterion. An alternative definition that is sometimes used is a birth weight at least 2 standard deviations below the mean for gestation.

Although the terms "Intrauterine Growth Retardation" and "Small-for-Gestational Age" tend to be used synonymously they do not actually mean exactly the same thing. The term "small-for-gestational age" includes both infants with IUGR and a few infants born to small mothers, who have not suffered sub-optimal uterine conditions, but who are genetically predestined to be smaller/lighter than the majority of their peers. Fortunately this discrepancy in terminology is less of a problem in research involving very preterm infants. This is because most of the variability in size that occurs due to genetic factors takes place during the last trimester of a normal pregnancy, which very preterm infants will not experience in utero. Thus the observed variation in weight for gestation among very preterm infants can be assumed to be almost entirely due to intrauterine conditions.

1.3.1 Developmental Consequences of Intra-uterine Growth Retardation

There is now a large body of research that shows that for full-term infants poor intrauterine growth is a risk factor for both long-term growth and development. For example, a follow-up study of term SGA infants (which used a cut-off criterion of the 3rd percentile) showed that only 63% of them had shown any catch-up growth at four months of age. As a group the SGA infants had significantly lower developmental scores than the AGA control group, and were rated as more manageable temperamentally, but there were no discernible differences in neuro-motor development (Newman et al 1997). However, other follow-up studies of term SGA infants have shown that, at pre-school age, SGA children exhibit significantly poorer language skills (both verbal, comprehension and expressive) (Walther & Ramaekers, 1982), have a higher incidence of eating problems, more health problems, and lag behind their AGA peers both physically and developmentally (Pryor, 1992).

Several studies that have followed up SGA infants into late adolescence have found that they are at an increased risk of short stature (Paz et al, 1993; Pryor et al, 1995; Frisancho et al, 1994), poorer cognitive outcome, poorer academic achievement (Paz et al, 1995; Pryor et al 1995) and of exhibiting behavioural problems (Pryor 1995). A recent study that assessed approximately 6,000 males born SGA at the age of 18 years, found an overall association between being SGA at birth and increased risk of subnormal intellectual and psychological performance. Within this group of individuals born SGA, the most important predictor of intellectual and psychological performance appeared to be the presence (or absence) of catch-up growth (Lundgren, 2001). Since this was a retrospective study, however, it was not clear whether the timing of the catch-up growth influenced outcome, which is an importance issue in view of the question of whether there is a "sensitive period" where good catch-up growth may ameliorate the effects of a poor intrauterine environment.

Even longer-term consequences of intrauterine growth retardation have been identified. A recent study has suggested that women who were born with IUGR may encounter fertility problems later in life (de Bruin et al, 1998) and an earlier menopause (Cresswell et al 1997). In men, similarly, there is some research evidence which suggests that previously unexplained male sub-fertility may be associated with low birth weight (Francois et al, 1997). Other long-term consequences of being born small-for-gestation include an increased risk of coronary heart disease (Osmond et al, 1993; Barker et al, 1993), stroke (Martyn,et al, 1996), diabetes (Hales, 1997) and hypertension (Law et al, 1993).

Barker (1997) has suggested that the sub-optimal intrauterine conditions that result in infants being born small-for-gestation necessitate the fetus having to adapt to a limited supply of nutrients, but by so adapting he/she may permanently change his/her physiology and metabolism. These changes may be the cause of the increased incidence of the various diseases later in life.

1.3.2 Intrauterine Growth Retardation in Conjunction with Very Preterm Birth

There has been less research published on infants who are born both very preterm and SGA. What literature there is, however, suggests that being IUGR in this group of already at-risk infants may increase the likelihood of neonatal mortality and long-term morbidity. Spinillo et al (1997) studied a group of 230 very/extremely preterm infants (born 24-31 weeks gestation) and discovered a significant linear trend linking a decreasing birth weight z-score with an increased likelihood of neonatal death, intra-ventricular haemorrhage (a major cause of later disability), severe Respiratory Distress Syndrome (RDS) and acidosis. Their findings did indicate, however, that a lower than expected birth weight was a less significant predictor of outcome than was gestational age. Conversely, another study reported that among preterm infants, those born small for gestation may do better in the first few minutes of life (i.e. have better Apgar scores) and be less likely to suffer from RDS requiring mechanical ventilation (Veelken et al, 1992).

In the longer term, more than one study has concluded that those infants born preterm and small-for-gestation are at an increased risk of minor neurological abnormalities, although not necessarily for the more major disabilities such as cerebral palsy. In fact, results of one study (Riegel et al, 1995) suggested that preterm SGA infants are at lower risk of cerebral palsy than the preterm AGA infants. Martikainen (1992) compared groups of preterm infants born SGA (either asymmetric or symmetric) or AGA with infants born at term and AGA. At 18 months of age the numbers of neurologically abnormal or suspect children in both the SGA groups were twice the number in the control group, although there were more diverse abnormalities in the symmetric SGA group. Veelken et al (1992) also reported an increased incidence of minor neurological abnormalities in preterm SGA infants, again at about 18 months of age.

There is scant literature available that reports on the specific types of difficulties that these children present with, although one study that compared a group of children born VLBW/SGA with a control group reported that the VLBW/SGA children scored significantly lower on measures of visuospatial ability, non-verbal reasoning, strategy formation and gross-motor co-ordination at 8-11 years of age. The children who were born most preterm had the highest incidence of behavioural and educational problems and subnormal performance in the tests (Smedler et al, 1992).

Two studies have compared very low birth weight, small-for-gestation infants with two "control" groups – one matched for gestation and one matched for birth weight. In the first study (Sung et al, 1993) the progress of the SGA group during the early neonatal period was comparable with that of the gestation-matched group, and better than the birth weight-matched group. However, during the first three years of life the developmental progress of the SGA group was slower than for the gestation-matched group, and more similar to the birth weight matched group. Interestingly though, by 3 years of age the SGA infants were performing similarly to the gestation-matched controls and better than the birth weight matched controls.

No further follow-up has been reported and therefore it is not possible to ascertain whether the SGA group would exhibit more educational difficulties than the gestation-matched group. Similar results were reported by the second study (Gutbrod et al, 2000), which also used these types of control groups, with the gestation-matched group showing the best growth and developmental performance at 5 and 20 months and 4.8 years of age. The SGA and birth weight-matched group performed similarly to each other at the first two time points, but the SGA group performed better than the birth weight-matched group at 4.8 years. However, when pre- and neonatal complications were taken into account the differences in developmental outcome between the groups disappeared after the 5-month assessment.

Interestingly, both the Sung study and other earlier ones have indicated that lack of catch-up growth among the SGA infants, in terms of head circumference, is strongly related to poorer cognitive function (Hack et al, 1989; Nelson et al, 1970). Unfortunately the issue of whether or not this catch-up growth needed to occur within a certain timeframe, and also what the direction of causality was for the children in these studies, was not addressed. This could have been accomplished by examining the weight of the subjects at, for example, term and/or 3-months of age corrected for gestation and relating that to both birth variables and later developmental outcome.

1.4. Growth and Failure to Thrive

As has already been discussed, poor growth in utero can have long-term consequences for later growth, health, cognitive development and behavioural functioning. Research findings have also shown that reduced growth during infancy and early childhood is related to poor developmental outcome. Experimental studies to ascertain the effects of under-nutrition and growth restriction have predominantly involved animals, since clearly it would be unethical to perform such research on human subjects. Observational studies on humans have, however, been carried out to ascertain whether under-nutrition and growth stunting result in poorer cognitive performance than is found among children who have been adequately nourished and have shown normal growth patterns. Generally it has been found that malnourishment is associated with lower cognitive scores, although in many studies there were several confounding variables which make it rather difficult to interpret the data (Morley & Lucas, 1997). For instance, a child who is undernourished may well also suffer from maternal neglect, lack of stimulation, environmental impoverishment etc., and it is no easy task to extrapolate the specific effects of under-nourishment per se.

Whether or not the timing of the growth faltering is an important factor in determining the effect on cognitive outcome is currently unclear. In a prospective study (Skuse et al, 1994) undertaken in a socially disadvantaged area of London, a birth cohort was followed for the first year of life. The sample did not include babies born preterm, or with severe intrauterine growth retardation. Children who showed growth faltering over the 12 months, i.e. failed to reach the anticipated growth trajectory for their birth weight, were followed up and matched with a control group (n=47 in each group). They were then assessed using the Bayley Scales at 14-15 months of age. Analyses showed that the regression coefficients between weight at 6 months and the Bayleys MDI and PDI were significant (p=.00 and p=.03 respectively), but those between concurrent weight and the Bayleys scores were non-significant. These results suggest that severely impaired growth during the first six months of life in this sample was associated with poorer mental and psychomotor development, but that growth faltering later in the first year of life did not adversely affect outcome. The authors concluded that these findings concurred with earlier studies that also suggested that the first six months of postnatal life might constitute a "sensitive period" (Lloyd-Still et al, 1974; Chase & Martin, 1970; Carmona da Mota et al, 1990).

However, two other studies, while also finding that growth faltering was associated with poor developmental outcome, have failed to find evidence of a "sensitive period". The first of these, by Wilensky (1996), reported on a group of children in Israel, and found age of onset of growth faltering was not related to the Bayley scores (possibly due to small sample size). The second study (Drewett et al, 2001) reported on a sub-sample of a birth cohort of Ethiopian children (n = 197), all of whom were born weighing at least 2.5 kg. The infants were categorised as (a) early growth falterers (their weight dropped below the 3rd percentile during the first four months); (b) late growth falterers were those not in the first group but whose weights were below the 3rd percentile by 10 and 12 months; and (c) the remaining group were a stratified random control sample whose weight remained above the 3rd percentile throughout the first year. At two years of age the children were assessed using the Bayley Scales, adapted for use in Ethiopia. The scores for the three groups were significantly different for both the mental and psychomotor scales, with the early growth-faltering group having the lowest scores on both scales. There was, however, a correlation between early growth faltering and weight at time of assessment, and after taking the latter into account there was no additional effect attributable to timing of the growth faltering. In other words, a low weight at 2 years of age was associated with developmental delay whatever the timing of the weight faltering. This finding was interpreted as the chronicity of the growth faltering being the critical issue for developmental outcome rather than the time of onset. The authors acknowledged, however, that the populations and therefore the causes of the growth faltering might have been different to those in the Skuse study. For example, there was a much higher proportion of early growth falterers in the Skuse et al sample, and evidence that some of these had oral-motor problems (Reilly et al, 1999). In contrast the Ethiopian study had a larger proportion of late growth falterers, possibly due in part to the very poor weaning diet available in the region. Indeed, Drewett highlighted the fact that, compared to the NCHS/WHO growth standards which are based on American children at one year of age, the <u>average</u> weight of the Ethiopian infants was 1.5 standard deviations below the mean (Asefa et al, 1996). Thus it is clear that there was widespread malnutrition among Ethiopian infants.

The above studies reported on findings from samples of term infants, but recently there have also been several studies of preterm infants that have linked post-natal growth to later developmental outcome. For example Cooke & Foulder-Hughes (2003) reported that poor cognitive outcome at seven years of age in a sample of very preterm infants was associated with poor post-natal growth, especial in terms of head circumference. Similarly, Latal-Hajnal et al (2003) reported that, at two years of age, there was an association between concurrent weight below the 10th percentile and performance on both the mental and psychomotor indices of the

Bayley Scales. In that study, children who had been born at a weight below the 10th percentile who were above that criterion by the age of two years performed better than the sub-group who remained small-for-age. Furthermore, of the infants who were born at a weight above the 10th percentile, those who had dropped below that criterion by two years of age performed significantly worse than those who remained at a weight appropriate for age. However, neither of these studies investigated the issue of whether the timing of catch-up growth (or conversely, growth faltering) was important, simply reporting on growth overall between birth and the later follow-up point.

Although it cannot be confidentally established that the growth faltering actually caused poorer outcome in any these children (since conversely some undiagnosed disorder might have resulted in the observed growth faltering, or a third factor might be responsible for both the growth faltering and the poor outcome), the two variables do, nonetheless, appear to be associated in some way. One approach to addressing the issue of causality would be the examination of early variables, including a range of medical, behavioural and social ones, in order to ascertain whether there were early differences between the individuals who exhibit failure to thrive and those who do not, which could provide an alternative explanation for the observed relationship between growth and development.

1.5. Nutrition

In this section the effects of early nutrition, in terms of health, growth and developmental outcome are examined, firstly for term infants, and then, in more detail, for infants born very preterm. As will become clear, research findings generally support the premise that breast milk is the best form of nutrition for term infants, but the picture is less clear for infants born very preterm, particularly in terms of growth and developmental outcome. Since these are the two main outcome measures used in this thesis, early nutrition is obviously an important factor to address.

1.5.1. Effects of Early Nutrition on the Health of Term Infants

There is a large body of research-based evidence that, for term infants, maternal breast milk is the ideal source of nutrition for the first few months of life (Campbell, 1996). The benefits of breast milk appear to be manifold, for example a large study (Howie et al, 1990) showed that term babies who were breast-fed, fully or partially, for the first 3 months of life had only one third the incidence of gastro-enteritis as babies receiving no breast milk (with the effect being maintained beyond the period of breast-feeding), and there was also a reduced rate of hospital admission. It has also been shown that breast-feeding offers significant protection again respiratory infections (Howie et al, 1990), ear infections (Dewey et al, 1995; Aniansson et al, 1994; Duncan et al, 1993) and urinary tract infections even if infants are only partially breast-fed, with the effect again extending beyond the period of breast-feeding (Pisacane et al,1992). Furthermore, exclusive breast-feeding, even if only for the first month,, has been shown to provide protection against atopic eczema, respiratory allergy and allergic food intolerance, (Saarinen & Kajosaari, 1995). There is also a reported reduced incidence of Sudden Infant Death Syndrome (SIDS) in breast-fed babies (Ford et al, 1993). In contrast, just one study has found that food allergies are more common in children who were breast-fed as infants (Savilahti et al, 1993).

1.5.1.2. Effects of Early Nutrition on the Growth of Term Infants

Patterns of growth are known to differ between breast and formula fed babies. An Australian study showed similar weight gains for breast and bottle fed full-term babies over the first 3 months of life, but from 3-6 months the weight gain was greater in bottle-fed group (Hitchcock et al, 1985). The DARLING Study in US followed babies to 18 months of age and throughout that period the mean weight of breastfed babies was lower than bottle-fed group. However, body length and head circumference among the two groups were similar throughout the period of study (Dewey et al, 1992).

1.5.1.3. Effects of Early Nutrition on the Developmental Outcome of Term Infants

Research evidence regarding the link between method of feeding and subsequent intelligence among term infants is contradictory. Some studies have suggested that breast-feeding is linked with subsequent increased intelligence at 18 months of age (Du V Florey et al, 1995); and also at five and 10 years of age (Pollock 1994). However, another study that reported on retrospective analyses of 994 individuals born 1920-1930, and which adjusted for other variables, found no association between adult intelligence and method of feeding (although the raw scores were higher before adjustments were made). The only independent predictors of adult intelligence that remained significant were dummy use in infancy, the number of older siblings, maternal age at birth and the father's occupational class (Gale (1996). Clearly a retrospective study of this kind, however, is based on the testimony of the subjects themselves as to how they had been fed as infants some 60 years previously and should be interpreted cautiously

Even with prospective, longitudinal studies it remains difficult to control for confounders, for example genetics, parenting effects and home environment. In a meta-analysis of the research to date, Anderson (1999) examined the results of 20 studies that examined the relationship between type of milk received in infancy and later developmental status. The results showed a statistically significant (and homogenous) difference in intelligence scores between subjects who had been breast-fed and those who had been formula-fed as infants, with the breast-fed group performing better. The mean difference across the studies of term infants was 2.7 points (95% CI: 2.2-3.2). Of course this difference, although significant statistically, is of questionable value clinically. Recent clinical trials by Willatts et al (1998, 2000, 2002) suggest that some of the differences in cognitive function that they found between breast-fed and formula-fed infants may be due to the presence of long-chain polyunsaturated fatty acids in breast milk which are not present in standard infant formulae. In addition to the possible cognitive benefits, there are other long-term benefits of breast-feeding, including (in addition to the medical benefits discussed above) earlier maturation of visual function (Birch, 1992; Carlson, 1993), earlier acquisition of motor skills (Dorner, 1978; Lucas, 1989), and fewer emotional and behavioural problems later in life (Menkes, 1977; Lanting, 1994), which all lead to the overall conclusion that human breast milk is superior to artificial formula for the nutrition of the majority of human infants.

1.5.2. Effects of Early Nutrition on Preterm Infants

For feeding low birth weight or preterm infants the situation would appear to be less clear-cut. Although human breast-milk naturally provides all the nutrients required by the term, healthy infant (who, during the later stages of pregnancy, has laid down stores of vital elements obtained via the placenta, e.g. iron), the needs of the preterm infant are more complex. There is, however, a range of commercially available fortifiers that can be added to expressed breast milk in order to increase its nutritional value. Some of these contain just one particular nutrient, for example protein, but others now provide extra protein, energy, vitamins and minerals. This large choice of different fortifiers makes it difficult to compare research findings.

One of the apparent advantages of human breast milk over standard infant formulae is that it is an excellent source of docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid that is present in large quantities in the brain and retina and is believed to be essential for normal neurodevelopment. This is particularly important for preterm infants since stores of DHA and other long-chain polyunsaturated fatty acids (LCPs) are normally accreted during the final trimester of pregnancy, and therefore these preterm infants are liable to a deficiency unless it is provided in their diet. Although special preterm infant formulae have now been developed that contain LCPs, these still require an extra step of synthesis before they can be incorporated into the infant's central nervous system. They nonetheless bridge the gap between breast-milk and standard formulae - prior to the LCP enriched formulae being developed, infant formulae only contained precursors of essential fatty acids, which resulted in the rapid depletion of LCPs in the preterm neonatal circulation. This in turn was shown to have an adverse effect on visual acuity (Birch et al, 1992; Carlson et al, 1993), mental development (Carlson et al, 1994) and possibly physical growth (Koletzko et al, 1991; Leaf et al, 1992; Carlson et al, 1992). The modern formulae developed specifically for preterm infants also provide higher concentrations of energy, protein, vitamins and minerals than standard formulae, in order to facilitate more rapid growth.

1.5.2.1. Effects of Early Nutrition on the Health of Very Preterm Infants

There is much evidence that maternal breast-milk, adequately fortified with specific nutrients, is the most appropriate source of nutrition for preterm infants from the point of view of health, particularly in the short-term. Schanler (2001), in a review of the literature to date, concluded that there was evidence that feeding of breast-milk to preterm infants resulted in decreased incidence of infection (Schanler, 1995), including necrotising enterocolitis (Yu, 1981; Lucas, 1990), diarrhoea, urinary tract infections and the use of antibiotics generally. It has also been shown to improve neurodevelopment (Lucas, 1992; 1994 – see below), improve visual function (Carlson, 1993), reduce the incidence of Retinopathy of Prematurity (Hylander, 1995), improve gastric emptying (Cavel, 1981), and decrease intestinal permeability (Shulman, 1996). Lucas et al (1990) reported on a study of 777 infants with a birth weight below 1850g, followed up at 18 months corrected age. Comparisons were made between infants who received breast milk, preterm formula and standard formula in the incidence of atopic disease (for example asthma, eczema, allergies etc). Overall, the feeding of infant formula did not increase the risk of allergy. However, for the subgroup of infants with a family history of atopy, early exposure to cows milk did cause a significant increase in the incidence of a variety of allergic reactions.

1.5.2.2. Effects of Early Nutrition on Growth in Very Preterm Infants

Because sick, very preterm infants are unable to take any nutrition enterally (i.e. via the gut) early in the neonatal period, they have to be fed intravenously (parenterally), until their medical condition allows for milk to be introduced, gradually, to the gut. This results in severe early growth faltering. Alexander (1996) compared the growth curves of infants born very preterm with those of fetuses that remained in utero. The preterm infants were classified according to degree of prematurity, 24-25 weeks gestation, 26-27 weeks gestation, and 28-29 weeks gestation. All the preterm infants lost weight initially, regaining their birth weight by about 2.5 weeks of age (whereas the fetal growth curves rose continuously during this period). By 32 weeks gestation, the growth curves for all three groups of preterm infants were below the 10th percentile on the fetal growth charts, with the growth deficits at that age equalling approximately 35-40% of the average weight of a fetus of that gestation. Thus the preterm infant needs to grow at a faster rate than an infant born at term if it is to catch-up with other infants. There have been many studies to date that compare growth rates between preterm infants fed human breast-milk, preterm formula and standard formula. Unfortunately the nutritional value of un-fortified breast-milk is now recognised as being insufficient to enable the vulnerable preterm infant to grow at this accelerated rate. Furthermore, as previously mentioned, the preterm infant has been born before the normal body stores of elements have been laid down in utero, and thus their diet needs to include these substances in order to compensate. For these reasons, most infants born very preterm whose mothers intend to breastfeed are now given fortified breast milk during the period before they are actually able to be put to the breast. There are a variety of fortifiers on the market. Wauben (1998, 1999) compared infants given breast milk supplemented with multi-nutrients with those supplemented just with calcium and phosphorous during hospitalisation. In a follow-up assessment at 12 months of age, the type of supplementation did not appear to have influenced growth or body composition during the first year of life.

Several studies have compared the growth of infants fed with breast milk (fortified or unfortified) with those fed a special preterm or standard formula, but the results are contradictory. Lucas et al (2001) reported on a prospective longitudinal study of 284 preterm infants. 113 of these infants were randomly assigned to an enriched post-discharge formula (protein, energy, mineral and micronutrient enriched), and 116 to a standard term formula. The remaining infants were breast fed until at least 6 weeks corrected age. Anthropometric measurements were performed at 6 weeks, 3, 6, 9 and 18 months corrected age. At 9 months of age the group fed the special formula were significantly heavier and longer than those fed the standard formula, and the difference in length persisted to 18 months. The advantage of the special formula was again shown to be greater for the boys in the study. When the breast-fed infants were compared to the formula-fed infants it was seen that by 6 weeks corrected age the breast-fed infants were significantly lighter and shorter than the infants fed special formula, and remained so at 9 months of age. Another study, by Schanler (1999), also indicated the advantage, in growth terms, of preterm formula. The author reported on 108 infants whose gestational age was 27-29 weeks. During hospitalisation 62 of these infants were given fortified breast-milk, and 46 were given a preterm formula. However, although the group who received breast milk showed significantly slower rates of weight and length gain, they also had a lower incidence of necrotising enterocolitis and late-onset sepsis, and were discharged home earlier than the formula fed infants. The author therefore concluded that the improved health benefits of receiving breast milk outweighed the slower growth and therefore should be actively encouraged for preterm infants.

However, in contrast to the growth benefits of preterm formulae reported by both Lucas and Schanler, Nicholl (1999) compared three groups of infants, one of which were fed breast milk, the second group were fed fortified breast milk and the third group were fed a preterm formula. During the period studied, the infants fed the fortified breast milk showed accelerated growth (lower leg length) compared to those fed unfortified breast milk, and in fact their growth rates were comparable to those fed the preterm formula. Unfortunately no information on follow-up has been published, and therefore it is unclear whether these effects persisted beyond the initial period during which the type of nutrition given to the infants differed.

Other studies have compared the relative value of prolonging the use of preterm formula beyond the initial period of hospitalisation. Cooke (1998) compared three groups of infants (n = 86). The first group (A) were fed on a preterm formula from discharge through to 6-months corrected age, the second group (B) were fed a standard formula from discharge, and the third group (C) were fed the preterm formula from discharge to term, and then the standard formula from term to 6-months corrected age. Interestingly the infants fed the preterm, enriched formula actually had a lower intake, although due to the higher calorific value for the formula the energy intake was similar. Between discharge and term the growth rate was greater for groups A and C than for B ($p < .01$). At 6 months of age the boys in groups B and C were lighter ($p < .05$) and shorter ($p < .05$) than those from group A. Their head circumferences were also smaller, but this difference failed to reach statistical significance. For the girls, however, there was no significant difference between the feed groups on anthropometric measurements. A follow-up study (Cooke, 2001) looked at anthropometric measurements for these infants at 18 months of age. Overall there were no group differences between the groups. However, when boys and girls were analysed separately there were highly significant differences for the boys between those in group A and those in groups B and C ($p < .0001$). The group A boys were, on average, 1 kg heavier, 2 cm longer and had 1 cm larger head circumference than the other groups. As at the 6-month assessment, however, for the girls there were no discernable group differences. The relevance of gender when assessing the importance of formula type was also shown in a study reported by Carver et al (2001). In that study 125 infants were randomly assigned to a post-discharge (special) formula or a standard formula, stratified by gender and birth weight (cut off = 1250g). The prescribed formula was fed to 12 months corrected age. Growth was fastest in the infants fed the special formula, especially in the first two months after discharge, with the benefit being greatest for the smaller infants (weighing < 1250g) and for boys. Again it appeared that the infants fed the standard formula took a greater volume of milk than the other group, and managed to achieve a similar energy intake despite a 10% difference in the calorific density of the feeds.

Whether there are real, long-term effects of formula type on growth is unclear. Cooper (1989), undertook a study following up 40 very low birth weight infants to 3 years of age. The infants who were not breastfed (BF) were randomly assigned to a whey-predominant formula (A), a casein-predominant formula (B) or a preterm formula (C) during hospitalisation. During the period of hospitalisation group C grew significantly better than the other groups, but at 3-year follow-up there were no significant inter-group differences with respect to anthropometric measurements. Furthermore, there was no gender difference in the effect of milk type reported in this study.

In conclusion, therefore, the findings of studies examining the growth of very preterm infants in relation to the type of early nutrition they received are inconsistent. It would generally appear that both preterm formulae and fortified breast milk are probably superior to standard infant formulae in terms of growth, although even this has not universally been found, and the longer-term effects of early nutrition also remain unclear. There is some suggestion that boys are more susceptible to the effects of milk type than are girls, but again this gender difference has not been found in all studies. It was therefore essential to examine early nutritional factors in the present study, since one of the main aims of the study was to build prediction models for rate of growth during the first few months of life.

1.5.2.3. The Effect of Early Nutrition on Later Developmental Status in Very Preterm Infants

As is the case for term infants, there have been many studies that attempted to ascertain the effect of early nutrition on later developmental or cognitive status in preterm infants. Again the results are rather ambiguous, although there does appear to be some benefit of breast-feeding to these at-risk infants in terms of developmental outcome. In a meta-analysis of effects of breast-feeding on cognitive development, Drane (2000) made the observation that many studies do not distinguish between partial and exclusive breast-feeding. The studies that do make the distinction (e.g. Lucas 1992) show that the benefits are most pronounced in infants who were exclusively breastfed. The author also emphasised the importance of controlling for a full range of confounders.

Morley et al (1988) reported an association between the use of breast-feeding for preterm infants and mental development at 18 months of age (average increase of 4.3 points on Bayley's). Lucas et al (1992) then reported the findings of a follow-up assessment at 7.5-8 years of age on 300 of the subjects. Using an abbreviated version of the WISC-R the authors reported an average 8.3 points IQ advantage for infants who had received maternal breast milk in the first few weeks. This represented an increase of over half a standard deviation, and took into account both maternal education and SES. The design of the study indicated that it was the milk itself that provided the benefit, rather than being put to the breast. In addition, there appeared to be a dose-response relationship between the proportion of mother's milk in the early diet and subsequent IQ. Similar results were reported by Horwood (2001) in New Zealand. 280 very low birth weight infants were followed up at 8 years of age using the WISC-R. Increasing duration of breast milk feeding was associated with increases in both verbal ($p < .001$) and performance ($p < .05$) IQ. Infants breast fed for at least 8 months had mean IQ scores 10.2 points (.56 sd) higher, and performance IQ scores 6.2 (.35 sd) points higher. After adjusting for a multitude of possible confounders (including medical, social and environment factors) a significant relationship still remained between breast milk and verbal IQ (a 6-point advantage, $p < .05$).

However, not all published results have shown this relationship between breast-feeding and developmental outcome. Jacobson et al (1999) reported on a sample of 323 children (of whom only a proportion were preterm) that was followed up at 4 years of age, and 280 of them assessed again at 11 years of age, using the WISC-R. At both ages the subjects who had been breast-fed as infants scored significantly higher than the formula fed infants even after adjusting for maternal education and SES. However, when further adjustments were made for maternal IQ and parenting skills as measured using the HOME questionnaire, the statistical significance of the difference between breast and formula fed infants disappeared. The authors suggested that findings from other studies (which in general only adjust for parental education and SES), might be attributing the higher IQ scores of children who were breastfed as infants to the nutritional benefits so gained, whereas they may in fact be due to genetic and socio-environmental factors that were not taken into account. The findings from this study should be interpreted with caution, however, since this study predominantly comprised term subjects (although some preterm infants were included), and may not apply to a very preterm sample of infants.

Research has also been undertaken to compare the relative value of preterm and standard formulas for very preterm infants in terms of developmental outcome, the results of which would indicate that the special preterm formulas are beneficial. Lucas et al (1989) reported the results of an 18-month assessment between infants fed preterm formula and those fed the standard formula. There was a significant advantage on the Bayley Scale PDI for children fed preterm formula, with the advantage being greatest when these diets were compared as sole diets. Sub-group analyses showed that the benefits were more pronounced in boys than girls, and in those born SGA rather than AGA. Interestingly, when the results of a study comparing preterm formula and donor breast milk were reported (Lucas, 1994) there were, surprisingly, only small developmental differences between the groups. This was particularly unexpected since the banked donor milk actually had the lowest nutrient content of all the milks used in the study, lower even than the standard formula. These findings do, however, support the hypothesis that human milk may contain factors, at that time unrecognised, that contribute to brain growth and maturation. A follow-up paper was published that reported on the subjects at 7.5-8 years, when they were tested using the WISC-R (Lucas et al, 1998). The authors reported a major sex difference on the impact of early diet. At follow-up the boys fed preterm formula had a 12.2 point advantage in verbal IQ and a 6.3 point on overall IQ compared to those fed the standard formula. The advantages were even greater in boys who received the highest intake of the trial diet. Furthermore, there were more reported cases of cerebral palsy, and more cases where the verbal IQ was < 85 in the boys fed the standard formula. No effect, however, was found among the girls. Interestingly, there were no apparent differences in developmental status between boys and girls who were fed the preterm formula. The findings suggest that preterm boys are particularly vulnerable to dietary deficiencies, although the reasons for this are not clear.

In conclusion, as with the effect of nutrition on early growth, the relationship between the type of nutrition received and later developmental outcome remains uncertain. Although there is some evidence that breast-milk confers a developmental advantage on very preterm infants, there is still a question mark over the issue of whether the infants who are breast-fed already differ in some subtle way from those who are formula-fed. Although most studies have controlled for some maternal and socio-economic status (SES), other unrecognised variables might explain the observed group differences. In a study examining very preterm infants, one important issue is whether the infants who received breast milk were more mature, and/or heavier at birth, or differed from the formula-fed infants in terms of severity of illness. Clearly these factors need to be taken into account, in relation to type of milk received, early growth pattern, and also later developmental outcome. In addition, the issue of maternal intelligence, in addition to other maternal variables such as educational level and SES should probably be addressed in order to ensure that the observed effects are not due to underlying genetic differences.

1.6. Summary of Chapter

Due to advances in medical technology, larger numbers of infants are surviving from increasingly extreme levels of prematurity. However, children born very preterm who survive the critical first few weeks of life remain at an increased risk of a multitude of long-term problems. For a small proportion of these individuals, it will be evident from very early in the neonatal course that gross neurological damage has occurred and therefore that impairment is almost inevitable. However, to date it has been difficult to predict from early infancy which of the remaining infants born very preterm will go on to exhibit significant deficits, particularly in the area of cognitive ability. As stated by Bennett & Scott (1997), infants with apparently very similar neonatal histories can develop totally differently. Although there is currently little evidence that early intervention studies can ameliorate developmental problems among very preterm infants (McCarton et al, 1997), early identification of children particularly at risk would nonetheless be of value in terms of social and educational support planning. In order to identify which individuals are at particular risk of deficits or delays, comprehensive prospective longitudinal research needs to be conducted that examines a multitude of early variables in relation to developmental outcome and can therefore determine pathways of influence.

For term infants, being born small-for-gestational age is a recognised risk factor for long-term problems in many spheres, for example cognitive, academic, social and behavioural as well as short stature as an adult. As already discussed, there is an increased incidence of intrauterine growth retardation in infants born very preterm, although among this group of at-risk infants the evidence for negative effects of intrauterine growth retardation is less clear-cut. It would, however, appear that small-for-gestational age very preterm infants are at an increased risk of minor neurological problems, even though the risk of major disabilities such as cerebral palsy may actually be reduced.

Failure to thrive, at least among term infants, has been shown to be associated with poor developmental outcome. Some researchers have found evidence of a specific "sensitive period" during the early months of life, when the relationship between growth faltering and developmental delay is particularly strong, although other studies have found that it is the chronicity of growth faltering that is the influential factor in determining outcome. There has, to date, been no research published on the effects of early growth faltering among a sample of very preterm infants although, based on studies of term infants, one might anticipate that growth faltering would be negatively associated with developmental outcome. What is already known is that, due to the medical condition of tiny infants, and the difficulties of providing them with adequate nutrition, their standardised weight almost inevitably drops during the first few week of life, often resulting in a major deficit by 32 weeks post-conceptual age. The rate of catch-up growth after the initial neonatal period clearly differs dramatically between infants. One of the research questions that is addressed in this thesis is whether actually being born SGA in an already high-risk sample automatically gives an additional risk of developmental delay, or whether good catch-up growth in the first few months of life can ameliorate this risk. Equally, based on the evidence from term infants, the intention is to ascertain whether those infants whose early growth is particularly poor are at an increased risk of negative developmental consequences.

For healthy, term infants breast-milk is almost universally accepted to be the ideal source of nutrients, offering clear protective benefits from disease, and possibly developmental advantages. However, for preterm and especially very preterm infants unfortified breast milk during the first few weeks of life does not provide sufficient nutrients to compensate for lack of body stores of vital substances, nor to allow catch-up growth to compensate for the observed initial weight loss associated with premature birth. Breast milk does, nonetheless, protect the preterm infant from some of the serious illnesses to which such individuals are prone (for example necrotising enterocolitis and retinopathy of prematurity) and in addition is a rich source of DHA (a long-chain polyunsaturated fatty acid), which is vital for neurodevelopment. There is growing (although not unanimous) evidence that breast milk bestows a greater developmental advantage on preterm infants than on term infants, although which constituent/s of breast milk are responsible for this benefit is not known. Several studies have concluded that male infants appear to be more sensitive to the effects of early nutrition, both in terms of growth rates and developmental consequences, than are female infants.

Breast-milk fortifiers are now available, which can be added to expressed breast milk prior to being fed to the infant, although how long breast milk should continue to be supplemented with fortifiers for preterm infants remains unclear. The advent of special, preterm formulae that contain long-chain polyunsaturated fatty acids, in addition to being a more concentrated source of nutrients than standard infant formulae, mean that there is now a viable alternative to fortified breast-milk for those infants whose mothers cannot or will not provide breast milk. Research suggests that infants fed preterm formulae grow faster and have a better developmental status at follow-up than those fed a standard infant formula (or, indeed, breast milk). The decision regarding when infants should be changed from preterm to standard infant formulae is again unclear, with several studies suggesting that at least short-term growth benefits are seen from continuation of the enriched preterm formulae after discharge from hospital. However, Griffin (2002) provides a summary of the use of enriched formula milks for preterm infants and concludes that, although they do improve early growth patterns (specifically in boys), most or all of the benefit appears to be lost by 18-months corrected age, and also that the improved early growth may not be associated with improved developmental outcome.

As shown by the foregoing pages, there is conflicting evidence as to the importance of nutrition during the early months of life for very preterm infants. Many of the cited studies have not looked at a wholly very preterm sample, and the effects on this type of particularly at-risk group may be different to those of a more homogenous sample. Ascertaining whether a relationship exists between early growth patterns and later developmental outcome, specifically among a sample of very preterm infants, was one of the main purposes of the present study, and therefore the identification of those factors that may contribute either to that early growth, or else directly to developmental outcome was vital. Early nutrition would appear, based on the published research, to be linked to both early growth and developmental outcome, although the precise nature and extent of the relationship remains unclear. For this reason the type of nutrition the Gain study infants received during the first few months of life was documented and analysed in relation to the outcome measures.

In addition to the type of milk an infant receives, there are other issues related to nutrition that may impact on growth and/or developmental outcomes. These include the individual infant's oral-motor abilities, and the number of feeds that the infant receives. These issues are among those addressed in the following chapter.

Chapter 2: Infant Characteristics in Relation to Growth & Development

2.0. Introduction to Chapter

In this second chapter the role of infant characteristics, particularly in relation to growth and development, are examined. Firstly feeding behaviour and technique in infancy is considered, both normal and abnormal, including the problems that can occur in relation to very preterm birth, and the ways in which feeding technique can be assessed in infancy. This is clearly an important issue to consider when attempting to understand the effect of nutrition on growth. Subsequently, research on infant temperament, i.e. irritability and crying, is reviewed, since temperamental differences among very preterm infants may be an important issue to examine in relation to growth and development. The review of research includes studies reporting on overall group differences between infants born full-term and preterm, and between those born small-for-gestational age and those born at a weight appropriate for gestational age.

2.1. Infant Feeding Technique

There have been several studies that have linked poor infant feeding technique with inadequate nutrition, resulting in poor weight gain. For example a paper, published in 1987 by Heptinstall et al, reported on a group of four-year old children who were chronically growth retarded, and found that the majority had begun to fail to thrive during the first year of life, and half of them showed abnormal feeding technique. Thus it would appear that assessment of infant feeding technique is an important issue when attempting to determine factors relating to growth in the first few months of life.

2.2.1. Background Information

The act of infant milk feeding is a very complex one, dependent on both anatomical structure and function. The relevant anatomy of the neonate differs slightly from that of an adult, including a relatively large tongue and soft palate; a relatively small oropharynx; an epiglottis that may overlap the soft palate and which helps protect against liquid aspiration; and the presence of sucking pads in the cheeks. The newborn, term infant has well developed rooting and sucking reflexes, and over time these reflexive movements become more refined and incorporated into more voluntary movements. Because the oral cavity in the newborn infant is only small, the tongue moves in an extension-retraction dimension. During feeding the infant is obliged to breathe through its nose due to the oral cavity is blocked by either the nipple or bottle teat (Stevenson & Allaire, 1991). The techniques required for successful bottle and breast-feeding differ slightly, and infants that become accustomed to one method may find it difficult to adjust to the other.

Healthy term infants suck in bursts of 10-30 sucks per burst (at a rate of approximately 1suck/second) with only brief pauses between bursts. The infant sucks, swallows and breathes during the sucking bursts in a 1:1:1 sequential pattern (Bu'Lock et al, 1990). Infants born preterm (i.e. <37 weeks), however, are unable to co-ordinate sucking, swallowing and breathing in this way, and instead show an immature sucking pattern of 3-5 sucks per burst, with respirations and swallows that occur before and after the sucking bursts. This type of early, immature sucking pattern, with bursts and pauses of equal lengths, has been seen in neonates from 32 weeks gestational age. Usually a mature sucking pattern is expected to emerge in preterm infants when they reach approximately 37 weeks gestation (Bu'Lock et al, 1990), and in term infants by the fifth day of life. The immature sucking pattern may persist for longer, however, in infants who had early respiratory difficulties during feeding, or if an infant has suffered neurological damage (Meyer Palmer, 1993).

Two types of abnormal sucking pattern have been identified – "disorganised", which describes a lack of rhythm of total sucking activity, and "dysfunctional", which describes the interruption of the feeding process by abnormal movements of tongue and jaw. Meyer Palmer has also described a "transitional sucking pattern", which has characteristics of both immature and mature sucking (that is a burst-pause pattern with sucking bursts of more than 3-5 sucks per burst; a variable length of burst e.g. 6-10 sucks; bursts and pauses of equal duration, but with apnoeic episodes following longer sucking bursts). This disorganised sucking pattern occurs because the infant cannot yet co-ordinate the suck-swallow action with respiration.

2.2.2. Methods of Studying Infant Feeding Technique

There have been many more studies on bottle-feeding than on breast-feeding infants, partly at least because it is technically more straightforward. Bottle-feeding involves the mother/carer holding the bottle at an appropriate angle and the infant sucking in order to receive the milk and, in simple terms, the more vigorous the sucking, the faster the rate of flow. In breast-feeding, however, the process involves the maternal physiology in addition to the infant's effort. The infant maintains some degree of control over milk ingestion by the rate and strength of sucking, but within a single feed, and also between individual mothers, the rate of milk expulsion varies widely and the detailed study of breast-feeding is therefore much more complex than when an infant is being bottle fed. In addition, whereas the composition of a bottle of formula when appropriately mixed with water is uniform, breast milk constituents vary across a feed. Initially there is a high water content (i.e. it is thirst quenching) and towards the end of a feed there is a higher fat content (i.e. it is hunger satiating). This change in fat content during a feed is said to be approximately linear (Hytten, 1954).

There are a variety of methods that can be used to study and analyse infant feeding techniques. Table 2 provides a brief description of the more commonly used methods, details the perceived advantages and disadvantages of the method, and cites publications describing their use.

Table 2: Methods of Studying Infant Feeding Technique

Instrument	**Advantages/*Disadvantages***	**Publications**
Modified teat connected to pressure transducer (measures positive and negative pressures of sucking)	Relationship between sucking and flow rate can be altered by experimenter, objective *Can't be used for breast-feeding, expensive and technically difficult to use*	Kron et al, 1963; Wolff, 1968; Dubignon & Cooper, 1980
Intraoral pressure measurement (measures the changing pressures in the mouth during sucking)	Can be used for both breast-and bottle-feeding infants, objective data *May interfere with normal feeding pattern as mildly invasive*	Woolridge & Drewett, 1986
Strain gauge beneath chin (measures sucking rate and rhythm rather than relative pressures)	Can be used for both breast- and bottle-feeding infants, non-invasive, objective data	De Monterice et al, 1992; Ramsay & Gisel, 1996
Direct observation (to record sucks and pauses)	Cheap and simple *Risk of experimenter error*	Kaye, 1977; Drewett & Woolridge, 1979
NOMAS (Neonatal Oral-Motor Assessment Scale)	Cheap and simple *Risk of experimenter error* *Comprehensive training required*	Braun & Meyer Palmer, 1985; Meyer Palmer, 1993; Blaymore Bier et al, 1993

Studies of bottle-fed infants frequently use adapted newborn teats with catheters that connect to external pressure transducers. These allow the measurement of expression and suction and of the positive and negative pressures of sucking. These measures then generate a waveform that reflects the pressure changes within the teat, and from this the rate and rhythm of individual sucks, together with the amplitude of the expression and suction, can be calculated. Using such equipment it has been observed that there is a rate difference between nutritive and non-nutritive sucking (e.g. on a dummy or finger). Normal nutritive sucking occurs at approximately one suck per second, while non-nutritive sucking occurs at two sucks per second (Wolff, 1968). There has, not surprisingly, been shown to be a strong correlation between milk consumption, sucking rate and sucking pressure (Kron et al, 1963). In another study that compared "good feeders" and "poor feeders" during a two minute feed session, the good feeder group had a much longer mean duration of sucking bursts (47.1s versus 10.3 s); there were more sucks per burst (60.4 versus 12.8); shorter pauses between bursts (2.42 versus 6.4s); and fewer bursts overall (4.58 versus 8.5) (Dubignon & Cooper, 1980). The criteria used for distinguishing " pauses" between sucking bursts varies between studies, from 1 second (Wolff, 1968; Dubignon & Campbell, 1969), through 1.3 seconds (Drewett & Woolridge, 1979; Woolridge & Drewett, 1986), to 1.5 seconds (Dubignon & Cooper,1980).

It is, of course, inappropriate to use equipment involving adapted teats for studying breast-fed infants and therefore other methods have had to be developed for this purpose. Sucking patterns in breastfed infants have been measured in various ways - using intra-oral pressure measurement (Woolridge & Drewett, 1986), by strain gauge (de Monterice et al 1992; Ramsey & Gisel, 1996) or by direct observation (Drewett & Woolridge, 1979). Both the strain gauge method and the direct observational method have been validated against pressure recordings. As previously mentioned, during a breast-feed the rate of milk flow varies continuously (starting fast, and slowing down over the feed). The more variable sucking pattern that is typically observed in breast-feeding infants may therefore not be a nutritive/non-nutritive dichotomy as in bottle-feeding, but just extremes of continuously varying pattern of sucking in response to the milk flow rate (Drewett & Young, 1998).

In the present study it was considered essential to measure the subject infants' feeding technique for two main reasons. The first was that it was anticipated that feeding competence might be associated with growth rate and therefore a measure of that feeding competence needed to be included. Secondly, abnormally poor feeding technique might be associated with underlying neurological damage and might therefore be associated with developmental outcome. The strain gauge was the instrument chosen to assess feeding technique in the present study for several reasons. An important factor was that, as discussed, it is appropriate for use with infants who are being breast-fed as well as those being bottle-fed, which was essential. In addition it could provide a really objective measure of an infant's feeding technique, and finally the equipment required was obtainable within the available budget. Personal communication with a researcher (M. Ramsay) who had experience with this type of equipment confirmed the belief that this was the most appropriate instrument to use in the present study.

An important variable in studying infant feeding efficiency is straightforward milk intake, and the simplest way of measuring this is by test weighing before and after feeds. This is essential for breast-feeders but is still valuable even with bottle-feeders, since some volume of milk may have been spilt or dribbled out by the infant, and therefore simply measuring the amount taken from the bottle can be misleading. The disadvantage of this pre- and post-feed weighing method, however, is that it only indicates weight of milk ingested, not its calorific value (and, as already mentioned, the nutritive value of breast milk is known to vary dramatically from the beginning to the end of a feed). It was nonetheless felt that measurement of milk intake would, in conjunction with other measures of feeding technique, add to the overall picture regarding feeding skills.

2.2.3. Hunger-Satiety Regulation

Infant feeding is an interactional activity, in which both mother and infant need to play their parts if it is to be successful. In healthy, full term infants it has been shown that when mothers increase the interval between feeds, the infants adapt by taking more milk at the subsequent feed, thereby maintaining the daily milk intake (Pinilla & Birch, 1993). It has also been shown that if the milk provided is of lower calorific value, the infants will attempt to compensate by ingesting a larger volume of it (Fomon et al 1975). Thus healthy, full-term infants are able to adapt to changing feeding conditions. This may not, however, necessarily be the case for preterm infants, particularly during the first few weeks after oral feeds have been introduced. Due to their fragility and in some cases medical complications, these infants may not initially be able to take in sufficient calories to ensure adequate growth. They often sleep for long periods and frequently have to be woken up for feeds because their hunger may not wake them. In addition, during feeds they become tired very quickly, i.e. they do not necessarily end a feed because they have consumed an adequate volume and are satiated - they may end it because they are too exhausted to continue. Even on discharge from hospital many of these infants have not yet reached sufficient maturity to control their own intake and, therefore, the onus is on the mother to ensure that her infant receives sufficient calories. This is usually achieved by advising the mother to wake the infant at regular intervals for feeds and, secondly, by giving the most appropriate (i.e. high energy) milk. Some neonatal units now recommend the use of preterm formula (with its higher calorific value) throughout the first year of life to ensure adequate growth. Thus with preterm infants the mother's role in ensuring adequate intake is potentially different to that of the mother of a full-term neonate. Although feeding is still an interactional activity, the mother of a preterm infant may need to take a more dominant role if adequate growth is to be achieved.

There are several factors that have been shown to contribute to poor early feeding in infants born preterm. One of these is medical complications associated with prematurity, for example broncho-pulmonary dysplasia (BPD - chronic lung damage) which results in difficulty co-ordinating the breathing with the sucking and swallowing, and also causes the infant to tire quickly (Singer et al, 1992); gastro-oesophageal reflux (when the valve at the top of the stomach is inadequate, permitting stomach contents to return to the oesophagus causing vomiting and oesophagitis) (Borowitz, 1997); and oral-tactile hypersensitivity (due to oral intubation for the purpose of mechanical ventilation) resulting in aversive conditioning (Wolf & Glass, 1992). Blaymore Bier et al (1993) compared the oral motor development of low birth weight infants intubated for (a) more than one week or (b) less than one week with (c) full-term controls. They reported that the best predictor of sucking ability at term was the number of days of oxygen use; the best predictor of sucking ability at 3 months corrected age was the number of days of oro-tracheal intubation. The authors did find, however, that the infants in group (a) showed significant improvement between the term and 3-month assessments and suggested that this might be due to various factors including improvement in chronic illness, practice at sucking and neurological plasticity. At term the poorer feeding skills associated with prolonged oxygen therapy (and later introduction of oral feeds) might have reflected lack of sucking practice, whereas poorer feeding at 3 months was more likely to be due to medical or neurological involvement.

There continues to be a higher than normal prevalence of feeding problems in infants and children who were born preterm, beyond the first few months of age. Douglas el al (1996), describing a feeding clinic at a large children's hospital, reported that 22% of the children referred to the clinic had been born preterm, with 33% weighing less than 2500g at birth (n.b. these low birth weight infants only account for 7% of births in the UK).

Because one of the main aims of the present study is to establish whether there is a causal link between early growth rate and later developmental outcome, it is essential to examine early factors that might reveal an underlying problem (e.g. neurological damage) that might actually be the cause of both observed growth faltering and developmental delay. As the foregoing sub-section highlights, abnormal infant feeding behaviours may be an early indicator of such an underlying neurological problem and is therefore an important factor to take into account.

2.2. Infant Temperament

In attempting to explore factors relating to early post-natal growth it is important to consider character traits, since these may influence weight gain. For example, a very active, fretful infant is likely to have greater energy expenditure than a more placid, sleepy infant. Conversely, an infant who sleeps for long periods may "miss" feeds and thereby ingest fewer calories during a given period than an infant who is awake and irritable much of the time. There is some research evidence that infant temperament may influence weight gain. Carey (1985) compared a group of term infants who showed good weight gain with a group who showed poor weight gain, and found that the first group had a much higher proportion of infants rated as "difficult", who cried and fussed significantly more than in the slower growing group of infants. A possible explanation for this effect would be that when an infant cries, a mother is likely to attribute this (rightly or wrongly) to hunger, and will therefore feed it, whereas if a baby is contented, she is likely to delay feeding it until either it begins to cry or she considers that it *should* be hungry. If there is indeed an association between being "difficult" and showing particularly good weight gain, then it could be speculated that being irritable might be an adaptive, positive characteristic among very preterm infants, leading to better growth during the first year of life.

2.2.1. Definition of Temperament

Infant temperament has been described as "the set of characteristic individual differences in the intensive and temporal parameters of behavioural expression of affect-related states" (Goldsmith & Campos, 1982). In other words, the term describes the latency and the strength of the infant's expression of its emotions.

2.2.2. Factors Related to Infant Temperament

The origins of infant temperament have been the subject of much research over the past few decades. Many years ago there were two opposing views. The first was that the young child was simply at the mercy of his environment, and could be passively moulded by experiences whether good or bad, (e.g. Watson, 1928). The second viewpoint was that the personality was fixed at birth and would develop independently of outside influences (e.g. Gesell, 1928). It is now generally accepted, however, that there is an interaction between biological (genetic) and environmental factors although, even at birth, there are clear individual differences in patterns of behaviour. Research has been published that suggests that a variety of factors may contribute to early infant temperament, including genetic make-up (Buss & Plomin, 1975); prolonged periods of stress in a NICU for sick or preterm infants (Bates, 1980); cognitive abilities (Goldsmith & Campos, 1982); and environmental experiences "that do not support behavioural organisation" (Gorski, Davison & Brazelton, 1979). The suggestion is that interaction between these factors will influence an infant's behavioural style, although this behavioural style can change as the infant matures and is influenced by his/her environment (Thomas & Chess, 1977).

2.2.3. Methods of Assessing Infant Temperament

The instrument selected to measure temperament depends, of course, on the age at which the assessment is taking place. The revised Neonatal Behavioral Assessment Scale (Brazelton, 1995) is an examiner-rated instrument that has been used in several studies of infant behaviour for assessing infant "irritability" (eg Crockenberg, 1981; Van den Boom, 1988, 1991, 1995; Keefe, 1998). It can be used from 37-48 weeks post-conceptual age, and includes several elements that can be combined to form the "Irritability" cluster (Kaye, 1978). Many of the other instruments that measure infant temperament rely on parental perceptions rather than being objective measures. One that has been developed for use in the neonatal period is the MABS (Mother and Baby Scales, Wolke & St James-Roberts, 1987), which includes a subscale of "unsettled-irregular" behaviours. Behavioural diaries, in which the mother records the frequency and duration of the infant's fussing and crying behaviour, have also been widely used, as they are inexpensive and enable large numbers of infants to be observed. Correlations between crying behaviour as measured by behavioural diary and by voice activated tape-recording are reportedly high (Barr et al, 1988). Use of behavioural diaries does, however, necessitate high levels of maternal compliance and commitment to the research project. The Crying Pattern Questionnaire (CPQ, St. James-Roberts & Halil, 1991) is a simple device, developed to measure the amount of time that the infant cried during a 24 hour period, with the each day being divided into four 6-hour periods (morning, afternoon, evening and night). This instrument, as with the behavioural diaries, does of course involve high levels of maternal commitment if it is to be accurate.

2.2.4. Differences in Temperament between Term and Preterm Infants

Although the present study is specifically looking at temperament differences within a group of very preterm infants in relation to growth and development, it is interesting to briefly review the research on group differences between these particularly vulnerable infants and infants born at term. There have been a number of studies that compare temperament in infancy between term and preterm infants, which have produced somewhat contradictory findings.

Several studies have found preterm infants to be at a higher risk of being classified as "irritable" or "difficult" than infants born at term. Medoff-Cooper (1982) in a small study of 26 very low birth weight infants, followed up at 8 months of age using the Infant Temperament Questionnaire, showed that as a group they were significantly more difficult than term infants. A further study by Medoff-Cooper (1986) again compared the temperaments of very low birth weight infants (n=41) to those of term infants at 6 months (using the ITQ) and 12 months (using the TTQ) corrected age. At 6 months of age there were significantly more "difficult" infants, and fewer "easy" infants, in the preterm group. The preterm group were significantly less adaptable and more intense than the term group but, interestingly, there did not appear to be a relationship between severity of neonatal illness and "difficultness". By 12 months the number of infants rated as "difficult" overall had decreased from thirteen to just seven, but as a group the preterm infants were significantly less "persistent" than the term group. The correlation coefficients between the ITQ and the TTQ varied from .03 to .49, indicating that overall there was poor stability across the nine temperament dimensions measured using these instruments between the ages of 6 and 12 months. The authors suggested that this finding might be due to each of the temperament dimensions being influenced by differing combinations of medical, biological, social and environmental factors. Thus those dimensions that were most strongly influenced by early perinatal experience could be expected to change the most, since this influence should diminish over time. Washington (1986) followed up 74 preterm infants at 3, 6 and 12 months of age, using the revised ITQ at 3 and 6 months, and the Toddler Temperament Scale (Fullard et al, 1984) at 12 months. In comparison with normative data (Carey & McDevitt, 1978), a significantly higher proportion of infants were rated as difficult at 6 months of age, but, as in the Medoff-Cooper study (1986) this difference was less pronounced by 12 months of age. Again no relationship was found between "difficultness" and degree of prematurity or severity of medical problems. The only significant factor was mode of delivery (infants delivered by caesarian section were rated as more irritable at 3 months of age), although this effect had gone by 6 months corrected age. A more recent study by Case-Smith (1998) compared 45 preterm and 22 term infants and again showed a significantly higher proportion of preterm infants being categorised as "difficult".

Although the Medoff-Cooper and Washington studies described above did not find a relationship between severity of early medical condition and "difficultness", other research has found such a link. A study by Spungen (1986) compared 3 groups: 44 high-risk preterm infants (who had been mechanically ventilated), 24 low-risk preterms (who only had minor problems associated with prematurity) and 24 term infants. Again the Infant Temperament Questionnaire was used, completed by the mothers at 6 months corrected age. There was a significant difference between the proportion of high-risk infants described as difficult compared to the other two groups (21% versus 0% of low risk preterms, and 4% of term infants). The differences were on the subscales of mood, adaptability, persistence and distractibility, although these differences disappeared when duration of hospitalisation was taken into account.

However, not all the research evidence points to significant differences between rates of "difficult" temperaments in preterm and term infants. In Australia, Oberklaid (1985) compared 110 preterm and 240 term infants at 4-8 months of age, using the ITQ. They found no differences between the two groups on proportions of "easy", "difficult" and "slow to warm up" infants. Even when infants born before 33 weeks gestation were analysed separately, they still failed to find any significant differences. The authors did acknowledge, however, in a subsequent paper (Oberklaid et al, 1986) that the preterm infants used in the study had not been unduly sick neonatally, and acknowledged that the results could not necessarily be generalised to all preterm infants. Interestngly a follow-up report (Oberklaid et al, 1991), analysing the subjects' temperaments as toddlers, discovered that those born preterm were actually significantly more likely to be categorised as "easy" and significantly less likely to be rated "difficult". Ross (1987) assessed 98 preterm and 89 term infants at 12 months corrected age using the Toddler Temperament Scale. No differences were discovered on overall temperament types, or any of the nine separate dimensions assessed, although she did note that degree of Respiratory Distress Syndrome (RDS, i.e. severity of lung damage) was significantly correlated with scores on some of the temperament dimensions. A study by Hertzig (1982), found that although preterms were not more difficult than their term peers on overall temperament at 12 months corrected age, they did appear to be less adaptable, less distractible, more intense and had a higher threshold to sensory stimuli. In addition, infants with diagnosed central nervous system (CNS) disorders were significantly more likely to be classified as "difficult" than other preterms. Similarly Hermanns (1981) found that at 2-4 years of age preterms were not more likely to be "difficult" overall, but did show significantly higher levels of activity and intensity, were more persistent and distractible, and had a lower threshold to sensory stimuli. Finally, a study by Riese (1988) followed up 109 term and 81 preterm infants at 6, 9, 12, 18 and 24 months of age. At each time point the subjects were assessed on emotional tone, attentiveness, activity and orientation to staff. Generally there were no significant differences between the two groups at any age, except that at 6 months the preterms were rated as less positive towards staff than the term infants. Interestingly, at 12 months of age the term infants were rated as more upset and less attentive to stimuli in the laboratory than the preterm infants, and became upset when their mothers left the room. However, this reaction to the disappearance of the mother did not appear in the preterm infants until the 18-month assessment. Another interesting point was that the term infants showed a significant stability in temperament across consecutive age groups, whereas with the preterm infants the stability from age to age was not observed as early, or as consistently, as for the term infants. When the pre-term group was split into infants born before and after 35 weeks gestation, the more mature sub-group performed more like the term group.

In summary, then, there appears to be continuing controversy about the relative prevalence of "difficult" temperament among infants born preterm and term. This may, in part, be due to differences in degree of prematurity/sickness of the infants assessed, the ages at which they were assessed, and what temperament dimensions are actually being assessed. More studies found differences on specific dimensions than in global temperament type (differences in adaptability, rhythmicity, activity, attention, persistence and soothability being the most common findings). There is some evidence to suggest that it is the sicker preterm infants (who were mechanically ventilated and/or were hospitalised for prolonged periods) who contribute most to the increased incidence of "difficultness" found in some studies. In addition, it would appear that preterm infants tend to be less stable temperamentally, at least in the first years of life, than their term peers. This would be logical if the "difficult" temperament were due to adverse early medical/environmental factors rather than innate genetic predisposition, since over time the influence of the neonatal experiences might recede. Previous research would therefore suggest that, within a group of very preterm infants, excessive irritability might be associated with severity of neonatal illness (and therefore perhaps with poorer outcome due to neurological damage), but also that irritability might not be a stable character trait over the first few months of life. These issues are addressed in the present study in order to ascertain whether irritability has any direct link with growth and/or developmental, or whether, if a relationship is observed, it is simply due to an underlying factor.

2.2.5. Differences in Temperament between AGA and SGA Infants

There have been fewer studies that have examined temperamental differences between infants born at a size appropriate for gestational age (AGA) and those born small for gestational age (SGA). This may be due partly to the issue of sample size, since particularly among term infants only a small proportion are born SGA, and in studies that are examining differences between both term and preterm infants, subdividing these groups into those born AGA and SGA would involve either very small sub-groups or a very large overall sample. Those papers that have been published support the idea that infants born SGA are "easier" than their AGA peers. Riese (1988), as part of a twin study, looked at temperament during the neonatal period. Among the term infants, those born SGA were classified as being less irritable than their AGA peers, although when the preterm infants were included in the analysis there were no differences overall between those born AGA and those born SGA. Newman (1997) also included both term and preterm infants in a study to compare the temperaments of AGA and SGA infants, with the subjects being assessed at 4 months corrected age. There were very few differences temperamentally between SGA and AGA infants (measured using the Short Temperament Scale for Infants – adapted from the ITQ), with the only significant difference being on "co-operation" – the SGA infants were classified as more co-operative. In an observational study of term infants, Parkinson (1986) compared 21 children born SGA with 21 children born AGA, at 5-9 years of age. At the follow-up assessment the children born SGA were rated as quieter, more compliant and less active than the AGA controls, and their play behaviour suggested that they were less advanced developmentally. Watt (1987) performed a three-way comparison, using 10 term AGA infants, 9 term SGA infants, and 13 AGA preterm infants. They were assessed using the Revised ITQ at 6 months corrected age, and the Toddler Temperament Scale at 20 months. Overall, more infants were rated as "difficult" at 6 than 20 months, with very few of the preterm infants being rated as difficult at either time point. At the 6-month assessment a large proportion of the SGA infants were rated as "slow to warm up", but by 20 months none of the SGA group fell into this category. There were no group differences at either age on total temperament scores. The preterm infants showed no consistency on any of the 9 temperament dimensions between the two time points, but for the other groups there was consistency on three (SGA) or five (AGA) dimensions.

None of the foregoing studies were specifically of very preterm infants, and therefore the question of whether, within a very preterm (and therefore already high risk) sample, being born SGA makes an infant more or less likely to be classified as irritable or difficult remains unanswered.

2.2.6. Differences in Temperament between Breast- and Bottle-fed Infants

It has been suggested that there are behavioural differences between breast- and bottle-fed babies in terms of crying levels in the early weeks of life. In a recent study of 97 babies who were either breast or formula fed, mothers completed 3-day behavioural diaries at 2 and 6 weeks of age. Total duration of overall crying increased over the 4-week period between the diaries in breast fed babies, but decreased in the formula fed group. At 6 weeks of age the breastfed babies cried on average 40 minutes more, and slept nearly 80 minutes less, per day than the formula fed group (Lucas, 1998). The difference in crying levels between breast-fed and formula-fed infants is therefore an important factor to take into account when examining the relationship between temperament and growth and/or development. This issue is particularly relevant because of the fact that type of feeding may also be related directly to growth rate (and, indeed, developmental outcome) and therefore ascertaining the specific effects of temperament on the outcome measures will necessitate the analysis of potential co-variates.

2.3. Summary of Chapter

There is research evidence that abnormal oral-motor function can adversely effect infant growth rates and contribute to the incidence of failure to thrive. Infants born very preterm are at particular risk of abnormal oral-motor function and may exhibit either disorganised (i.e. immature) or dysfunctional feeding patterns, with the former being temporary and more likely to improve significantly as the infant matures. There are several ways of studying infant feeding technique, but not many of these are both objective and appropriate both for infants who are being bottle-fed and those being breast-fed.

Feeding is an interactional activity between the mother and the infant. In healthy term infants, who are fed on demand, the infant can control the daily intake according to the nutritional value of the milk being received. Among those infants born very preterm, however, the issue of physical frailty may be critical, with some immature or weak infants ceasing to feed not due to satiety, but due to exhaustion. The mother's role in the feeding activity may therefore be particularly important in the case of these at-risk infants. In view of the foregoing, a study investigating the contribution of early factors to rate of growth during the first few months of life needs to consider both the objective measurement of the infant's oral-motor function, and also the effect of maternal compensatory behaviours, for example, the regular waking of infants for feeds.

The relationship, if any, between temperament and preterm birth remains unclear. There is some suggestion that the degree of prematurity (i.e. the gestational age at birth), and the severity of early neonatal illness may be contributory factors to levels of "irritability" or "difficultness". Once again, one of the main difficulties in interpreting the available publications is the diversity of the samples examined. Some are preterm, but include the higher gestation and therefore lower risk infants, which may dilute the effects of prematurity on temperament. Furthermore, the instruments used to measure "temperament" vary between studies, and therefore may actually be measuring different traits.

There is no research evidence currently available that reports on whether or not there are temperamental differences, among very preterm infants, between those who were born SGA and those born AGA. It has been suggested that, at least among term infants, being more "irritable" may lead to more rapid growth. If this were also true for very preterm infants then irritability could be viewed as a positive, adaptive attribute, facilitating catch-up growth among these at-risk infants. Conversely, if there is a link in very preterm infants between severity of early illness and irritability levels, then the more irritable infants might also be at a higher risk of oral-motor problems, which could negate the potential growth benefits. Many possible factors that may influence early growth and subsequent development are likely to be inter-related (for example crying levels and type of feeding; crying levels and severity of neonatal illness). Clearly the issue is a very complex one, and the specific contribution of early temperamental factors to the observed rate of growth among a sample of very preterm infants needs to be addressed.

Chapter 3: Aims of the Present Study

3.0 Introduction

In this third and final chapter of Section I the shortcomings of previous studies and the current gaps in knowledge regarding the individual differences in growth rates among very preterm infants are highlighted. Subsequently the Aims of the Study, in terms of the major research questions to be addressed, are described.

3.1. Overview of Previous Research

Research to date suggests that the early experiences of very preterm infants and their mothers differ in many respects from those of healthy term infants. The very preterm infant may have endured weeks of treatment in the neonatal unit for a variety of problems attributable to its precipitate birth. Unfortunately, a proportion of these infants will go on to suffer from chronic problems, in some or all of the spheres of cognitive function, motor performance, social and behavioural function or general health. Many factors, including gender, gestation at birth and birth weight, will have a major influence on neonatal and later progress. Very preterm infants have specific nutritional needs over and above those of healthy, term neonates. This is due, in part, to them not remaining in utero during the final months of pregnancy, during which time stores of certain vital substances are normally laid down in the body, and fine-tuning of systems (e.g. vision) takes place. Infants born very preterm have a high incidence of oral-motor problems both in the early months of life, and in the longer term, due in part to medical interventions resulting from their prematurity (e.g. oro-tracheal intubation to facilitate mechanical ventilation). There is some research evidence that abnormal oral-motor function may adversely affect growth rates, and it might also be associated with developmental outcome since abnormal oral-motor function has been linked to severity of early neonatal illness. There are conflicting reports regarding the proportion of very preterm infants who are classified as "irritable" or "difficult" by their mothers in comparison with term infants. It is possible that a higher level of irritability is an adaptive trait for these infants, as there is some research evidence (from term infants) that those who are more irritable are likely to grow better than their more placid peers. Conversely, it is possible that excessively irritable infants may be that way because they have experienced a more difficult neonatal course, including neurological damage, which could result in poorer growth and/or developmental outcome.

3.2. Limitations of Previous Research

There are several major shortcomings that are evident among studies that have been reported to date. Firstly many studies report on the differences between term and preterm, or very preterm, infants (i.e. between group differences), and of course in most respects there are significant group differences. However, there has generally been much less research into within-group differences among a sample that is solely comprised of very preterm infants. The present study is specifically examining such within-group differences whilst investigating the mechanisms of early growth and later developmental outcome.

Secondly, many studies are retrospective in design and investigate the origins of problems that are discovered at a later stage. This can create difficulties both of lack of detailed information on the period prior to identification, and also distortion of the overall picture.

Thirdly, as the foregoing chapters have made clear, there are many diverse factors that appear to be implicated in the observed variance in early growth rates and/or developmental outcome among very preterm infants. However, most of the research studies that have been cited in the preceding chapters report on only one or two of these factors (e.g. oral-motor function, or severity of neonatal illness). Furthermore, much of the evidence is contradictory, possibly due to the fact that other confounding factors were not taken into consideration.

Finally, many studies either have a very small sample size, which presents difficulties in terms of statistical power, or include larger, more mature infants who by definition are likely to be lower-risk and will therefore dilute the observed effects.

The intention of the present study was to address, insofar as is possible, these design shortcomings and thereby to prospectively and comprehensively examine the relative contribution of all of the factors implicated in previous research both to early growth rate, and to later developmental outcome. As has already been discussed, the long-term developmental outcome for very preterm infants is extremely variable and, except in cases where there is obvious major neurological damage, it is difficult to make early predictions with any accuracy. However, the ability to predict, at an early stage, which infants were at particular risk of suffering from such delays would be of both clinical and practical value in terms of resource planning.

3.3. Aims of the Present Study

The aims of this thesis are to address two major research questions:

Research Question 1: What is the relative extent to which various medical, nutritional, infant behavioural and maternal factors predict early growth rates (i.e. between birth and 3-months corrected age) in a sample of very preterm infants.

The relationship between early growth and a variety of antecedent factors that fall into each of these categories will be explored, in order to establish their relative association with growth in the first few months of life. An attempt will be made to develop prediction models.

Research Question 2: Within this very pre-term sample, what is the extent to which early post-natal growth and/or weight status at specific time points predict developmental status at 18 months corrected age.

In addition to these weight variables, early infant, maternal and medical factors will also be analysed in relation to developmental status at 18 months of age. Most importantly, the relationship between early growth and developmental status will be examined.

SECTION II. METHOD

Introduction to Section II

This Method Section is divided into three chapters. In the first chapter there is background information about the setting up of the GAIN Study, the recruitment procedures and sample characteristics. There are then two chapters describing the instruments used at the various assessment points. The first of these relates to the three early assessments (i.e. pre-discharge, term and 3-months) and the second one relates to the 18-month assessment. Some of the procedures/instruments were administered at more than one assessment point. In these cases a full description is given in the sub-section covering the first instance of that procedure being used, and is only mentioned briefly in the subsequent sub-section.

Chapter 4: The GAIN Study

4.1. Study Design

The mothers and infants were seen at four separate time points: pre-discharge (from hospital); at or around term (i.e. due date of delivery); at 3 months corrected age; and at 18 months corrected age. See table 3 for details.

Table 3: Assessment Time Points

Assessment Point	Location	Time-point Criteria	Infant age Mean (SD)	Infant age Min-Max
Pre-discharge (T1)	In Hospital	When infant in stable medical condition, about 2 weeks before discharge home	35.6 (2.0)	32.0 - 39.6 (post-conceptual weeks)
At term (T2)	Home (89%) Hospital (11%)	As near to term as possible, but no later than 44 wks	41.1 (1.2)	38.6 – 44.0 (p-c weeks)
At 3 mths corrected age (T3)	At home	As near to 3 months (52.6 wks post-conceptual age) as possible	53.7 (1.6)	50.4 – 58.0 (p-c weeks)
At 18 mths corrected age (T4)	At University/ Child Dev Unit	As near to 18 months corrected age as possible	1.59 (.10) yrs	1.35 – 2.00 years

Assessment T2 (term) was conducted in the family home, except in cases when the infant was still hospitalised. Assessment T4 was conducted in special observation laboratories either at the University of Hertfordshire, Hatfield Campus, or at the SPS Department, University of Cambridge.

All assessments were designed to take a maximum of 2-3 hours to complete, in order to avoid being too taxing for either the infants or the mothers.

4.2. Procedure

4.2.1. Identification of suitable Neonatal Intensive Care Units (NICUs)

The GAIN study was based at the University of Hertfordshire's Hatfield campus, and the selected NICU's needed to be within practical travelling distance of the campus. The most suitable Units were consequently identified as: Rosie Maternity (Cambridge), QEII (Welwyn Garden City, Herts), and Luton & Dunstable (Luton, Beds). These are Units that retain infants from the lowest gestation (rather than transferring them out to larger Units), and are in fact referral Units for other smaller Special Care Baby Units.

4.2.2. Consultant and Ethical Approval

Ethical approval for the GAIN Study was granted by the Ethics Committee of the Psychology Department at the University of Hertfordshire (PSY9627, 12 June 1998). Consultant Neonatologist and NICU Nursing Manager consent was obtained at each hospital, and subsequently ethical approval from the three relevant NHS Trusts was obtained (Addenbrooke's Hospital, 15 August 1997, LREC97/212; Luton & Dunstable Hospital, 30 January 1998; and Queen Elizabeth II Hospital, 21 November 1997, JCA/11.97). Honorary contracts were then obtained from all three Trusts for both of the researchers, in order to gain access to the neonatal intensive care wards and to view maternal and neonatal records.

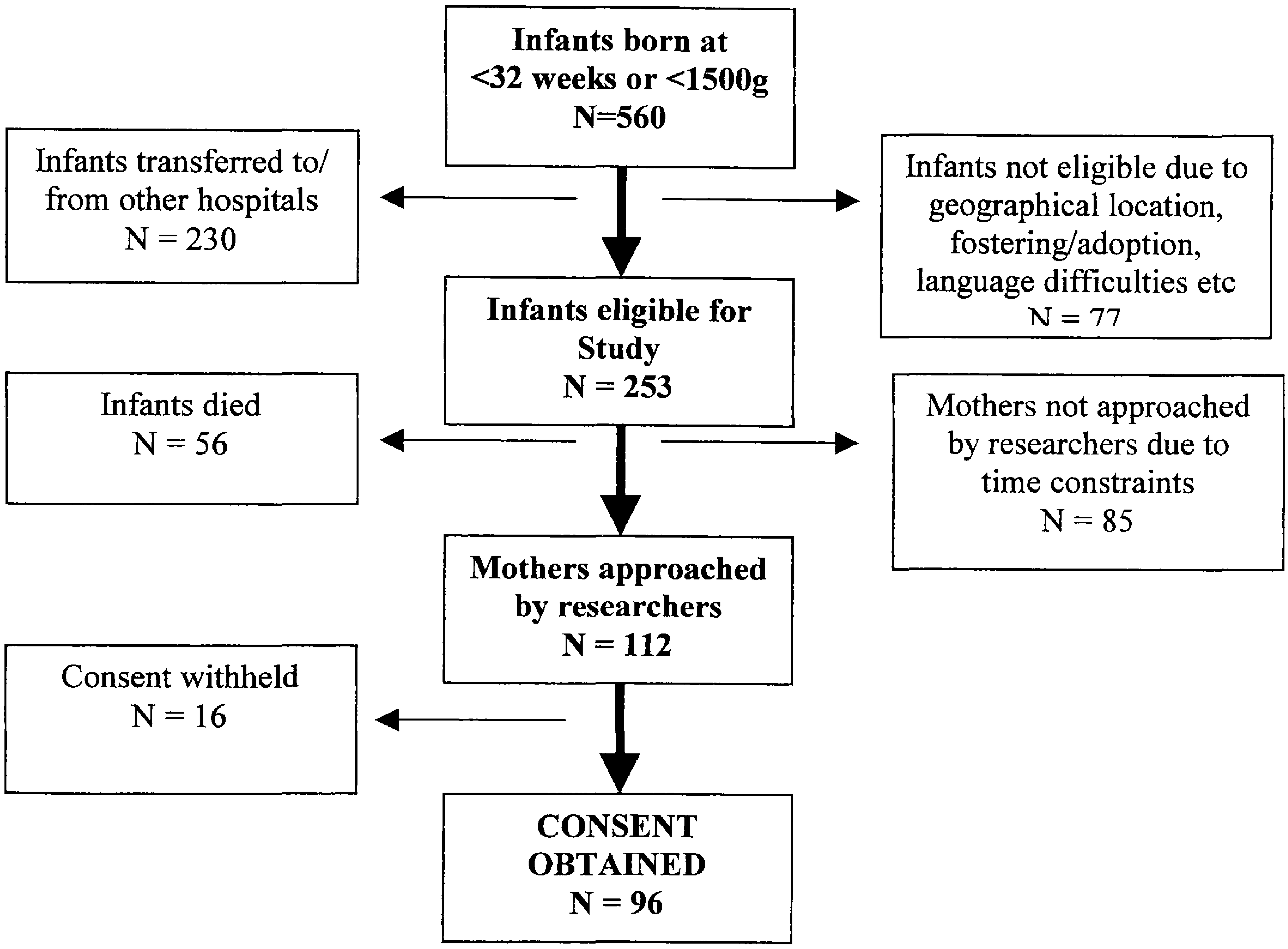
4.2.3. Selection Criteria

The principal selection criterion for entry into the Study was that the infants had to have been born at or before 32 completed weeks of gestation, or weighing less than 1500g, at one of the three participating hospitals in the South East of England. There were, however, certain exclusion criteria:

- If the infant was transferred into or out of the participating Unit after birth and prior to discharge home (medical notes remain at hospital of origin, and would therefore not be available);
- If the parental home was more than 2 hours drive from the hospital (impracticality of follow-up assessments);

- If the infant's mother only had limited English (interviews would have been difficult);
- If the infant was being sent for fostering/adoption.

Figure 1: Recruitment Procedure



As the flow chart above shows, after excluding infants on the basis of the stated exclusion criteria there were 253 potential participants for the Study. Unfortunately, 56 of these infants died within the first few weeks after birth. In addition, due to time constraints, a maximum of just six infants per month could be recruited (based on due date of delivery). Thus there were 112 infants eligible to be recruited into the Study.

The two researchers each recruited and followed up approximately half of the final sample up to, and including, the 3-month assessment. A team of researchers followed up the infants at 18 months. Designation of a particular researcher to each hospital simplified recruitment procedures and also facilitated good relationships with the hospital staff.

4.2.4. Recruitment Procedure

Once a target infant's condition had stabilised and he/she no longer required mechanical ventilation, the researcher introduced herself to the mother and explained the aims of the Study and what participation would involve should she agree to the inclusion of her infant. An information sheet was also given to her at this time. A few days later, the mother was approached and asked whether she had had a chance to read the information sheet, had any questions about it, and was prepared to participate. If she agreed, written consent was obtained in the presence of an independent witness, and the infant was thus recruited into the study. Copies of the GAIN Study information sheet and consent form can be found in Appendices 1 and 2.

4.2.5. Consent Rate

The final consent rate was 86% (96 out of 112). Sixteen mothers declined to take part in the study: two cited cultural/religious objections to the research; six cited lack of willingness to put themselves or their infants through any more stress; four felt that they could not afford the time due to demands of older children and/or work commitments; and three did not wish to be involved in research due to dissatisfaction with the hospital care. One mother refused to participate because her infant was suspected of having serious brain damage.

The infants who were eligible to participate in the study but for whom maternal consent was not obtained did not differ from the study sample as regards gestational age or birth weight (see table 4). Of the 96 infants actually recruited into the study, five were lost prior to the term assessment (in four cases they were not possible to contact and/or repeatedly failed to attend appointments, in the fifth case the mother developed a psychiatric illness and the infant was temporarily fostered before the father became the primary care-giver). One infant unfortunately died before the 3-month assessment. Thus the final sample of the GAIN Study (birth – 3 months corrected age) comprised 90 infants out of the 270 who were born eligible for inclusion.

Of these 90 infants, 81 were followed up at 18 months corrected age. Of the nine who were lost to follow-up, the reasons were loss of contact due to moving home; declining to participate in a further assessment; and in two cases agreeing to participate but failing to keep appointments. Table 4 also shows the mean gestational age and birth weight of the drop-outs between 3 and 18 months.

Table 4: Comparison of Final Samples with Non-Consents/Drop-outs

	N	Gestation (wks)	t	Birth weight (g)	t
Non-consents	16	29.6	.43	1287	.27
Sample	96	29.7		1282	
Drop-outs	6	29.2	1.03	1249	.50
Sample (birth-3m)	90	29.4		1266	
Drop-outs	9	28.9	.90	1120	1.47
Sample (3-18m)	81	29.4		1283	

4.3. Sample Characteristics

As can be seen from Table 5, the birth-3 month sample had a mean gestational age of 29.4 weeks, a mean birth weight of 1271g and an average hospitalisation of 56 days. Thus the sample can be classified as being born at moderate to high risk (e.g. Landry et al, 1990). The inclusion criteria was for infants <32 weeks or <1500g, and consequently there were some small-for-gestation infants of more than 32 weeks, and some large-for-gestation infants of <32 weeks, but who weighed >1500g. The study exclusion criteria did not include severity of early illness, or suspected long-term sequelae and, as is shown in the Table, some of the subjects were hospitalised for extremely long periods.

Maternal characteristics were well distributed within the sample, with 50% of infants being firstborns, and a wide range of both maternal age and SES. 90% of the mothers were in stable relationships, either married or co-habiting with the infant's father. Maternal IQ, which was measured at the third assessment (T3), ranged from 68-150, with a mean of 99.2 and a standard deviation of 16.4.

Table 5: Sample Characteristics

INFANT CHARACTERISTICS	N = 90
Sex	
Female	37 (41%)
Male	53 (59%)
Multiple Birth	
Singleton	64 (71%)
Twin / Triplet	26 (29%)
Gestation (completed weeks)	
Mean (SD)	29.4 (1.8)
Range	24-33
Birth Weight (grams)	
Mean (SD)	1271 (327)
Range	521-2158
Hospitalisation (days)	
Mean (SD)	55.9 (26.2)
Range	15 - 166
MATERNAL CHARACTERISTICS	
Maternal age (years)	
Mean (SD)	30.4 (5.7)
Range	17 - 43
Parity	
Primiparous	45 (50%)
Marital Status	
Married/co-habiting	81 (90%)
Maternal SES*	
Mean (SD)	56.3 (8.9)
Range	36 - 72
Maternal IQ	
Mean (SD)	99.2 (16.4)
Range	68 - 150

* Osborn Index (1987)

Further analyses showed that there were no significant gender differences with regard to birth weight, gestation or SGA status (see Table 6).

Table 6: Gender Differences in Relation to Birth Data

Birth Variable	**Male (n=53)** Mean (Std Dev)	**Female (n=37)** Mean (Std Dev)	**Statistical Test**	**p**
Birth Weight (g)	1291 (343)	1243 (304)	t =.69	.50
Gestational Age (wks)	29.4 (1.6)	29.3 (2.0)	t = .29	.77
SGA status	26.4%	22.0%	Chi-Sq = .27	.63

4.1.4.2. Assessment Procedures

The majority of the assessment instruments used in the study were developed and standardised in previous studies, and were used in their original state. Other instruments were developed and piloted specifically for this study. The assessment procedures are outlined in detail below, in chronological order according to the time-point at which they were used and the order in which they were usually administered.

Chapter 5: Birth – 3-Month Assessment Procedures

5.1. Pre-discharge Assessment

This sub-section describes the instruments used at the first (pre-discharge) assessment point. The purpose of this assessment was to provide base-line information on the subjects, i.e. their birth data (gestation, weight etc), the extent of early medical complications, and their socio-economic background. These were all independent factors that were analysed in relation to post-natal growth rate and later developmental status. Unlike the later assessments, the various components of this first assessment were completed at different times, for example, the Intensity of Care summary sheets could not be finalised until the infant had been discharged. Information required was either supplied by the mothers (in the case of socio-demographic data) or from the medical records. It should be noted that the infants themselves were not examined/assessed at this time-point.

In Table 7 the first column shows the type of information obtained, and the second column indicates the actual assessment instrument used to access that information.

Table 7: Assessment T1 (Pre-Discharge) Components

Information Obtained	Instruments Used
Anthropometric data	Baseline measures (obtained from neonatal medical notes)
Medical Risk	PABRAS (derived from maternal and infant's medical notes), used to produce Composite Ante-natal and Neonatal Risk Scores, and also scoring for ultrasound brain scans
Respiratory and Nutritional support during hospitalisation	Intensity of Care records (derived from infant's medical and nursing notes)
Socio-demographic information	Osborn Index (Osborn, 1987)

5.1.1. Anthropometric Measures

Anthropometric measurements were taken at each of the later assessment points, by the Gain Study researchers. These were needed to ascertain the rate of growth between time-points, one of the two principal outcome measures examined in this thesis.

5.1.1.1. Actual Birth Weight

At birth all pre-term infants are weighed routinely in order to calculate their fluid, nutritional and drug dose requirements and to monitor subsequent fluctuations in weight. This information is always recorded in the infants' medical records, and was obtained from that source for the purposes of this thesis, in order to establish baseline measures.

Although with term infants head circumference at birth is also routinely recorded, this measurement was not available on many of the infants in the study because they were too sick at the time of birth. In addition, body length is no longer routinely recorded in hospital due to the recognised unreliability of the measurement. Consequently only birth weight was available for the purposes of this thesis. Table 8 gives the descriptive statistics for birth weight, and further analysis showed that the values were fairly normally distributed and that there were no outliers.

Table 8: Descriptive Statistics of Birth Weight (N = 90)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Birth weight (g)	1271.3	327.2	521 – 2158	.08	-.24

5.1.1.2. Z-Score Values of Birth Weight

Although Table 8 above gives the descriptive statistics for actual birth weights, which are of some interest, they do not take into account the gestation of the individual infants. The infants were not all born at the same gestation and, due to the nature of the study, were not re-assessed at exactly the same ages. It was therefore necessary to standardise the anthropometric measurements in some way to take these anomalies into account. This was done using the British 1990 growth reference for height, weight, BMI and head circumference (software version available from the Child Growth Foundation), which provides data for infants from 24 completed-weeks gestational age. Using this database z-scores for all the anthropometric data obtained at each assessment point were calculated, providing an accurate weight-for-age (or height/head circumference-for-age) score. An average z-score would be 0, with infants who were small for age getting a minus score, and those who were above average for age getting a positive score. The z-score measures were used in all the analyses presented in the results sections.

Z-score values were calculated for the birth weights of all the 90 infants in the study, and the descriptive data is shown in Table 9. Again, further analysis of the scores confirmed that the values were fairly normally distributed, and that there were no outliers.

Table 9: Descriptive Statistics of Birth Weight Z-Scores (N = 90)

Variable	**Mean**	**Std Dev**	**Min-Max**	**Skewness**	**Kurtosis**
Birth weight Z-score	-.37	1.14	-2.54 – 2.04	.16	-.79

5.1.1.3. Weight Status Cut-off Criterion

For some of the analyses performed, it was necessary to categorise the subjects as "small-for-gestational age" (or at later assessment points "small-for-age"). The decision was made to use the 10^{th} percentile of the z-score measures as the cut-off criterion (i.e. 1.28 standard deviation below the mean). Using this criterion, 22 (24.4%) of the infants in the study were classified as small for gestational age (SGA), with the remaining 68 being AGA (weight appropriate for gestational age).

As mentioned in Section I, there is a difference between infants who are small-for-gestation and those who are "growth-retarded" - the terms are not actually synonymous since the classification of small-for-gestation will include both infants who have suffered from intrauterine growth retardation, and also those who genetically are predestined to be at the lower end of the weight spectrum due to parental size. However, this is less of an issue for infants born very preterm, since most of the variance in growth rate due to genetic factors occurs during the final trimester of the pregnancy. Distinction was not made in this study between these sub-groups of small-for-gestation infants, although in some of the analyses parental height was taken into account.

5.1.2. Medical Risk –PABRAS

5.1.2.1. Maternal Obstetric Notes

The mother's obstetric notes were reviewed to obtain detailed information, both about previous pregnancies and their outcomes, and details of this latest pregnancy and birth i.e. chronic/acute maternal disease; antenatal complications; reason for preterm birth; gestation at birth (and whether based on ultrasound scan or calculated by dates); type of delivery etc. The information was recorded in the first section of a document (PABRAS) adapted from Riegel et al (1995), and was subsequently used to compute the composite antenatal-risk score (see Section 5.1.2.3. below).

5.1.2.2. Infant Medical Notes

The infant's medical notes were reviewed in order to obtain detailed information, first about the birth, any resuscitation required and anthropometric measurements, but also about routine management, any medical complications (e.g. infections) which arose and all subsequent diagnostic tests and care (eg ultrasound brain scans, medications, surgery etc). This information was recorded in the second section of the PABRAS document, and was used to compute the composite neonatal risk score.

5.1.2.3. Composite Risk Scores

A Medical Risk Index was computed from information recorded on the PABRAS forms, based on that used in the Bavarian Longitudinal Study, with additional input from Consultant Paediatricians acting as advisors to the present study. It comprised 20 ante-natal, and 20 peri/neonatal items. The ante-natal items were risk factors for preterm birth, and possible later sequelae, and the peri/neonatal items were risk factors for both short and longer-term progress. Each of the 20 items within the composite was scored 0 or 1, giving a maximum score of 20 (with high scores denoting high risk) (see Table 10).

Table 10: Antenatal and Peri/Neonatal Risk Factors

Antenatal	**Perinatal/Neonatal**
Maternal age <20/>30	Emergency c/section/instrumental delivery
Infertility treatment	Opiates
Previous Terminations (>1)	Epidural/spinal
Previous miscarriage (>1)	General Anaesthetic
Previous preterm birth	Resuscitation (> bag & mask)
Severe chronic illness	Ventilation
Parity 0/>2	Oxygen for > 28 days (BPD)
Pre-eclampsia	Respiratory Distress Syndrome/ Hyaline Membrane Disease
Urinary tract infection	Pulmonary interstitial emphysema (PIE)
Other acute infections in pregnancy	Hypoglycaemia (<2.5 mmol)
Multiple pregnancy	Platelets < 100
Smoker	Blood transfusions > 1
Drug abuse	Major infection (eg septacaemia/ necrotising enterocolitis (NEC))
Antenatal hospitalisation (> 1 day)	Surgery
Polyhydramnios/oligohydramnios	Seizures
PROM (> 24 hours prior to delivery)	Ultrasound scans: Cerebral cysts
Placenta praevia/abruption/infarction	Ultrasound scans: Ventricular dilation
Intrauterine growth retardation	Ultrasound scans: Haemorrhage
Corticosteroids 0/<24 hours pre-delivery	Phototherapy
Fetal distress	Oxygen > 50% after day 1

The descriptive statistics for the two composite risk variables are given in Table 11. Both variables were fairly normally distributed and, not surprisingly, they were quite highly inter-correlated (r=.35, p < .01).

Table 11: Composite Ante-natal and Peri/Neonatal Risk Scores (N = 90)

Variable	Mean/Sd	Min- Max	Skewness	Kurtosis
Ante-natal Risk Score	4.40 / 1.77	1 – 8	.21	-.59
Peri/Neonatal Risk Score	6.19 / 2.89	0 – 13	.35	- .49

5.1.2.4. Ultrasound Scans of Brain

Although the results of ultrasound brain scans of the subjects were included in the composite risk variable described above, that was only a very crude measure and, because abnormal brain scans are known to be such important predictors of outcome, it was decided to also examine these variables separately and in more detail. For the majority of infants (83 out of 90) one or more ultrasound scans of the brain were performed during initial hospitalisation. Scans performed during the first week of life were analysed separately from those performed at a later date, on medical advice (Prof N Marlow, UKOS Trial). Some infants had both early and late scans, others just one or the other. Table 12 describes the classification system used to score the scans. For the subsequent analyses, the haemorrhage scores and ventricular size scores were amalgamated into one variable. For example, an infant with an intraventricular haemorrhage and ventricular dilatation of less than 4 mm would have had a combined haemorrhage/ventricular size score of 3.

Table 12: Scoring of Ultrasound Scans of the Neonatal Brain

Score	Haemorrhage	Ventricular Size	Parenchymal Cysts
0	No haemorrhage	No dilatation	No cyst
1	Subependymal/choroidal	< 4mm	Porencephalic cyst
2	Intraventricular	> 4mm	Cystic leucomalacia
3	Parenchymal		

As can be seen in Table 12, the combined haemorrhage/ventricular size variable had a maximum possible score of 5, and the cyst variable a maximum of 2. In addition, a further variable was included which showed whether the abnormalities were unilateral or bilateral (and if unilateral, which side of the brain was affected).

Table 13 shows the frequency data for the variables described above. As can be seen, the majority of infants had no discernable abnormalities on either early or late scans. There were four infants who had no indication of haemorrhage/ventricular dilation on early scan, but had developed such abnormalities by the time the later scan was performed. Of the 25 infants who did not have late scans performed, 5 didn't have early scans either. All those infants whose early scans were scored >1 had repeat scans at a later date. Regarding cyst formation, of the six infants who on late scan had developed cysts four of them had early haemorrhage/ventricular scores >0.

Table 13: Frequency Data on Neonatal Ultrasound Scans of Brain

Variable	Score	Frequency	Percentage
Early scan – Haemorrhage/ ventricular size	0	48	53.3
	1	9	10.0
	2	2	2.2
	3	3	3.3
	4	0	0
	5	0	0
	missing	28	31.1
Early scan – Cysts	0	61	67.8
	1	0	0
	2	1	1.1
	missing	28	31.1
Late scans – Haemorrhage/ ventricular size	0	49	54.4
	1	6	6.7
	2	2	2.2
	3	5	5.6
	4	0	0
	5	0	0
	missing	28	31.1
Late scan – Cysts	0	55	61.1
	1	5	5.6
	2	2	2.2
	missing	28	31.1
Abnormalities :	None	59	65.6
	Left-sided	6	6.7
	Right-sided	9	10.0
	Bilateral	5	5.6
	Missing	11	12.2

For the 36 infants on whom both early and late scans were performed, the correlations between haemorrhage/ventricular size scores on early and late scans was high (r = .66, p < .01), but for the cyst variables there was no correlation (r = -.07), and neither was there a correlation between haemorrhage/ventricular size score during the first week and later cyst score (r = .12).

There were six subjects upon whom ultrasound scan after the first week of life showed evidence of neurological damage.

5.1.2.5. Intensity of Care Summary Sheets

Three forms were used. The first form recorded the level of respiratory support that the infant required on a daily basis from birth until discharge from hospital. There were four possible levels that defined the amount of assistance the infant required, ranging from full mechanical ventilation to independent breathing of air. The second form recorded the level of nutritional support that was required each day, and again there were four possible levels, ranging from intravenous feeding to independent oral feeding. See Table 14 for details of scoring used. These forms were scored using an ordinal scale, that is the score descended with the level of assistance required, but the difference between scoring three and two was not necessarily comparable with the difference between 2 and 1.

Table 14: Intensity of Care Scoring

Level of Assistance Required	Score
Respiratory/breathing	
Full Ventilation (IPPV/HFOV)	3
Assisted Ventilation (CPAP)	2
Supplementary Oxygen	1
Breathing air independently	0
Nutritional/feeding	
Intravenous fluids only (TPN)	3
Combined IV and naso-gastric feeding (TPN/NG)	2
Combined naso-gastric & oral feeding (NG/oral)	1
Independent oral feeding	0

A third scale provided a composite of the other two scales, giving a rating of level of overall care each day, which varied between 0 and 6. This information was subsequently used to compute the following variables:

Duration of Intensive Care

Duration of Intensive Care (DIC) was the number of days during which the infant was receiving intensive care. This variable was computed on the basis that an infant was classified as receiving intensive care if the composite score (ventilation + nutritional support) was greater than or equal to 2. An infant was considered to have reached criterion for no longer receiving intensive care when the composite score was less than 2 for three consecutive days, with the first day of the lower score counting in the total duration of intensive care.

Level of Care over first 10 days

This was calculated by totalling the composite scores recorded on each of the first ten days of life; thus the maximum possible score would be 60 (maximum score each day being 3 for ventilatory support and 3 for nutritional support).

Duration of Specific Support Variables

This was a calculation of the total number of days during which the infant received the specified support (e.g. full mechanical ventilation) for any period during the day. An infant who on a given day was on CPAP for 3 hours, and on supplementary oxygen for the remaining 21 hours, would be designated as receiving CPAP on that day (i.e. the higher level of support).

The descriptive statistics of these Intensity of Care variables are shown in Table 15 below.

Table 15: Descriptive Statistics of Scores on Intensity of Care Variables (N = 90)

Intensity of Care Variable	Mean	Std Dev	Range	Skewness	Kurtosis
Duration of IC	27.8	30.4	2-162	2.1	4.6
Level of Care 1st 10 days (max 60)	36.1	14.4	12-60	0.2	1.3
Days of Hospitalisation	55.9	26.2	15-166	1.4	2.9
Days of Ventilation	3.8	7.4	0-53	4.2	22.4
Days of CPAP	8.3	15.2	0-82	3.1	10.3
Days of TPN	15.2	13.0	0-62	1.9	3.7
Days of naso-gastric feeds	34.8	18.9	7-123	1.5	4.3

As can be seen from the foregoing table, none of the intensity of care variables were normally distributed. Further analyses revealed that in all but one case (Level of Care over first 10 days, which had a maximum score of 60) there were between one and seven outliers.

As shown in Table 16, the inter-correlations between the intensity of care variables were extremely high, all being significant at the $p < .01$ level.

Table 16: Inter-correlations between Intensity of Care Variables

	Duration of Intensive Care	**Level of Care over First 10 days**	**Total days In Hospital**	**Total days of Ventilation**
Duration of Intensive Care	-	-	-	-
Level of Care over 1st 10 days	.83**	-	-	-
Total days in Hospital	.67**	.62**	-	
Total days of Ventilation	.69**	.81**	.62**	-

** Significant at the .01 level

5.1.3. Socio-Demographic Data

Osborn Index (Osborn, 1987)

Description

The Osborn index is an instrument for assessing socio-economic status, developed for use in the Child Health and Education Study (CHES) which followed a birth cohort born in 1970 and comprised approximately 16,000 children.

The Index is comprised of seven items:

- Father's occupation (or mother's occupation if a single parent)
- Highest educational qualification of either parent
- Housing tenure (owned, privately rented, council rented etc)
- Type of accommodation

- Number of persons per room
- Car ownership
- Telephone ownership

For each of the above items the subject is scored according to individual circumstances, and the scores totalled and added to a base of 50, in order that all scores are positive – high scores indicating high socio-economic status.

The Osborn Index has distinct advantages over the OPCS classifications based on father's occupation. Firstly, there is a significant minority of children being brought up in one-parent families, where there is no information available on the father. Secondly, the Osborn Index resolves potential anomalies inherent in the OPCS system. For example, an extremely well-paid, but poorly educated professional footballer, who owned and lived in a large detached house and had all the modern luxuries would, under the social class system, be classified as group III (manual worker), which does not distinguish between this individual and a factory worker living in council accommodation in relatively deprived circumstances.

For the original birth cohort the mean Osborn Index value was 50.0, with a standard deviation of 10.2. The subjects on whom paternal occupation was not available ("no information" group) had the same mean value as SC IV.

Procedure

The seven items that comprise the Osborn Index were incorporated into the initial Parent Interview that was completed pre-term, while the infant was still hospitalised. The questions were repeated in the third Parent Interview, which was completed at T3 (3 month assessment).

Psychometric Evaluation

Data was available on all but one subject. Table 17 shows the descriptive statistics for the Osborn Index scores. As can be seen, the scores were fairly normally distributed, and further analysis revealed no outliers or extreme cases.

Table 17: Descriptive Statistics of the Osborn Index (N = 89)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Osborn Index	56.30	8.89	36 – 72	-.56	-.65

5.2. Term Assessment

5.2.1. Background Information

This section describes the instruments and procedures used in the Term assessment. The order of administration of the various elements of this assessment was flexible, depending primarily on the infant's behavioural state at the time. In the ideal situation, the infant would be asleep initially, but expected to wake within the next hour for a feed. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) would therefore be performed first (which would invariably wake up the infant), followed by the anthropometric measurements and the feeding session, and the Parent Interview could be completed at the end of the visit. If, however, the baby was awake and hungry, the anthropometric measurements would be taken, then the feeding assessment would be done, followed by the maternal interview and other paperwork, with the BNBAS being done at least one hour after the end of the feed.

Table 18: Assessment T2 (Term) Components

Assessment T2	Instruments used
Outcome Measure:	
Growth	**Anthropometric form:** weight, head circumference and length/height
Independent Variables:	
Feeding:	
Nutrition	Feeding Questions in Parent II Interview (derived from Ramsay & Gisel, 1996; Skuse et al, unpublished)
Infant Feeding Technique	**Whitney Strain Gauge** (feeding technique) **Pre- and post-feed weighing** (intake)
Infant Behaviour:	
Sleeping	Sleep questions in Parent II Interview (derived from Seifer, 1992. See also Wolke, 2003)
Crying/irritability	**Crying Patterns Questionnaire** (St.James Roberts & Halil, 1991) **Neonatal Behavioral Assessment Scale** (Brazelton, 1995)

5.2.2. Anthropometric Measurements

A form was designed to record pre- and post-feed weights; body length and head circumference. The equipment used was that recommended by the Child Growth Foundation. The actual measurements on day of examination were recorded for each infant, but these could not be directly compared since infants were of varying post-conceptual ages when the Term assessment was carried out. The measurements were later entered onto a Microsoft Excel spreadsheet and converted into z-scores using the software version of the British 1990 Growth reference database.

5.2.2.1. Weight

Procedure

The infant was undressed, and the nappy changed. The infant was weighed on a set of Soehnle electronic baby scales (accurate to 5 grams), and the weight of a clean nappy deducted from the total weight displayed.

Psychometric Evaluation

As can be seen from Table 19, the term weight z-scores were fairly normally distributed, although further analysis revealed that there were three outliers at the top end of the distribution. The table shows that the mean weight z-score had decreased considerably since birth (when it was -.37), indicating that as a group these infants had not grown well.

Table 19: Descriptive Statistics of Term Weight & Weight z scores (N = 87)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Term weight (g)	3238	577	1961 - 4900	.42	.33
Term weight z-score	-1.06	1.11	-3.65 – 1.70	.11	.20

5.2.2.2. Length

Procedure

Body length was measured using a device marketed by the Child Growth Foundation called the "Pedobaby". This comprised a metal tape measure with vertical struts at each end. The mother held the baby's head against one vertical strut while the investigator fully extended the baby's leg to touch the other, adjustable, end.

Psychometric Evaluation

As can be seen from Table 20, the mean weight at term was approximately one standard deviation below the mean, but with a wide range of scores. The scores were fairly normally distributed, although there were two outliers, one at the top end of the distribution, and the other at the bottom end. As with the weight z-scores, the mean value was well below that expected, although it was not possible to compare with birth measurements since these were not being routinely performed in hospital.

Table 20: Descriptive Statistics of Term Length & Length z scores (N = 87)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Term Length (cm)	49.56	2.95	42 – 58	.34	.82
Term length z-score	-1.12	1.41	-5.60 – 2.75	-.16	.63

5.2.2.3. Head circumference

Procedure

The head circumference of each infant was measured using a disposable paper measuring tape, of the type distributed to maternity units by Cow & Gate (considered to be both more hygienic and more accurate than a cloth one since the latter stretch with repeated use). The tape was placed around the infant's head at its widest point (at a time when the infant was inactive) and the measurement recorded.

Psychometric Evaluation

As can be seen from Table 21, the head circumference z-scores at term were also fairly normally distributed, and further analysis revealed just one outlier at the top end of the distribution. Unlike the weight and length measurements, the mean head circumference was very close to normal.

Table 21: Descriptive Statistics of Term Head Circumference & Head Circumference Z-scores (N = 87)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Head circumference (cm)	35.66	1.47	32.5 – 40.0	.16	-.01
Head circumference z-score	.04	1.04	-1.92 – 3.05	.19	.03

5.2.3. Feeding

Two areas of infant feeding were assessed during this study – these being factors relating to nutrition and then factors relating to the infant's actual feeding technique.

5.2.3.1. Nutrition

A section of the maternal interview given at T2 (term assessment) comprised questions regarding type of milk given, frequency of feeds, and the infant's feeding competence in an attempt to obtain detailed information on these factors that were expected to be crucial to early growth. For the purposes of this thesis, however, only four of the questions have been used in analyses, which are the following:

Table 22: Nutrition Questions asked at Term

- **What milk is your baby receiving at present** (scored 1 – 5: 1= solely breast milk; 3 = half and half; 5 = solely formula)?
- **If your baby receives formula, what type is it** a) pre-term formula; b) full-term formula; c) special formula (eg soya, Efamil etc)?
- **How many feeds does your baby have during an average 24-hour period**?
- **Do you regularly wake your baby for feeds?**

5.2.3.1.1. Type of Milk at Term

As shown in Table 23, the majority of infants were only receiving formula at term (n=57, 63%), with just 15 (17%) receiving solely breast milk. The remaining 20% of the infants received a combination of breast milk and formula.

Table 23: Type of milk received at Term (N = 90)

Just Breast Milk	Mainly Breast Milk	50% breast, 50% formula	Mainly Infant Formula	Just Infant Formula
15 (17%)	8 (9%)	5 (5.5%)	5 (5.5%)	57 (63%)

Of the infants who were given some or all formula at term, 67% were given pre-term formula, 29% full-term formula, and the remaining 4% (ie 3 infants) received a "special formula". Special formula is usually prescribed due to some intolerance of the infant, for example Efamil is given to infants who suffer from gastric reflux (which causes excessive vomiting), because it solidifies when it reaches the stomach.

Data Reduction

Due to the small number of infants receiving special formula (n = 3), it was decided to combine this group with the group receiving full-term formula. Table 24 shows the numbers of infants receiving (predominantly) each type of milk at term. For this purpose, those infants who received totally or mainly breast milk were included in the breast milk group.

Table 24: Predominant Milk Received at Term (N = 90)

Breast Milk	Pre-term Formula	Full-term/special formula
23 (26%)	45 (50%)	22 (24%)

5.2.3.1.2. Number of feeds given in 24 hours at Term

The responses to this question are shown in Table 25. As can be seen, the range of number of feeds in a normal day was large, and further analyses showed that the scores were skewed towards the lower scores, with a number of outliers/extreme cases at the top end of the scoring range. This suggests that generally infants were fed between four and six times in 24 hours, but a few infants received much more frequent feeds.

Table 25: Descriptive Statistics of Number of Milk Feeds in 24 hours at Term (N = 90)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
No. of milk feeds	6.81	1.75	5 – 15	2.47	7.06

5.2.3.1.3. Maternal Waking of Infant for Feeds

This question again required a simple "yes/no" response, but data was only available on 84 of the infants, as the other six were still hospitalised. Of the 84 responses, 32 (38%) did not regularly wake their infants for feeds, and 52 (62%) did do so.

5.2.3.2. Infant Feeding Technique

5.2.3.2.1. Feeding Problem Index

Background

The Feeding Problem Index comprised a checklist of 10 disorganised/dysfunctional feeding behaviours that might have occurred during a milk-feed, together with an 'other' option, giving a total possible score of 11 (see Table 26).

The primary purpose of this Index was for within-group comparison. It was anticipated that, particularly at the term assessment, the majority of infants would exhibit some of the behaviours, but that a high score on the FPI would be indicative of a problem above and beyond that of simple immaturity.

Table 26: Components of the Feeding Problem Index

Fighting against breast/bottle
Crying/fussing during feed
Difficulty 'latching on'
Stopping after just a few sucks
Excessive dribbling/difficulty swallowing
Sucking weakly
Wriggling about excessively during feed
Gagging/choking during feed
Vomiting (as opposed to 'possitting')
Falling asleep during feed
Other behaviour (specify)

Procedure

The FPI was incorporated into the maternal interviews. The mother was asked "does your infant do any of the following during most or all milk feeds", and then answered "yes" or "no" to each of the above items. The Index was used as a repeated measure, being given at both the term (T2) and 3 month (T3) assessments.

Missing Data

There were two infants for whom the FPI was not available, because they were not receiving oral feeds at the time of the term assessment.

Psychometric Evaluation

The descriptive statistics for the scores on the FPI are shown in Table 27. Further analysis revealed that there was one high scoring outlier.

Table 27: Descriptive Statistics of the FPI at Term (N = 88)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
FPI at term	3.27	1.97	0 – 9	.79	.21

Data Reduction

The scores on the Feeding Problem Index were dichotomised into high and low scores (the high scorers exhibiting more dysfunctional/disorganised feeding behaviours). A score of 4 was used as the cut-off, which resulted in 31 (35%) of infants being classified as "high scorers" and 57 (65%) as "low scorers".

5.2.3.2.2. <u>Examiner-rated Infant Feeding Technique using Whitney Strain Gauge</u>

Background

Previous research in Montreal, Canada, (Ramsay, 1996) has been undertaken using a mercury-filled strain gauge attached to the baby's face with medical tape. This recorded movement has been shown to correlate very highly with data obtained using a teat-mounted pressure sensor (de Monterice et al, 1992) and has the advantage of being appropriate for both breast and bottle fed infants. It was decided to use this method of assessing sucking patterns since the sample would include both breast and bottle fed infants, and the equipment could be used both at term and at 3 months of age.

Procedure

Approval for the use of the equipment was obtained from the Medical Engineers in the Technical Departments of each of the participating hospitals. It was then piloted on both term and three-month old infants in order to familiarise the researchers with its use, and to confirm that it was appropriate for the age of the infants being studied. The use of the equipment was discussed with the pilot mothers, who all reported that having the gauge attached to their infant's face had not noticeably affected the way the infant fed.

The mercury-filled strain gauge was connected to the plethysmograph (Parks Medical Electronics, model 273), which measured the amount by which the gauge was stretched during movement of the baby's lower jaw while sucking The plethysmograph was connected to a lap-top computer, which recorded the data both in numerical and graphical form using a Pico software program. Each time the infant moved its jaw to suck, a peak was formed on the graph, with the line returning to baseline when the infant relaxed its jaw at the end of a suck. Both the plethysmograph and the computer ran on re-chargeable batteries, and therefore none of the equipment needed connection to mains electricity during the assessment. The equipment was re-calibrated at the beginning of each assessment, when the infant's jaw was closed.

The feeding assessment took place when the infant was due for a feed anyway, in order to ensure that the data obtained represented a typical feed. Prior to the feed taking place, the infant was weighed. The equipment was then set up, and the strain gauge attached to the infant's face with hypoallergenic tape (Transpore, 3M) as used in the neonatal units. Once the mother and infant were ready for the feed to begin, the recording was commenced and the time noted. Although only the first five minutes of the feed were analysed, the equipment was left in situ until the feed finished in order not to disturb the normal feeding process. A form was completed at the time of the feed, with notes of incidents affecting the recording e.g. tape working loose, feed being interrupted for "winding" etc., together with information regarding the physical situation of the feed (e.g. the number of people present, noise level, number of interruptions). The mother was asked to indicate when the feed was finished and the time again noted, in order to record the total length of the feed. The infant was re-weighed as soon as possible after the end of the feed in order to be able to calculate the precise intake.

The recording of the feed was initially saved onto the hard drive of the computer on site, and then copied onto disk for printing out and coding at a later date. The information sheet, which was completed concurrently with the feed, supplemented the graphical recording of the feed.

Missing Data

Unfortunately, although the strain gauge assessment was carried out on almost all the infants, not all the resulting data could be coded. Considerable technical difficulties were experienced, which were not apparent until the assessments were underway, and this resulted in less than optimum data being obtained in most cases. The equipment, although appropriate for the task, was unreliable, on occasions failing to record at all, or beginning recording correctly, then stopping doing so for no apparent reason. Some of these feeds could be repeated on a subsequent occasion, but this was not always possible due to time-constraints, or lack of maternal co-operation.

It was therefore necessary to grade each print-out with a score between 1 and 5, according to how reliably it could be coded. Those graded 1 were optimal, with it being possible to code continuously for five minutes. Those graded 2 were adequate, with a total of five minutes being available for coding although with some uncodable sections, which were excluded. Those graded 3 were inadequate, with less than 5 minutes of the feeding being available for coding once uncodable sections had been excluded. Those graded 4 were not codable due to mechanical or operator error; and those graded 5 were uncodable or not performed due to subject disability (for example, one infant had a cleft lip and palate and was unable to suck). See Table 28 for frequency data.

Table 28: Quality of WSG Output at Term and 3 months

Code	**Frequency (term)**	**Cumulative Frequency (t)**	**Frequency (3 mths)**	**Cumulative Frequency (3m)**
1 – good	12	12	21	21
2 – satisfactory	18	30	28	49
3 – inadequate	31	61	29	78
4 – unusable	27	88	9	87
5 – not done	2	90	3	90

It was decided that only feeds coded 1 or 2 could be used for the analyses, and thus, despite having 90 subjects at each time-point, only 30 feeds were analysed at term, and 49 at 3 months.

N.B. Data on total duration of feed, and quantity taken at observed feed (based on pre- and post-feed weight), were available on a larger number of infants, and therefore intake/minute could be computed and used as a further "feeding efficiency" indicator. This variable was used in later analyses.

Coding Procedure

As already mentioned, only five minutes of the feed were coded and used for analysis. This was the minimum duration of feed for any of the subjects, and was considered an appropriate cut-off point. The total duration of each infant's feed was, however, recorded together with the quantity ingested over the total feed. It was initially intended that the first five minutes would be used, but in some cases, due to technical difficulties, it was necessary to discard either the initial part, or small sections of the feed that had not been recorded accurately. It was not possible to measure the amplitude of the sucks accurately since this varied according to how stretched the strain gauge was. Although several sizes were available, the precise degree of stretch varied from infant to infant, according to the size of the head. For this reason each infant acted as his/her own control, with the criterion for defining a suck being a deflection from baseline which exceeded 10% of the height of the largest suck of the recording period for that individual subject.

Previous researchers have used a variety of values for defining an inter-burst pause, including 1.0 seconds (Wolff, 1968; Dubignon & Campbell, 1969); 1.3 seconds (Drewett & Woolridge, 1979; Woolridge & Drewett, 1986); and 1.5 seconds (Dubignon & Cooper, 1980). In this study pauses were defined as breaks exceeding 1.3 seconds in duration (accurate to .1 of a second). When the feeds were printed out prior to being coded by hand, each page displayed 60 seconds of the feed, and measured 228 mm in length. Thus a linear measurement of 5mm corresponded with a 1.3 second period, the conversion being performed using the statistics software SPSS in order to avoid the risk of human error.

Coding of the feeds was done by hand. This was done using a 30cm ruler and fine-pointed pencil. The first priority when coding was to identify the largest suck during the coding period, and thus the smallest true suck (10% of the height of the largest suck). Any movement that did not reach this 10% criteria was discounted. Subsequently the linear length of each sucking burst and pause was measured (in millimetres), together with the number of sucks in each burst. These were then recorded on a coding sheet. The coding was completed at the end of the burst/pause that was in progress when the 5-minute criterion was reached. Thus the exact duration of coding varied slightly from subject to subject. (see Appendices 7-9 for a detailed explanation of coding procedure, a copy of a coding sheet and an example of a print-out, including the markings showing how it was coded). This was the raw data that was available, and from which the following variables were computed:

- total number of sucking bursts and pauses
- total number of sucks
- duration of each pause and sucking burst (and number of sucks per burst)

- total sucking duration, and pause duration
- number of single sucks.

As already explained, the exact duration of coding for each of the subjects varied, so this raw data was then transformed into the following variables in order that inter-subject comparisons could be made:

- mean burst length
- mean pause length
- mean number of sucks per burst
- rate of sucking (i.e. mean duration of each suck)
- percentage of coded time spent sucking.

Establishing Coding Reliability

It was necessary to devise a coding protocol that could standardize the method of coding and it was also necessary to ensure that coding reliability could be achieved using this protocol. Consequently, a second researcher (Anne Hagues) was trained in the coding procedure and, after several feeds had been coded together, reliability testing was undertaken. Ten feeds (five term and five 3-month) were coded independently by the two researchers, and the resulting data analysed. See Table 29 for analyses.

Table 29: Inter-Rater Reliability of Coding Procedure

Variable	**Rater A**	**Rater B**	**Correlation**
	Mean & (SD)	Mean & (SD)	
Mean burst length (secs)	30.91 (40.07)	31.19 (40.05)	1.00
Mean pause length (secs)	4.94 (2.50)	5.02 (2.78)	.99
Mean sucks per burst (secs)	43.79 (56.54)	44.46 (56.93)	1.00
Percentage of time sucking	73.56 (19.41)	72.79 (18.98)	.99
Mean duration of suck (secs)	0.72 (0.06)	0.72 (0.06)	.96

From the above table it can be seen that the inter-rate reliability was extremely high on the variables being used for analyses, the lowest correlation being for the mean duration of a suck, which was .96.

Psychometric Evaluation

Once coding reliability had been established the remaining feeds were coded and the data obtained was analysed. Table 30 shows the descriptive statistics of these variables. As can be seen by the standard deviation scores, the 30 subjects upon whom this data is available varied widely in their feeding technique. These five variables are not normally distributed, as indicated by the skewness and kurtosis values. Further analysis revealed three (high) outliers for the mean burst length and sucks/burst variables, one of whom was also an outlier for the individual suck duration variable.

Table 30: Descriptive Statistics of Feeding Variables at Term (N = 30)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Mean burst length (secs)	20.65	20.83	4.95 – 104.21	2.74	8.59
Mean sucks/burst	25.70	23.09	6.41 – 100.67	2.08	3.85
Mean pause length (secs)	5.23	2.29	2.58 – 10.09	1.00	-.07
Length of suck (secs)	0.78	0.08	0.65 – 1.04	.60	1.39
% of coded time spent sucking	73.70	15.55	45.9 – 98.26	-.30	-.97

5.2.3.2.3. Fluid Intake per Minute

This was a simple calculation based on feed duration and the difference between pre- and post-feeding weights. Table 31 shows the descriptive statistics for this variable. Further analysis revealed that the values were skewed towards the lower end, with one outlier.

Table 31: Descriptive Statistics for Intake per Minute at Term

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Intake per Minute (g)	5.36	3.29	.57 - 16.00	.96	.86

5.2.4. Infant Behavioural Regulation

The assessment of infant behavioural regulation included variables relating to both sleep patterns and levels of irritability and crying.

5.2.4.1. Sleep Behaviour

Questions regarding infant sleeping behaviour were incorporated into the maternal interview at term, and repeated at 3 months corrected age. As with the feeding questions, only four questions were used in these analyses, which were as follows:

Table 32: Sleep Questions asked at Term

- **On average, how many hours does your baby sleep in a 24 hour period?**
- **Where does your baby usually sleep most of the night?**
- **How many times does your baby usually wake him/herself up at night?**
- **Do you usually wake your baby for feeds?**

The latter two questions were amalgamated to produce a further variable to identify those infants who had regular feeds, and those who neither woke nor were woken by their mothers.

Six infants were still hospitalised at the term assessment, and therefore this information was not available, leaving a sample of 84 infants.

5.2.4.1.1. Total Sleep Duration in 24 Hours

The descriptive statistics for total sleep duration in 24 hours are shown in Table 33. As can be seen, the scores are fairly normally distributed (although slightly skewed towards higher scores) and further analysis revealed no outliers.

Table 33: Descriptive Statistics of Total Sleep Duration (N = 84)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Total sleep duration (hrs)	15.49	3.33	7 – 21	-.49	-.34

5.2.4.1.2. Co-sleeping

Co-sleeping refers to the infant sharing the parental bed for most or all of the night on a regular basis. Data was missing on one infant. The mothers of 8 infants, from the 83 who responded (10%), said that they regularly co-slept, with the remaining 76 (90%) saying that co-sleeping did not regularly occur.

5.2.4.1.3. Self-waking

At term it was expected that infants would wake themselves for feeds at least twice during the night, and this was used as the criterion for "self-waking". Of the 84 infants upon whom data was available, 58 (69%) reached this criterion, with the remaining 26 (31%) waking a maximum of once per night.

5.2.4.1.4. Maternal Waking of Infant for Feeds

10 (12%) of the infants were being woken by their mothers for night feeds at Term, with the remaining 74 (88%) being demand fed.

5.2.4.1.5. Infants who do not Self-wake, and are not Woken by Mother

This was the composite variable calculated in order to ascertain how many infants were fed regularly (either infant or mother-instigated) and how many were allowed to sleep for long periods without a feed. Of the 84 infants who were at home at the time of assessment, 61 (73%) received at least two feeds during the night period, with the remaining 23 (27%) receiving one feed or less during this period.

5.2.4.2. Infant Irritability

5.2.4.2.1. Crying Pattern Questionnaire (St. James-Roberts & Halil, 1991)

Description

The CPQ is a brief, simple questionnaire that assesses the duration of crying during an average day, divided into morning, afternoon, evening and night periods. The mother indicates how much time during each of these periods her baby has cried, and a total crying time can thus be computed. A copy of the CPQ is given in Appendix 6.

Procedure

The CPQ was administered during the maternal interview as a repeated measure at both Assessment 2 (term) and Assessment 3 (3 months).

Missing Data

Data was not available on six of the infants at T2 (term) as they were still hospitalised and the mothers were therefore not with them for 24 hours each day.

Psychometric Evaluation

The four time periods were combined to produce a composite score "Crying Duration at Term" (in minutes). Table 34 shows the descriptive statistics for this variable. The high standard deviation reflects the large within-group differences in daily crying duration. The high skewness and kurtosis values reflect the non-normal distribution of these crying scores. Further analyses showed than there were four outliers, and that the scores were skewed towards the lower end.

Table 34: Descriptive Statistics of Crying Duration at Term (N = 84)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Crying Duration	180.5	151.2	0-720	1.45	2.1

Data Reduction

Because of the skewed distribution of scores and the presence of outliers, the total crying duration scores were dichotomised into "excessive criers" (those who cried >180 minutes/day) and "normal criers" (who cried <181 minutes per day), according to Wessel's modified criteria of excessive crying (Wessel et al, 1954). Using this dichotomy, 34 (40%) of the infants were classified as excessive criers, with the remaining 50 (60%) classified as normal criers.

5.2.4.2.2. Brazelton Neonatal Behavioral Assessment Scale (Brazelton & Nugent, 1995, 3rd edition)

Background

This is a standardised neonatal examination of neonatal behavioural competence, complex motor organisation and the ability to interact with environmental stimuli. It has been used widely in both research and clinical settings over the past 20 years. It has previously been used in studies researching the effects of intrauterine growth retardation, preterm birth and maternal substance abuse. The BNBAS gives scores on 28 nine-point behavioural items and 18 reflex items, and an additional seven supplementary items were added to the second edition which are especially designed to capture the behaviours of frail, at-risk infants. These supplementary items rate the infant's general responsiveness, the facilitation required by the examiner to organise the infant's responses, and the extent to which the infant's physiological system is stressed during the examination.

The assessment is based on the principle of "best performance", that is the administrator is required to elicit the infant's best possible performance at the time of the examination, and consequently the sequence in which the items are administered can be varied to accommodate the infant's changing behavioural state.

Training in the NBAS

Both researchers who worked on the GAIN Study (the author and T Gutbrod) were formally trained in the administration and coding of the Brazelton NBAS by D. Wolke (European Trainer for NBAS), and were officially certified as being able to administer and code the NBAS to the required level of reliability. Both researchers received a scholarship from the Brazelton Institute UK to fund their training in the NBAS.

Procedure

The NBAS was usually administered in the family home or, in the case of infants who remained hospitalised, in a room on the NICU. The examination ideally took place a) half way between two feeds, in order to minimise irritability due to hunger, or post-feed drowsiness, and b) in a quiet, shaded, warm room to maximise infant comfort and alertness.

The mothers were usually present at the examination, and were given general feedback on their infant's relative strengths and weaknesses by the examiner.

In general, the behavioural and reflex items are combined into seven clusters that are derived from factor-analysis or existing a priori cluster schemes. Only one cluster deals with irritability as it occurs during the examination (Prechtl, 1982) and is included in this thesis.

Irritability Cluster

Kaye (1978) identified an irritability cluster from three of the items in the BNBAS – Peak of Excitement, Rapidity of Build-up, and Irritability, which has subsequently been used by many researchers (e.g. Crockenberg, 1981; Van den Boom, 1988). This cluster is computed by totalling the means of these three items: Peak of Excitement, Rapidity of Build-up and Irritability. In addition, one of the supplementary items that were added to the second edition of the assessment manual, "general irritability", has been added to the irritability cluster used in this study. Descriptions of the four items used to compute the irritability score are given in Table 35.

Table 35: Irritability Items in the NBAS

"Peak of Excitement" is a measure of the overall amount of both motor and crying activity observed during the whole examination, and gives an indication of the length and intensity of excitement. This item is scored from 1 ("low level of arousal to stimulation") to 9 ("infant achieves insulated crying state; unable to be quieted or soothed").

"Rapidity of Build-up" is a measure of the number of stimuli which are necessary before the infant changes from an initially calm state to an agitated one, i.e. the amount of control shown by the infant in the face of increasingly aversive stimuli, and the point during the examination at which loss of this control occurs. This item is scored from 1 ("never cries") to 9 ("never quiet enough to score this")

"Irritability" measures the number of stimuli (out of a list of increasingly aversive stimuli) to which the infant responds by becoming irritable (ie audible fussing or crying) for periods of at least three seconds during the examination. This item is scored from 1 ("no fussing to any of the above") to 9 ("irritable fussing to 8 or more of the stimuli")

"General Irritability" is one of the supplementary items from the examination, which measures how irritable the infant is overall, to both aversive and non-aversive stimuli. This item is scored from 1 ("irritable to all degrees of stimulation throughout the examination") to 9 ("no irritability; infant responds to all stimuli with well-maintained self-control").

Missing Data

Full NBAS data was only available on 83 infants. Two infants could not be assessed due to their medical condition, and for the other infants the assessment could not be completed in its entirety due to deterioration in their physiological state during the examination.

Data Reduction

The General Irritability item was re-coded so that the values corresponded with those of the other items (ie 1 = low irritability and 9 = high irritability) and then correlations were performed between the four items. These inter-correlations were all above r >.75 (highly significant). The four items were then added (and divided by the number of scales) to compute a sum score reflecting "Neonatal Irritability in the NBAS".

Table 36: Neonatal Irritability (NBAS) (N=83)

	Alpha	**Mean/SD**	**Min – Max**	**Skewness**	**Kurtosis**
Neonatal Irritability	.94	4.64 / 1.91	1.25 – 8.25	.08	-1.2

The internal consistency for the four items was very high (alpha =.94), and further analysis showed that the scores were normally distributed, with no outliers.

Irritability Classification

Previous studies have used a score of 6 as the cut-off criterion for irritable/non-irritable classification (Crockenberg, 1986; Murray et al, 1996; Van den Boom, 1988). Using this criterion, 24 (29%) of the 83 infants were classified as irritable, with the remaining 59 (71%) being non-irritable.

5.2.4.2.3. Irritability: Inter-instrument correlations

From Table 37 it can be seen that the two variables described above, both believed to measure irritability, were significantly correlated. The Crying Patterns Questionnaire was maternally-assessed, whereas the NBAS was examiner-assessed.

Table 37: Inter-instrument Correlation at Term (Irritability)

	NBAS Irritability	CPQ Cry duration
NBAS Irritability	1.00	
CPQ Cry duration	**.24***	1.00

* correlation is significant at .05 level

5.3. 3-Month Assessment

5.3.1. Background Information

This section describes the instruments and procedures used in the assessment performed at 3 months of age, corrected for gestation. This assessment took place in the parental home for all the subjects. As with the Term assessment, the order of administration was dependent on the infant's routine on that particular day.

The mothers were again given a structured interview, which included questions about the baby's health since the last meeting and also repeated many of the questions on feeding, sleeping and crying behaviours that were asked at Assessment 2. It also repeated questions from the earlier interviews about socio-demographic details and social support networks to ascertain any changes that had taken place.

Table 38: Assessment T3 (3-month) Components

Assessment T3 (3 months)	**Instruments used**
Outcome Measure:	
Growth	**Anthropometric form** recording weight, body length, and head circumference
Independent Variables:	
Feeding:	
Nutrition	Feeding Questions in Parent II Interview (derived from Ramsay & Gisel, 1996; Skuse et al, unpublished)
Infant Feeding Technique	**Whitney Strain Gauge** (feeding technique) **Pre- and post-feed weighing** (intake)
Infant Behaviour:	
Sleeping	Sleep questions in Parent II Interview (derived from Seifer, 1992. See also Wolke, 2003)
Crying/irritability	**Crying Patterns Questionnaire** (St.James Roberts & Halil, 1991) **Neonatal Behavioral Assessment Scale** (Brazelton, 1995)
Maternal Intelligence	**WAIS-R** (Wechsler, 1981)

5.3.2. Anthropometric Measurements

Background and procedural information for the anthropometric measures can be found in Section 5.2.2 (T2 assessment).

5.3.2.1. Weight

Table 39 shows the descriptive statistics for the 3-month weight z-scores. They were fairly normally distributed, and further analysis revealed just one high scoring outlier.

Table 39: Descriptive Statistics of 3-month Weight & Weight Z-scores (N = 89)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
3-month weight	5601	869	3690 – 9105	.96	2.22
3-month weight z-score	-.86	1.18	-3.74 – 2.50	.20	.13

The Pearson correlation between the weight z-scores at term and 3 months of age was r = .77 (p< .01).

5.3.2.2. Length

Table 40 shows the descriptive statistics for the 3 month length z-scores. They were fairly normally distributed, and further analysis revealed two outliers, one high scoring and the other low scoring.

Table 40: Descriptive Statistics of 3-month Length & Length Z-scores (N = 89)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
3-month length	59.76	2.98	52.2 – 67.0	.25	-.02
3-month length z-score	-.49	1.26	- 4.1 – 3.1	.11	.37

The Pearson correlation between the length z-scores at term and 3 months of age was $r = .71$ ($p < .01$).

8.3.2.3. Head Circumference

Table 41 shows the descriptive statistics for the 3-month head circumference z-scores. They were fairly normally distributed, and further analysis revealed one high scoring outlier.

Table 41: Descriptive Statistics of 3-month Head Circumference & Head Circumference Z-scores (N = 89)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
3-month head circumference	40.97	1.54	37.9 – 45.4	.50	.36
3-month head circumference z-score	-.05	1.20	- 2.36 – 3.86	.46	.54

The Pearson correlation between the head circumference z-scores at term and 3 months of age was $r = .76$ ($p < .01$).

8.3.3. Feeding

As at the Term assessment the feeding factors examined at the 3-month assessment included those relating to both nutrition and infant feeding technique.

8.3.3.1. Nutrition

As at T2 (term assessment) a large section of the maternal interview given at T3 (3 month assessment) comprised questions regarding feeding and nutrition. The same four questions were used in analyses as for the previous time point, but with one extra one added, relating to solid feeds:

Table 42: Nutrition Questions asked at 3 Months

- **What milk is your baby receiving at present** (scored 1 – 5: 1= solely breast milk; 3 = half and half; 5 = solely formula)?
- **If your baby receives formula, what type is it** a) pre-term formula; b) full-term formula; c) special formula (eg soya, Efamil etc)?
- **How many milk feeds does your baby have during an average 24 hour period**?
- **How many solid feeds (if any) does your baby have during an average 24 hour period?**
- **Do you regularly wake your baby for feeds?**

5.3.3.1.1. Type of Milk at 3 months

As shown in Table 43, the majority of infants were receiving just formula at 3 months (n=68, 75%), with only 7 (8%) receiving just breast milk. The remaining 17% of the infants received a combination of breast milk and formula.

Table 43: Type of milk received at 3 months (N = 90)

Only Breast Milk	Mainly Breast Milk	50% breast, 50% formula	Mainly Infant Formula	Only Infant Formula
7 (8%)	9 (10%)	0	6 (7%)	68 (75%)

5.3.3.1.2. Type of Formula Received at 3 months

Of the 83 infants who were given some or all formula at 3 months, 34% were given pre-term formula, 45% full-term formula, and the remaining 11% (ie 9 infants) received a "special formula".

Data Reduction

As with the term data, due to the small number of infants receiving special formula it was decided to combine this group with the group receiving full-term formula. Table 44 shows the numbers of infants receiving (predominantly) each type of milk at 3 months. For this purpose, those infants who received totally or mainly breast milk were included in the breast milk group.

Table 44: Predominant Milk given at 3 months (N = 90)

Breast Milk	Pre-term Formula	Full-term/special formula
16 (18%)	28 (31%)	46 (51%)

5.3.3.1.3. Number of milk feeds given in 24 hours

The responses to this question are shown in Table 45. As can be seen, the range of number of feeds in a normal day remained large, and further analysis revealed that the scores were bunched in the middle, with a number of outliers/extreme cases at both ends of the scoring range. There was one infant who received no milk feeds, receiving instead just very "sloppy" solid feeds.

Table 45: Descriptive Statistics of Number of Milk Feeds in 24 hours (N = 90)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Milk feeds in 24 hours	5.63	1.55	0 – 12	.70	4.12

5.3.3.1.4. Solid Feeds

Solid feeds are generally introduced at or around 3-4 months of age. Of the 90 infants in the GAIN Study, 64 (71%) were receiving at least one solid feed per day. The remaining 26 infants (29%) had not started receiving regular solid feeds to supplement their nutritional intake. Table 46 shows the descriptive statistics for the number of solid feeds given each day. Further analysis showed that although the scores were not normally distributed, there were no outliers.

Table 46: Descriptive Statistics of Number of Solid Feeds in 24 hours (N = 90)

VARIABLE	MEAN	STD DEV	MIN-MAX	SKEWNESS	KURTOSIS
Solid feeds in 24 hours	1.52	1.14	0 – 3	- .11	- 1.4

5.3.3.1.5. Maternal Waking of Infant for Feeds

This question again required a simple yes/no response. The mothers of 25 (28%) of the infants replied that they usually woke their infant at least once during a 24-hour period, with the remaining 65 (72%) responding that they did not wake their infants for feeds.

5.3.3.2. Infant Feeding Technique

The three measures of feeding technique that were used at the Term assessment (T2) were repeated at the 3-month assessment (T3), i.e. the Feeding Problem Index, the Whitney Strain Gauge and intake per minute.

5.3.3.2.1. Feeding Problem Index

Background information and procedural explanation on the FPI is given in Section 5.2.3.2.1.

Missing Data

There were three infants on whom the FPI was not available at the 3-month assessment.

Psychometric Evaluation

The descriptive statistics for the FPI at 3 months are shown in Table 47. Further analysis confirmed that the scores were fairly normally distributed, with one high scoring outlier.

Table 47: Descriptive Statistics of the FPI at 3 months (N = 87)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
FPI	1.98	1.63	0 – 6	.57	- .63

Data Reduction

The scores on the Feeding Problem Index were again dichotomised into high and low scores (the high scorers exhibiting more dysfunctional/disorganised feeding behaviours). The score of 4 was used as the cut-off, which resulted in 18 (21%) of infants being classified as "high scorers" and 69 (79%) as "low scorers".

Longitudinal Analysis

Although the mean score on the FPI improved across the two time points, the scores on the FPI at term and 3 months of age were highly correlated ($r = .31$, $p < .00$). The proportion of infants who scored more than 3 (out of a possible 11) dropped from 35% at term to 21% at 3 months corrected age. Again, there was a high correlation between high and low scoring classification at the two time points ($r = .30$, $p < .00$).

5.3.3.2.2. Examiner-rated Infant Feeding Technique using Whitney Strain Gauge

Background and procedural information on the Whitney Strain Gauge can be found in Section 5.2.3.2.2. (T2 assessment).

Missing Data

As previously discussed, it was only possible to code a proportion of the WSG data. At the 3-month assessment, data was coded and analysed for 49 infants.

Psychometric Evaluation

The descriptive statistics for the WSG variables at 3 months are shown in Table 48. The reason that there is only pause data on 46 of the 49 infants is that three infants sucked non-stop for the full five minutes used for coding, and therefore no pause occurred. As at T2 assessment, it can be seen by the standard deviation scores that the infants varied widely in their oral-motor function. None of the five variables are normally distributed, as indicated by the skewness and kurtosis values. Further analysis revealed five (high) outliers/extreme cases for the mean burst length and sucks/burst variables, two for pause length, four for suck duration (3 high, one low) and one low outlier for percentage of time spent sucking.

Table 48: Descriptive Statistics of Feeding Variables at 3 months

Variable	N	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Mean burst length (s)	49	52.1	79.8	6.7 – 370.5	3.3	10.2
Mean sucks/burst	49	82.3	157.3	9.5 – 964	4.4	21.8
Mean pause length (s)	46	3.7	2.6	1.6 – 18.2	4.2	22.9
Mean suck length (s)	49	0.7	0.1	0.4 - .9	-0.4	3.4
% of coded time spent sucking	49	86.9	12.0	51.1 – 100	-1.1	0.5

Longitudinal Analysis

The Whitney Strain Gauge equipment was used at both term and 3 months corrected age. As can be seen from Table 49, overall there was a dramatic increase in burst length (and consequently in number of sucks per burst) between term and 3 months corrected age. The pause length decreased slightly, suck length remained largely unchanged, and the percentage of coded time spent sucking increased. These findings would appear to reflect normal maturational changes.

Table 49: Comparison of WSG Variables at Term and 3-Months

Variable	N	Mean	Std Dev
Mean burst length (secs)			
Term	30	20.7	20.8
3 months	49	52.1	79.8
Mean sucks/burst			
Term	30	25.7	23.1
3 months	49	82.3	157.3
Mean pause length (secs)			
Term	30	5.2	2.3
3 months	46	3.7	2.6
Mean suck length (secs)			
Term	30	0.8	0.1
3 months	49	0.7	0.1
% of time spent sucking			
Term	30	73.7	15.6
3 months	49	86.9	12.0

There were just 17 infants on whom analysable data was available at both term and three months, and information derived from this sub-group is shown in Table 50.

Table 50: Repeated Measure Analysis Term to 3 months (N = 17)

Variable	Term mean (sd)	3 month mean (sd)	t-value	p
Mean burst length (secs)	16.05 (13.43)	34.30 (29.02)	-2.35	.03
Mean no of sucks/burst	20.55 (16.85)	47.09 (38.97)	-2.55	.02
Mean pause length (secs)	4.92 (1.59)	4.53 (3.82)	0.39	.70
Mean duration of suck	0.78 (.07)	0.73 (.07)	2.94	.01
% time spent sucking	72.00 (14.39)	86.30 (12.17)	-3.42	.01

In the case of most of the variables, it can be seen that the repeated-measures data that is available supports the findings of the overall groups at each time-point, i.e. there were significant improvements in feeding technique between the term and 3-month assessments. Both the mean burst length and the number of sucks per burst more than doubled, although in this sub-group the mean pause length did not change significantly. The rates of sucking by this sub-group closely reflect the whole group at each assessment point, as do the percentages of time spent sucking.

5.3.3.2.3. Fluid Intake per Minute

This was a simple calculation based on feed duration and the difference between pre- and post feeding weights. Table 51 shows the descriptive statistics, and further analysis revealed that the values were skewed towards the lower end, with 3 outliers and one extreme case.

Table 51: Descriptive Statistics of Intake per Minute at 3 Months

Variable	N	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Intake per minute (g)	49	10.6	8.3	.01 – 56.0	2.5	10.3

Longitudinal Analysis

As can be seen from Table 52, the mean intake per minute has doubled between the two time points. This increased intake, as with the changes in the WSG variables, would appear to reflect normal maturational changes. The variance between the scores has increased, however, and the scores are even less normally distributed at 3 months than they were at term.

Table 52: Comparison of Intake/Minute at Term and 3 Months

Variable	N	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Intake/minute at term	78	5.4	3.3	.6 - 16	1.0	.9
Intake/minute at 3 months	84	10.6	8.3	0 - 56	2.5	10.3

The Spearman Rho(non-parametric) correlation between the scores at the two time points was calculated at .35 ($p < .00$).

5.3.4. Infant Behavioural Regulation

As at the Term assessment, both sleep behaviour and irritability levels were examined at the 3-month assessment.

5.3.4.1. Sleep Behaviour

5.3.4.1.1. Total Sleep Duration in 24 Hours

The descriptive statistics for total sleep duration in 24 hours are shown in Table 53. Data was missing on one infant. As can be seen, the scores are fairly normally distributed (although slightly skewed towards higher scores), and further analysis revealed no outliers. The mean number of hours slept had dropped from 15.49 at term, to 13.74 at 3 months corrected age. The correlation between hours slept at the two time points was r =.22 (p<.05).

Table 53: Descriptive Statistics of Total Sleep Duration at 3 Months (N = 89)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Total sleep duration (hrs)	13.74	2.02	9 – 19	.06	-.14

5.3.4.1.2. Co-sleeping

Data was available on all 90 infants at the 3 months assessment. Of these, the mothers of 5 infants (6%) said that they regularly co-slept, with the remaining 85 (94%) saying that co-sleeping did not regularly occur. Two infants who were not co-sleeping at term had started to do so by 3 months of age, and five who had been co-sleeping at term were no longer doing so three months later.

5.3.4.1.3. Self-waking

At 3 months of age the criterion used was waking at least once during the period from 10pm to 6am. Of the 90 infants, 49 (54%) reached this criterion, with the remaining 41 (46%) not being fed during this night period. Nine infants who had not self-woken at term were doing so at 3 months of age, and 19 who had woken at term were sleeping through at 3 months.

5.3.4.1.4. Maternal Waking of Infant for Feeds

At 3 months of age, seven (8%) of the infants were still being woken by their mothers for night feeds, with the remaining 83 (92%) being demand fed. Nine of the mothers who were waking their infants for feeds at term had stopped doing so by 3 months of age, and six who were not waking their infants at term had begun doing so at 3 months of age.

5.3.4.1.5. Infants who do not Self-wake, and are not Woken by Mother

This was the composite variable to ascertain how many infants were fed regularly (either infant or mother-instigated) and how many were allowed to sleep for long periods without a feed. Of the 90 infants, 52 (58%) received at least one feed during the night period, with the remaining 38 (42%) not being fed between the hours of 10pm and 6am. 19 infants who had been fed at least twice during the night at term were not being fed between 10pm and 6am at 3 months. Nine infants who had not been receiving night feeds at term were receiving them at 3 months of age.

5.3.4.2. Crying

5.3.4.2.1. Crying Pattern Questionnaire (St. James-Roberts & Halil, 1991)

The CPQ was re-administered at the 3-month assessment, in order to compare the amount of crying at the two time-points (see Section 5.3.2.1 for background information).

Psychometric Evaluation

Table 54 shows the descriptive statistics for the total Cry Duration at 3 months. The large standard deviation indicates wide variance around the mean of the individual subject scores. Further analyses revealed that the scores were skewed towards the lower end, and that there were three high scoring outliers.

Table 54: Descriptive Statistics of Cry Duration at 3 Months (N = 90)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Total Cry Duration	105.44	85.66	10 – 440	1.60	3.14

Data Reduction

Because of the skewed distribution of scores and the presence of outliers, the total crying duration scores were again dichotomised into "excessive criers" and "normal criers" (<181 minutes per day), using Wessel's modified criteria of excessive crying as at the Term assessment (Wessel et al, 1954). Using this dichotomy, 12 (13%) of the infants were now classified as excessive criers at 3 months corrected age, with the remaining 78 (87%) infants classified as normal criers.

Longitudinal Analysis

The correlation between total Cry Duration at term and 3 months was .31 (significant at the $p< .00$ level), and the correlation between cry classification (excessive vs normal) was .26 (significant at the $p< .01$ level).

5.3.5. Maternal Intelligence - Wais-R (1981)

Background

The Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981) is the most recent version of the WAIS, which was published in 1955. Its predecessor, the Wechsler Bellevue Intelligence Scale was published in 1939. The Scale defines a level of intelligence by comparing the performance of an individual of a given age with average scores attained by other people in that age group (Wechsler, 1981). Identical IQs do not have the same meaning at different ages, since average test scores rise to a peak in young adulthood, and then fall away later in life. Therefore more ability is required to obtain a given IQ at 21 years of age than at 60.

The WAIS-R is composed of 11 tests – six verbal and five non-verbal. An individual's raw scores on the tests are converted to scaled-scores based on the reference group (aged 20-34), regardless of age. The sums of scaled scores are then converted into

Verbal, Performance and Full Scale IQs according to age. Within every age group the mean score is 100 and the standard deviation is 15.

Procedure

The WAIS-R was administered to the mothers of the GAIN subjects at the T3 assessment (3 months). An abbreviated form of the Scale was used due to time constraints – administering two of the six verbal, and two of the performance tests. These were: Information (v), Vocabulary (v), Block Design (p) and Object Assembly (p). These four tests were selected because they correlated most highly with the overall verbal/performance IQ scores (r = .75 - .90).

The Scales were administered at a point during the assessment when the infant was either asleep or otherwise occupied so that the mother could give her full attention. The scaled scores were later computed from the raw scores of the tests, and verbal, performance and full-scale IQ calculated.

Missing Data

Data was available on the mothers of 83 of the infants, the remaining 7 declining to be assessed.

Psychometric Evaluation

The descriptive statistics for Maternal IQ are shown in Table 55. As can be seen the scores are fairly normally distributed, and the mean and standard deviation are close to those expected. Further analysis revealed one high scoring outlier.

Table 55: Descriptive Statistics of Maternal IQ (n = 83)

Variable	Mean	Std Dev	Min - Max	Skewness	Kurtosis
Maternal IQ	99.2	16.4	68 - 150	.59	.15

Chapter 6: 18-Month Assessment

6.1. Background Information

Efforts were made to contact the mothers of all the original 90 subjects at approximately 18 months corrected age, and 81 were reached and agreed to attend this follow-up assessment. The infants lost to follow-up did not differ from those who were seen at this stage in terms of gestational age, birth weight, twin status, severity of illness (as measured by days of hospitalisation), or maternal factors (Osborn Index, maternal IQ, age and marital status). More boys were lost to follow-up than girls, but as there had been more boys in the original sample, this resulted in a more equal proportion of male and female subjects (54% and 46% respectively). In addition, slightly more firstborns were lost to follow-up. Although the average age at follow-up was 18.48 months (standard deviation of 1.15), the age of the infants at assessment actually ranged from 16-22 months of age, with the majority being assessed at 18-20 months.

This section describes some of the instruments and procedures used in the 18-month assessment. The assessments were carried out in observations rooms, either at the University of Hertfordshire Hatfield Campus, or in the SPS Department at the University of Cambridge, depending on the hospital unit where the subjects had been recruited. These rooms were set up with cameras, one-way mirrors etc., which enabled the assessments to be carried out in a standardised way. The complete assessments took approximately 2-2.5 hours to complete, including intervals for the young subjects to have drinks and/or biscuits if required.

Table 56: Assessment T4 (18-Month) Components

Assessment T4	Instruments used
Outcome Measure:	
Developmental Quotient Mental	**Bayley Scales of Infant Development,** 2nd Edition, 1993 (BSID-II)
Independent Variable:	
Growth	**Anthropometric form:** weight, head circumference and length/height

6.2. Bayley Scales-II (BSID-II, 1993)

Background

The original Bayley Scales of Infant Development (BSID) were published in 1969. The updated BSID-II added several new items, extended the age range and improved the accuracy of administration and scoring. It is used for clinical, educational and research purposes, on children aged 1-42 months.

It is an assessment of development rather than intelligence – that is, it assesses whether an ability has been acquired or not rather than the degree to which an ability is displayed at given age. As a developmental assessment it is not attempting to predict in the same way as an intelligence test, which assumes a curvilinear function between age and level of ability. However, among infants at biological risk, performance on BSID-II as early as 12 months of age has been shown to correlate with scores of verbal and motor performance at 4.5 years (Crowe, Deitz & Bennett, 1987). Results of the assessment can be used to identify areas of relative developmental delay (and subsequently to assess outcome of any intervention measures).

For a normal population, parental level of education is moderately positively correlated with infants' mental and motor development at 12 months of age, and IQ for infants up to 6 years of age (Rose & Wallace, 1985). However, infant temperament, state of arousal, affect and motivation can also affect performance on assessment.

Procedure

The BSID-II specifies groups of items that are administered to the infant according to his/her chronological age. However, if developmental delay is anticipated, or if a set of items is "failed", then a set of items from a younger age group can be presented. Similarly, if an infant/child succeeds on all the items appropriate for his/her age, then the next set of items can be given. Raw scores are converted into the mental and psychomotor index scores by referring to exact age at time of assessment. It should be noted that statistically significant differences between MDI and PDI scores can occur within normal populations – development rates vary and some aspects may get ahead of others.

Studies have been undertaken to assess the equivalence of the BSID-II with other scales of development, which provide evidence of both convergent and discriminant validity of the Scales. The correlations with the McCarthy Scales of Children's Abilities (MSCA, McCarthy, 1972) were .79 and .59 respectively for mental and psychomotor scales. When compared with the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R, Wechsler, 1989) the correlations were .73 and .37 respectively.

Normative Data

The norms given in the BSID-II manual were derived from a national, stratified random sample representative of the US population. The sample of 1,700 cases included 50 males and 50 females within each of 17 age groups between 1 month and 42 months of age.

Psychometric Evaluation

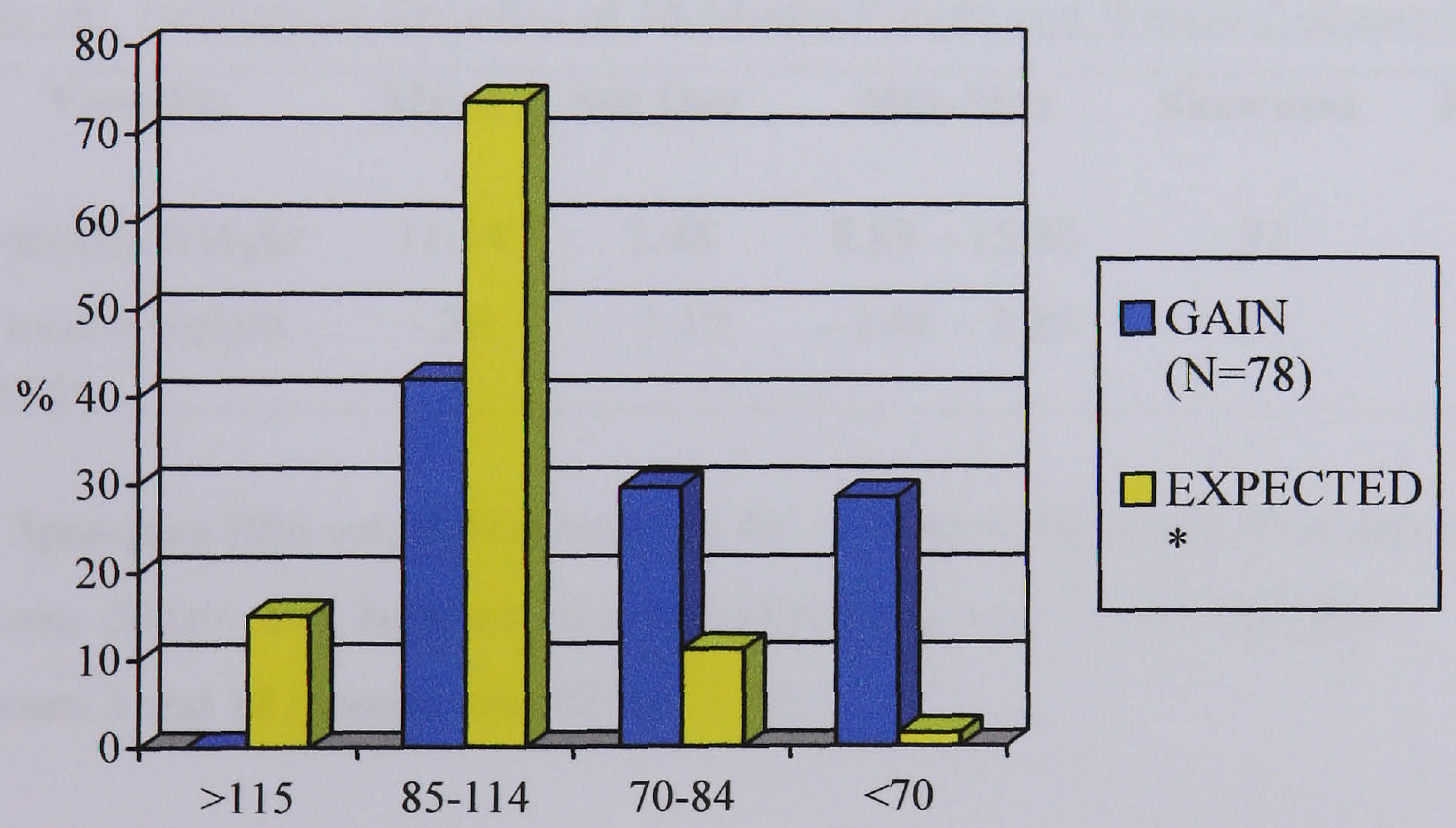
Table 57 shows the descriptive statistics of the BSID-II Index scores for the GAIN Study sample. As can be seen, the mean score on the MDI are below that expected of a normative sample. This is not surprising as the GAIN Study sample comprises a moderate-high risk group of infants. The scores are flatter than a normal distribution (see Kurtosis values), and slightly skewed, but further analysis revealed no outliers. Only the MDI scores were used in this thesis, although psychomotor scores were also computed for the infants. The correlation between the two scales was $r = .70$.

Table 57: Descriptive Statistics of BSID-II Mental Development Index Scores (N = 78)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Mental Index	78.31	16.09	50 - 109	- .25	- .77

As can be seen very clearly in Figure 2, the sample as a whole performed below the expected levels.

Figure 2: Performance on the MDI at 18 months of age: Comparison between GAIN Study Infants and Normative Sample



When Chi-square analyses were performed, the difference between the observed and expected frequencies (based on the Bayley data, 1993) was highly significant (Chi-Square = 286.16, $p < .001$).

In summary then, the GAIN subject scores were significantly lower overall than would be expected in a normative sample, and in addition were not normally distributed.

6.3. Anthropometric Measurements

Background and procedural information for the anthropometric measures can be found in Section 5.3.5 (T2 assessment).

6.3.1. Weight

Table 58 shows the descriptive statistics for the 18-month weight z-scores. They were fairly normally distributed, but further analysis revealed five high scoring outliers.

Table 58: Descriptive Statistics of 18-Month Weight and Weight Z-scores (N = 78)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
18-month Weight	11.14	1.48	8.89 – 15.80	.93	.96
18 month weight z-score	-.26	1.19	- 2.46 – 3.20	.72	.59

The Spearman Rho correlation between the z-scores at birth and 18 months of age was .50 ($p < .01$), between term and 18 months was .53 ($p < .01$), and between 3 and 18 months was .68 ($p < .01$).

6.3.2. Height

Table 59 shows the descriptive statistics for the 18-month height and height z-scores. These scores were not normally distributed, and further analysis revealed one extreme case (low scoring).

Table 59: Descriptive Statistics of 18-Month Height and Height Z-scores (N = 78)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
18-month height	80.07	4.04	64.00 – 87.50	-.65	1.93
18 month height z-score	-.71	1.36	- 6.82 – 1.82	- 1.05	3.95

The Spearman Rho correlation between the z-scores at term and 18 months of age was .20 ($p < .05$), and between 3 months and 18 months of age was .43 ($p < .01$).

6.3.3. Head Circumference

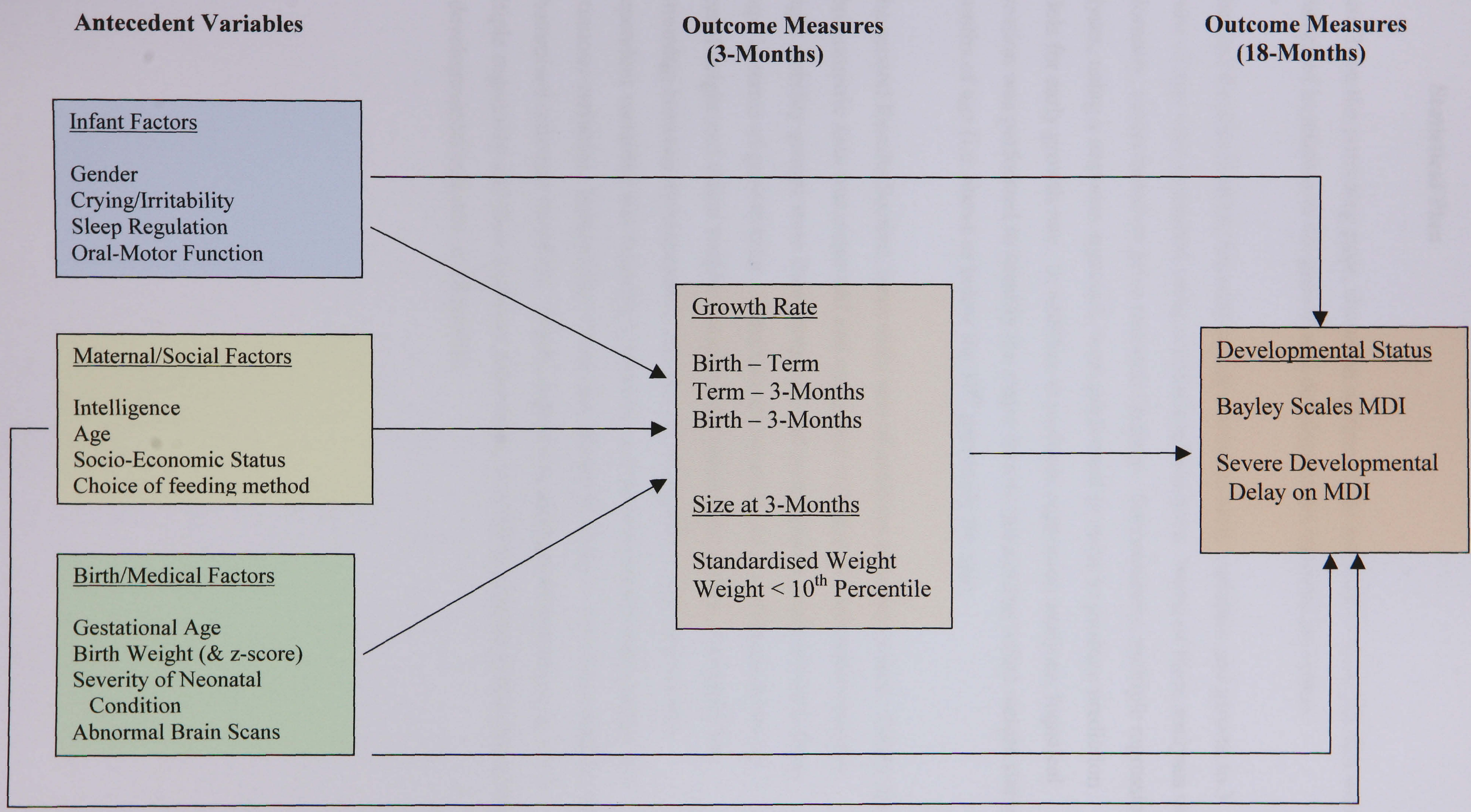
Table 60 shows the descriptive statistics for the 18-month head circumference Z-Scores. They were fairly normally distributed, but further analysis revealed one high scoring outlier.

Table 60: Descriptive Statistics of 18-Month Head Circumference and Head Circumference Z-scores (N = 78)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
18-month head circumference	48.26	1.67	45.00 – 52.50	.49	-.22
18 month head circ z-score	-.47	1.35	- 2.57 – 3.65	.59	.17

The Spearman Rho correlation between the z-scores at term and 18 months of age was $r = .59$ ($p < .01$), and between 3 months and 18 months was $r = .73$ ($p < .01$).

Figure 3: Identification of Variables to be Investigated in Relation to Growth & Developmental Outcomes



6.4. Statistical Plan

Figure 3, on the preceding page, shows an outline of the antecedent variables that were investigated in relation to the growth and developmental outcome measures.

In the first Results Section, the relationships between early variables and growth to 3 months of age were examined using correlational analyses. Some of these analyses were exploratory, others based on prior research findings. Subsequently, multiple regression analyses, using a stepwise approach, were performed in order to produce prediction models for early growth rate. In addition to multiple regression analyses, logistical regression was performed to identify the major factors influencing infant weight status at 3 months of age (i.e. above or below the 10^{th} percentile for age).

In the second Results Section, three main sets of analyses were performed. Firstly the anthropometric data was examined and compared with that of a normative sample. Weight stability groups were then computed and comparisons made between these groups in terms of growth rates. Correlational analyses were performed between parental height and infant weight at each of the assessment points. Secondly the relationship between developmental outcome at 18 months of age and various independent variables was examined, primarily using correlational analyses for the continuous variables. Independent t-tests and Mann-Whitney U tests were used for the dichotomised outcome variables. Finally regression analyses were performed, both multiple regression and then logistical regression, in order to produce prediction models for developmental outcome at 18 months.

SECTION III: BIRTH – 3 MONTHS

RESULTS & DISCUSSION

Introduction to Section III

In this Section the Results and Discussion for the period birth – 3 months are presented. The organisation of this Section reflects the first of the two primary research questions addressed in this thesis, that is, the nature of early post-natal growth in infants born very preterm, and the extent to which various medical, nutritional, infant behavioural and maternal factors contribute to this observed growth. The Section is divided into two Results chapters, followed by a Discussion chapter.

The first brief chapter introduces the concepts of growth and weight status, and then reports on the findings for the 90 infants included in the GAIN Study.

The second chapter firstly examines the relationship between the observed early growth patterns and various independent variables that fall into the categories of medical, nutritional, infant behavioural and maternal/social.

The medical variables that are analysed in relation to growth include birth data (gestational age and weight), several measures that reflect how sick the infant was during initial hospitalisation (duration of intensive care; level of care during first ten days; total duration of hospitalisation; and duration of mechanical ventilation), a composite neonatal medical risk index, and the presence of early abnormal brain scans.

The nutritional variables that are examined in relation to growth can be broadly divided into two categories – the type and quantity of milk that the infant receives; and the infant's actual feeding skill/technique. The latter was measured using a feeding problem index; measurement of intake per minute; and objective sucking analysis using a Whitney Strain Gauge.

Irritability, together with crying and sleeping patterns, are the aspects of infant behaviour that are examined in relation to early growth. The subject's scores on the irritability cluster of the Brazelton Neonatal Assessment Scale (NBAS) at term, together with cry duration over a 24 hour period were the measures of "irritability". Total hours slept in 24-hours, the relationship between the number of hours slept and the number of feeds received, together with information regarding whether the infant self-woke for feeds or had to be woken by the mother were the sleep variables used in the analyses.

Lastly the effects on growth of maternal and social factors were analysed. Variables that were examined in relation to growth included maternal age, maternal intelligence (using the Weschsler Adult Intelligence Scale) and socio-economic status (using the Osborn Index).

At the end of this second chapter, the most significant individual contributors to growth based on the reported findings are drawn together and entered into regression analyses to establish the specific effects of independent variables when co-variates were held constant. Models were constructed to predict patterns of early growth based on these independent variables.

The majority of the independent variables that were included in the analyses and are presented in this section have been selected because previous publications suggested that they were relevant to early infant growth. In many cases, however, the precise relationships between these variables and growth are unclear, with studies either producing ambiguous or conflicting results, or else failing to control for confounding variables. This thesis is intended to address these ambiguities in order to ascertain the specific contribution of each independent variable to the observed growth of this group of very preterm infants.

As already mentioned, the third chapter in this Section comprises the Discussion relating to the results presented in the previous two chapters.

Chapter 7: Early Growth

7.1. Weight and the Concept of "Growth"

In this chapter the growth data on the subject infants between birth and three months of age (corrected for gestation) is presented. The equipment and procedures used to collect the anthropometric data on the infants at each assessment point were described in Section II (Method). The anthropometric measurements were standardised into z-scores according to the British 1990 Growth Reference database. This is standardised according to actual age in completed weeks, and takes into account the gender of the infant. The intention initially was to compute "growth" between one assessment point and another using a formula devised by Cole (1995). This formula takes into account the starting point z-score (since there is always regression to the mean, and the further from the mean the infant's weight, the greater the expected regression). Unfortunately, however, the use of this formula was not possible because of the very early ages at which the anthropometric measurements were first taken, which were outside the parameters of the formula. Consequently, in this thesis the simple change in the z-scores between the time points have been used as measures of growth (measured between birth and term (Gain1), between term and 3 months (Gain2) and between birth and 3 months (Gain3)). Thus a positive "growth" z-score indicates that the subject has shown better growth than average in relation to it's peers, whereas a negative score indicates that the subject has grown more slowly than average compared to it's peers.

As can be seen from Table 61, the mean weight z-score at each assessment point for the infants in this study was below that expected using the British Growth Reference (BGR). This low mean weight z-score was most apparent at term, with the mean for the sample having fallen to more than one standard deviation below the mean given on the BGR. This fall in mean weight z-score reflects the generally poor growth of the subjects between birth and term compared to infants who remained in utero. Between term and three months corrected age, the infants on average showed some catch-up growth, which in turn is reflected in the improvement in actual mean weight z-scores.

Table 61: Weight and Growth Variable Data

Variable	N	Mean	Std Dev	Min-Max	Skewness	Kurtosis
Birth weight z-score	90	-.37	1.14	-2.54 – 2.04	.16	-.79
Term weight z-score	88	-1.03	1.13	-3.65 – 1.70	.17	.17
3 mth weight z-score	89	-.86	1.18	-3.74 – 2.50	.20	.13
Growth between birth and term	88	-.66	1.09	-4.14 - 2.08	-.42	.85
Growth between term and 3-months	87	.16	.79	-1.33 – 2.08	.41	-.30
Growth between birth and 3-months	89	-.51	1.08	-3.64 – 3.04	.26	.86

The three "growth" variables were fairly normally distributed, although further analysis revealed two outliers for Gain1 (birth to term), one high and one low; one high outlier for Gain2 (term to three months); and one high outlier for Gain3 (birth to 3 months).

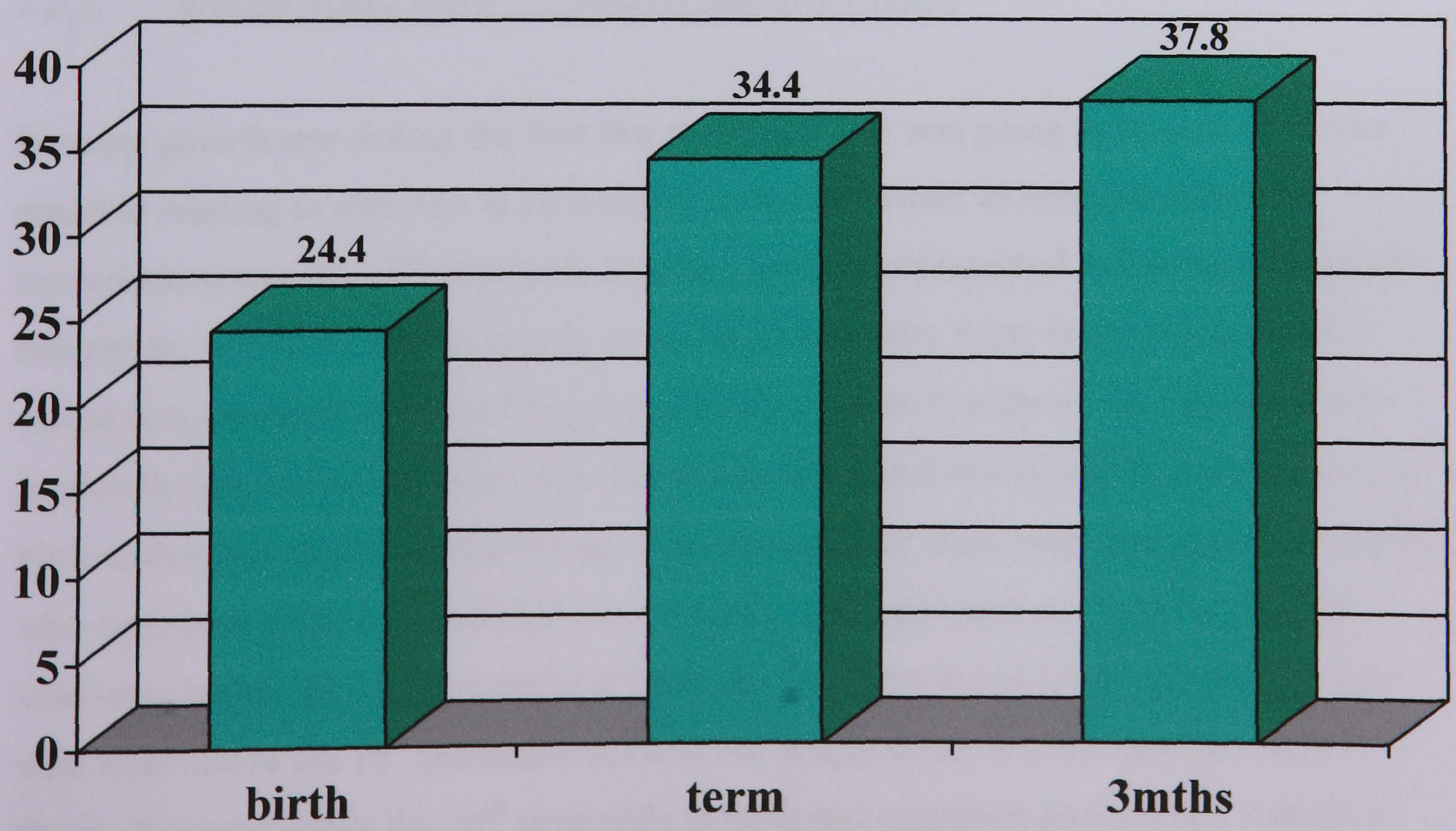
The correlation coefficients between the actual weight z-scores of infants over the three assessments were analysed: between birth and term $r = .55$; between birth and three months $r = .56$; and between term and three months $r = .77$ (all significant at the $p < .01$ level). In addition, the correlation coefficients between the three "growth" variables were also analysed. There was a significant negative correlation ($r = -.36$, $p < .01$) between Gain1 and Gain2 – that is, the infants who grew least well up to term tended to show better growth for the following three months, and vice versa. Between Gain1 and Gain3, however, the correlation was $r = +.74$ ($p < .01$), and between Gain2 and Gain3 was $r = -.36$ ($p < .01$).

7.2. Weight Status

As discussed in the Method Section, the infants in the study were categorised as being born at a weight appropriate for gestational age (AGA) or small-for-gestational age (SGA, i.e. below the 10^{th} percentile). Similarly, at term and three months of age infants were identified as being either an appropriate weight for age, or small-for-age (again using the 10^{th} percentile as the cut-off).

As can be seen from Figure 4, although all the infants were, of course, growing between the assessment points, the proportion of infants whose weight was below the 10^{th} percentile actually increased between birth and 3-months corrected age (from 24.4% to 37.8%). When Chi-square analyses were performed, the increase in the proportion of infants who were small-for-age between birth and term and for the overall period between birth and 3-months were both significant (Chi-square 5.54, $p < .05$; Chi-square 9.12, $p < .01$ respectively), although the increase between term and 3-months failed to reach statistical significance (Chi-square .35, $p < .56$).

Figure 4: Percentage of Infants with Weight < 10^{th} Percentile



7.2.1 Stability of Weight Status

The stability of weight status over time for the infants was subsequently analysed. Of the 22 infants in the study who were born at a weight below the 10th percentile for gestation, just five were above that criterion by 3 months corrected age, and of the 68 infants who were born above the 10th percentile, fourteen had fallen below the 10th percentile by 3 months corrected age. The relative risk of being below the 10th percentile at term and three months according to earlier weight status was calculated (using the EPI6INFO statcalc.exe public software, available from the Centre of Disease Control, Atlanta, USA). The relative risk of being below the 10th percentile at term for an infant born SGA compared to an infant born AGA was calculated as 2.02 (c.i. 1.36 – 3.0, $p < .000$). The relative risk of being below the 10th percentile at 3 months corrected age for an infant who was below the 10th percentile at term compared to an infant above the 10th percentile at term was calculated as 1.97 (c.i. 1.27 – 3.06, $p < .001$). The relative risk of being below the 10th percentile at 3 months corrected age for an infant born SGA compared to an infant born AGA was calculated as 1.59 (c.i. 1.17 - 2.18, $p < .001$). Thus there was a statistically significant greater risk of being below the 10th percentile for weight at 3 months corrected age for infants born SGA.

7.2.2. Weight Status Birth – 3-Months Stability Groups

Because growth rate during the first few months of life was going to be used in further analyses relating to outcome at 18 months, it was important to establish whether movement across the 10th percentile criterion actually represented a difference in growth rate per se, or whether it was simply a case of infants who were nearer to the criterion on the first occasion therefore being more likely to cross it without any real difference in growth rate. A variable was therefore computed which compared the weight status at birth to that at 3 months corrected age and consequently there were four groups, 1) those who were below the 10th percentile at birth and remained there at 3 months; 2) those who were below the 10th percentile at birth but had risen above it at 3 months; 3) those who were above the 10th percentile at birth but dropped below it by 3 months; and 4) those who were above the 10th percentile at birth and remained above it at 3 months of age (see Table 62b). In order to ascertain whether there were significant differences in birth weight z-scores between the four groups, a one-way analysis of variance was performed. As can be seen in Table 60, there were overall significant group differences ($F = 26.20$, $p < .000$), and a Scheffe's range test found that the only significant differences were between the AGA groups (3 & 4) and SGA groups (1 & 2), rather than between the AGA infants who remained above the 10th percentile and those who dropped below, or between the SGA infants who remained below the 10th percentile and those who rose above it by 3 months of age.

Table 62: Group Differences on Birth Weight Z-scores

GROUP	N	MEAN	STD DEV	MIN-MAX	F	SIG OF F
1	13	-1.79	.32	-2.28 - -1.35	26.20	.000
2	6	-1.64	.45	-2.54 - -1.35		
3	16	-.23	.94	-1.19 – 1.86		
4	46	.24	.90	-1.22 – 2.04		

Table 62b: Key to Weight Stability Groups

GROUP	WEIGHT STATUS AT BIRTH AND 3 MONTHS
1	Below 10th percentile at both birth and 3 months
2	Below 10th percentile at birth but above it at 3 months
3	Above 10th percentile at birth but below it at 3 months
4	Above 10th percentile at both birth and 3 months

Further analyses were subsequently performed to ascertain the actual mean growth rates of the subjects in each of the four groups, to see whether there were significant differences in rates of growth, or whether the starting point weight z-score was the cause of the movement across the 10th percentile criterion (as can be seen from the above table, the group 3 infants did have a somewhat lower mean birth weight z-score than their group 4 peers, although this difference did not reach statistical significance).

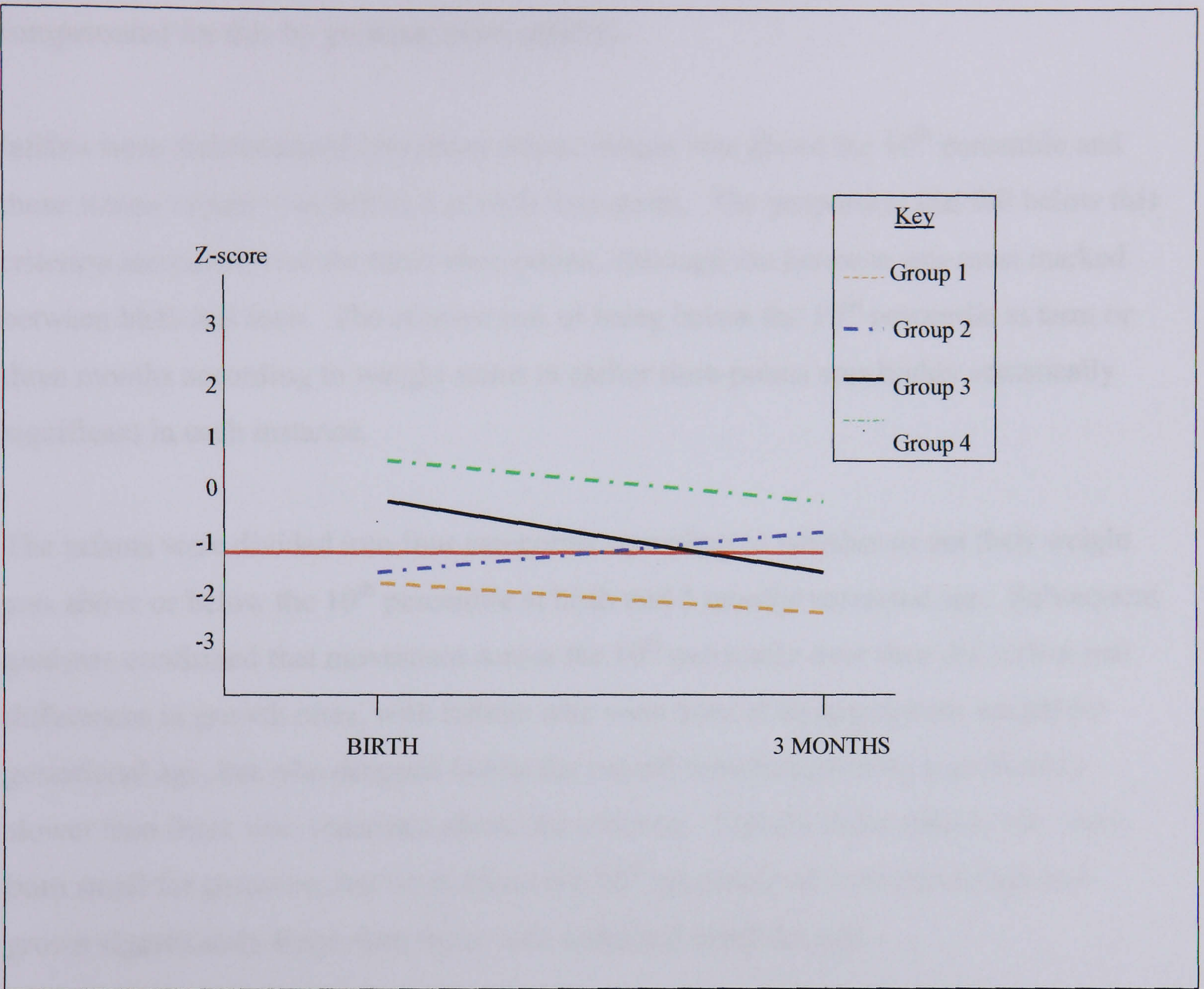
Table 63 confirms, however, that there were real and significant group differences in growth rate, with the group 3 infants showing the poorest rate of growth and the group 2 infants showing the fastest rate of growth. Further analysis revealed that the difference between groups 3 and 4 was highly significant ($p < .00$), as was that between groups 1 and 2 ($p < .01$), although that between groups 1 and 3 failed to reach statistical significance ($p < .70$). Thus it would seem that the differences between the four groups are real, and not simply an artefact of an arbitrarily assigned cut-off criterion.

Table 63: Group Differences on Growth Rate between Birth and 3 Months

GROUP	N	MEAN	STD DEVIATION	F	SIG OF F
1	13	-.47	.57		
2	6	.91	.36	7.82	.00
3	15	-1.33	.92		
4	46	-.38	1.13		

This difference in growth rates of the four groups is also shown in Figure 5, which depicts the change in weight z-scores between birth and 3 months for each of the groups.

Figure 5: Weight Z-score Changes from Birth to 3 Months for the Four Stability Groups



7.3. Summary of Chapter

Weight z-scores (based on completed weeks of age) were computed in order to compare infants who were seen and measured at slightly different ages. These z-scores showed that the infants in the Study were smaller than expected throughout the first few months of life, with this shortfall being most marked at the term assessment when the mean was more than one standard deviation below the mean.

Growth (as measured by change in weight z-score) between the three time-points was analysed, and correlational analyses showed that growth between birth and term was negatively correlated with growth during the subsequent three months (i.e. the infants who grew slowest during the first few weeks of life subsequently at least partially compensated for this by growing more rapidly).

Infants were dichotomised into those whose weight was above the 10^{th} percentile and those whose weight was below it at each time-point. The proportion that fell below this criterion increased over the three time-points, although the increase was most marked between birth and term. The relative risk of being below the 10^{th} percentile at term or three months according to weight status at earlier time-points was highly statistically significant in each instance.

The infants were divided into four categories according to whether or not their weight was above or below the 10^{th} percentile at birth and 3 months corrected age. Subsequent analyses confirmed that movement across the 10^{th} percentile over time did reflect real differences in growth rates, with infants who were born at an appropriate weight for gestational age, but who dropped below the cut-off criterion growing significantly slower than those who remained above the criterion. Equally those infants who were born small for gestation, but were above the 10^{th} percentile at 3 months of age had grown significantly faster than those who remained small for age.

Chapter 8: The Relationship between Independent Variables and Growth from Birth to 3-Months

8.1. Medical Risk Variables in Relation to Growth

In this sub-section, the effects of intra-uterine and early neonatal medical risk on growth are examined. There is evidence from previous research that infants born very preterm frequently fail to grow at the rate expected (based on in utero data) during the first few weeks of life (Alexander, 1996). Furthermore, in the longer term, a proportion of very preterm infants fail to achieve normal growth, particularly those who have had severe neonatal complications or were born small-for-gestation (Campbell, 1997). In this chapter, therefore, an attempt is made to ascertain whether, within this sample of very preterm infants, there is a significant relationship between gestational age and/or birth weight and early growth rate. In addition, a variety of measures of severity of early illness are explored as potential predictors of growth during the first few months of life.

There were several measures of medical risk that were examined in relation to subsequent growth, these being Composite Antenatal Score ("Comppreg"), Composite Peri/neonatal Score ("Compneon"), birth weight, birth weight z-score, gestation, Level of Intensity of Care over the first 10 days, Duration of Intensive Care, and Total Days of Hospitalisation (all described in detail in Section II – Methods).

Table 64 shows the correlations between the growth and weight measures and the early medical variables. Spearman non-parametric correlations were performed due to the non-normally distributed nature of several of the variables. As can be seen, the only early variable that was significantly correlated to growth between birth and term was birth-weight z-score, and the negative direction of the correlation indicates that the infants who were heavier for gestation at birth grew less well during the following few weeks. For the period between term and 3 months corrected age, the only early variable that was significantly correlated with growth was gestational age, with the more mature infants tending to grow better during this period than infants born at an earlier gestation. For the overall period birth to 3 months corrected age, both gestational age and birth weight z-score remained significantly correlated to growth (in the directions described above). In addition, however, several of the variables indicating how sick the infant had been during initial hospitalisation were also significantly correlated to growth. These were all in the expected direction, with the sicker infants growing less well. It must be recalled, however, that the medical variables that correlated significantly with growth were also highly inter-correlated. The only medical variables not significantly correlated with growth during this overall period were total days of hospitalisation and brain scan scores.

The variables that were significantly correlated with weight z-score at 3 months of age were actual birth weight and birth weight z-score, Level of Care over first 10 days, and Duration of Intensive Care.

Table 64: Relationship between Early Risk Variables and Growth

Variable	**Growth Birth-term** (N = 88)	**Growth Term-3-mths** (N = 87)	**Growth Birth-3-mths** (N = 87)	**3-mth weight z-score** (N=89)
Birth Risk				
"Comppreg"	.16	-.04	.05	-.14
Gestational Age	.06	**.22***	**.21***	.10
Birth Weight	-.26*	.18	-.11	**.51****
Birth Weight z-score	**-.46****	.01	**-.41****	**.58****
Medical factors				
"Compneon"	-.13	-.09	**-.22***	-.17
Level of Care of 1st 10 days	-.13	-.21	**-.32****	**-.26***
Duration of Intensive Care	-.13	-.18	**-.28****	**-.29****
Duration of Ventilation	-.17	-.07	**-.26***	-.12
Total days in hospital	-.07	-.13	-.16	-.30
Abnormal Brain scan (haemorrhage /ventricular dilation)	-.09	-.08	-.12	-.09
Abnormal Brain scan (cyst formation)	.10	-.13	.04	-.03

* significant at p < .05 level
** significant at p < .01 level

8.2. Infant Feeding in Relation to Growth

Previous research has suggested that two aspects of infant feeding are important in relation to growth. There is a substantial amount of evidence that the type of milk that an infant receives in the first few months of life influences at least the concurrent rate of growth (Lucas et al, 2001; Carver et al, 2001; Nicholl, 1999 etc), and can also affect later developmental status (Morley et al, 1988; Lucas et al, 1992; Horwood, 2001). In addition, previously published research has linked abnormal infant feeding technique to failure to thrive (i.e. slow growth rate) (Ramsay et al, 1993). Both these aspects of infant feeding are addressed in this sub-section. Firstly, infant nutrition, i.e. the type of milk the infants were receiving at each assessment point in relation to growth rate is presented, and subsequently the relationship between the infant feeding technique and rate of growth.

8.2.1. Nutrition

At the beginning of this section on nutrition, the relationship between the type of milk received at term and 3 months corrected age on concurrent weight and growth rate up to the relevant assessment point is reported. Subsequently, correlational analyses were performed to ascertain whether there was a relationship between the number of feeds an infant received during a 24-hour period (at both Term and 3-months of age) and the growth/weight variables. Finally, analyses were performed to examine the relationship, if any, between the birth and early medical history of the infants and the subsequent method of feeding that was used. It should be noted that the decision as to whether an infant will be breastfed or bottle-fed is usually made by the mother during the antenatal period. Of the infants included in the present study, 93% of the mothers had decided on their preferred method of feeding prior to the birth of the infant, even though all the infants were born at least eight weeks earlier than expected.

8.2.1.1. Relationship between Type of Milk Received and Growth

8.2.1.1.1. Term Data

For the following analyses examining the relationship between type of milk received and growth, differentiation was made between preterm formulae and standard infant formulae, the latter being grouped together with the "special" formulae that have been developed to assist with the feeding of infants with specific problems (e.g. gastric reflux or cow's milk allergy). The reason for this dichotomising of formula milks is that previous research has generally shown that infants fed preterm formula, at least until term, grow better during that period than infants fed standard formula (Cooke, 1998) or breast milk (Lucas et al, 2001; Carver et al, 2001). Preterm infants receiving breast milk are usually fed it fortified with added nutrients during the initial period when milk is being passed into the stomach using a naso-gastric tube. There is some evidence that infants fed such fortified breast-milk can grow at a rate similar to that shown by infants given preterm formula (Nicholl, 1999).

As can be seen from Table 65, there were significant differences in the growth trajectories of infants depending on whether they were receiving predominantly breast milk or formula at term. Within this sample, early growth, i.e. from birth to term, was adversely affected if the infant was receiving mainly breast milk at term. However, subsequent growth (from term to 3 months) was significantly better for these infants.

When one-way analysis of variance was performed, the main milk being given at term was shown significantly to affect both growth from birth to term and, prospectively, from term to 3 months. When post-hoc analysis was performed using Scheffe's test, it was discovered that the difference was only significant between breast and formula overall, with no difference in growth according to type of formula received (difference between breastfed and preterm formula-fed infants was significant at the $p < .01$ level, and between breastfed and standard formula-fed infants was significant at the $p < .05$ level).

As far as growth for the overall period birth to 3 months was concerned, however, the contrasting effects of milk type on early and later growth appeared to cancel one another out, and the overall effect of milk type was slight. For this overall growth measure, although the results were statistically non-significant, the trend was for infants fed preterm formula at term to grow best, followed by breastfed infants, with infants receiving standard formula at term showing slowest growth for the period between birth and 3 months.

As Table 65 shows, there was no relationship between type of milk being received at term and weight z-score at 3 months of age.

Table 65: Relationship between Type of Milk Received at Term and Growth

	Breast mean (sd) (n=22)	**Pre-term** mean (sd) (n=44)	**Full-term/Special** mean (sd) (n=22)	F	p
Growth birth-Term	-1.43 (1.04)	-.29 (.92)	-.62 (1.08)	9.65	**00**
Growth term-3 months	.81 (.61)	.02 (.71)	-.19 (.75)	12.79	**.00**
Growth birth-3 months	-.68 (.99)	-.29 (1.18)	-.80 (.87)	2.11	.13
3-month weight z-score	-.84 (.96)	-.78 (1.29)	-1.03 (1.16)	0.33	.72

8.2.1.1.2. Type of Milk Received at 3 months and Growth

Growth between term and 3 months was also significantly related to the main type of milk being received at 3 months, with infants who were still receiving breast milk exhibiting much greater growth velocity than either of the two formula sub-groups. Nonetheless, all the infants in the study were showing positive growth z-scores between term and three months, which suggested that they were beginning to "catch-up" weight-wise after their slow start (n.b. a z-score of 0 represents average growth rate). Again, however, the type of milk being received at this time point does not seem to be related to overall growth from birth to 3 months (see Table 66).

Analyses were also performed using the concurrent weight z-score at 3 months corrected age as the outcome measure. As can be seen in Table 64, by this age there was no discernible difference in size between the infants who were being breastfed, those being fed preterm formula, or those who were being fed a standard infant formula.

Table 66: Relationship between Type of Milk Received at 3 months and Growth

	Breast mean (sd) (n=16)	**Pre-term** mean (sd) (n=28)	**Full-term/Special** mean (sd) (n=45)	**F**	**p**
Growth term-3 months	.77 (.57)	.01 (.53)	.05 (.90)	6.02	**.01**
Growth birth-3 months	-.52 (.97)	-.50 (1.12))	-.52 (1.11)	.00	1.0
3-month Weight z-score	-.93 (.97)	-.90 (1.17)	-.80 (1.26)	.10	.91

8.2.1.2. Relationship between Number of Feeds and Growth

Correlational analyses were performed to ascertain whether there was a relationship between the number of feeds given during a 24-hour period, and any of the growth/weight variables. As can be seen from Table 67, the only significant correlation is between the number of milk feeds given at term and growth during the following three months.

Table 67: Relationship between Number of Feeds and Growth

Variable	**N**	**Growth Birth-Term**	**Growth Term-3 mths**	**Growth Birth-3 months**	**3-mth weight z-score**
Term					
Number of milk feeds		-.21	**.40****	.11	.01
3 month					
Number of milk feeds		-	**.24***	.07	-.18
Number of solid feeds		-	.04	-.03	.11

** Significant at the .01 level
* Significant at the .05 level

8.2.1.3. Relationship between Number of Feeds and Type of Milk Received

Analyses were performed to ascertain whether there was a relationship between the type of milk the infants were receiving and the number of feeds during a 24-hour period. As expected, there was a significant relationship, both at term and at the 3-month assessment, with infants being breast-fed receiving more feeds than those being formula-fed.

Table 68: Relationship Between Number of Feeds and Type of Milk Received

Variable	Breast Milk Mean (SD)	Formula Mean (SD)	Mann-Whitney U test p
Term	*(N=23)*	*(N=66)*	
Number of Feeds	8.17 (2.64)	6.35 (0.98)	**.00**
3-Months	*(N=16)*	*(N=74)*	
Number of Feeds	7.69 (1.58)	5.19 (1.13)	**.00**

8.2.1.4. Relationship between Type of Milk and Early Medical Variables

8.2.1.4.1. Term Data

Since the type of milk received by the infants was related to rate of growth, it was considered important to ascertain whether birth factors and factors representing the severity of illness of the infant significantly influenced the type of milk that the infant was receiving at term. For these analyses the type of milk being received was dichotomised into "mainly breast milk" versus "other", which included any of the possible artificial formulae.

As can be seen from Table 69, there were no significant differences between infants being given breast milk at term and those receiving formula on any of the birth or intensity of care variables. For several of the variables there was, however, a tendency for the infants receiving breast milk to have been less sick than those receiving formula, although this did not include gestational age at birth for which the two groups were almost identical.

Table 69: Relationship between Birth & Neonatal factors and Type of Milk at Term

Variable	**Breast milk** mean (sd)	**Formula** mean (sd)	**t-value**	**p**
Birth weight (grams)	1347 (278)	1242 (341)	1.38	.17
Birth weight z-score	-.20 (1.23)	-.43 (1.11)	0.87	.39
Gestation (weeks)	29.7 (1.9)	29.3 (1.7)	0.97	.34
Level of IOC 10 days	32.3 (13.4)	37.6 (14.8)	-1.55	.13
Duration of IOC	21.7 (19.3)	30.1 (33.5)	-1.49	.14
Total days in hospital	51.8 (19.9)	57.5 (28.2)	-0.92	.36

8.2.1.4.2. Relationship between Type of Milk at 3 Months and Birth/Early Medical Variables

The foregoing analyses were repeated, using the type of milk given at 3 months corrected age. Interestingly, by this time point, there did seem to be a relationship between some of the early medical variables and the type of milk being received. The infants who had been of a lower gestation, and subsequently sicker during the neonatal period, were significantly more likely to be receiving formula milk at 3 months corrected age.

Table 70: Relationship between Birth & Neonatal factors and Type of Milk at 3-Months

Variable	**Breast milk** mean (sd)	**Formula** mean (sd)	**t-value**	**p**
Birth weight (grams)	1399 (221)	1243 (340)	1.75	.08
Birth weight z-score	-.42 (1.21)	-.36 (1.14)	-0.18	.86
Gestation (weeks)	30.38 (1.15)	29.18 (1.81)	3.37	**.01**
Level of IOC 10 days	28.50 (13.54)	37.77 (14.30)	-2.37	**.02**
Duration of IOC	14.69 (16.69)	30.62 (31.95)	-2.85	**.01**
Total days in hospital	46.38 (10.79)	57.99(28.04)	-2.75	**.01**

8.2.2. Infant Feeding Technique

Feeding disorganisation and dysfunction have been shown in previous research to adversely affect growth (e.g. Ramsay et al, 1993; Heptinstall et al, 1987) and this was therefore an important area of infant behaviour to examine in the present study. As indicated in Section II (Method), there were three assessments of infant feeding technique, each administered at term and 3 months of age. These were the Feeding Problem Index (FPI), intake per minute and the feed analysis using the Whitney Strain Gauge. The first measure was maternally-rated, incorporated in the Parent Interview conducted at each assessment point. The latter two measures were objective measures.

Firstly, the relationship between infant feeding technique (as assessed using the three measures mentioned above) and growth variables was examined. Then the inter-correlations between the various measures were examined, first for the term and then for the 3-month data. Finally, the relationship between early medical variables and infant feeding technique was investigated, since previous research has suggested that various medical complications can have an adverse effect on feeding skills (e.g. oral intubation to facilitate mechanical ventilation, chronic lung damage etc).

As discussed in Section II (Method) data obtained using the Whitney Strain Gauge was unfortunately only available on a relatively small number of subjects (n=30 at term and 49 at 3-months). This was due to technical difficulties, which resulted in it not being possible to code a large proportion of the feed printouts.

8.2.2.1. Infant Feeding Technique and Growth

8.2.2.1.1. Term Data

Correlations were performed between the various measures of infant feeding technique, both at term and 3 months of age, and the three growth variables and weight status below the 10^{th} percentile at each assessment point. As can be seen from Table 71, very few of the feeding technique measures at term correlated significantly with any of the growth or weight status variables. One exception to this was intake per minute, which correlated significantly with growth for the overall period birth to 3-months corrected age and with actual weight at 3 months of age. It would appear that faster feeding, i.e. more efficient feeding, was related to increased growth rate. Finally, individual suck duration was positively correlated with 3-month weight, showing that infants who took longer sucks tended to be heavier by the 3-month assessment point.

Table 71: Correlations between Measures of Infant Feeding Technique at Term and Growth

	Growth Birth-Term	**Growth Term-3 mths**	**Growth Birth-3 mths**	**3-mth weight z-score**
FPI (n=88)	-.03	-.16	-.08	-.06
Intake/ Min (n=86)	.21	.16	**.30****	**.25***
Burst Length (n=30)	-.13	.21	.09	-.10
Sucks/Burst (n=30)	-.12	.23	.13	-.05
Pause Length (n=30)	-.30	.14	-.26	.14
% Time Sucking (n=30)	.13	.02	.21	-.11
Individual Suck Duration (n=30)	.07	.19	-.19	**.44***

** significant at the .01 level
* significant at the .05 level

In addition to the whole group analyses shown in the table above, the infants were also dichotomised into breast-feeders and bottle-feeders in order to eliminate possible effects of method of feeding and type of milk received. The majority of infants were being bottle-fed formula, and indeed the number of breast-fed infants upon whom WSG data was available was so small (n = 5) that statistical analyses were not possible on this group. For the bottle-fed infants sub-group, however, the results of the analyses were in line with those from the whole group analyses.

8.2.2.1.2. Three-Month Data

Similar correlational analyses were performed between the measures of infant feeding technique assessed at 3 months and the growth and weight variables up to and including that time point. As can be seen from Table 72, there were no statistically significant correlations between the feeding measures and growth/weight outcome variables.

Table 72: Correlations between Measures of Infant Feeding Technique at 3-Months and Growth

	Growth Term-3 mths	Growth Birth-3 mths	3-mth weight z-score
FPI (n=87)	-.13	.01	-.19
Intake/ Min (n=85)	-.15	-.07	.13
Burst Length (n=49	-.02	-.02	-.03
Sucks/Burst (n=49)	.00	-.07	-.06
Pause Length (n=46)	.19	.24	.00
% Time Sucking (n=49)	-.07	-.03	-.01
Individual Suck Duration (n=49)	-.05	-.22	-.14

8.2.2.2. Inter-correlations between measures of Infant Feeding Technique

8.2.2.2.1. At Term

As can be seen from Table 73, there were several statistically significant inter-correlations between the different instruments measuring infant feeding technique at the Term assessment. The Feeding Problem Index was significantly negatively correlated with intake per minute, i.e. the more feeding problems that the infants had, the lower the intake per minute.

Intake per minute, in addition to being correlated with the Feeding Problem Index, was also significantly correlated to individual suck duration, i.e. the slower the individual suck, the greater the intake per minute. Individual suck duration was the only strain gauge variable that correlated significantly with other measures of feeding technique although, not surprisingly, several of the strain gauge variables were highly inter-correlated. The burst length, sucks per burst, and pause length were all significantly inter-correlated, but with the burst length and sucks per burst being negatively correlated with the pause length.

Although the Feeding Problem Index was completed for 88 of the 90 subjects and the intake per minute variable was also available for most of the infants, the strain gauge variables, as discussed in the Method Section, were only available on 30 of the infants at term due to technical difficulties.

Table 73: Inter-correlations between Measures of Infant Feeding Technique at Term

	FPI	Intake /Min	Burst Length	Sucks/ Burst	Pause Length	% Time sucking	Ind Suck Duration
FPI	-	-	-	-	-	-	-
Intake/ Min	**-.35****	-	-	-	-	-	-
Burst Length	-.17	.07	-	-	-	-	-
Sucks/Burst	-.18	-.06	**.96****	-	-	-	-
Pause Length	-.24	.14	**-.40***	**-.37***	-	-	-
% Time Sucking	-.02	.02	**.88****	**.84****	**-.74****	-	-
Individual Suck Duration	-.05	**-.42***	-.03	.16	.08	-.03	-

** signficant at the .01 level
* significant at the .05 level

8.2.2.2.2. At 3 Months

The inter-correlations at the 3-month assessment between the various measures of infant feeding technique were very similar to those at the Term assessment. The Feeding Problem Index was again highly negatively correlated with intake per minute and to a lesser extent with individual suck duration. Intake per minute, in addition to being correlated with the Feeding Problem Index, was again significantly correlated with individual suck duration. The other strain gauge variables, i.e. burst length, sucks per burst and pause length were again very highly inter-correlated, but did not correlate significantly with any of the other measures of feeding technique.

At the 3-month assessment, strain gauge data was only available on 48 of the 90 subjects, but the other measures were available for over 95% of the infants.

Table 74: Inter-correlations between Measures of Infant Feeding Technique at 3 Months

	FPI	Intake /Min	Burst Length	Sucks/ Burst	Pause Length	% Time sucking	Ind Suck Duration
FPI	-	-	-	-	-	-	-
Intake/ Min	**-.30****	-	-	-	-	-	-
Burst Length	-.06	-.01	-	-	-	-	-
Sucks/Burst	-.00	-.05	**.99****	-	-	-	-
Pause Length	-.00	-.28	**-.45****	**-.47****	-	-	-
% Time Sucking	-.00	.04	**.93****	**.93****	**-.67****	-	-
Individual Suck Duration	**.29***	**-.31***	.08	**.19**	**-.23**	**.12**	-

** signficant at the .01 level
* significant at the .05 level

8.2.2.3. Infant Feeding Technique & Early Medical Variables

8.2.2.3.1. Term Data

Correlational analyses were performed to ascertain whether there was a relationship between early medical variables and feeding technique at the Term assessment. As can be seen from Table 75, there were few statistically significant correlations. Gestation at birth correlated with intake per minute at term. Pause length at term was highly correlated with birth weight. None of the other correlations were statistically significant, however, although small sample size might be accountable for this as some of the correlations were of a reasonable magnitude (e.g. birth weight with percentage of time spent sucking).

Table 75: Correlations between Early Medical Variables and Infant Feeding Technique At Term

	Gestation	Birth Weight	Birth Weight Status	Duration of Intensive Care	Days of Mechanical Ventilation
FPI	.09	.05	.11	.08	-.03
Intake/ Min	**.28***	.20	-.09	**-.25***	-.11
Burst Length	.16	-.08	-.01	-.09	-.06
Sucks/Burst	.14	-.10	-.01	-.01	-.04
Pause Length	.23	**.51****	-.22	-.25	-.18
% Time Sucking	-.01	-.32	.09	.05	-.00
Individual Suck Duration	.03	.08	-.03	-.12	.07

** signficant at the .01 level
* significant at the .05 level

8.2.2.3.2. Three-Month Data

Similar correlational analyses were performed between early medical variables and infant feeding technique at 3 months corrected age, since by this age feeding disorganization due to immaturity might be expected to have alleviated, leaving only those infants with more chronic feeding dysfunction to display abnormal feeding behaviours. As can be seen from Table 76, none of the measures of infant feeding technique were related to the early medical variables. These findings are in contrast to previous published findings, and will be considered in the Discussion Chapter.

Table 76: Correlations between Early Medical Variables and Infant Feeding Technique At 3 Months

	Gestation	Birth Weight	Birth Weight Status	Duration of Intensive Care	Days of Mechanical Ventilation
FPI	-.09	-.15	.05	.04	.08
Intake/ Min	-.06	.02	.00	.03	-.08
Burst Length	-.10	-.02	-.11	.24	.14
Sucks/Burst	-.10	-.02	-.12	.25	.14
Pause Length	.21	.01	.18	-.14	-.26
% Time Sucking	-.12	-.02	-.20	.25	.19
Individual Suck Duration	-.04	-.01	.00	.20	.02

** signficant at the .01 level

* significant at the .05 level

8.3. Infant Behaviour Regulation in Relation to Growth

This section examines the relationship between variables measuring individual infant behavioural characteristics and concurrent growth and weight z-score at 3 months corrected age. The traits that are examined are irritability and sleep patterns. Some of these analyses are exploratory: for example, Carey (1985) reported that there were more irritable infants in a fast growing group of infants than in the slower growing group, and it was therefore hypothesised that irritable infants might be fed more frequently, resulting in accelerated growth rates, and conversely that infants who slept for long periods might be fed less frequently and therefore exhibit slower growth.

8.3.1. Infant Irritability

Infant irritability was measured using a variety of instruments, both at term and at 3 months corrected age (see Section II - Method). Firstly, the relationship between these measures of irritability and growth are presented using the same growth variables as in the previous sub-sections. Secondly, the relationship between irritability and feeding frequency are presented.

Unfortunately, as will be seen from the following tables, irritability data was not available on all 90 subjects. At the term assessment the missing data was due to infants still being hospitalised at the time of assessment, and the mothers therefore not being able to complete the questionnaires accurately. It was also not possible to complete the NBAS on some of the infants due to their fragile medical condition. At the 3-month assessment, however, the CPQ was completed for all the subjects.

8.3.1.1. Irritability and Growth

Analyses were performed to ascertain whether the infants rated as irritable showed different rates of growth from their less irritable peers. As can be seen from Table 77, however, there were no significant correlations between growth or weight and any of the irritability measures, either at term or 3 months of age.

Table 77: Correlations between Irritability and Growth

Variable	N	Growth Birth-Term	Growth Term-3 mths	Growth Birth-3 months	3-mth weight z-score
Term					
Cry Duration	81	-.06	.05	-.02	.-3
NBAS Irritability Cluster	80	-.05	.03	.03	-.01
3 month					
Cry Duration	87	-	-.06	-.04	.09

8.3.1.2. Irritability and Feeding

As previously mentioned, one of the a priori hypotheses of the study had been that the infants who were rated as irritable would be fed more frequently and should therefore show better growth rates than their more placid peers. The foregoing sub-section shows that the second part of this hypothesis was not supported by the available data, and in this sub-section the first part of that hypothesis, i.e. that irritable infants would be fed more frequently than their more placid peers, is examined. The same measures of infant irritability at each time point were used in these analyses as in the previous section. Spearman Rho correlations were performed since the data was not normally distributed. As can be seen from Table 78, there were no significant correlations between irritability or crying measures and the number of feeds an infant was given, either at term or 3-months of age.

Table 78: Correlations between Irritability and Concurrent Number of Feeds

Variable	N	Number of Feeds
Term – Milk Feeds		
Cry Duration	84	.06
NBAS Irritability Cluster	83	.11
3-Months – Milk Feeds		
Cry Duration	90	.07
3-Months – Solid Feeds		
Cry Duration	90	-.17

Previous analysis had revealed that there was a significant relationship between the number of feeds per day and the type of milk given at term ($t=3.44$, $p<.01$). As Table 79 shows, however, there were no significant differences between breast- and formula-fed infants in terms of irritability at term.

Table 79: Irritability and Method of Feeding at Term

Variable	Breast mean (sd)	Formula mean (sd)	t-value	p
Cry Duration (minutes)	167.4 (130.9)	185.5 (159.0)	-.49	.63
NBAS Irritability Cluster	19.5 (7.3)	18.2 (7.8)	.71	.48

8.3.2. Infant Sleeping

The second infant characteristic that was analysed in relation to early growth was sleeping behaviour, which was measured at both the Term and 3-Month assessments. The main reason for exploring this issue was that mothers of preterm infants are generally advised to wake them regularly for feeds when discharged from hospital, in the belief, presumably, that this will increase calorific intake and thereby enhance growth. First, the relationship between sleep patterns and growth/weight z-score is presented. Subsequently the relationship between sleeping and feeding variables was examined. Exploratory analyses were then performed to ascertain whether birth or early medical characteristics had an influence on the sleeping patterns of the infants, both directly (i.e. on self-waking behaviour) and indirectly (i.e. on whether or not the mother chose to wake her infant for feeds).

8.3.2.1. Relationship between Hours Slept and Growth

Correlational analyses were initially performed to see whether there was a relationship between the number of hours slept during a 24-hour period and an infant's concurrent weight or rate of growth. The outcome variables used were as previously, i.e. growth birth to term, term to 3 months, birth to 3 months and weight z-score at 3-months. Table 80 shows the correlations between these variables, and as can be seen the positive correlation between total hours slept during a 24-hour period at term and the growth variable is statistically significant. This indicates that the infants who slept for more hours overall during a 24-hour period at term actually grew better during the following three months, but the relationship between hours spent sleeping and growth had disappeared by the 3-month assessment. The correlation between hours slept and concurrent weight z-score was not significant.

Table 80: Correlations between Total Sleep Duration and Growth

Variable	**Hours slept at Term** (N=82)	**Hours slept at 3-mths** (N=87)
Growth birth-term	-.07	-.12
Growth term-3mths	**.22***	-.07
Growth birth-3mths	.09	-.16
3-month weight z-score	.09	-.18

* Significant at the .05 level

8.3.2.2. Relationship between waking/being woken and growth

Subsequently, independent t-tests were performed to ascertain whether waking or being woken regularly for feeds was related to growth and, as can be seen from Table 81, although the trend was for the infants who were waking/being woken for feeds at term (at least 4-hourly) to grow better, this difference failed to reach statistical significance. The results were very similar for the 3-month data, although at this age the criterion for waking/being woken had been increased to six hours.

Table 81: Relationship between Waking/Being Woken at Night and Growth

	Wakes/Woken Mean (SD)	**Over-sleeps** Mean (SD)	**t-value**	**p**
Term Assessment	**N=59**	**N=23**		
Growth birth-term	-.68 (1.02	-.57 (1.23)	-0.40	.69
Growth term-3-mths	.22 (.69)	-.05 (.93)	1.18	.24
Growth birth-3-mths	-.48 (1.06)	-.58 (1.17)	0.34	.73
3-mth weight z-score	-.88 (1.17)	-.65 (1.19)	-0.80	.43
3-mth Assessment	**N=51**	**N=38**		
Growth term-3-mths	.26 (.75)	.02 (.38)	1.40	.17
Growth birth-3-mths	-.57 (1.15)	-.44 (.98)	-.55	.59
3-mth weight z-score	-.85 (1.22)	-.86 (1.13)	.05	.97

8.3.2.3. Characteristics of Infants who fail to self-wake, and whose mothers leave them to sleep

Further exploratory analyses were then performed to ascertain whether there were differences between the infants who self-woke or were woken for feeds by their mothers, and those who failed to self-wake and were left to sleep for prolonged periods by their mothers.

8.3.2.3.1. At Term

Receiving four-hourly feeds was the criterion used at term principally because this is the rule generally applied in neonatal units. If an infant is fed approximately every four hours, then the average number of feeds per day should be six. Some infants are demand-fed (i.e. the infant initiates feeds), others are schedule-fed (i.e. the mother initiates feeds), and some combine the two. As already mentioned, however, mothers of infants who have been born very preterm are often advised to wake them at least four-hourly, to ensure an adequate daily intake.

At term 61 of the 84 infants were either self-waking or being woken by their mothers every four hours. That, however, left 23 infants who were left to sleep for longer periods until they woke of their own accord. As can be seen from Table 82, there were generally only slight differences between the infants who wake/get woken for feeds every four hours and those who are left to sleep for longer periods of time. The birth weight of those who self-woke/were woken was lower than for those who were left, and they required intensive care for longer. The difference in term weight z-score was in the same direction as for birth weight, with the smaller infants being more likely to self-wake/be woken for feeds. None of these differences, however, reached statistical significance. The only medical variable that was significantly related to the infant self-waking/being woken was the overall composite neonatal complications score of the two groups, with infants with higher composite scores (i.e. sicker neonatally) being more likely to wake/be woken. Due to the number of analyses that were performed, however, this one significant result might have been due to chance.

Table 82: Differences between Infants Fed/not Fed 4-hourly at Term

Variable	Wakes/Woken mean (sd) (N =61)	Left > 4 hrs mean (sd) (N = 23)		p
Birth risk				
Birth weight (g)	1254 (286)	1385 (370)	-1.72 (1)	.09
Gestation (weeks)	29.4 (1.7)	29.7 (1.7)	-0.81 (1)	.42
SGA	16	3	1.66 (2)	.25
AGA	45	20		
Medical care				
"Compneon"	45.7	34.0	505.5 (3)	**.05**
Duration of IC	44.7	36.8	570.5 (3)	.19
Level of care 1st 10 days	44.6	36.8	571.0 (3)	.19
Total days in hospital	44.2	38.1	599.5 (3)	.31
Days of ventilation	44.4	37.4	584.5 (3)	.22
Miscellaneous				
Feeding - breast	19	4	1.59 (2)	.28
- formula	42	19		
Term weight z-score	-1.11 (1.7)	-.64 (.94)	-1.72 (1)	.09

1 = t-value
2 = Chi-square
3 = Mann-Whitney U

8.3.2.3.2 Characteristics of Infants who fail to self-wake, and whose mothers leave them to sleep at 3mths

At the 3-month assessment, the criterion for waking/being woken was increased to six hours, since by this age the majority of infants would be expected to be sleeping for longer periods during the night than during the day. Of the 90 infants in the study, 52 were still either waking themselves or being woken at least every 6 hours (i.e. once during the night) for a feed at 3 months of age. The majority of infants who were waking/being woken at term remained in this category at 3 months of age ($r = .22$, $p < .05$). Analyses using the medical variables showed that, at this time, it was actually the babies who had been sicker during the neonatal period who were more likely to be left more than six hours between feeds (reversing the trend seen at the term assessment). As regards the concurrent method of feeding, the difference between breast-fed and formula-fed infants was highly significant, with formula-fed infants being much more likely to sleep/be left to sleep longer than 6 hours than their breast-fed counterparts.

This difference, however, is due to the fact that all 16 of the breast-fed infants were still self-waking.

Table 83: Differences between Infants Fed/not Fed 6-hourly at 3-Months

Variable	Wakes/Woken mean (sd) (N = 52)	Left > 6 hrs mean (sd) (N = 38)	t-value/Chi-square/ Mann-Whitney U	p
Birth risk				
Birth weight (g)	1313 ((320)	1215 (333)	1.41 (1)	.16
Gestation (weeks)	29.6 (1.6)	29.1 (2.0)	1.43 (1)	.16
SGA	12	10	0.13 (2)	.81
AGA	40	28		
Medical care				
"Compneon"	42.3	49.8	823.0 (3)	.17
Duration of IC	43.9	47.8	902.0 (3)	.48
Level of care 1st 10 days	42.0	50.3	807.0 (3)	.14
Total days in hospital	42.4	49.7	827.5 (3)	.19
Days of ventilation	42.4	49.8	825.5 (3)	.17
Miscellaneous				
Feeding: breast	16	0	14.22 (2)	**.00**
Formula	36	38		
3 mth weight z-score	-.85 (1.22)	-.86 (1.13)	0.05 (1)	.97

1 = t-value
2 = Chi-square
3 = Mann-Whitney U

8.3.2.4. Relationship between Waking/Being woken at night and Number of Feeds in 24 hours

Analyses were performed to ascertain whether self-waking/being woken at night affected the number of feeds an infant was given during a 24-hour period. Table 84 shows the results of these analyses both at term and at 3 months of age. As can be seen, at both ages there was a significant relationship between waking/being woken at night and total number of milk feeds in 24 hours. This finding may be explained, however, by the significant relationship between method of feeding (i.e. breast or formula) and the number of feeds per day (at term t=3.18, p< .01; at 3-months t= 7.43, p< .00). As already discussed, all the breast-feeding infants were still waking for feeds at 3 months of age, whereas less than half of the formula-fed infants were doing so.

Table 84: Relationship between Waking/Being woken at Night and Total Feeds in 24 Hours

Variable	Wakes/Woken	Left to sleep	Mann-Whitney U test	p
Milk feeds/24 hrs (term) (n=84)	45.3	35.0	530.0	**.05**
Milk feeds/24 hrs (3 months) (n=90)	52.6	35.7	617.0	**.00**
Solid feeds/24 hrs (3 months) (n=90)	46.1	44.7	957.5	.80

Self-waking/being woken at night was not related to the number of solid feeds given per day, the average for each group being approximately 1.5. There was, however, a statistically significant negative correlation between the number of milk feeds and the number of solid feeds given per day at 3 months of age ($r = -.25$, $p < .05$). Thus the infants who naturally slept for longer than 6 hours and were left to do so may have been the infants who were receiving solid feeds at this stage.

8.3.2.5. Relationship between Sleeping and Feeding Variables

As shown in Section 8.2.1, the number of hours slept during a 24-hour period at term was related to rate of growth during the following three months. It was therefore decided to establish whether there was a relationship between the number of hours slept and the total number of feeds received during an average 24-hour period

8.3.2.5.1. Sleeping Behaviour and Number of Feeds Received

Spearman's Rho correlations revealed that there was no significant relationship between the number of hours that the infants slept and the number of feeds they received at term. At 3 months of age there was still no significant correlation between the total hours slept during a 24-hour period and the number of milk feeds given, nor with the number of solid feeds (see Table 85).

Table 85: Correlations between Hours Slept and Number of Feeds in 24 hours

	Number of milk feeds (Term)(n=84)	**Number of milk feeds** (3-mths)(n=89)	**Number of solid feeds** (3-mths)(n=89)
Hours slept in 24 hours (term)	-.09	-	-
Hours slept in 24 hours(3mths)	-	.03	-.06

8.3.2.5.2. Differences between Breast- and Formula-fed infants on Sleeping Variables

The subjects were dichotomised into those who were predominantly breast-fed and those who were mainly or fully formula-fed at each assessment-point, and the relationship between feeding type and sleeping variables was examined using chi-square analysis. The sleeping variables included self-waking by the infant (at least every four hours at term, every 6 hours at 3 months), being woken by the mother for 4-hourly (6-hourly at 3 months) feeds, and being left to sleep for periods longer than four hours (6 hours at 3 months). As can be seen in Table 86, at term a larger proportion of breast-feeders than formula-feeders did wake for feeds at least four hourly, but this difference did not reach statistical significance. For the maternal waking at term variable the proportions were similar. The proportion of infants in each group who neither self-woke nor were woken by their mother at term also failed to reach statistical significance.

When the three-month data was examined, however, the proportion of infants who neither self-woke nor were woken by the mother was dramatically different for the two groups, since all the breast-feeders were still waking themselves during the night period whereas 51.4% of the formula-fed infants slept for longer than six hours.

Table 86: Feeding Method and Waking Variables

Variable	Breast-feeders	Formula-feeders	Chi-Square	p
Term	**(n = 25)**	**(n = 65)**		
Self-waking	21	43	2.80	.12
Maternal waking	3	11	0.33	.75
Neither wakes nor woken	4	19	1.66	.28
3 Months	**(n = 16)**	**(n = 74)**		
Self-waking	16	33	16.28	**. 00**
Maternal waking	1	6	0.06	.10
Neither wakes nor woken	0	38	14.22	**.00**

8.3.2.5.3. Relationship between Where Infants Sleep and Type of Feeding

It was anticipated that there would be a relationship between where the infant slept and the method of feeding at that time (i.e. breast or formula feeding). At term a similar proportion of infants in each feeding group slept in a cot in the parents' room (69.6% compared to 72.1%), but a much larger proportion of breast-feeders actually co-slept (i.e. in parents' bed) (21.7% compared to 4.9%). When the variable was dichotomised into co-sleeping versus not co-sleeping, the difference between the breast-feeding and the formula-fed infants was statistically significant (Chi-square = 5.49,p < .05). At 3 months of age the proportions sharing the parental bed were 18.8% and 2.7% respectively, and again this difference was statistically significant (Chi-square= 6.46, p < .05).

8.4. Maternal & Social Factors in Relation to Growth

In the following sub-section, the relationship between various maternal or social factors and growth are examined. The variables that are analysed in relation to growth include maternal age at time of infant birth, maternal intelligence (as measured using the WAIS at the 3-month assessment), and the Osborn Index (see Section II - Method for further details on these instruments). It was anticipated that there would be significant inter-correlations between the various factors included in this chapter, and, as Table 87 shows, this proved to be the case. The inter-correlations were all highly significant.

Table 87: Inter-correlations between Maternal and Social Variables

	Maternal Age	Maternal IQ	Osborn Index
Maternal Age	-	-	-
Maternal IQ	.37**	-	-
Osborn Index	.50**	.50**	-

** $p < .01$

8.4.1. The Relationship between Maternal & Social Factors and Growth

The maternal and social variables were examined in relation to all three growth measures and weight z-score at the 3-month assessment. It was not anticipated that there would be a relationship with early post-natal growth (i.e. from birth-term) since for much, if not all, of that period the infants were hospitalised. As can be seen from Table 88, two of the three maternal/social variables were significantly correlated with growth between term and three months of age (as already shown, however, these maternal variables are also highly inter-correlated). There were no significant correlations between the maternal/social variables and the other two growth variables, nor with 3-month weight.

Table 88: Relationship between Social Factors and Growth

Variable	**N**	**Growth Birth – Term**	**Growth Term – 3mths**	**Growth Birth-3mths**	**3-mth Weight z-score**
Maternal Age	86	-.19	.19	-.05	-.01
Maternal IQ	81	-.09	**.24***	.08	.12
Osborne Index	86	-.18	**.29****	.03	.12

** significant at the .01 level
* significant at the .05 level

8.4.2. Relationship between Maternal/Social Factors and Method of Feeding

Independent t-tests were then performed to identify any significant differences between breast-fed and formula-fed infants on any of the maternal and social variables. As shown in Table 89, the type of milk received at term was significantly correlated with both maternal IQ and Osborn Index score, with breast feeding mothers having a higher mean IQ and scoring higher on the Osborn Index (i.e. higher SES). The difference between breast- and formula-feeding mothers in terms of maternal age was not significant, although the tendency was for breast-feeding mothers to be older. These differences were no longer significant when type of feeding at 3 months of age was examined, although the trends continued to be in the same direction with older, more intelligent and higher socio-economic status women being more likely to still be predominantly breast-feeding.

Table 89: Correlations between Method of Feeding and Maternal/Social Factors

	Breast Mean (SD)	**Formula** Mean (SD)	**t-value**	**p**
Term				
Maternal Age	31.4 (5.2)	30.0 (5.9)	1.04	.30
Maternal IQ	106.8 (14.6)	96.1 (16.2)	2.79	**.01**
Osborn Index	59.8 (6.7)	54.9 (9.3)	2.74	**.01**
3 months				
Maternal Age	31.6 (5.5)	30.1 (5.7)	0.93	.35
Maternal IQ	103.0 (13.1)	98.3 (17.1)	1.04	.30
Osborn Index	59.2 (6.0)	55.7 (9.3)	1.90	.15

8.5. Summary of Relationship between Independent Variables and Growth

8.5.1. Birth and Medical Variables

Although there was a significant relationship between birth-weight z-score and growth between birth and term, none of the other birth or medical variables used in this study were significantly correlated to growth between birth and term. Between term and 3 months the only early variable that was related to growth was gestational age at birth, with the more mature infants growing better. For the overall period birth–3 months corrected age several of the medical factors seem to be significant (the composite Neonatal Risk Score, Intensity of Care of first 10 days, Duration of Intensive Care and Days of Ventilation). It should be noted, however, that these variables are also highly inter-correlated (see Section II – Methods). For weight z-score at 3 months of age, the birth weight and birth weight z-score were both highly correlated, and of the medical variables, both Level of Care over first 10 days and Duration of Intensive Care were significant.

8.5.2. Feeding Variables

The type of milk that the infants were receiving at both term and 3-months had a significant impact on their growth rates. Infants being breast-fed at term showed a significantly slower rate of growth from birth-term than infants who were being formula-fed, but had a much faster rate of growth from term to 3-months of age. Overall from birth to term the contrasting effects cancelled one another out and there was no difference in growth rate depending on type of milk received, nor was there a difference in whether or not infant weight was below the 10th percentile according to milk received. The infants who were still being breast-fed at 3-months showed better growth from term to 3-months, but overall from birth-3 months there was no difference, and again type of milk was not related to whether 3-month weight was above or below the 10th percentile.

There was a significant relationship between the number of feeds that an infant received at term and at 3-months and growth between these two time points, but there was also a significant relationship between the number of feeds and the type of milk that the infant was receiving, with breastfed infants receiving more feeds per day than formula fed infants.

There was no relationship between the type of milk that the infants received at term and early medical risk, although the tendency was for the breastfed infants to have been less sick than the infants receiving formula milk. The type of milk being received at 3-months, however, was significantly related to several of the medical risk variables, with breastfed infants having been less sick during the neonatal period (although the medical risk variables were also highly inter-correlated, as already discussed).

The only feeding technique measures at term that were related to growth were intake per minute (with faster feeders growing better and being less likely to have a weight below the 10^{th} percentile at 3-months), and suck duration (infants exhibiting long sucks were less likely to have a weight below the 10^{th} percentile at 3-months). There were no significant relationships between measures of infant feeding technique at 3-months and growth.

There were significant inter-correlations between measures of feeding technique at both term and 3-months. At term the FPI and intake per minute were negatively correlated (i.e. infants with more abnormal feeding behaviours on the FPI were less efficient feeders), and several of the strain gauge variables were inter-correlated. Individual suck duration was correlated with intake per minute. The pattern of inter-correlations was very similar at the 3-month assessment.

There were few significant correlations between measures of infant feeding technique and medical risk variables. Intake per minute was related to gestation (infants of a higher gestation at birth had a greater intake per minute) and duration of intensive care (sicker infants had a lower intake per minute). There were no significant correlations between feeding technique at 3-months and early medical risk.

8.5.3. Infant Behavioural Characteristics

There was no apparent relationship between irritability at term or 3 months and growth between these time-points.

Neither of the irritability measures used at term was significantly related to number of feeds. At 3 months of age there was again no significant relationship between irritability and number of milk or solid feeds. There was no apparent difference between breast-fed and formula-fed infants in terms of irritability levels.

There was a statistically significant relationship between total number of hours slept during a 24-hour period at term and growth during the following three months, with the infants who slept for longer growing faster. There was no correlation, however, between the number of hours slept at either term or 3-months of age and concurrent weight z-score.

There was no correlation between the total number of hours slept in 24 hours and total number of feeds received during that period. Despite the fact that the infants who self-woke/were woken by their mothers for night feeds did receive significantly more milk feeds during the 24 hour period, there was no significant difference between the growth rates of infants who self-woke/were woken regularly by their mothers and those who slept for prolonged periods (at either term or 3 months), although the trend was for infants who were fed regularly to grow faster.

At term infants who were sicker during the neonatal period were more likely to feed regularly, but this trend was reversed at 3 months. None of these relationships reached statistical significance.

8.5.4. Maternal/Social Variables

The three maternal/social variables that were analysed in relation to growth were maternal age, maternal IQ and socio-economic status. All three of these variables were significantly correlated with growth between term and 3-months of age, although not with either of the other growth periods, nor with actual weight z-score at 3 months of age. The three variables were also, however, very highly inter-correlated.

8.6. Predictors of Growth

8.6.1. Introduction

In this sub-section, the independent variables that had been shown in the preliminary analyses to be significantly related to early growth have been brought together. Using multiple regression analyses, prediction models for preterm infant growth up to 3-months of age, corrected for gestation, have been produced.

As already discussed, there were three growth variables available for analysis. The first, birth to term, was primarily a period during which the infant was hospitalised and receiving vital medical and nursing care in order to ensure survival, although many of the infants included in the study were discharged several weeks before term. The second growth variable, term to three months, encompassed a period during which the majority of the subjects were at home, and no longer dependent on medical support, although a small number of infants did remain on ancillary oxygen and/or supplementary naso-gastric feeds while at home during part or all of this period. The third growth variable was for the total period from birth to three months corrected age, i.e. a period of 5-7 months, encompassing both the early neonatal period of medical dependency and the later period of relatively normal infancy in the care of the mother. As with the individual analyses, weight z-score at 3-months of age was also used as an outcome measure, and a further outcome measure was included which was 3-month weight below the 10^{th} percentile. As previously mentioned, one of the a priori hypotheses considered in this study was that good catch-up growth between birth and 3 months of age might ameliorate the long-term negative effects of intrauterine growth retardation and, conversely, that particularly poor early growth might be related to poor cognitive outcome. As described in Section 10.2.2, the 10^{th} percentile for weight z-score was selected as the cut-off criterion, and will be used in the analyses in relation to cognitive outcome at 18 months. For this reason it was included as one of the outcome measures for early growth.

Factors that were significantly related, individually, to the first four outcome variables mentioned above were entered into multiple regression analyses. Subsequently logistical regression analysis was performed on the dichotomised outcome variable "weight below the 10th percentile at 3 months corrected age".

8.6.2. Growth from Birth to Term

As can be seen from the foregoing chapter, there were few obvious predictors for this early growth period. Although none of the early medical variables were significantly correlated with this growth variable, Duration of Intensive Care was included in the regression analyses since it was highly correlated with growth over the whole period (which in turn was highly correlated with growth during the initial period). The type of milk given at term was included, dichotomised into breast or formula. The assumption was made that the infants who were receiving predominantly breast-milk at term had received greater amounts of it, over a longer duration, during the preterm period than the infants who were receiving wholly or mainly formula milk at term. Table 90 shows a prediction model comprising these three independent variables and shows their relative contribution to growth during this early period. The three variables were entered simultaneously into the regression analysis.

Table 90: Prediction Model for Growth Birth – Term

Variable	B	Std Error	Beta	t	p
Birth weight z-score	-.43	.08	-.46	-5.42	**.00**
Milk received at Term	1.06	.20	.44	5.19	**.00**
Duration of Intensive Care	-4.47E-03	.00	-.13	-1.48	.14

Model	R = .65	R square = .43	Adjusted R square = .40	p < .00

As can be seen, the only significant contributors to the model were the type of milk received at term (with infants fed predominantly breast milk growing more slowly than the infants fed any form of artificial formula), and birth weight z-score (with infants who were lighter for gestation growing faster). Duration of Intensive Care explains only a small amount of variance, with infants who required intensive care for longer growing less well in these early weeks of life. The model shown above, adjusted for size of sample and number of variables, accounts for some 40% of the variance in growth. Although this is statistically significant, it still leaves 60% of the variance unexplained.

8.6.3. Growth Term – 3-Months

A prediction model for growth during this second period was computed, which included variables that individually had been significantly related to growth between term and 3 months of age. As with the regression for growth between birth and term, the variables were entered simultaneously.

As can be seen from Table 91, the variable that contributed most to the model was the type of milk given at term, with infants being breast-fed showing faster growth rate during the subsequent three months. The number of hours slept during a 24-hour period also explained a significant amount of the variance, with infants sleeping for longer growing more rapidly. The cut-off criterion for maternal IQ continued to make a significant contribution to growth, even when type of milk being given was held constant. Gestational age and number of feeds per day, although contributing to the model, did not, when other variables were controlled for, continue to be statistically significant. The overall model explains 35% of the variance in the rate of growth of the subject infants between term and 3 months corrected age, which is highly statistically significant.

Table 91: Prediction Model for Growth Term – 3 Months

Variable	B	Std Error	Beta	t	p
Gestational age	.07	.04	.16	1.60	.11
Milk at term	-.61	.19	-.36	-3.21	**.00**
Hours slept/day at Term	.05	.02	.21	2.19	**.03**
Number of feeds/day at Term	.04	.05	.10	.91	.37
IQ cutoff (< 85)	.38	.19	.20	2.06	**.04**

Model	R = .63	R square = .39	Adjusted R square = .35	p < .00

8.6.4. Growth Birth – 3-Months

Although the two growth variables birth-term and birth-3 months were highly inter-correlated (r=.74, p< .01), the foregoing chapters have shown that they differ in the early variables with which they are correlated. Consequently a separate regression analysis was performed for this overall period. As already mentioned, the type of milk being received during this overall period is not included in the regression, since the first and second time periods cancel one another out as far as this variable is concerned. As can be seen from Table 92, the variable that explains most of the variance is the birth weight z-score, with infants who were lighter for gestation at birth growing best during the following 5-7 months. The only other variable that remained significant was the volume of milk ingested per minute at term, i.e. the efficiency of the infant's feeding.

Table 92: Prediction Model for Growth Birth – 3 Months

Variable	B	Std Error	Beta	t	p
Birth weight z-score	-.45	.10	-.47	-4.51	**.00**
Gestational Age	-.03	.09	-.05	-.36	.72
Level of Care over first 10 days	-.06	.01	-.15	-1.11	.27
Intake/minute at Term	.08	.04	.24	2.33	**.02**

Model	**R = .53**	**R square = .28**	**Adjusted R square = .24**	**p < .00**

8.6.5. 3-Month Weight Z-score

Actual weight z-score at 3-months was examined using the same multiple regression technique as in the previous analyses. As can be seen in Table 93, the only variable that remains significant within the model when the other variables were held constant was the birth weight z-score, i.e. infants who were light for gestation at birth were likely still to be light for age several months later.

Table 93: Prediction Model for 3-Month Weight Z-score

Variable	B	Std Error	Beta	t	p
Birth weight z-score	.67	.15	.68	4.50	**00**
Duration of Intensive Care	3.73E-03	.01	.07	.47	.65
Intake/minute at Term	.07	.07	.17	1.07	.30
Individual Suck Duration	-3.79	2.11	-.29	-.80	.09

Model	**R = .75**	**R square = .56**	**Adjusted R square = .47**	**p < .00**

8.6.6. Three- Month Weight Z-score below 10th Percentile

The final regression analysis performed was on the outcome measure 3-month weight below the 10th percentile. As previously discussed, this outcome measure was selected because it would be used at the 18-month assessment to test the a priori hypothesis that good catch-up growth post-natally is related to better cognitive outcome. Logistical regression analysis was used since the outcome measure was a dichotomised variable. The variable "sub-optimal milk at term" differentiates between infants receiving breast milk or preterm formula from those receiving a standard infant formula or special formula. As can be seen from Table 94, by far the most powerful contributor to the model for weight status at 3 months corrected age is the weight status at birth (with infants who were small for gestation being seven times as likely still to be small for age at 3 months as infants whose weight was above that criterion at birth) when other factors were held constant. The other variable that contributes significantly to the model is the Level of Care required over the first ten days of life, with the sicker infants being more likely to be below the 10th percentile for weight at 3 months of age. Both the type of milk at term and low maternal IQ fail to reach statistical significance when other variables were held constant.

Table 94: Prediction Model for 3-Month weight below 10th Percentile

Variable	**Wald**	**df**	**Sig**	**Exp (B)***	**95% C.I. for Exp (B)**	
					Lower	**Upper**
Birthweight < 10th percentile	10.33	1	**.00**	7.55	2.20	25.92
Level of Care during First 10 days	4.66	1	**.03**	1.04	1.00	1.08
Sub-optimal milk at term	1.46	1	.23	2.13	0.62	7.24
Maternal IQ < 85	1.32	1	.25	2.03	0.61	7.84

Model Chi-Square = 18.21; df = 4 ; p< .001;*adjusted odds ratio

8.6.7. Summary of Regression Analyses

Five sets of regression analyses were performed, one on each of the three “growth” variables, one on 3-month weight z-score, and lastly logistical regression analysis with the outcome measure being weight below the 10^{th} percentile at 3 months of age.

The prediction model for growth between birth and term included three independent variables: birth weight z-score, type of milk received at term and duration of intensive care during initial hospitalisation. Of these, only the first two remained significant to the model when the other variables were held constant. Infants who weighed less for gestation grew better during the following few weeks of life, and infants who were still being breast-fed at term had grown less well in the weeks up to that point.

For the period term to 3 months of age, the independent variables were different, and more were included. Gestational age, type of milk given at term, number of feeds per day at term, number of hours slept per day at term, and maternal IQ (cut-off 85) were entered into the analysis. Only the type of milk, hours slept and maternal IQ remained significant when the other variables were held constant. For this time period, infants who were receiving breast milk at term, and infants who slept for longer, grew significantly better during the following three months. Low maternal IQ adversely effected growth between birth and term, even when type of milk being received was held constant. Gestational age and number of feeds per day, however, failed to maintain signficance when included in the model.

For the total period between birth and 3 months corrected age, four independent variables were entered into the analysis: birth weight z-score; gestational age; level of care during first 10 days of life; and milk intake/minute at term. Of these, only birth weight z-score and milk intake/minute remained significant contributors to the model when the other variables were held constant. Infants who were lighter for gestation at birth and those infants who fed more efficiently at term grew faster during the following 5-7 month period.

When 3-month weight z-score was used as the outcome measure, the independent variables that were entered into the regression model were birth weight z-score, duration of intensive care, milk intake/minute and individual suck duration (i.e. whether individual sucks were long or short). Although all these variables had individually been significantly correlated with 3-month weight z-score, when they were entered into the regression analysis, only the birth weight z-score remained a significant contributor, i.e. infants who were lighter for gestation at birth were significantly more likely still to be lighter at 3 months of age, despite the fact that (as indicated in the previous paragraph) they showed better growth than infants born larger for gestation.

Finally, logistical regression analysis was carried out to ascertain the variables contributing significantly to a weight below the 10^{th} percentile at 3 months of age. The independent variables entered into the regression analysis were birth weight below the 10^{th} percentile; level of care over first 10 days; sub-optimal milk (i.e. neither breast nor preterm formula) at term; and maternal IQ below 85. Of these, only birth weight below the 10^{th} percentile and the level of care in the first 10 days remained significant contributors to the model. Infants whose weight was below the criterion at birth, and those who required higher levels of intensive care were more likely to have a weight below the 10^{th} percentile at 3 months of age.

Chapter 9: Discussion

9.1. Overview

There has been much research indicating that sub-optimal growth in utero, for both term and preterm infants, can have long term negative implications, particularly in terms of cognitive development (e.g. Walter & Ramaekers, 1982; Newman et al, 1997; Martikainen, 1992; Smedler et al, 1992). There has also been research suggesting that slow growth during the first few months of life (i.e. early growth faltering) , in term infants, is related to poorer developmental outcome (Skuse et al, 1994; Carmona da Mota et al, 1990). The relevance of early post-natal growth in terms of cognitive development at 18 months of age is addressed in the next Results and Discussion Section. In the present Section, however, the principal research questions were "how well did this sample of very preterm infants grow, and which were the principal early variables that were related to growth rates". In this chapter the findings relating to these issues are discussed in relation to previously published research.

In the foregoing Results chapters, firstly the general growth patterns for this sample of very preterm, high-risk infants was presented, indicating that as a group they did not grow well in comparison to infants who remained in utero. Subsequently the relationship between specific independent variables and early growth measures was examined in order to ascertain their relative importance. The results indicated that the importance of these independent factors varied according to the time period that was being analysed. To some extent, growth rate appeared to be pre-determined, depending on birth weight in relation to gestation (with the smaller infants growing better); how sick the infant had been during the first few weeks of life (with the sicker infants growing slower); and the level of feeding competence (with the less competent feeders growing more slowly). Nonetheless, there were other significant predictors, particularly for the time period from Term to 3-months, that could potentially be manipulated in order to maximise weight gain, if indeed this is shown to be important for later outcome. Such variables included the type of milk given and the number of hours of sleep that the infant achieved during a 24-hour period.

Recognising the risk factors for poor growth (which include severe illness during the neonatal period, poor oral-motor function, and mother of below average intelligence) can in itself be of value in highlighting those infants who are likely to grow poorly. Ideally professional input could be provided for these particularly at-risk individuals, since from a clinical viewpoint the idea of improving weight gain is an attractive one, but this may not, in practice, be possible.

Despite a rigorous attempt to include a broad range of independent variables that were expected to be related to growth rate, the prediction models that were produced accounted for less than half the variance observed in growth rate during each time period.

This Discussion chapter is set out in the same order as the Results chapters. Firstly the growth of these very preterm infants is discussed and compared with that reported in previous studies. Subsequently the relative importance of the various medical, feeding, infant behavioural and maternal/social factors are addressed, again in relation to what was anticipated based on previously published work. The prediction models attempt to address the deficiencies apparent in some previous studies, which have concentrated on specific issues without controlling for other, confounding factors.

At the end of the Thesis, following the Results and Discussion sections pertaining to the 18-month assessment, there is a final drawing together of the most important findings to come out of this study, the implications for future research and potentially for the clinical care of very preterm infants.

9.2. An At-Risk Sample

The inclusion criteria for the study specified that infants were to be either less than 32 weeks gestation (i.e. very preterm), and/or less than 1500g at birth (i.e. very low birth weight). These are two of the most commonly used criterion in studies of this type. As previously presented in the Method Section, the 90 infants who were followed from birth to 3 months corrected age had a mean gestational age of 29.4 weeks (range 24-33 weeks); and mean birth weight of 1271g (range 521-2158g). The upper end of the gestational age range represented small for gestation infants who despite their maturity fulfilled the birth weight criterion. The upper end of the birth weight range includes several infants who weighed over 1500g (the heaviest being born to a diabetic mother), but all these large infants were born before 32 completed weeks' gestation. This sample would therefore normally be classified as moderate to high risk.

There were a slightly larger proportion of boys (53) compared to girls (37), but there were no gender differences with regard to birth weight, gestational age or birth weight status (SGA/AGA). Half of the infants were firstborns, the other half having older siblings. Previous, quite recent, research has indicated that a disproportionate number of very preterm infants are still being born to women who are of low socio-economic status, have a poor level of education, are aged over 35 (or under 20), or are single (Ancel et al, 1999). In the present study, however, 90% of the women were either married or co-habiting, and maternal age (mean 30.4 years, range 17-43) and IQ (mean 99.2, range 68-150) were normally distributed. The average maternal SES, as measured using the Osborn Social Index (described in Section II - Method) was actually slightly higher than the figures given for the National Birth Cohort used to standardise the instrument (Osborn, 1987). The wide range of maternal age, and relatively high SES of the mothers compared to anticipated data might reflect the relatively new sub-sample of very preterm infants being born to older women who became pregnant using assisted conception technology (e.g. IVF). The mothers of the subject infants were routinely asked whether they had conceived naturally or not, and answers were given by 82 of the 90 women, the remaining 8 declining to reply to this question. Of the 82 who replied, three had received hormonal treatment to assist conception, and 10 infants were born as a result of in-vitro fertilisation. These thirteen infants, who represent nearly 16% of the sample for whom the data was made available, would probably not have been conceived 20 years ago, before this type of fertility treatment became widely available.

9.3. Patterns of Growth among Very Preterm Infants

It had been intended to measure growth between assessment points based on the formula devised and described by Cole (1995). This formula provides "a weight velocity reference that compensates for regression to the mean". This is an important issue, since infants whose weights are at the extreme ends of the percentile charts would be expected to gradually regress towards the mean weight for age over time. Unfortunately, however, the formula had not been standardised for, and therefore could not be applied, to infants below four weeks of age (i.e. four weeks post-term). It was therefore decided simply to measure the change in weight z-score between the assessment points, and to use this as the measure of "growth". This is obviously a cruder measure than would have been available using the Cole formula, but in the circumstances was unavoidable. The British 1990 weight reference database was used to ascertain the weight z-scores for the infants at each age. The use of this modern database is important because it has been shown that growth patterns have altered considerably over the past 30 years, probably as a result of changes in infant nutrition (Wright, Waterston & Aynsley-Green, 1993).

The decision was made to investigate the independent variables contributing to growth between each of the three assessments. Although it would have been simpler just to look at growth between birth and three months corrected age, it was anticipated, correctly, that different variables would be influential during the first weeks, much of which was spent in the neonatal unit, compared to the period from term onwards, when most of the infants were at home in the care of their mothers. Thus three separate "growth velocity" measures were used in this study – growth velocity between birth and term (a period ranging from 7 to 16 weeks), between term and 3 months corrected age, and then overall between birth and 3 months corrected age (i.e. a period of approximately 5-7 months). Z-scores were used in all the analyses, as the measurements were not actually carried out at precisely the prescribed ages, since for administrative reasons this was not possible. The actual age in completed weeks at time of measurement, together with the infant's gender, were used in calculating standardised weight scores (z-scores).

Despite the fact that "growth" velocity varied quite dramatically within the sample, the overall change in standardised weight was not great in the majority of cases. Indeed, there was a highly significant correlation between the weight z-scores at birth, term and 3 months corrected age, and of all the independent variables examined the strongest predictor of 3-month weight z-score was the birth weight z-score.

The mean birth weight z-score for the sample was below that expected using the reference database. This fact probably reflects the fact that a proportion of these infants were electively delivered due to conditions that affect intrauterine growth – e.g. pre-eclampsia and placental insufficiency. Comparison of weight z-scores at birth and 3-months shows, however, that instead of "catching-up", the mean weight z-score was even lower at the latter time than it had been at birth. Closer inspection of the data revealed that this was due to particularly poor growth during the period between birth and term, i.e. the initial hospitalisation period. The mean growth rate during this period, for the sample as a whole, was -.66 (when 0 would represent a maintaining of weight z-score for age). This observed poor growth within the present sample is consistent with previous research. Berry et al (1997a) also reported that growth of very preterm infants fell considerably behind the expected rate for intrauterine growth during the first eight weeks of life, particularly during the first two weeks. Thereafter the growth rate was parallel with intrauterine growth, but without catch-up. Alexander (1996) reported that this pattern of growth results from initial physiological weight loss (also experienced by healthy, term neonates), delay in commencing parenteral nutrition, and use of milk not adequate for the needs of these tiny infants. In addition, in many neonatal units, including those used in this study, the accepted practice is to feed according to actual body weight rather than expected body weight for gestation (Alexander, 1996). This practice, while permitting growth, does not facilitate catch-up growth to compensate for the initial downturn.

When analyses were performed comparing the first and second growth periods, it transpired that there was a highly significant negative correlation between the two measures. Thus those infants who grew particularly poorly during the period from birth to term tended to grow fastest during the following three months. Early growth (i.e. between birth and term) is to a large extent dependent on external factors, since these very preterm infants are initially unable to take any active role in their nutritional intake.

Thus individual hospital policy regarding type of parenteral (ie intravenous) nutrition, the fortifying of expressed breast milk (if the mother had opted to breastfeed), the availability and quality of pre-term formula and the method of calculating daily nutritional requirement will all influence growth rate. In addition, the medical condition of the infant influences the timing of the introduction of milk feeds.

In contrast, by the term assessment most of the infants had been discharged home into the care of the mother, were taking oral feeds and were therefore taking a much more active role in determining their own growth rate. During this second period, between term and 3-months, the average weight z-score increased, and the mean growth rate was +.16, indicating a degree of real catch-up growth.

As regards actual weight (as opposed to growth rate) the number of infants whose standardised weight was below the 10th percentile increased between birth to 3 months corrected age, and by the end of this period in excess of a third of the infants fell into the small-for-age category. It has previously been shown that weight z-score of very preterm infants reaches a low-point approximately three weeks post-natally, with very little improvement up to discharge (Embleton, 2001). One of the limitations of the present study was that weight data was only available at three time points, and thus it is not possible to ascertain precisely when the lowest mean weight z-score occurred. What can be confirmed is that the mean weight z-score at term (-1.03, sd 1.13) was significantly lower than the mean at birth (-.37, sd 1.14, $p < .00$)). Although there had been a small improvement in mean weight z-score at 3 months corrected age (-.86, sd 1.18), this improvement did not reach statistical significance ($p = .06$). Thus the observed more rapid growth between term and three months of those infants who had grown particularly poorly during the initial postnatal period still did not compensate entirely for the early disadvantage. The similarity in standard deviation scores (and the relatively normal distribution of scores) at each time point indicate that these findings are not likely to be due to occasional outliers distorting the overall picture.

Despite the occurrence of movement across the 10th percentile line between time points (19 subjects moved between birth and term, and 24 infants moved between term and 3 months) the calculation of the relative risk of being small for age at term and/or 3 months corrected age according to birth weight status showed that there is a significantly greater risk of being below the 10^{th} percentile at the later time points if the infant was born small-for-gestation. Although the present data only examines the infants between birth and three months corrected age (a period of some 5-7 months in total), these findings are in accordance with those of previous researchers which suggest that infants born SGA have a increased risk of remaining small at 3 years of age (Sung et al, 1993) and even through to adulthood (Paz et al, 1993; Pryor et al, 1995).

9.4. Relationship between Birth & Early Medical Factors and Growth

The birth variables used in the statistical analyses included weight, gestational age, and birth weight z-score. Early medical variables included the two composite risk scores (antenatal and neonatal), together with several variables pertaining to severity of illness and the amount of medical intervention required during initial hospitalisation. Although these variables did measure different aspects of the infants' condition and care, they tended to be highly correlated (see Section II – Methods). Results of ultrasound brain scans were also used in the analyses. Interestingly, antenatal complications did not appear to have an effect on any of the three growth measures. This might have been due to the use of the composite scoring system – which gave equal weighting to such diverse events as "previous miscarriage" and "pre-eclampsia". If specific antenatal "risk factors" had been analysed individually then some effect on growth might have been found.

The three growth measures will be considered separately, as they were in the Results chapter.

9.4.1. <u>The Relationship between Birth/Early Medical Risk Variables and Growth Birth-Term</u>

The only early variables that were significantly related to growth between birth and term were actual birth weight and birth weight z-score, with the latter having a higher correlation. In each case the correlation was negative, indicating that the smaller infants and those who were smaller for gestation grew faster than the larger and larger-for-gestation infants. This latter finding is consistent with previously published studies, the proposed explanation being firstly that infants who were smaller-for-gestation lose less weight in the first few days after birth because the observed weight loss comprises mainly fluid loss which is greater in larger-for-gestation infants. In addition, as they grow these smaller-for-gestation infants store more fluid within their bodies than larger-for-gestation infants (Berry et al, 1997; Cheek et al, 1984; Chessex et al 1984; Bauer et al, 1993). Unlike birth weight, gestational age at birth was not related to growth during the initial postnatal period, but was significantly positively correlated with both growth between term and 3-months, and overall from birth to 3-months. This indicates that the more mature infants tended to grow better once the initial postnatal period was over and they were in the care of their mothers. This result contrasts with those reported by Berry et al, who somewhat surprisingly found a significant negative correlation between gestational age at birth and growth rate. The Berry study, however, included only infants with a birth weight below 1kg, and therefore presumably constituted an even higher-risk sample, which might explain the different findings.

There were no significant correlations between the variables measuring severity of the infant's condition and growth during hospitalisation (birth to term), although the trend was in the expected direction (with sicker infants growing more slowly). This lack of a significant relationship between early medical condition and growth is somewhat surprising if, as suggested, initial slow growth is often due to delay in commencing parenteral feeding, intolerance of feeds etc. One explanation is that, since compared to a group of normal term infants all of the subject infants were of moderate to high risk and required neonatal intensive care, the relative difference between the "healthiest" and "sickest" of these subjects was not particularly dramatic. The medical variable that correlated most highly with this early phase of growth was duration of mechanical ventilation ($r = .17$), which was also found to be of significant predictive value in the Berry study (1997b).

Interestingly, the identification of abnormal brain scans (after the first 7 days) was not related to this or either of the other growth outcome measures. This was surprising, since the infants with apparent brain damage were among the sickest of the infants, and based on the findings discussed above, would have been expected to show slower rates of growth.

9.4.2. The Relationship between Birth/Early Medical Risk Variables and Growth Term-3 Months

The only one of the birth variables that correlated significantly with this second period of growth was gestational age, with the infants born at a higher gestation growing better between term and 3 months of age. The correlation was not particularly high, however, ($r = .22$, $p < .05$) and, due to the number of analyses performed, might have occurred by chance. As with the earlier growth period, there tended to be a negative relationship between the variables measuring how sick the infants had been and growth term-3 months, although none of these correlations reached statistical significance.

The observed lack of relationship between these early risk variables and growth once the majority of infants had been discharged home can be viewed in a very positive light. It would indicate that, at least for this group of very preterm infants, the severity of their early condition did not impact negatively on their growth once they had progressed beyond the initial period of hospitalisation.

9.4.3. The Relationship between Birth/Early Medical Risk Variables and Growth Birth-3 Months

Several of the neonatal medical variables were related to overall growth between birth and three months of age, specifically the Composite Neonatal Risk Score, Level of Care over the first 10 days of life, Duration of Intensive Care, Duration of Ventilation and Duration of Hospitalisation. These correlations, as with the growth period birth-term, were again all negative, that is, the sicker the infants, the slower the rate of growth. It should be remembered, however that these variables were also highly inter-correlated, and therefore the findings should be viewed with caution. Level of Care during the first 10 days was the variable most strongly correlated with growth (-.30, $p < .01$). The mechanism for this relationship is not clear. It would not appear to be due to poor oral-motor function, since there were no correlations between medical variables and the measures of oral-motor function, nor were there observable differences in the number of feeds received at term or 3 months according to severity of early illness.

9.4.4. The Relationship between Birth/Early Medical Risk Variables and Weight Z-Score at 3 Months

Weight z-score at 3-months of age was used as a fourth outcome measure, because this was later used to test the second major research question addressed in this thesis, i.e. can early catch-up growth ameliorate the adverse effects of intrauterine growth retardation on a subject's cognitive development. Not surprisingly, strong correlations were observed between both birth weight and birth weight z-score and subsequent weight z-score at 3-months of age, the latter being marginally greater. This would indicate that although the infants who were lighter for gestation at birth did show better rates of growth during the subsequent months than the larger-for-dates infants, this accelerated growth was not sufficient to dramatically alter their weight compared to the norms. Interestingly, however, there were also significant negative correlations between 3-month weight z-score and Duration of Intensive Care and Level of Care during first 10 days of life, with infants who were sicker during the initial post-natal period being smaller at 3 months of age. This result was not due to the observed correlation between birth weight z-score and 3-month weight z-score, since the former was not itself significantly correlated with the two medical variables.

9.4.5. Inter-correlations between Birth and Medical Variables

The majority of analyses of early medical variables gave rise to results that had been anticipated. For example, the high positive correlation between antenatal and neonatal composite risk scores. However, one surprising result was that there was no significant correlation between antenatal risk score and gestational age, which would imply that complications of pregnancy did not greatly influence timing of delivery. A large proportion (40% of those on whom information was available) of mothers went into spontaneous premature labour, which might explain these findings. There was, however, a significant correlation between antenatal risk score and birth weight, although not with birth weight z-score, the latter suggesting that composite antenatal risk did not contribute to intrauterine growth retardation (IUGR).

The negative correlation between the composite neonatal score and both gestational age and birth weight (which were highly inter-correlated) indicates that, not surprisingly, the more immature the infant, the more problems occurred during the neonatal period. Interestingly there was not a significant correlation between the composite neonatal score and birth weight z-score, or birth weight status (AGA/SGA), which would suggest that the infants who had suffered from IUGR were not significantly more at risk of neonatal complications than the infants who had been adequately nourished in utero. This conflicts with the findings of Spinillo et al (1997), who discovered a linear trend among similarly pre-term infants between birth weight z-score and early morbidity/mortality. The reason for this difference is unclear, although the fact that the Spinillo study used a slightly different criterion for identifying SGA infants might be one explanation (-1 sd below the mean for gestational age, as opposed to –1.28 sd used in the present study). In addition, a different growth reference database was used since the cited study took place in Italy.

9.5. The Relationship between Infant Feeding and Growth

In the preceding Results chapters, two main aspects of infant feeding were analysed in relation to early growth, these being nutrition (i.e. what the infant was fed, and how frequently) and infant feeding technique (i.e. how competently the infants fed). Each of these aspects of feeding will be discussed in relation to the growth variables previously described.

9.5.1. Nutrition

9.5.1.1. The Importance of the Type of Milk Received

Despite the fact that each of the three neonatal units involved in the Gain Study had a policy of encouraging mothers of the very preterm infants initially to express breast milk for their infants and subsequently to commence breastfeeding, the proportion of infants who were still being predominantly breast fed at term and three months was small (26% and 18% respectively). Interestingly, the type of milk being given to the infants at term was not significantly related to how sick they had been during the early postnatal period. The infants who were still being predominantly breastfed at 3-months, however, had been significantly more mature and less sick during the neonatal period than the infants who by that time were being formula-fed.

The predominant source of nutrition did appear to have a significant impact on growth within this sample of very preterm infants, although the direction of the effect was different for the two time periods.

Birth to Term – As shown in the Results chapters, infants who were receiving predominantly breast milk at the Term Assessment showed much slower growth up to that time than those who receiving predominantly formula at term. Many of the previous studies that have investigated the comparative growth rates of very preterm infants receiving breast or formula milk have focussed on the period following discharge from hospital. There have, however, been some studies that have included the period of hospitalisation, and these have produced conflicting results. The study by Schanler (1999) showed, as with the present study, that the infants given fortified breast milk did have significantly slower rates of growth than those fed a preterm formula, but considered that the advantages gained in terms of improved health outweighed this disadvantage. A study by Nicholl (1999), on the other hand, found that fortification of breast milk resulted in growth rates comparable to those seen in infants given preterm formula, although the infants fed unfortified breast milk grew less well. A similar finding was also reported in a paper by Morley & Lucas (2000), which compared unfortified breast milk, preterm formula and standard formula, although they reported that the differences in early growth rate had disappeared by nine months of age.

One explanation for these conflicting findings is that the type of "fortification" used may have been different in each study, and in the case of both the present study and that of Schanler, were inadequate to support optimum rates of growth. Unfortunately the type of the fortifiers used at each hospital was not recorded, and therefore this avenue of enquiry is not feasible. A second interpretation was that breast milk fortification did not continue for long enough. The majority of infants in the present study were discharged from hospital some weeks before the Term Assessment, and from discharge onwards were breastfeeding normally, with (at most) liquid vitamins and minerals given separately by mouth, but no calorific supplementation. As discussed in Section I, initially pre-term infants may not feed until satiated but rather stop due to fatigue, and consequently may not ingest sufficient quantities to facilitate catch-up growth. This would particularly affect breastfeeding infants since breast-feeds typically take longer than bottle feeds, and the greatest nutritional and calorific value is gained from the hind milk (at the end of a feed). Thus a relatively frail pre-term infant may not continue feeding for long enough to receive this more nutritious, calorie-dense milk.

Within the sub-group of infants who were receiving formula milk at term, the infants fed preterm formula did show slightly better growth from birth to term than those fed standard or special formula, but this difference did not reach statistical significance. This result contrasts with previous research that has indicated the value of preterm formulae in facilitating more rapid growth than standard formulae (e.g. Cooper, 1989; Cooke, 1998; Morley & Lucas, 2000). There are several possible explanations for the failure of the present study to replicate previous findings. The first is that the only data analysed is on the type of milk being given at the time of the term and 3-months assessments. Therefore a proportion of the infants receiving standard formula at term may have been receiving preterm formula during hospitalisation, the period of which would constitute most of the time between birth and term. No distinction was made between infants who had just been swapped to standard formula from those who had been on it for several weeks. Secondly, a proportion of the infants who were receiving one of the formula milks at term may have been receiving breast milk until just before the assessment, and again this might have confounded the findings. Finally, the number of infants receiving the standard and/or "special" formula at term was quite small (n=22) and therefore the difference in growth rate would have needed to be greater in order to reach statistical significance.

Term to 3 Months – In contrast with the initial growth period, between term and 3 months of age the sub-group of infants within the present sample who were being breast-fed at term showed very significantly better growth during the following 3 months than those who were being formula fed (either pre-term or standard/special). This finding is in contrast to previous studies examining the growth of very preterm infants post-discharge from hospital, that have consistently shown that continuation of preterm or enriched formulae post-discharge does offer advantages over breast milk or standard formula in terms of enhanced growth for these infants (Cooke, 1998; Lucas, 2001; Carver, 2001). A paper by Lucas et al (1997) reporting on the growth rates of term, small for gestation infants may offer an explanation for this finding. The authors reported that the breast-fed infants showed a much better rate of catch-up growth than those fed on formula (although the comparison was only with standard formula), particularly during the first three months of life. There were several possible mechanisms for this observed effect, including higher intake (since the infants would stop feeding when satiated rather than when the bottle was empty); specific beneficial nutrients in the breast milk; better nutrient absorption, or a combination of these factors. Since the breast-fed infants in the present study had shown particularly poor growth trajectories during the early weeks of life, i.e. to term, they might in some ways be comparable with term infants born small for gestation, and similar mechanisms might explain their subsequent catch-up growth which compensated for earlier deficiencies.

As with the earlier growth period, in the present study there was no significant difference between mean growth rates of the sub-groups of infants fed pre-term as opposed to standard formula at term, although the trend was for the sub-group fed the preterm formula to grow more quickly than the standard/special formula group. Possible reasons for results that contrast with previous studies have been discussed above, and relate equally to this time period. Previous studies have found that the effect of the milk on growth is more pronounced in boys (Lucas et al, 2001; Carver et al, 2001). In the present study, however, the effect of milk at term on growth during the following three months is very similar for both boys and girls.

Interestingly, when type of milk being given at 3 months corrected age is analysed in relation to growth, the infants who were still being breast-fed at that time showed significantly better growth during the previous three months than either of the formula fed sub-group. Of the 23 infants who were being predominantly breast fed at term, seven were swapped to formula feeding by the 3-month assessment. Again, the timing of the change of milk is not known, and therefore it is difficult to draw conclusions from these findings, for example it might be that it was the breastfeeding infants who were not growing particularly well who were swapped onto formula feeding between the two assessment points.

Among the formula fed infants, the sub-group still being given preterm formula at 3 months actually had a slightly lower mean growth rate than the infants being given standard formula. One possible explanation of this finding, which is in contrast to previously cited studies, is that the standard formula sub-group were changed to standard formula specifically because they were showing good growth, and it was therefore deemed unnecessary to continue with the enriched formula. As already discussed, the timing of the change from one type of milk to another is not known, which unfortunately means that it is not possible to pursue this avenue of enquiry.

<u>Birth to 3 Months Corrected Age</u> - For the overall time from birth to 3 months corrected age, there was no apparent difference in growth rates between formula and breast-fed infants, with the differing growth trajectories for the two periods cancelling one another out. By 3 months of age the type of milk that had been fed at term, or indeed

concurrently (i.e. at 3 months), had no effect on either weight z-score or weight status being above or below the 10th percentile. This finding is surprising, based on previous research (see above). It would have been anticipated that the infants fed preterm formula beyond discharge from hospital would have shown significantly better growth than those fed either breast milk or standard formula. It is unclear why the findings from this study differ from previous research. One explanation might be that, due to the relatively small sample size, and the small numbers of breast-fed infants (particularly at 3 months), the results were simply due to chance.

9.5.1.2. The Irrelevance of the Number of Feeds per Day

The number of feeds per day being given at term was not related to growth during the preceding weeks of life, but there was a highly significant correlation between the number of feeds being given at term and growth during the following three months. Further investigation revealed that there was also, however, a significant correlation, at both term and 3-months, between the number of feeds being given and the type of milk being given, with the breastfed infants receiving more feeds per day than those who were formula-fed. When both the type of milk being received and the number of feeds being given were subsequently included in the multiple regression analyses, the independent contribution of each variable while the other variables were held constant could be calculated, and this revealed that the number of feeds given, when the type of milk was held constant, did not contribute significantly to the model. This finding is of considerable clinical relevance, since mothers of infants born very preterm are usually advised to wake them regularly for feeds, on the assumption that this will increase their calorific intake and thereby enhance growth. The value of this practice would appear, based on the present study, to be worthless.

9.5.2. The Lack of Relationship between Infant Feeding Technique and Growth

Infant feeding technique was measured using a) a checklist of possible abnormal feeding behaviours (the Feeding Problem Index); b) objective analysis of sucking pattern using the Whitney Strain Gauge; and c) calculation of intake/minute. In general the results were surprising, with none of the measures of feeding technique being related to growth during the period from birth to term or from term to 3-months, only intake per minute being related to growth for the overall period birth-3 months and intake per minute and individual suck duration related to weight z-score at 3 months of age. These findings, and possible explanations for them, are discussed below, with each of the outcome measures in terms of growth being considered in turn.

There were inter-correlations, both at term and 3-months, between the scores on the FPI and mean individual suck duration, with the poorer feeders exhibiting shorter sucks, and in turn mean individual suck duration was significantly positively correlated with intake per minute. Thus it would seem that the instruments used did effectively measure some oral-motor function.

9.5.2.1. Growth from Birth-Term

As mentioned above, there was no significant correlation between any of the feeding technique variables and growth rate between birth and term. The most likely reason for this is that for a considerable proportion of the time between birth and term the infants were not relying on their feeding skills in order to receive nutrition. During the first few weeks of life they were usually being fed firstly parenterally (i.e. intravenously) and then by naso-gastric tube direct into the stomach. By the latter few weeks of this period many of the infants had started to take oral feeds, but this gradual change is carefully monitored, and if intake isn't adequate (for example due to poor feeding skills) further milk is given via the naso-gastric tube. Some of the infants even went home whilst still receiving naso-gastric supplementation. It can be seen, therefore, that it is quite feasible for the infant's feeding competence not to be directly related to growth during this period.

9.5.2.2. Growth from Term – 3-Months

More surprisingly than the lack of significant findings during the period from birth to term, was the fact that there was also no significant relationship between any of the measures of feeding technique and growth between term and 3-months, a period when almost all of the infants were taking oral feeds normally and it could be anticipated that a relationship would be found.

The lack of a significant relationship between the FPI scores and growth could have several causes. The FPI was a composite variable, comprising feeding behaviours that would indicate poor feeding, e.g. dribbling excessively, gagging or choking etc. The higher the score, the more of the disorganised or dysfunctional feeding behaviours the infant displayed on a regular basis. Although this would seem to be a reasonably accurate way of distinguishing feeding competence, it does require the mothers accurately to recall normal infant feeding behaviour. In addition, it was unfortunately not possible, prior to the onset of the study, to pilot this instrument. Thus it is possible that the instrument simply was not an appropriate one for this type of infant sample. Another possible reason for the lack of relationship between FPI scores and any of the growth measures is that the mothers of the infants who were experiencing feeding problems compensated for these difficulties by adapting their feeding technique and thereby ensured adequate nutritional intake. This second hypothesis is supported by the highly significant relationship between FPI and milk intake per minute, which would suggest that the FPI did actually reflect feeding competence. The mean scores on the FPI did decrease between term and three months, which suggests that the infants who at term were exhibiting abnormal feeding behaviours (for example excessive dribbling, choking etc) had improved during the subsequent three months, presumably as a result of maturity, and increased co-ordination.

The lack of a significant relationship between any of the Whitney Strain Gauge variables and growth from term to 3-months could also be due to several causes. The first might be that the sample size was simply inadequate for a clear pattern to emerge and reach statistical significance. The correlations were all in the expected direction, however, with infants who demonstrated longer sucking bursts, longer pauses and longer individual sucks showing better growth. These trends were in accordance with previous research (Dubignon & Cooper, 1980; Wolff, 1968; Young, personal communication). Unfortunately one of the drawbacks of the strain gauge equipment was that it was not possible to measure actual sucking pressure, which is one of the other oral-motor variables commonly associated with feeding ability (e.g. Kron et al, 1963). The equipment was difficult to use and, particularly at the term assessment, many of the feed printouts could not be coded. Coding of the feeds did not commence until the data collection phase of the study had been completed, and the extent of the unusable data was not therefore apparent until it was too late to take remedial action.

The strain gauge equipment had been piloted, with few technical difficulties, and the fact that more of the 3-month feeds could be coded (49 compared to just 30 at term) suggests that possibly the equipment was not adequate to cope with the disorganised sucking patterns still exhibited by many very preterm infants at the term assessment. This possibility is also supported by the fact that there was a much larger proportion of unusable data among infants rated as poor feeders on the FPI. Whatever the cause of the equipment failure, the lack of subjects upon whom data was available was a disappointment and, on the basis of the present study, the use of this type of equipment in future studies of very preterm infants might be deemed inappropriate.

Separate analyses were also performed on bottle and breast-feeding infants when examining the relationship between WSG variables and growth between term and 3 months (due to known differences in both sucking patterns and growth trajectories of the two sub-groups). As previously explained, due to the very small number of breast-fed infants upon whom WSG data was available at term statistical analyses could only be performed on the bottle-fed subjects. For this sub-group, the results were very similar to those for the whole group.

9.5.2.3. Growth from Birth to 3 Months

Only one of the infant feeding technique variables at term was significantly correlated with growth during the overall period from birth to 3 months of age, that being milk intake per minute. The correlation was positive, indicating that infants who fed more efficiently grew faster. Again, as with the two shorter time periods, none of the WSG variables nor the FPI were significantly related to growth rate. The possible reasons for this have already been discussed.

9.5.2.4. 3-Month Weight Z-score

When the feeding technique variables were examined in relation to the final outcome measure, actual weight z-score at 3 months of age, there were two significant correlations. Firstly, as with growth from birth to 3 months, the intake per minute was significant and in the expected direction with infants who fed more efficiently at term being heavier at 3 months of age. Secondly, the only WSG variable to be related to any of the outcome measures was mean individual suck duration, with infants who took longer sucks being larger at 3 months of age. This finding is consistent with previous research which shows that nutritive sucks are longer than non-nutritive sucks (i.e. on a dummy or finger) (Wolff, 1968), and also that there is a strong correlation between sucking rate and milk intake (Kron et al, 1963). Bearing in mind, however, the number of correlational analyses that were performed, this single significant finding from the WSG data might simply be the result of a type I error, although as it is in accordance with previous findings it may be that the observed correlation is genuine.

9.5.3. The Relationship between Infant Feeding Technique and Medical Variables

Previous research has suggested that there might be a link between severity of early medical condition (e.g. duration of mechanical ventilation) and later infant feeding skill (e.g. Meyer Palmer, 1993; Blaymore Bier et al, 1993). When exploratory correlational analyses were performed, however, there were very few significant findings. At the term assessment there was a significant correlation between gestational age at birth and milk intake per minute (with more mature infants feeding faster); between birth weight and pause length (with heavier infants taking longer pauses between sucking bursts); and between duration of intensive care and intake per minute (with infants who had been sicker being slower feeders). None of the feeding technique variables were correlated with duration of mechanical ventilation.

The findings from this study are clearly not as would be expected based on prior research. One possible reason for this discrepancy is that the sample size, particularly for the strain gauge variables, was not large enough to enable the correlations to reach statistical significance. For the Feeding Problem Index, however, the sample size was much bigger at both term and 3-months, but it still did not correlate with medical variables to any discernable extent.

Another possible explanation for these findings is that advances in neonatal intensive care have been such that there is less likelihood of oral-motor sequelae. For example, the recent use of naso-tracheal intubation rather than the oro-tracheal intubation that was shown to effect sucking ability adversely to a very significant extent (Blaymore Bier, 1993). The relative frequency of abnormal feeding behaviours at the term assessment may therefore be simply a continuation of the disorganised sucking behaviour usually exhibited by preterm infants, and which may be seen during the first few days of life even in healthy, term infants. The observed reduction in reported problems, and the improvement shown on the strain gauge variables between the term and 3-month assessment, may be indicative of maturity and the absence, in general, of the longer-term, dysfunctional feeding behaviours that were more prevalent in the past.

9.6. The Lack of a Relationship between Infant Behavioural Factors and Growth

The two aspects of infant behaviour that were examined in relation to growth, and presented in the foregoing Results chapters, were irritability (and crying) and sleep patterns.

9.6.1. Infant Irritability

A paper by Carey (1985) reported that in a study of normal, term infants, those who had more difficult temperaments showed a significantly faster rate of growth, the proposed explanation being that "fussy" infants would have been fed more frequently, in order to quieten them. It was anticipated that the present study would produce similar findings, since the idea that the more irritable infants would be fed more frequently, and that their total daily intake would therefore be greater, seemed plausible. However, the Carey findings were not replicated in the present study. Interestingly the explanation for the expected findings was supported by the data analysis, i.e. the more irritable infants were fed more frequently, but this did not actually lead to increased growth rates. The discrepancy between the results of the present study and the Carey study might be due to the fact that the samples were very different – the Carey sample comprising normal, low risk infants, and examining growth between 6 and 12 months of age, rather than during the first few months of life.

There are two possible explanations for the findings reported in this thesis. Firstly, that although the infants in the present study fed more frequently, they did not actually have a greater daily intake (for example, taking smaller feeds, possibly due to fretfulness, or possessing poorer oral-motor skills). Secondly, that although they fed more frequently, and possibly did have a greater intake, their energy output was greater due to their irritability and therefore there was no net benefit to their increased calorific intake.

9.6.2. Sleeping and Feeding Patterns

There were several interesting, and perhaps surprising, findings in respect of sleeping and feeding patterns among the very pre-term infants followed in this study, and the relationship between these variables and growth. There has been little published research on sleeping patterns of very preterm infants in relation to growth, and therefore the analyses reported in this thesis are exploratory in nature.

Most importantly and of clinical significance, there was no relationship between infants who were/were not woken for feeds at term and growth in the subsequent 3 months. This would suggest that, generally speaking, the usual advice to wake infants for feeds, if they naturally sleep for long periods of time, is ineffective in promoting more rapid weight gain. Furthermore, although there was a high correlation between number of feeds given at term and growth between term and 3-months, multiple regression analyses revealed that the relationship was no longer statistically significant if the type of milk being received was held constant. An important conclusion that can therefore be drawn from these results is that more frequent feeds does not necessarily imply greater daily intake. If infants are woken for feeds, when they would have been asleep if left to their own devices, they may feed ineffectively, and therefore the benefit of the extra feed might be minimal. Infants who are allowed to follow their natural sleep patterns may, on the other hand, feed better when they do feed, and thereby have a comparable daily intake.

Interestingly there was no correlation between the number of hours slept and the number of feeds given in a 24-hour period, either at term or at the 3-month assessment. This implies that infants who were good sleepers did not actually miss out on feeds as a result of their sleepiness, merely that they presumably spent less time awake but not being fed. In addition, there was no relationship between the number of feeds given in a 24-hour period and whether or not the infants were woken for feeds at night. Thus it would appear that infants who were left to sleep for prolonged periods during the night compensated by having more frequent feeds during the day.

It would be expected that all the infants in the study would, at term, be waking for feeds during the night since their post-conceptual age was equivalent to that of full term newborns. This was not the case, however, and surprisingly it was the infants who had weighed less at birth, and who had been sicker during the neonatal period, who were significantly more likely to self-wake at term than their heavier, more robust peers. This might have been due to their relatively recent discharge from hospital and that therefore they were still behaving according to hospital routine, i.e. being fed every four hours, day and night.

Thus there would appear to be no clear relationship between infant behavioural patterns and growth among this sample of infants born very preterm. An infant who is irritable or cries more than average is not likely to have either an accelerated or diminished rate of growth than its less irritable peers. Furthermore, on the basis of this, albeit small, study it does not appear that waking very preterm infants for night feeds post-discharge is particularly beneficial, since this does not appear to increase either the total number of feeds in a 24-hour period, or indeed the growth rate between term and 3 months of age.

9.7. Relationship between Maternal & Social Factors and Growth

The three variables representing maternal/social factors that were used in analyses with growth variables and reported in the foregoing Results chapters were maternal age, maternal IQ, and Osborn Index. These measures were analysed only in relation to growth between term and 3 months, because this was the period when the infants were at home, in the care of their mothers. All three of the maternal/ social measures were shown to be significantly correlated with growth between term and 3 months but they were also, as expected, highly inter-correlated.

It has long been recognised that there are strong correlations between maternal factors and type of feeding, with older, better educated and higher SES women being more likely both to initiate and persevere with breastfeeding (e.g. Foster et al, 1997; Pollock, 1994). Despite the complication of very preterm birth, this relationship was also found in this study, with mothers who were breast-feeding at term having both significantly higher Osborn Index scores and significantly higher IQ scores - in fact further analysis showed that the sub-group of breast feeding mothers had a mean IQ 10 points higher than the mothers who were formula feeding. This relationship between type of feeding and maternal or social factors was no longer significant, however, at the 3-month assessment, although the trend persisted in the expected direction.

Thus the relationship between social factors and growth might have been due, partly or entirely, to the inter-correlation with method of feeding since, as already reported, during the period from term to 3 months the infants who were being breastfed at term grew significantly better than those who were being formula-fed. The problem of the type of milk confounding the findings in relation to social factors was addressed in the multiple regression analyses, which are discussed in the following section.

9.8. The Significance of the Prediction Models

One of the primary intentions of the present study was to develop models that could be used to predict early growth, in order to identify infants who were believed to be particularly at risk of poor growth. In much previously published research, specific factors have been examined, often in relation to growth, for example nutrition (Cooke, 1998, 2001; Lucas et al, 2001; Carver et al, 2001 etc), temperament (Carey, 1985), oral-motor function (Ramsay et al, 1993; Reilly et al, 1999), medical complications (Campbell, 1997). Although all these studies have contributed to the current body of knowledge about growth in early infancy, not all have specifically examined very preterm infants, and not all have controlled for possible confounding factors. It was hoped that the present study would provide a more comprehensive view of the early growth of these high-risk infants, and clarify the relative importance of a whole range of variables on observed growths rates. After the initial analyses had been performed examining the relationships between the various factors and growth, it was necessary to perform regression analyses in order that the specific effect of particular independent variables could be established, taking into account other confounding variables. As already discussed, although some of the early analyses had been exploratory, the majority were based on findings from previous research (even if not on a very preterm sample of infants, as in this instance).

Prediction models were computed for each of the three growth periods, together with weight z-score at 3 months of age, and weight status (i.e. above or below the 10^{th} percentile) at 3 months. This was necessary because the significant "predictors" were different for the early postnatal period and the later period between term and 3-months.

9.8.1. <u>Growth from Birth to Term</u>

Only two significant predictors of growth between birth and term were found, these being birth weight z-score and the type of milk being received at term. The duration of intensive care, although included in the regression model, failed to contribute significantly to it when the other variables were held constant.

Infants who were lighter for gestation at birth were likely to grow better during the weeks immediately after birth than those infants who had been heavier for gestation. One likely explanation for this finding has been presented in Section 13.4.1, and relates to apparently reduced fluid levels at birth in infants who are lighter-for-gestation. The finding is also concordant with more general research that suggests that there is a deviation towards the mean for infants at both ends of the weight for gestation spectrum (Cole, 1995). It must be remembered, however, that overall the sample showed very poor growth during these early weeks, and therefore the better growth rate of lighter for gestation infants is only a within-group comparison. This finding of generally poor early growth in very preterm infants in comparison to intra-uterine growth rate is in keeping with previous research (Alexander, 1996).

Infants within the present sample who were still being breast-fed at term were likely to exhibit poorer growth up to that point than infants who by term were being predominantly formula fed, regardless of the type of formula or other factors (e.g. severity of neonatal illness). One of the recognised limitations of the study, however, was the fact that precise duration of breastfeeding was not known, i.e. a proportion of the "formula" fed group would also have received expressed milk for at least part of the period of hospitalisation, but information about when they were changed onto formula milk was not available. It might be expected that one of the main reasons for changing infants from breast milk to formula is that the mother was unable to produce enough milk, but in this case the formula-fed group growth rate would have been reduced. This suggests that the observed advantage of formula feeding during the first weeks of life might actually be conservative in its magnitude. As discussed in section 13.5.1.1, the type of formula being received at term does not significantly predict growth, but this might be because even those fed a standard formula at the term assessment would have been receiving preterm formula up until discharge from hospital, which constitutes the greater part of the time period under examination. This finding that infants who were fed formula at term grew significantly better than those who were fed breast-milk, regardless of other factors, is again in accordance with previous research (e.g. Lucas et al, 2001; Schanler, 1999).

Finally, although the predictive value of the model was statistically significant, it in fact only explained 40% of the variance in growth rate between birth and term, leaving the other 60% of variance unexplained. Thus, despite the attempt to analyse comprehensively the effects of many early variables on growth, it was obviously not possible to identify all such variables.

9.8.2. Growth from Term to 3-Months

Five independently significant variables were entered into the regression model for growth between term and 3 months, but due to inter-correlations only three of these continued to make a statistically significant contribution to the model when the other variables were held constant.

The type of milk being given at term was the greatest contributor to the regression model, with infants who were being breastfed growing significantly better during the following three months. This was in dramatic contrast to the earlier growth period, and also at odds with much of the previous research which, as discussed in section 13.5.1.1, generally finds that infants fed preterm formula grow faster than those fed on breast milk. One explanation for this discrepant finding might be that, due to cell size, type of milk was simply dichotomised into breast or formula, and infants fed on standard (or "special" formula) would be expected to grow slower than those on preterm formula. Another reason for this finding, again mentioned in section 13.5.1.1, may be that the breastfeeding infants, having become stronger, more competent feeders, were now compensating for earlier poor weight gain by showing rapid catch-up growth. In addition, although breast milk is known not to contain sufficient levels of nutrients for very preterm infants (e.g. Nutrition Committee, 1995) and therefore during the period up to term there is a risk of inadequate augmentation of the breast milk with additional nutrients, this is not an issue once the infant is post-term and the breast milk is sufficient to satisfy the infant's nutritional requirements.

The second significant contributor to the model was the number of hours the infant slept during a 24-hour period at term, with infants who slept for more hours in total showing better growth rates. The most likely mechanism for this finding is that while infants are asleep they are using very little energy compared to when they are awake and active, and therefore those who sleep for longer are able to use more of their calorific intake to grow. Another possible explanation is that the infants who are well rested are able to feed more efficiently and therefore their actual calorific intake is greater. Infant sleep patterns are an issue that have not been examined in detail in relation to growth among very preterm infants, and therefore these findings are of particular interest from a clinical perspective. Further research would seem to be warranted, which if it replicated these findings might have implications for management of these at-risk infants post-discharge from hospital.

The third and final independent variable that contributed significantly to the model was maternal intelligence, with infants whose mothers were less intelligent (specifically those whose IQ, as measured using the WAIS when the infant was 3 months old, was below 85) being particularly at risk of poor growth between term and 3 months. Although there was a correlation between maternal IQ and type of milk being given at term, when the latter was held constant within the regression analyses maternal IQ still was an significant predictor for growth between term and 3-months. The precise mechanism for this effect is unclear, but it is possible that the less intelligent mothers (who by definition were at least one standard deviation below the mean for the general population) were less sensitive to their infants' demands, and/or more rigid in their feeding behaviours, e.g. giving a specified quantity of milk rather than allowing the infant to determine intake.

The other two independently significant variables that were entered into the regression analysis, i.e. number of feeds per day and gestational age, were no longer significant when all other variables were held constant, the former presumably because of the high correlation between type of milk and number of feeds being given.

The prediction model that was presented explained 35% of the variance in growth between term and 3 months, which again was statistically significant, but still leaves 65% of the variance unexplained.

9.8.3. Birth to 3 Months

When discussing the prediction model for growth during the overall period from birth to 3 months corrected age (a total period of 5-7 months) it must be taken into consideration that one of the strongest predictors for each of the sub-periods discussed above, i.e. the type of milk being given at term, was not included because the contrast in direction of influence for the two shorter periods cancelled out the effect for the overall period.

As with the period from birth to term, birth weight z-score was the most significant contributor to the model, with infants who were lighter for gestation tending to grow faster during the subsequent months. Explanations for this have been discussed in section 9.8.1 above.

The only other significant contributor to the model was feeding efficiency (i.e. milk intake per minute) at term, with the more efficient feeders showing better growth for the overall period.

Surprisingly, and rather reassuringly, the other independent variables that were entered into the regression analysis, i.e. gestational age and intensity of care in the immediate postnatal period, failed to contribute significantly to the model once the other variables were held constant. This suggests that the less mature, and sicker infants were not likely to suffer, at least in growth terms, any more than the more mature robust infants in the study.

9.8.4. 3-Month Weight Z-score

Although four independent variables were entered into the regression model for this outcome measure, the only one that remained significant when the others were held constant was birth weight z-score. This indicates that, although the infants who were lighter for gestation at birth generally showed better growth during the following months than infants born heavier for gestation (as discussed above in sections 9.8.1 and 9.8.3), they were still likely to be lighter at 3-months corrected age.

9.8.5. 3-Month Weight Below 10th Percentile

As previously indicated, a significantly larger proportion of the 90 infants included in the study were below the 10th percentile cut-off at the 3-month assessment than were below this criterion level at birth. The rationale behind using this outcome measure is the second major research question (addressed in the next Results chapter), i.e. whether good catch-up growth can ameliorate the adverse effects on cognitive development of intrauterine growth retardation. In other words, will infants who cross the 10th percentile line during the early months of life perform differently to those who remain (or fall) below that criterion at 3-months corrected age?

Four independent variables were entered into the logistical regression analysis, but only two of these remained statistically significant contributors to the model when the others were held constant. The greatest contributor was birth weight status, i.e. whether or not the infant was born small for gestation, with a seven-fold increased risk of being below the 10th percentile at the 3-month assessment if below it at birth, when all other factors were held constant. This finding is concordant with previous research that suggests that within full-term samples being born small-for-gestation leads to an increased risk of remaining small even into adulthood (Paz et al, 1993; Pryor et al, 1995; Frisancho et al, 1994).

The only other independent variable that appeared to contribute significantly to the model was the level of intensive care required during the first 10 days of life, with the infants who had required more intensive care (i.e. were sicker) being more likely to have a weight below the 10th percentile at 3 months of age. This medical variable was also significantly correlated with growth between birth and 3 months corrected age, although it failed to contribute significantly to the final regression model. As previously discussed, the mechanism for this effect is unclear, since early medical condition did not appear to be related to type of feed, number of feeds, or oral-motor function. Nonetheless, whatever the mechanism, there does appear to be a relationship between severity of early medical condition and weight at 3 months corrected age.

The other two independent variables that were entered into the regression analysis were sub-optimal milk and low maternal IQ. Type of milk being given, rather than being dichotomised between breast milk and formula, was dichotomised between breast milk (which was fortified during hospitalisation) or preterm formula and standard infant or special formulas, the latter two not being optimal in terms of nutrient value for preterm infants. Neither milk type nor maternal IQ was a significant independent contributor to the model.

9.9. Summary of Chapter

In this chapter the relative influence on growth and later weight status of various early variables have been discussed in relation to previously published research. One of the most significant findings, ironically, was that despite the number of early variables that were examined in relation to growth, the prediction models that resulted from these analyses only explained a relatively small proportion of the variance in growth/weight outcome measures. Many of the findings were concordant with previous studies, although there were exceptions – notably that infant feeding technique did not appear to be adversely effected by early medical treatment (e.g.. mechanical ventilation), and that for the overall period from birth to 3 months corrected age the type of milk was not an important factor (although it was for each of the sub-periods). It was also clear that there were different factors influencing growth rate during the first and second (and consequently overall) periods under investigation.

During the initial period from birth to term all the infants grew poorly, but the infants who were light for gestation grew faster than those who were heavier for gestation, and the breast-fed infants grew much worse than those receiving formula. The clinical implications of these findings will be discussed at the end of the thesis.

During the second growth period from Term to 3 months corrected age, when the majority of infants were at home in the care of their mothers, the factors influencing growth were again type of milk at term (with breast milk now having a positive influence on growth); how much sleep the infant had (with those who slept for longer growing better; and maternal IQ (with infants whose mother's IQ was more than one standard deviation below the mean growing more slowly).

For the overall period birth to 3 months corrected age, birth weight z-score and feeding efficiency at term were the only early variables that contributed to the prediction model, with lighter-for-gestation infants, and those who fed more efficiently, growing better.

As far as 3-month weight z-score was concerned the overwhelmingly significant early variable was birth weight z-score, with infants who were born light for gestation remaining lighter-for-age, despite the fact that they had showed better growth between time points than their heavier peers.

Finally, for 3-month weight status below the 10^{th} percentile, there were two early variables that contributed significantly to the prediction model. Firstly weight status at birth (i.e. if the infant's weight was below the 10^{th} percentile at birth there was a high risk that it would still be below it at 3 months corrected age); and secondly how sick the infant was in the first 10 days of life (with infants who were sicker being more likely to be below the 10^{th} percentile at 3 months corrected age).

SECTION IV: 18 MONTH ASSESSMENT

RESULTS & DISCUSSION

Introduction to Section IV

As discussed in the Section II (Method), the design of the Gain Study included an 18-month follow-up assessment. At this assessment each subject's developmental progress was examined and then analysed in relation to some of the early variables presented in the preceding chapters. The primary issue was whether it was possible to devise prediction models that explained the variance in developmental status among the subjects, and more specifically, to ascertain whether variations in early rates of growth were related to developmental outcome at 18 months of age. In addition to the developmental assessment that took place at this time, further anthropometric measurements were taken, in order to ascertain whether there had been further fluctuations in rates of growth among the infants, and to establish concurrent anthropometric data for use in the analyses with the developmental outcome data.

This Section comprises the outcome of the 18-month assessment, presented in a single Results chapter, followed by a Discussion chapter in which the important findings relating to this assessment are addressed.

In the Results chapter firstly the results of the developmental assessments that took place using the Bayley Scales MDI (see Section II - Method) are presented. These developmental outcomes are then examined in relation to many of the variables used in the previous Section examining the predictors of early growth, i.e. birth/early medical factors, anthropometric measurements, early infant feeding and maternal/socio-economic variables in order to ascertain whether there were significant relationships between any of these antecedent factors and developmental outcome at 18 months of age. Regression analyses are presented which were used to devise prediction models for developmental outcome at 18 months, and specifically for severe developmental delay at this time.

Following on from the developmental outcome analyses, the anthropometric measurements of the subjects at the 18-month assessment are presented. These are compared to those of a normative sample and the stability of weight status (i.e. above or below the 10^{th} percentile for age) between the early period of study and the 18-month assessment is examined. 18-month anthropometric measurements and their relationship with neonatal and maternal/social variables are also presented. Finally, the relationship between parental height and subject weight at each assessment point is investigated.

The subsequent Discussion chapter first addresses the most important findings, i.e. the significant early predictors of developmental outcome, and those early variables that were not related to outcome.

Chapter 10: Outcome at 18 Months – Development & Anthropometry

10.0. Introduction

In this chapter the data obtained at the 18-month assessment is presented. Firstly developmental outcome is considered, and its relationship with early variables examined. Subsequently the anthropometric outcome is addressed, again in relation to early variables.

10.1. Developmental Outcome at 18 Months

As discussed in the Method Section, each subject's cognitive development was assessed using the Mental Development Index (MDI) of the Bayley Scales. The mean score was 78, with a standard deviation of 16. Scores ranged from 50-109. Three infants had such severe cerebral palsy that they were unable adequately to perform the assessments due to their physical condition, and they were therefore excluded from the subsequent analyses, leaving a total of 78 infants upon whom developmental scores were available. The minimum possible score was 50, and this was allocated to those infants who failed to co-operate sufficiently to perform the tasks (n=7).

According to the BSID-II reference data, approximately 15% of the sample would be expected to score 115 or above on the MDI. However, within the study group none of the infants performed within this range. As previously indicated in Section II (Methods), when chi-square analyses were performed there was a significant difference between the expected and observed frequencies within each of the four classification categories.

10.1.1. Gender

10.1.1.1. The Relationship between Developmental Scores and Gender

Independent t-tests were performed to ascertain whether there were significant gender differences on the MDI scores, since previous research has shown that boys are more vulnerable to the adverse effects of preterm birth and sub-optimal early feeding than girls (e.g. Whitfield et al, 1997; Campbell, 1997; Lucas et al, 1989 and 1998).

As can be seen from Table 95, girls performed significantly better. Mann-Whitney U-tests (rank-ordering of scores) were also performed to confirm the findings, as the scores were not normally distributed. These tests confirmed the results of the t-tests.

Table 95: Gender Differences on BSID-II MDI (N = 78)

		N	Mean	Std Dev	t- value	p
MDI	male	43	74.23	16.50	-2.57	.01
	female	35	83.31	14.27		

10.1.1.2. The Relationship between Severe Developmental Delay and Gender

The subjects were subsequently dichotomised into two groups, one of infants whose MDI scores were below 70 (i.e. > two standard deviations below the mean) and the other of infants whose scores were 70 or above. Of the 78 infants who were tested using the Bayley Scales MDI, there were 20 infants in the low scoring group and 58 in the higher scoring group. This dichotomy has clinical relevance since there is an increased risk that infants born very preterm who score at this level at 18 months of age will continue to show developmental delay as they mature (Kopp et al, 1982; Wolke et al, 1994; Wildin et al, 1997) and thus are likely to require special education and other support services.

Analyses were performed to ascertain whether there were sex differences in the severely developmentally delayed group. There was a significantly higher proportion of boys than girls in the severely delayed group (Chi-square 6.73, df 1, $p < .01$) and these differences were apparently not due to birth or early medical variables, since there were no significant gender differences on these variables.

10.1.2. Neonatal Variables

10.1.2.1. The Relationship between Developmental Scores and Neonatal Variables

Analyses were performed to ascertain whether there were any significant relationships between any of the early neonatal variables and developmental scores at 18 months corrected age. Initially the whole group was looked at using their MDI scores. As can be seen from Table 96, neither gestational age nor actual birth weight were significantly correlated with the Mental Development Index. Furthermore, the neonatal variables that measured how sick the infants had been (duration of intensive care and level of care over first 10 days) were not correlated with later development, and nor were the two composite risk scores – antenatal or neonatal (the foregoing variables all comprised continuous data). Ultrasound brain scans during initial hospitalisation that showed evidence of cyst formation were highly correlated with MDI scores, with infants who had abnormal scans scoring lower than those with normal scans (despite the prior exclusion of the severe cerebral palsy infants from the analyses).

Table 96: Correlations between BSID-II MDI and Neonatal Risk Variables (N=78)

Birth/Neonatal Variable	**Bayley Scales Mental Index**
Gestational age	.06
Birth weight	.11
"Compneon"	-.02
"Comppreg"	-.03
Duration of Intensive Care	-.04
Level of Care over 1st 10 days	-.06
Abnormal Ultrasound Scan > 1 week of age	**-.25***

* significant at the .05 level

10.1.2.2. The Relationship between Severe Developmental Delay and Neonatal Variables

Analyses were performed to ascertain whether the infants who were classified as severely developmentally delayed differed from the rest of the sample in terms of neonatal and medical risk variables. Mann-Whitney tests were performed because the medical risk indices were not normally distributed.

Table 97: Differences between infants with and without Severe Developmental Delay (SDD) on Neonatal Variables (N=78)

Neonatal Variable	MDI (cut-off 70)	Mean Rank	Mann-Whitney U	p
Gestation	Non-SDD SDD	41.93 32.45	439.0	.10
Birth weight	Non-SDD SDD	42.39 31.13	412.5	.06
"Compneon"	Non-SDD SDD	38.51 42.38	522.5	.51
"Comppreg"	Non-SDD SDD	39.76 38.75	565.0	.86
Duration of Intensive Care	Non-SDD SDD	36.34 44.97	418.5	.14
Total days of Hospitalisation	Non-SDD SDD	35.58 47.26	**375.0**	**.05**
Total days of Ventilation	Non-SDD SDD	37.48 41.55	483.5	.47
Level of care 1st 10 days	Non-SDD SDD	36.08 45.76	403.5	.10

As can be seen from Table 97, the trend was for the infants who were in the severely developmentally delayed group to have been less mature and lighter in weight at birth, and to have required higher levels of intensive care during the neonatal period. However, this trend only reached statistical significance in the case of total days of hospitalisation and in view of the number of variables tested this one significant finding (at the $p < .05$ level) might have been due to chance. There was very little difference between the two groups on the composite medical risk variables "Compneon", "Comppreg".

Chi-square analysis was performed to ascertain whether abnormal ultrasound scans of the brain were associated with severe developmental delay, and the results showed that there was a significant relationship between the two variables, with three of the four infants with abnormal brain scans being classified as severely delayed compared with 17 of the 74 with normal brain scans (75% compared to 23%, Chi-square = 5.39, $p < .05$).

10.1.3. Anthropometric Variables

10.1.3.1. The Relationship between Developmental Scores and Anthropometric Data

Based on previous research (e.g. Martikainen, 1992; Smedler et al, 1992; Sung et al, 1993) it was anticipated that there would be a significant relationship between early weight (for age) and developmental status at 18 months of age. Correlations were therefore performed to ascertain whether there was a significant relationship between developmental status at 18 months corrected age and weight/ head circumference up to and including that time.

As can be seen from Table 98, the correlation between 3-month weight and the MDI was significant, as was that between the 3-month head circumference and the Mental Index. The concurrent weight (i.e. 18 month measurement) was also significantly correlated with the MDI, although the correlation between 18-month head circumference and MDI failed to reach statistical significance.

Table 98: Correlations between Developmental Scores and Anthropometric Data

Anthropometric Variable	Bayley Scales Mental Index
Birth weight z-score	.09
Term weight z-score	.21
Term head circumference z-score	.13
3 mth weight z-score	**.26***
3 mth head circumference z-score	**.28***
18 mth weight z-score	**.29***
18 mth head circumference z-score	.22

* Correlation significant at the .05 level

Independent t-tests were performed to ascertain whether dichotomising the subjects weight z-scores (using the 10th percentile as the cut-off criterion) resulted in significantly differing scores. As can be seen from Table 99, being below the 10th percentile for weight/head circumference at birth and/or at term was not significantly related to the developmental scores. Being below the 10th percentile criterion for weight at 3-months_was, however, significantly related to the MDI score. Being below the 10th percentile for weight at 18-months wasn't significantly related to the MDI score, but head circumference was (although to a lesser extent than 3-month weight).

Table 99: Developmental Scores and Dichotomised Anthropometric Data

VARIABLE		N	BAYLEY MDI MEAN (SD)	t-value	p
Birthweight	> 10th C	59	78.19 (16.36)	-.12	.91
	< 10th C	19	78.68(15.66)		
Term weight	> 10th C	48	79.69 (16.98)	-.91	.37
	< 10th C	28	76.14 (14.48)		
Term hc	> 10th C	72	78.28 (16.13)	.94	.96
	< 10th C	6	78.67 (17.11)		
3mth weight	**> 10th C**	**51**	**81.65 (15.42)**	**2.73**	**.01**
	< 10th C	**26**	**71.42 (15.72)**		
3mth hc	> 10th C	69	79.03 (16.08)	1.10	.28
	< 10th C	9	72.78 (16.08)		
18mth weight	> 10th C	64	79.53 (15.58)	1.45	.15
	< 10th C	14	72.71 (17.19)		
18mth hc	**> 10th C**	**56**	**80.68 (14.90)**	**2.12**	**.04**
	< 10th C	**22**	**72.27 (17.76)**		

10.1.3.2. The Relationship between Severe Developmental Delay and Anthropometric Variables

The relationship between anthropometric variables and severe developmental delay was examined using independent t-tests. As can be seen in Table 100, the only two anthropometric variables on which there were significant differences between the groups of infants who did and did not exhibit severe developmental delay were weight z-score at 3-months and weight z-score at 18-months (i.e. concurrent weight).

Table 100: Differences between Infants with and without Severe Developmental Delay on Anthropometric Variables (N=78)

Anthropometric Variable	MDI >69	MDI <70	t-value	p
Birth weight z-score	-.24	-.53	1.05	.30
Term weight z-score	-.91	-1.32	1.43	.16
Term head circumference z-score	.13	-.15	1.10	.27
3-Month weight z-score	**-.61**	**-1.31**	**2.50**	**.01**
3-Month head circumference z-score	.15	-.34	1.66	.10
18-Month weight z-score	**-.08**	**-.73**	**2.21**	**.03**
18-Month head circumference z-score	-.30	-.92	1.84	.07

Chi-square analyses were then performed to examine the extent of the relationship between severe developmental delay and anthropometric measurements below the 10^{th} percentile at each time point. The only dichotomized anthropometric measurement that was significantly related to severe developmental delay was 3-month weight, with 13 of the 26 infants below the 10^{th} percentile classified as severely developmentally delayed, compared to seven of the 44 infants whose weights were above the 10^{th} percentile (50% versus 16%, Chi- square = 12.96, $p< .00$). None of the other dichotomised anthropometric variables showed a significant relationship to the dichotomised MDI, although the trend for each variable was in the expected direction (i.e. small infants being more likely to be severely developmentally delayed).

10.1.3.3. Interaction effects of Weight Status at Birth and 3 months

It was necessary to ascertain whether there was an interaction effect between the weight status at birth and at 3 months of age, that is, whether being below 10th percentile at 3-months was related to MDI scores, by virtue of being highly correlated with birth weight status. Univariate analysis of variance was performed, which showed that it was only weight status at 3 months that significantly predicted MDI score, regardless of weight status at birth (see Table 101).

Table 101: Effect of Weight Status at Birth and 3 months, and the interaction effect between the two time-points on MDI scores

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2516.75a	3	838.92	3.53	02
Intercept	275810.64	1	275810.64	1160.25	.00
TINY3MTH	**1382.16**	**1**	**1382.16**	**5.81**	**.02**
SGA	427.66	1	427.66	1.80	.18
TINY3MTH * SGA	218.94	1	218.94	0.92	.34
Error	17353.33	73	237.72		
Total	490681.00	77			
Corrected Total	19870.08	76			

a R Squared = .127 (Adjusted R Squared = .091)

10.1.3.4. Developmental scores and stability of weight status

One of the a priori hypotheses of the present study, based on previous research, had been that poor early growth would be related to poor cognitive outcome (e.g. Skuse et al, 1994; Carmona da Mota et al, 1990) and that, conversely, early catch-up growth might facilitate improved cognitive outcome for infants born small for gestational age. This supposition was tested using 1-way ANOVA to examine differences in developmental scores of infants. There were four groups: 1) small at birth (ie < 10th percentile) and remaining so at 3 months of age; 2) small at birth but exceeding the 10th percentile at 3 months (good catch-up growth); 3) above the 10th percentile at birth but dropping below it by 3 months (sub-optimal growth); 4) above the 10th percentile at birth and remaining so at 3 months of age.

Table 102 shows the results of this analysis, and the associated graph clearly depicts the group differences. Post-hoc analysis using Scheffe's range test showed that the only significant difference on the MDI was between groups 3 and 4 ($p < .01$). The failure of the difference between groups 1 and 2 to reach significance might have been partly due to the small size of the second small-for-gestational age group (n=6) since the mean difference was 6.6 points, which would be of clinical relevance.

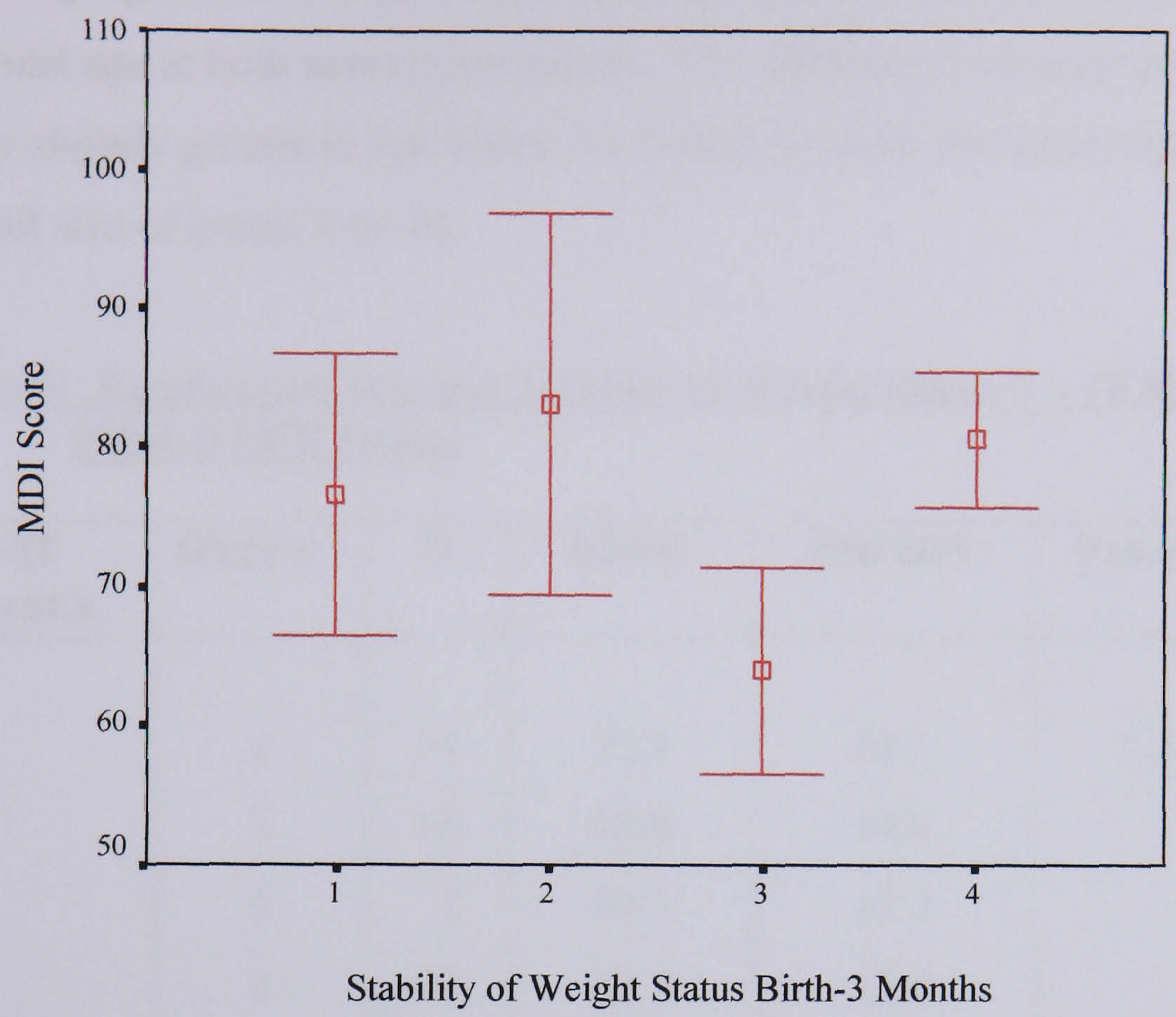
Table 102: Relationship between Stability of Weight Status Birth – 3 months and Developmental Scores

BSID-II Variable	Group	N	Mean	Std Dev	F-Ratio	P
MDI	1	13	76.6	16.8		
	2	6	83.2	13.1	3.53	.02
	3	13	66.2	13.2		
	4	45	81.4	15.8		

Table 102b: Key to Weight Stability Groups

Group	Weight Status at Birth and 3 Months
1	Below 10th percentile at both birth and 3 months
2	Below 10th percentile at birth but above it at 3 months
3	Above 10th centile at birth but below it at 3 months
4	Above 10th centile at both birth and 3 months

Figure 6: Relationship between Stability of Weight Status Birth – 3 months and BSID-II MDI Score



Similar analyses in relation to MDI scores were performed for the other weight status stability measures (ie birth to term; term to 3-months, 3-18 months and birth-18 months). For birth to term the group differences were non-significant; for term to 3 months the pattern was similar as for birth to 3 months (shown in the foregoing table and graph). The ANOVA showed an overall difference between the four groups (MDI $F=3.72$, $p=.02$; PDI $F=3.15$, $p=.03$), with Scheffe's range test showing that, again, the only significant difference on the MDI scores was between groups 3 and 4 ($p< .02$). This would suggest that it is the period after discharge from hospital when growth rate is most important, rather than the first few weeks of life when the infants were in the neonatal intensive care units.

Interestingly the pattern for the period 3-18 months was different, with the infants who rose above the 10th percentile criterion after the 3-month assessment performing slightly worse than those who remained small and similarly to those whose weight dropped below the 10th percentile during this period. Scheffe's post-hoc range test showed that the only significant difference was between group 2 and group 4 on the MDI ($p < .02$), with the infants who had been small at 3-months and then showed late catch-up growth performing significantly worse than those who had remained an appropriate size for gestational age at both assessment points. The difference between groups 3 and 4 was actually slightly greater in real terms, but failed to reach statistical significance due to the small size of group 3 (n=4).

Table 103: Relationship between Stability of Weight Status 3 – 18 Months and BSID-II MDI Scores

BSID-II VARIABLE	GROUP	N	MEAN	STD DEV	F-RATIO	P
MDI	1	11	75.3	18.1	3.55	.02
	2	16	69.8	14.0		
	3	4	69.3	17.7		
	4	47	82.7	15.0		

Finally, the overall period from birth to 18 months again showed the same trend of developmental scores as the period from birth to 3 months, although the group differences were not statistically significant for this longer period.

10.1.3.5. Stability of Weight Status and Early Medical Variables

Analyses were performed in order to ascertain whether weight status stability was related to early medical risk variables, and thus that it could be medical risk that actually linked weight status and later developmental status. Univariate ANOVAs were performed on both the stability between birth and 3 months, and that between term and 3 months. Gestation, birth weight, Composite Neonatal Risk score, Duration of Intensive Care, Intensity of Care over first 10 days, total days of Hospitalisation and total days of Mechanical Ventilation were used in the analyses. As shown in Table 104, for both the periods of stability only birth weight varied significantly (groups 1 and 2 differed from group 4 from birth-3 months; group 1 and 4 varied significantly from term-3 months). Mann-Whitney U-tests were also performed, since the medical variables were not normally distributed, and these confirmed the ANOVA findings.

Thus the relationship between early weight stability/rate of growth and later developmental scores cannot be attributed to the interaction effects of early medical variables.

Table 104: Relationship between Stability of Weight Status Groups and Early Medical Risk Variables

	F-ratio	p
Stability Birth-3 Months		
Gestational Age	.48	.73
Birth Weight	**10.82**	**.00**
Composite Neonatal Risk Score	.49	.69
Duration of Intensive Care	2.07	.11
Level of Care in first 10 days	.91	.44
Total Days of Hospitalisation	2.62	.06
Days of Mechanical Ventilation	2.36	.08
Stability Term-3 Months		
Gestational Age	.22	.88
Birth Weight	**4.75**	**.01**
Composite Neonatal Risk Score	.89	.45
Duration of Intensive Care	1.11	.35
Level of Care in first 10 days	1.30	.28
Total Days of Hospitalisation	1.86	.15
Days of Mechanical Ventilation	1.75	.17

10.1.4. Feeding Variables

10.1.4.1. The Relationship between Developmental Scores and Feeding Variables

10.1.4.1.1. Type of Milk Received

Past research has suggested that the type of milk received during the first few months of life can influence the developmental progress of preterm infants (Morley et al, 1988; Lucas et al, 1992; Horwood 2001). Consequently one-way Analyses of Variance were performed to ascertain whether the type of feeding at term and/or three months of age was related to the developmental scores at 18 months of age within the present sample. The categories were breast, preterm formula, and standard/special formula. As can be seen, neither the type of milk being received at term nor at 3-months corrected age was significantly related to the developmental scores at 18-months corrected age, with the group differences being minimal.

Table 105: Developmental Scores and Type of Milk Received

	N	MDI Score		F-Ratio	p
		Mean	Std Dev		
Milk at Term					
Breast	22	76.7	14.4	0.15	.86
Preterm Formula	38	79.0	17.2		
Full-term/Special Formula	18	78.8	16.5		
Milk at 3 Months					
Breast	16	77.6	13.9	0.25	.78
Preterm Formula	25	76.8	15.4		
Full-term/Special Formula	37	79.7	17.1		

When Chi-square analyses were performed to ascertain whether there was a relationship between the type of milk received at either term or 3-months and severe developmental delay the results indicated that there was absolutely no relationship between these variables (Chi-square .05, p=.98 and Chi-square .16, p=.92 respectively).

10.1.4.1.2. Infant Feeding Technique

Correlations were performed to see whether there was a statistical relationship between the Feeding Problem Index or intake per minute at term/three months and the 18-month developmental scores. As can be seen in Table 106, neither of the feeding technique variables at either term or 3-months were correlated with later developmental score.

Table 106: Correlations between Infant Feeding Technique and BSID-II MDI Scores

Feeding Technique Variable	**MDI** (n =78)
FPI at Term	.02
Volume/minute at Term	.17
FPI at 3 months	-.16
Volume/minute at 3 months	.04

When further analyses were performed to establish whether there was a difference on feeding technique variables between subjects who were severely developmentally delayed and the rest of the sample, there were again no significant differences between the groups on any of these variables.

10.1.5. Parental/Social Variables

10.1.5.1. The Relationship between Developmental Scores and Parental Variables

Correlations were performed to ascertain whether various parental/socio-economic variables were significantly correlated with the developmental scores at 18 months corrected age. As can be seen from Table 107, there was no statistically significant correlation between maternal height, IQ or Socio-Economic Status as measured using the Osborn Index. There were, however, significant correlations between the MDI and both paternal and mean parental height.

Table 107: Correlations between Maternal Variables and BSID-II MDI Scores

Parental/SES Variable	BSID-II MDI
Maternal Age	-.16
Maternal IQ	.20
Osborn Index	.10
Maternal Height	.15
Paternal Height	.34**
Mean Parental Height	.38**

** Correlation significant at the .01 level

10.1.5.2. The Relationship between Severe Developmental Delay and Parental/Social Variables

Independent t-tests were performed to see whether the infants who showed severe developmental delay at 18-months differed significantly from the rest of the sample on any of the parental or social variables. As can be seen from Table 108, the two groups were very similar in terms of these variables, although the tendency was for the infants who were severely developmentally delayed to have shorter fathers, and therefore a smaller mean parental height.

Table 108: Differences between Infants with and without Severe Developmental Delay on Parental/Social Variables (N=78)

Parental/Social Variable	**MDI >69**	**MDI <70**	**t-value**	**p**
Maternal Age	30.41	31.30	-.61	.54
Maternal IQ	101	95	1.36	.18
Osborn Index	57	55	0.69	.49
Maternal Height	1.63	1.63	-.02	.98
Paternal Height	1.79	1.75	1.90	.06
Mean Parental Height	1.71	1.69	1.90	.06

10.1.6. Significant Predictors of Infant Development at 18 Months

One of the aims of the present study was to predict later developmental status, in particular significant developmental delay, from factors evident during the first few months of life. The beginning of this chapter has highlighted some of the individual factors that were related to developmental status at 18 months of age, but many of these early factors were inter-correlated, and it was therefore necessary to establish the specific relationships between these and the later developmental scores when other factors were held constant.

Multiple regression analyses were performed in order to devise prediction models for the BSID-II Mental Development Index at 18 months of age by the antecedent factors previously described. Based on the preliminary analyses already performed and presented, infant gender, gestational age, gross neurological pathology (as shown on ultrasound scan after the first week of life), the 3-month and 18-month anthropometric measurements and mean parental height were the independent variables used in the regression. Stepwise regression analysis was used, with the variables being added in a pre-determined order specifically to ascertain additive effects of 3-month data when 18-month data had already been incorporated into the regression. For these analyses, the 3-

month weight z-scores and the 3-month head circumference z-score were used in a separate regression analysis because they were very highly correlated (r = .68). Similarly mean parental height was not included in the same regression model as 18-month weight z-score because these two variables were also highly inter-correlated. Table 109 shows all the inter-correlations between the predictors used in the following regression analyses.

Table 109: Inter-correlations between Predictors included in the Regression Analyses

	MDI	Gender	Scan	3mth weight	3mth head circ	18mth weight	Parental height
MDI	1.00						
Gender	**.31****	1.00					
Scan	**-.25***	.02	1.00				
3mth weight	**.26***	-.05	-.01	1.00			
3mth head circ	**.28***	.01	-.09	**.62****	1.00		
18mth weight	**.29***	.08	-.02	**.69****	**.44****	1.00	
Parental height	**.38***	.02	-.05	**.27***	**.28***	**.35****	1.00

* Correlation significant at the .05 level
** Correlation significant at the .01 level

10.1.6.1. Stepwise Multiple Regression Analysis

10.1.6.1.1. Regression using Weight Z-score Variables at 3- and 18-Months

As already indicated, stepwise regression analysis was performed with the independent variables added in a pre-defined order to ascertain the added value of extra variables. As can be seen from Table 110, the 18-month weight z-score just failed to add significantly to the model, which already took into account infant gender and history of abnormal ultrasound scans. When the 3-month weight z-score was subsequently included, however, this did add significant value to the overall model.

Table 110: Stepwise Multiple Regression Model for BSID-II MDI (Weight) (n = 77)

Model	R	R Sq	Adj. R Sq	F	Sig. of F	Sig F Change
1	.40	.15	.13	6.70	.00	.00
2	.44	.19	.16	5.81	.00	.06
3	.49	.24	.20	5.68	.00	.04

Model	Predictor	B	Std. Error	Beta	t	Sig. of t
1	Gender	9.24	3.46	.29	2.67	.01
	Abnormal Scan	-19.83	7.75	-.27	-2.56	.01
2	Gender	8.35	3.43	.26	2.44	.02
	Abnormal Scan	-19.68	7.62	-.27	-2.58	.01
	18 mth weight z-score	2.71	1.44	.20	1.88	.06
3	**Gender**	**9.30**	**3.38**	**.29**	**2.74**	**.01**
	Abnormal Scan	**-20.21**	**7.45**	**-.28**	**-2.71**	**.01**
	18-mth weight z-score	.16	1.85	.01	.08	.93
	3-mth weight z-score	**3.96**	**1.87**	**.29**	**2.12**	**.04**

10.1.6.1.2. Regression using Mean Parental Height and 3-Month Weight

Due to the highly significant inter-correlation between weight z-score at 18 months and mean parental height, a separate regression model was calculated using the latter, and excluding the former predictor. As shown in Table 111, all four of the predictors entered continued to contribute signficantly to the model even when the other predictors were held constant.

Table 111: Stepwise Multiple Regression Model for BSID-II MDI (Weight & Parental Height (n = 77)

Model	R	R Sq	Adj. R Sq	F	Sig. of F	Sig F Change
1	.41	.17	.15	7.29	.00	.00
2	.52	.27	.24	8.74	.00	.00
3	.56	.31	.27	7.95	.00	.04

Model	Predictor	B	Std. Error	Beta	t	Sig. of t
1	Gender	10.18	3.48	.31	2.93	.01
	Abnormal Scan	-19.33	7.73	-.27	-2.50	.02
2	Gender	9.96	3.29	.31	3.03	.00
	Abnormal Scan	-17.89	7.31	-.25	-2.45	.02
	Mean parental height	107.42	34.26	.32	3.14	.00
3	**Gender**	**9.96**	**3.21**	**.31**	**3.10**	**.00**
	Abnormal Scan	**-18.46**	**7.15**	**-.26**	**-2.58**	**.01**
	Mean parental height	**90.05**	**34.50**	**.27**	**2.61**	**.01**
	3-mth weight z-score	**2.97**	**1.43**	**.21**	**2.08**	**.04**

10.1.6.1.3. Regression using Head Circumference Status

The regression analysis was repeated, substituting the head circumference z-score at 3-months for the previously used weight 3-month weight z-score and again including mean parental height. As can be seen from Table 112, the results were very similar to those for the model using the 3-month weight z-score, with all four predictors remaining significant contributors to the model when the other three were held constant.

Table 112: Stepwise Multiple Regression Model for BSID-II MDI (Head Circumference & Parental Height (n = 77)

Model	R	R Sq	Adj. R Sq	F	Sig. of F	Sig F Change
1	.41	.17	.15	7.29	.00	.00
2	.52	.27	.24	8.74	.00	.00
3	.56	.31	.27	7.87	.00	.05

Model	Predictor	B	Std. Error	Beta	t	Sig. of t
1	Gender	10.18	3.48	.31	2.93	.01
	Abnormal Scan	-19.33	7.73	-.27	-2.50	.02
2	Gender	9.96	3.29	.31	3.03	.01
	Abnormal Scan	-17.89	7.31	-.25	-2.45	.02
	Mean parental height	107.42	34.26	.32	3.14	.00
3	**Gender**	**9.87**	**3.22**	**.31**	**3.07**	**.00**
	Abnormal Scan	**-17.76**	**7.15**	**-.25**	**-2.48**	**.02**
	Mean parental height	**90.06**	**34.60**	**.28**	**2.60**	**.01**
	3-mth head circ z-score	**2.96**	**1.46**	**.21**	**2.03**	**.05**

10.1.6.1.4. Regression excluding Subjects with Neuropathology

The regression analyses were repeated excluding the extra four infants who had been shown to have abnormal brain scans after the first week of life. Two of the three cerebral palsy infants also had abnormal scans, but these infants had already been excluded from the analyses. The removal of these subjects from the analyses did not change the results.

10.1.6.2. Logistic Regression Analysis

The foregoing sub-section described the multiple regression analyses performed in order to establish the antecedent factors that are related to developmental outcome at 18 months of age. What is of particular interest, however, is the prediction of those infants whose development will be severely delayed by 18 months, since this group is likely to require ongoing professional support. It was also felt that ideally the antecedent variables should be dichotomised, in order that risk factors could be easily assessed.

Logistic regression analysis was therefore used to determine the best combination of factors predicting severe developmental delay at 18 months of age. The dichotomised dependent variable was the Bayley Mental Development Index (MDI), with the cut-off being a score below 70 (i.e. more than two standard deviations below the mean). The predictors were primarily identified by their individually significant relationship with the dichotomised MDI and were: (1) gender (Chi-square = 6.73, $p< .01$); (2) abnormal ultrasound scan (Chi-square 5.39, $p< .05$); (3) weight z-score < 10^{th} percentile at 3 months (Chi-square 11.79, $p < .01$); (4) weight z-score < 10^{th} percentile at 18 months (Chi square 2.65, $p<.17$). The weight at 18 months was included in the regression because there was a significant correlation between being below the 10^{th} percentile for weight at 3 months and 18 months, and the effect of the weight criterion at 3 months needed to be ascertained independent of concurrent weight criterion. Although head circumference at 3 months of age correlated with MDI, when each of the variables was dichotomised the relationship was no longer significant and therefore head circumference was not incorporated into a logistic regression model.

As can be seen from Table 113, the only variables that were significantly related to severe developmental delay were gender, and weight status at 3 months of age, with infants who were below the 10^{th} percentile for weight at 3-months being more likely to show severe developmental delay at the 18-month assessment. 3-month weight data was added to the model after the 18-month data, in order to assess whether the effect was simply due to chronicity of low weight. The results of this analysis would suggest that this is not the case.

Table 113: Final Logistic Regression Model of Variables Contributing to Severe Developmental Delay on the MDI at 18 Months of Age (n = 77)

Variable	B	S.E.	Wald	df	p	Exp (B)*	95% C.I. for Exp (B) Lower	Upper
Gender	**1.91**	**.76**	**6.32**	**1**	**.01**	**6.77**	**1.53**	**30.10**
Abnormal Scan	2.80	1.51	3.45	1	.06	16.42	.86	315.28
Weight < 10^{th} Centile at 18 mths	0.89	.79	1.28	1	.26	2.45	.52	11.49
Weight < 10^{th} Centile at 3 mths	**1.50**	**.66**	**5.21**	**1**	**.02**	**4.47**	**1.24**	**16.19**

Model Chi-Square = 22.27; df = 4; p< 001.; *adjusted odds ratio
R square = .37

10.2. Anthropometric Outcome at 18 Months

Fourteen of the 81 subjects (17%) who were followed up at 18-months were below the 10th percentile for weight at this age. The figure had been 37.5% at 3 months corrected age, which suggests that there was some catch-up growth between these two time points. However, 23 (28%) of the children still had a head circumference below the 10th percentile.

10.2.1. Relationship between Anthropometric Measures at Birth, Term, 3-Months and 18-Months

As can be seen from Tables 114 and 115, both the weight and head circumference variables at each time point were very highly correlated. Head circumference measurements were only available from term onwards since most infants did not have this measurement taken at birth due to their fragile state, which required urgent medical intervention.

Table 114: Correlations between Weight Z-Scores at each Assessment Point

	Birth Weight	Term Weight	3-Mth Weight	18-Mth Weight
Birth Weight	-	-	-	-
Term Weight	**.51****	-	-	-
3-Month Weight	**.54****	.77**	-	-
18-Month Weight	**.51****	.47**	.64**	-

** Significant at .01 level

Table 115: Correlations between Head Circumference Z-Scores at each Assessment Point

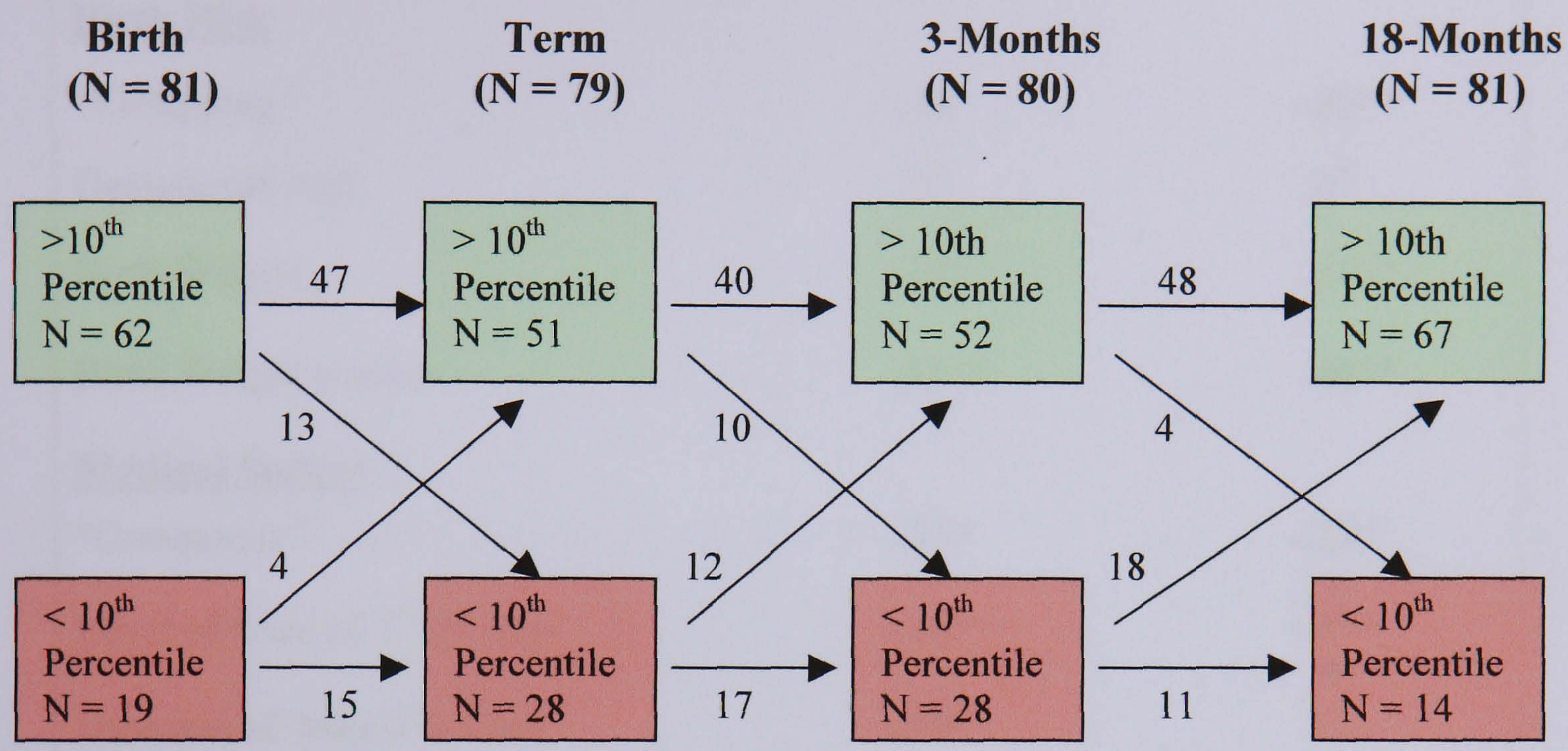
	Term Head Circ	3-Mth Head Circ	18-Mth Head Circ
Term Head Circumference	-	-	-
3-Month Head Circumference	.78**	-	-
18-Month Head Circumference	.59**	.74**	

** Significant at .01 level

10.2.1.1. Stability of Weight Status between birth and 18 months

Although the correlation between weight z-scores at 3 months and at 18 months of age was .64 ($p < .01$), there were actually considerable amounts of movement across the 10th percentile criterion by many of the infants. Figure 7 is a flow diagram showing the stability of weight status over time for the 81 infants who were re-assessed at 18 months of age. Although it is not shown in the diagram, a large number of infants were above the 10th percentile at birth, and remained so throughout the four assessments periods (n=38). Conversely, only four of the 19 infants who were below the 10th percentile at birth remained so throughout the four assessments. The remaining 40 infants moved across the 10th percentile point on one occasion (n=19), two occasions (n=18) and two of them on all three possible occasions. It can be seen that there were some infants on whom weight data was missing from either the term or the 3-month assessment, which is the reason that the numbers do not all tally as would otherwise be expected.

Figure 7: Stability of Weight Status between Birth and 18-Months



10.2.2. Relationship between Anthropometric Measurements at 18-Months and Early Medical Risk

Correlational analyses were performed to ascertain whether birth and early medical risk variables were significantly related to anthropometric measures at 18 months corrected age. As can be seen from Table 116, weight z-score at 18 months was significantly related to the majority of early variables, with the exceptions only of gestational age and duration of ventilation. Head circumference at 18 months was also significantly correlated to the majority of the early variables.

Table 116: Correlations between and 18-Month Anthropometric Measures and Early Risk Variables

Variable	Weight z-score at 18-Months	Head Circ z-score at 18-Months
Birth Risk		
"Comppreg"	**-.22***	**-.30****
Gestational Age	.20	.07
Birth Weight	**.51****	**.37****
Birth Weight z-score	**.51****	**.40****
Medical factors		
"Compneon"	**-.27***	**-.22***
Level of Care of 1st 10 days	**-.35****	**-.27***
Duration of Intensive Care	**-.29***	-.11
Duration of Ventilation	-.16	-.21
Total days in hospital	**-.38****	**-.24***

* Significant at .05 level
** Significant at .01 level

10.2.3. Relationship between and Infant Anthropometric Measurements at 18-Months and Parental/Social Factors

10.2.3.1. Maternal/Social Factors

As can be seen from Table 117, although infant weight at 18-months was not significantly correlated to any of the three maternal or social factors used in the earlier analyses, there were significant correlations between infant head circumference at 18-months and both maternal IQ and score on the Osborn Index.

Table 117: Correlations between 18-Months Anthropometric Measurements and Maternal/Social Factors (n= 75)

	Maternal Age	Maternal IQ	Osborn Index
Weight Z-score	-.18	.06	-.13
Head Circumference Z-score	.09	**.25***	**.25***

* Significant at the .05 level

10.2.3.2. Parental Height and Infant Weight

Correlations were performed to ascertain whether there was a significant relationship between parental height and infant weight at any of the assessment points – i.e. birth, term, 3 months or 18 months. Parental height data was only available for 75 of the subjects. As Table 118 shows the correlations were smallest at term, but from term onwards the correlations increased, and although by 18 months there was still no significant relationship between the infant weight and maternal height, there was between infant weight and both paternal height and the mean combined height of both parents.

Table 118: Correlations between Parental Height and Infant Weight Z-scores (n= 75)

	Maternal Height	Paternal Height	Mean Parental Height
Infant Weight Z-score at Birth	.06	.19	.19
Infant Weight Z-score at Term	.11	-.05	.04
Infant Weight Z-score at 3 Months	.21	.12	**.24***
Infant Weight Z-score at 18 Months	.11	**.30****	**.32****

* Significant at the .05 level
** Significant at the .01 level

10.3. Summary of Chapter

10.3.1. Developmental Outcome

81 of the original 90 infants who were participated in the study up to 3-months corrected age were followed up at the 18-month assessment. However, there were three subjects who had been diagnosed with severe cerebral palsy and these individuals were excluded from the developmental outcome analyses described at the beginning of this chapter because they were unable to perform the tasks required to assess their development. These analyses were therefore carried out on a sample of 78 subjects.

As a group, there were significant differences between the expected and observed frequencies within each category of MDI score (i.e. delayed, severely delayed etc.), with the subject infants being at a significantly higher risk of developmental delay than a normative sample.

10.3.1.1. Relationship between Early Variables and Developmental Outcome at 18-Months

Female subjects performed significantly better than male subjects in analyses using continuous MDI scores and male subjects were significantly more likely to be classified as severely developmentally delayed (i.e. scoring below 70) than were female subjects.

There were no significant correlations between birth/early neonatal risk variables and MDI scores when continuous data were analysed. The presence of abnormal ultrasound scans after the first week of life was significantly correlated with the MDI scores, however, despite the exclusion of the three severe cerebral palsy subjects from the analyses. As would be expected, the subjects who had a history of abnormal brain scans were likely to have lower MDI scores.

When dichotomised MDI scores were analysed (i.e. above or below 70), the trend was for the infants classified as severely developmentally delayed to have been more preterm and sicker. This trend only reached statistical significance, however, in the case of total days of hospitalisation.

When early anthropometric measurements were analysed in relation to later developmental score, both weight and head circumference at 3 months of age were significantly correlated with the MDI, as were concurrent weight and head circumference (i.e. at 18 months of age). Earlier anthropometric measurements, at birth and term, were not related to later developmental score. When the anthropometric measurements were dichotomised into above/below the 10^{th} percentile, there were significant differences in MDI scores according to weight status at 3 months, and to a lesser extent to concurrent (i.e. 18-month) head circumference status. In each case the subjects who were lighter/smaller had a significantly lower mean MDI score.

Because there was a high correlation between birth weight status and weight status at 3 months of age, univariate analysis of variance was performed to establish whether the apparent relationship with weight status at 3 months was actually influenced by birth weight status. The analysis confirmed, however, that it was only weight status at 3 months of age that was important, regardless of birth weight status. When Chi-square analyses were subsequently performed these showed that infants whose weight was below the 10^{th} percentile at 3 months of age were significantly more likely to be severely developmentally delayed at 18 months of age than infants whose 3-month weight was above the 10^{th} percentile.

Subjects were classified according to what had happened to their weight status between birth and term. There were four groups, subjects born below the 10^{th} percentile who remained there at 3-months (group1); subjects born below the 10^{th} percentile who rose above it by 3-months (group 2); subjects born above the 10^{th} percentile who fell below it at 3-months (group3); and finally subjects born above the 10^{th} percentile who remained above it at 3-months (group 4). When Analyses of Variance were performed on these groups, with the MDI score as the outcome measure, there were significant group differences. The second group (who had shown good catch-up growth) had the highest mean MDI score, and the third group (who had shown particularly poor growth) had the lowest mean MDI score. Similar analyses were performed using change in weight status between 3 and 18 months of age. During this period, however, stability of weight status appeared to be related to better MDI scores, with both groups 1 and 4 scoring better than groups 2 and 3. Further analyses was carried out that showed that the changes in weight status as indicated by group membership described above were not apparently due to birth or early medical risk variables – the only variable upon which the groups differed significantly was birth weight.

There was no apparent relationship between the type of milk being received either at the term or the 3-month assessment and later developmental score. Analyses of variance showed very similar mean scores for the groups of infants who were breastfed, fed preterm formula or fed standard formula at either time point. Similarly there appeared to be no relationship between early oral-motor function and later MDI score.

Finally, there was no significant correlation between maternal age, maternal IQ or socio-economic status (as measured using the Osborn Index) and the subjects' MDI scores at 18 months of age.

10.3.1.2. Identification of Significant Predictors of Developmental Outcome using Regression Analyses

Two sets of regression analyses were performed. Firstly multiple regression analyses were performed using the continuous variables, and secondly logistic regression was performed using dichotomised variables in an attempt to build a prediction model for severe developmental delay at 18 months of age.

Stepwise multiple regression analysis was performed, with neonatal data being entered in the first block, 18-month anthropometric measurement or parental height in the second block, and 3-month anthropometric measurement in the third block. This was in order to ascertain the additive value of the 3-month anthropometric measurement even when the concurrent or parental measurement was already in the model. The results showed that gender, abnormal ultrasound scan, and the 3-month anthropometric measurements were the three significant contributors to the model, regardless of concurrent anthropometric measurements or parental height measurement. The analysis was repeated excluding the four subjects who had abnormal ultrasound scans during initial hospitalisation (in addition to the original three severe cerebral palsy cases), but this did not noticeably alter the model – only gender and 3-month anthropometric measurement remained significant.

Logistic regression analyses were subsequently performed, in order to build a prediction model for severe developmental delay at 18 months of age. The independent variables were also dichotomised. These analyses showed that only gender and weight status at 3 months of age were significant contributors to the final model, with male gender multiplying the risk of being severely developmentally delayed by more than six times, and weight below the 10^{th} percentile at 3 months multiplying the risk by four. Neither abnormal ultrasound scan nor 18-month weight status was a significant contributor to the prediction model for severe developmental delay.

10.3.2. Anthropometric Outcome

At the 18-month assessment the 81 very preterm infants who were followed up at this time point remained below the mean expected weight, height and head circumference, although there had been catch-up growth between 3 and 18 months as shown by the improved mean z-scores. Both weight and head circumference at 18-months were significantly correlated to many of the birth and early medical variables.

Approximately half of the total sample had remained above the 10^{th} percentile for weight at all four of the assessment points, but only a small minority of the infants who were born below the 10^{th} percentile remained there throughout the total study period.

There was no discernable relationship between infant weight z-scores at birth, term or 3 months corrected age and maternal, paternal or mean parental height. By 18 months of age, however, there was a highly significant positive correlation between infant weight and both paternal and mean parental height.

Chapter 11: Discussion

11.0. Introduction

This second discussion section focuses on the results of the 18-month assessment presented in the foregoing two chapters, specifically the developmental assessment using the Bayley's Mental Developmental Index and the concurrent anthropometric measurements. The influence of various antecedent factors on developmental status at 18 months of age within this sample of very pre-term infants is considered in relation to previously published research. In particular, the second main research question is addressed, i.e. whether early growth rate is associated with later developmental outcome, specifically whether good early catch-up growth can ameliorate the developmental effects of a poor intrauterine environment and whether poor growth during the early months is associated with a poorer developmental outcome.

The chapter is divided into sub-sections. Firstly, and most importantly, the significant predictors of developmental outcome at 18-months are discussed (i.e. gender, abnormal cranial ultrasound scans during initial hospitalisation, 3-month anthropometric measurements and parental height). Secondly, the early variables that were not shown to be related to later developmental outcome within this sample of infants born very preterm are addressed (including medical, feeding and maternal/social factors). The group results are examined in relation to a normative sample, and the 18-month sample characteristics are briefly considered in relation to the original sample of infants who were followed from birth to 3-months corrected age. Finally the anthropometric measurements at the 18-month assessment are considered in relation both to those at previous assessment points, and to birth and early medical risk variables.

11.1. Significant Predictors of Developmental Outcome at 18-Months

11.1.1 Gender

Within this sample of very preterm infants female subjects performed significantly better than their male counterparts on the Bayley's Scale MDI at 18-months of age, both when analysed in isolation and when included in regression models. Furthermore, when the infants were dichotomised into those who were/were not severely developmental delayed, there was a significantly larger proportion of boys who were in the severely delayed group.

Further analyses showed that this gender difference was not attributable to differences in birth or early medical variables, since there were no significant differences between the sexes on these variables. Although outcome at 18-months is not definitive, these findings are consistent with previous research that has indicated that, within the very low birth weight population, boys are at an increased risk of requiring special education facilities. For example, in a review of the relevant research, Campbell (1997) concluded that one of the two strongest risk factors associated with a requirement for special education among very low birth weight infants was male gender. Similarly a large retrospective study by Andrews et al (1995), which examined the background of children who were receiving special education, revealed that being male was the strongest risk factor.

It should be noted, of course, that developmental quotient at 18-months of age will measure not only the actual developmental outcome, but also the subject's level of social competence and maturity. It has been suggested that, within the population of children born very preterm, boys are more likely to exhibit behavioural and attentional problems than girls (e.g. Hille et al, 2001; Schothorst et al, 1996). As previously mentioned, seven of the 78 infants who were assessed using the Bayley's Scale MDI were allocated the minimum score of 50 due to failure to co-operate in the assessment, and of these seven, six were boys. Although these scores, and others at the bottom end of the range, might reflect true developmental delay, it might equally or to a greater extend reflect lack of maturity.

Although it is known that correlations between early developmental testing and later intelligence and school performance testing are generally poor, it is generally accepted that there is a strong tendency for low to remain low (e.g. Largo et al, 1990; Liaw et al, 1993). Thus it is reasonable to anticipate that, as with previous studies, there will be a higher proportion of boys than girls from the present sample who will continue to be developmentally delayed and, once of school age, require special educational support.

11.1.2. Weight at 3-Months

One of the main a priori hypotheses addressed in this thesis was that there might be a sensitive period during the early months of life for very preterm infants when the negative long-term effects of a poor intrauterine environment (leading to growth retardation) could be ameliorated, and conversely when poor growth in the post-natal months could adversely influence developmental outcome. This hypothesis was tested by examining the relationship between weight/weight status at birth and at 3 months corrected age (a period of 5-7 months depending on gestation at birth), and then analysing the relationships between these variables and later scores on the MDI.

The analyses showed that there was no apparent relationship between being born small for gestation and subsequent performance on the MDI at 18 months of age. There was, however, an observed relationship between weight at 3-months of age and performance on the MDI.

When dichotomised variables were examined, weight status at 3-months corrected age was significantly related to later developmental status, with infants who were below the 10^{th} percentile for weight at 3-months performing significantly worse than those infants whose weight was above that criterion. This relationship between 3-month weight and developmental outcome was significant both when examined in isolation, and when incorporated into a prediction model. Importantly, although there was a correlation between being born small-for-gestation and still being below the 10^{th} percentile at 3-months of age, univariate analysis confirmed that it was 3-month weight status, irrespective of birth weight status, that was related to later score on the MDI.

Further analysis in which the sample was categorised according to change in weight status between birth and 3 months of age showed that those infants whose birth weight was above the 10th percentile but whose weight fell below that criterion at 3-months corrected age, performed significantly worse on the MDI than those infants whose weight remained above the 10th percentile. Conversely infants who began life small-for-gestation (and therefore at an increased risk of developmental delay) but then showed sufficient catch-up growth to exceed the 10th percentile at 3-months of age had an average 6.6 point advantage on the MDI over those infants whose weight remained below that criterion. Although this difference failed to reach statistical significance due to small group size (n=6), it might nonetheless be of clinical relevance. These results were not explained by early medical variables, or by any of the variables associated with oral-motor function.

These findings would appear to support the hypothesis that there is a "sensitive period" during the first few months of life among very preterm infants during which rate of growth may influence developmental progress, either for the better or for the worse. Interestingly, and also consistent with the theory of a sensitive period limited to the first few months of life, movement across the 10th percentile for weight between three and eighteen months was not related to MDI score. In fact the infants who showed good catch-up growth after 3-months and rose above the 10th percentile by 18-months performed very similarly to those whose weight dropped below the 10th percentile over the same period, and both these groups performed worse, on average, than the infants whose position relative to the 10th percentile remained constant between the two time points. It should be noted that, although the use of the 10th percentile to identify infants as small-for-age at each assessment point was arbitrary, movement across this criterion over time did actually reflect a difference in growth rate between the groups of infants.

The observed relationship between early growth rate and developmental outcome is consistent with most of the previously published research, although this has generally concentrated specifically on the relationship between poor growth in the early months of life and cognitive outcome. Papers were published as long ago as the 1960's that highlighted the relationship between growth failure in childhood and impaired cognitive development (e.g. Pollitt & Granoff, 1967). A study by Skuse, Wolke & Reilly (1992) again associated growth faltering in infancy with lower developmental scores (using the

Bayley Scales), and a subsequent study by Skuse et al (1994), supported the suggestion that there appeared to be a specific "sensitive period" early in post-natal life when slow growth was related to poor cognitive outcome. Growth faltering after the first six months of life didn't, in that study, appear to have these negative effects. Two studies reported by Drewett et al (1999 and 2001), however, produced very different results. The first found that failure to thrive (i.e. slow growth during the first 18 months of life), although associated with reduced physical size at 7-9 years, was not related to cognitive deficits or educational disadvantages. That study was, however, based on a sample of normal, term infants, and differentiation was not made between those infants who exhibited poor growth during the first few months of life and those whose growth faltering occurred later in the period under investigation. In the more recent paper, Drewett et al (2001) presented the results of a study examining the effects of early versus later onset growth faltering. The study was undertaken in Ethiopia, again using normal, term infants whose weight was over 2.5 kg at birth. The results of that study, although showing a definite link between failure to thrive and cognitive outcome, contradicted the suggestion that there is a sensitive period during the first few months of life. Their data showed that this period was only important because early onset of growth faltering is associated with longer-term growth faltering, and it is this chronicity that had detrimental effects. Similarly a study by Wilensky et al (1996), while reporting a link between growth faltering and developmental outcome, failed to find cognitive differences between those who had early rather than late onset growth faltering. The results of the regression analyses presented in the present thesis, however, suggest that weight at 3-months corrected age is predictive of later mental development score even when weight at 18-months is taken into account, which suggests that within this sample the predictive value of weight status at 3-months cannot simply be explained in terms of chronicity.

The present study does, of course, examine a very different population of infants to the studies mentioned above; indeed, all of the Gain Study subjects would be considered to be at an increased risk of adverse developmental consequences due to their very preterm births. It is interesting to note that, within this particularly at-risk group of infants, there does appear to be a "sensitive period"; the group of infants whose weight dropped below the 10^{th} percentile between birth and 3-months of age had a mean developmental score more than 15 points lower than the group whose weight remained above that weight criterion. Conversely, there was no such deficit among those infants whose later growth was slow in relation to the rest of the sample (i.e. between 3- and 18-months corrected age).

In addition, whereas the Skuse study, the Wilensky study and both the Drewett studies only examined the relationship between particularly poor early growth and later outcome, the present study also examined the relationship, among infants who were born small-for-gestational age, between rate of catch-up growth and later developmental outcome. The results of the univariate analysis of variance indicated that being born small-for-gestation was not a risk factor in respect of developmental outcome, but being small-for-age at 3-months of age was. This would suggest that catch-up growth which was sufficient to enable infants born small-for-gestation to rise above the 10^{th} percentile for weight at 3-months of age ameliorated the negative effects of sub-optimal intrauterine growth.

11.1.3. Head Circumference at 3-Months

When correlational analyses were performed between head circumference at 3-months and later MDI score there was a significant relationship, and when 3-month head circumference was included in the regression analysis in place of 3-month weight this anthropometric variable still contributed significantly to the prediction model (although to a lesser extent than the weight variable). This is not surprising since the two measurements were highly correlated, as indeed they were at term and 18-months of age. Furthermore, this finding is consistent with previous research that has suggested that head circumference measurement is linked to cognitive outcome in a similar way to weight change (e.g. Drewett et al, 2001; Piecuch, 1988).

Unlike the 3-month weight variable, however, dichotomising the concurrent head circumference measurements using the 10^{th} percentile did not result in significant differences in mean MDI scores for the two groups, and there was no significant difference in mean 3-month head circumference between the infants who were or were not severely developmentally delayed (although the trend was for the severely delayed group to have smaller head circumferences).

11.1.4. Abnormal Brain Scans

The presence of identified abnormalities on ultrasound scans of the neonatal brain during initial hospitalisation, but after the first week of life, was individually correlated with the developmental scores, even when the three subjects who had severe cerebral palsy were excluded from the analyses. Furthermore, when regression analyses were performed, this variable continued to contribute significantly to the model for developmental outcome even when other early variables were held constant. When the subjects were dichotomised into those who were or were not severely developmentally delayed, there was a significantly increased risk of being in the delayed group if there had been an abnormal brain scan. However, when this variable was included in the logistic regression analysis, it failed to contribute significantly to the final model when other variables were held constant.

It is known that neurological insults that are visible on ultrasound scan (both major intracranial haemorrhage and periventricular leucomalacia) do increase the risk of handicap (e.g. Leonard et al, 1990). However, it has also been observed that it is difficult to predict with certainty which of the infants who have suffered visible neurological insult will go on to exhibit developmental problems in childhood and beyond, due to the plasticity of the infant brain which may actually allow normal development of function (Leonard & Piecuch, 1997). The fact that, in the present study, the "abnormal brain scan" variable was not a significant predictor in the model for severe developmental delay might be due to the extremely small number of children within the study who had abnormal scans (four, excluding the known cerebral palsy cases), and/or the fact that, at 18-months of age, some significant disabilities are not yet discernable. For example, previous research has suggested that abnormal neonatal brain ultrasound scans are associated with attention deficit hyperactivity (Whitaker et al, 1997; Hille et al, 2001), and also that infants who have scored within the average range in the first year of life may subsequently have significant language difficulties at 3 years of age and reading problems when at school that adversely affect performance (Vohr &

Msall, 1997). Furthermore, the variable used in this study did not distinguish between the levels of severity of damage visible on the ultrasound scan, simply being a dichotomised variable of normal/abnormal.

11.1.5. Parental Height

Interestingly there were significant correlations between both paternal height and mean parental height and developmental outcome at 18-months of age. Because there were also significant correlations between mean parental height and infant anthropometric measurements (especially at 18-months of age) separate regression analyses had to be performed. These analyses indicated that mean parental height contributed significantly to the prediction model for developmental outcome at 18-months. There was not, however, a significant difference in the mean parental height between those subjects who were or were not severely developmentally delayed, and therefore this variable was not included in the logistic regression analysis.

It is not immediately clear why there should be this relationship between mean parental height and the developmental status of the subjects in this study, and there is little previous research to compare with these findings or which can shed light on this result.

11.2. Early Variables that were not Significantly Related to Developmental Outcome

11.2.1. Birth Weight, Gestation and Early Medical Variables

It has been suggested that the relationship between birth weight and IQ is approximately linear within low birth weight groups (Lagercrantz, 1997), although another study, by Piecuch et al (1997), found there to be no such association between birth weight and outcome. As in the Piecuch study, in the present study there appeared to be no discernable relationship between birth or neonatal medical variables and overall developmental scores, the only significant relationship with developmental outcome being the presence of an abnormal brain scan after one week of age. For the dichotomised outcome (distinguishing subjects who were severely developmentally delayed), there was a trend for the subjects in the severely delayed group to have been sicker during the neonatal period, although the difference only reached statistical significance for duration of initial hospitalisation and, as emphasized in the results section, this one significant finding might well have been due to chance bearing in mind the number of analyses that were performed.

It has been suggested that motor deficits tend to be picked up early, but often the more subtle deficits associated with language and behaviour may not be obvious at this early stage, and indeed may not become apparent until school age (Kaplan, 1997; Vohr & Msall, 1997). This may explain the lack of relationship between birth variables and the MDI in the present study. As already mentioned, although it is generally accepted that overall there is little predictive value in tests undertaken in infancy, frequently "low stays low" (Largo et al, 1990; Liaw et al, 1993). Conversely, for those infants who scored within the average to borderline range at this age the later outcome is less clear.

There have been several studies that have compared the outcome of very low birth weight infants born at a weight appropriate for their gestational age with infants who were born small-for-gestation, and therefore presumed to have suffered from a sub-optimal intra-uterine environment. The results have generally suggested that being born small-for-gestation is an added risk factor for long-term cognitive deficits (in addition to other behavioural and social difficulties) (e.g. Korkman et al, 1996; Lagercrantz, 1997;

Hutton, 1997). In the present study, however, there has not been shown to be any significant correlation between birth weight status and developmental status at 18-months corrected age. The reasons for this lack of correlation are unclear, although the foregoing section (16.2.2) may explain this inconsistency with previous research. In addition, it might be that the skills that are measured at 18-months of age are not those in which infants born small-for-gestation tend to exhibit deficits.

11.2.2. Nutrition

There have been a number of studies that have examined the relationship between type of milk given to preterm infants and later developmental status. There is now quite strong evidence that breast milk is particularly advantageous to these small infants (e.g. Lucas, 1992; Morley et al, 1988; Lucas et al 1998; Drane & Logemann, 2000), although the advent of special preterm artificial formulae may have improved the outcome for infants whose mothers are unwilling or unable to provide breast milk. In the present study, however, the previous findings were not replicated, with no discernable difference on the MDI between the groups fed different milks. The reason for this anomalous result is unclear. It may be due to the fact that the analyses were based on how the infants were being fed at the specific assessment point (term and 3-months), and did not take into account how long the infants had been receiving that type of milk, or when they had been changed from one type to another. Some of the formula-fed infants at term or 3-months might, therefore, have been being breast-fed until just days before the assessment. It has been suggested that there is a dose-response relationship between breast-milk and later intelligence quotient (Lucas et al, 1992), and infants in the present study who had only been changed onto formula shortly before the term assessment (and were therefore categorised as formula-fed), might actually have received significant amounts of breast-milk. This would obviously have reduced the apparent positive effect of breast-milk (since the change from one milk to the other could only be in one direction). In addition, the lack of obvious developmental benefits of breast-milk may be partly due to the small group size – at 3-months corrected age there were only 16 infants who were still being predominantly breast-fed. Finally, most of the reports of advantage in IQ terms of breast milk have been based on developmental assessment at a later age, and with the poor predictive value of early assessment (as discussed above), the long-term benefits of breast milk for cognitive development may simply not have become apparent by 18-months corrected age.

11.2.3. Infant Feeding Technique

The early measures of infant feeding technique used in the present study were not related in any way to developmental outcome at 18-months corrected age. This is somewhat surprising since there has been previous research that suggests that abnormal feeding technique may be associated with neurological impairment (e.g. Ramsay et al, 1993). This cited research, however, analysed feeding dysfunction at a later age than in the present study, and it may be that during the early months of life the group of very preterm infants exhibiting abnormal feeding technique included those who had simply not yet matured, in addition to those who may have actually neurological impairment (i.e. some may have shown disorganised rather than dysfunctional feeding behaviour). Alternatively, it may be that the observed lack of relationship is due to the fact that the MDI at 18-months of age reflects mental rather than motor development, the latter of which might relate more strongly to abnormal feeding technique.

In this study, the use of the mercury strain gauge to objectively assess infant feeding technique was less than satisfactory. The reasons for this were unclear, although the fact that in the past such equipment had only been reported as being used on "normal" infants (i.e. born at term) might indicate that the disorganised/dysfunctional sucking behaviours frequently seen in infants born very preterm could not accurately be recorded using this equipment. This explanation is supported by the fact that the use of the equipment was more successful at the 3-month assessment, when many of the infants had matured sufficiently to suck in a more normal way.

11.2.4. Social Factors

In the present study there was found to be no significant relationship between maternal IQ or SES (as measured by the Osborn Index) and infant developmental status at 18 months of age. It would seem therefore, that in contrast to the observed relationship between parental and child intelligence quotients among normal term samples, the effects of very pre-term birth and the associated neonatal complications outweigh the genetic influence on the development of these infants at least up to 18-months of age. This conclusion is consistent with findings from the IHDP intervention study (Infant Health and Development Program), which indicated that there was no discernable developmental benefit to a community based support programme for very low birth weight infants and their families (McCarton et al, 1997). Other research has, however, shown that socio-economic factors can affect the development of these vulnerable infants, with low SES home environment increasing the risk of requiring special education, although this may be due to behavioural issues rather than actual cognitive outcome (Leonard & Piecuch, 1997; Piecuch et al, 1997). As previously discussed, developmental outcome at 18-months is not definitive and does not identify those individuals who go on to exhibit subtle deficits such as ADD, language difficulties etc, which can present difficulties during the school years.

11.3. Poor Performance Compared to Normative Sample

There is much evidence to suggest that being born very preterm is a risk factor for developmental delay, and it has been suggested that some10-25% of children born very preterm are found to have severe cognitive impairments (Wolke, 1998). It was therefore anticipated that there would be an increased incidence of developmental delay within the present sample, compared to a normative sample. Three of the infants were excluded from analyses due to severe cerebral palsy which prevented them participating in any meaningful way. Seven further infants were assigned the minimum score (50) on the assessment due to failure to co-operate, which made it impossible to gauge accurately their true level of functioning. The distribution of scores was skewed, with no infants performing at a level above average, and a disproportionately large number who performed below the level expected for their chronological age. As already discussed, developmental outcome at 18-months is not definitive, and there may be considerable change over time. The infants who were given the minimum score due to lack of co-operation might, at re-testing, perform at a level that truly reflects their abilities. Despite popular belief, however, evidence suggests that mean intelligence quotients do not increase over time for these individuals compared to their peers (Breslau, 1995; Botting, 1997; Wolke, 1998), and that many subjects who scored within the "normal" band during pre-school years go on to exhibit deficits when reaching school age. As already discussed, the group of infants who were severely delayed at 18-months, perhaps excluding those who failed to co-operate, are highly likely to remain severely delayed as they grow older.

11.4. Non-Significance of Study "Drop-outs"

Of the original 90 subjects, 81 were successfully contacted and followed up at this assessment. This constitutes a 90% follow-up rate, which compares favourably with other longitudinal studies of infants (e.g. Wolke et al, 1994; Wildin et al, 1997; Schendel et al, 1997). It has been suggested that a follow-up rate of 70-80% is adequate for valid interpretation of outcome measures, with a 90% follow-up rate being considered optimal (Vohr & Msall, 1997).

Analysis of the "drop-outs" revealed that there were no significant differences between those infants lost to follow-up and those re-assessed at 18 months of age in terms of birth weight, gestation, severity of early illness or maternal and social factors. Although it is reassuring to know that the subjects lost to follow-up did not appear to differ in any particular respect from those who were successfully re-assessed at 18 months of age, it obviously does not guarantee that the drop-outs would have conformed to the patterns of growth and development exhibited by the follow-up group.

11.5. Improved Anthropometric measurements at 18-Months

There had been considerable catch-up growth in terms of weight between 3- and 18-months with the mean weight z-score improving from -.86 to -.26 during that period, although there was still a highly significant correlation between weight z-scores at the two time points. In addition, the proportion of infants whose weight was below the 10^{th} percentile had decreased from 37.5% at 3 months, to 17% at 18 months. However, compared to a normative sample, the mean weight, height and head circumference of this group of infants born very pre-term were still below the level expected at 18 months of age, as indicated by the negative z-score values. Interestingly the improvement in weight z-score was not mirrored in changes of height and head circumference, z-scores for both of which had decreased over the period 3-18 months. Although there has been considerable prior research on the long-term consequences of being born very preterm, most of it has concentrated on cognitive, behavioural, social or medical outcomes rather than on size per se. A review paper by Campbell (1997) does, however, indicate that normal growth is potentially a problem, particularly for the very preterm infants who were born small for gestation, and also for those who were particularly ill after birth. This was confirmed in the present study, with the results showing a significant relationship between size at 18 months, in terms of weight and head circumference, and early medical risk variables (with infants who had been sicker during the neonatal period being smaller at 18 months of age). There also continued to be a highly significant correlation between birth weight z-score and weight z-score at 18-months.

There was no significant relationship between infant weights z-scores at birth or term and parental height. By 3-months the relationship had become statistically significant, and by the age of 18 months the relationship was highly significant. This suggests that infant size during the first few months of life was probably unduly influenced by non-genetic factors, i.e. being born very preterm, but by 3-months corrected age the genetic influence on subject size had begun to be apparent.

11.7. Summary of Chapter

There were four significant predictors of developmental outcome at 18-months of age. Firstly gender, with girls significantly out-performing boys developmentally and boys at a higher risk of being classified as severely developmentally delayed. This finding is consistent with previous research of preterm populations, which show that girls are generally more developmentally mature than boys of the same age (e.g. Campbell, 1997; Leonard & Piecuch, 1997).

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Secondly, although being born small for gestation was not directly related to developmental outcome at 18 months, weight status at 3 months corrected age was a significant predictor of outcome, with infants below the 10th percentile at this time showing a significantly poorer performance, and being more likely to be classified as severely developmentally delayed. These findings are consistent with the theory of a "sensitive period" during the first few months of life when brain growth is rapid and good catch-up growth can be beneficial and, conversely, inadequate growth may have long-term negative consequences.

Thirdly, the presence of abnormal brain scans during initial hospitalisation was a significant predictor of MDI score at 18-months, and this observed importance of neurological insult as shown on ultrasound scan was as expected. Interestingly, however, although there was an increased risk of being severely developmentally delayed if there was a history of abnormal brain scan, the presence of an abnormal brain scan did not contribute significantly to the regression model for predicting severe developmental delay among the very preterm subjects within the present study.

Fourthly, there appeared to be a significant positive relationship between developmental outcome at 18-months and mean parental height, which was predominantly accounted for by paternal height. No real explanation could be given for this finding.

There were no apparent effects of early nutrition on developmental status at 18 months. This is in contrast to previous research (e.g. Morley, 1988; Lucas 1992). Possible reasons for these divergent results were small sample size (particularly the sub-sample of breast-fed infants) and lack of information regarding duration of specified feeding type.

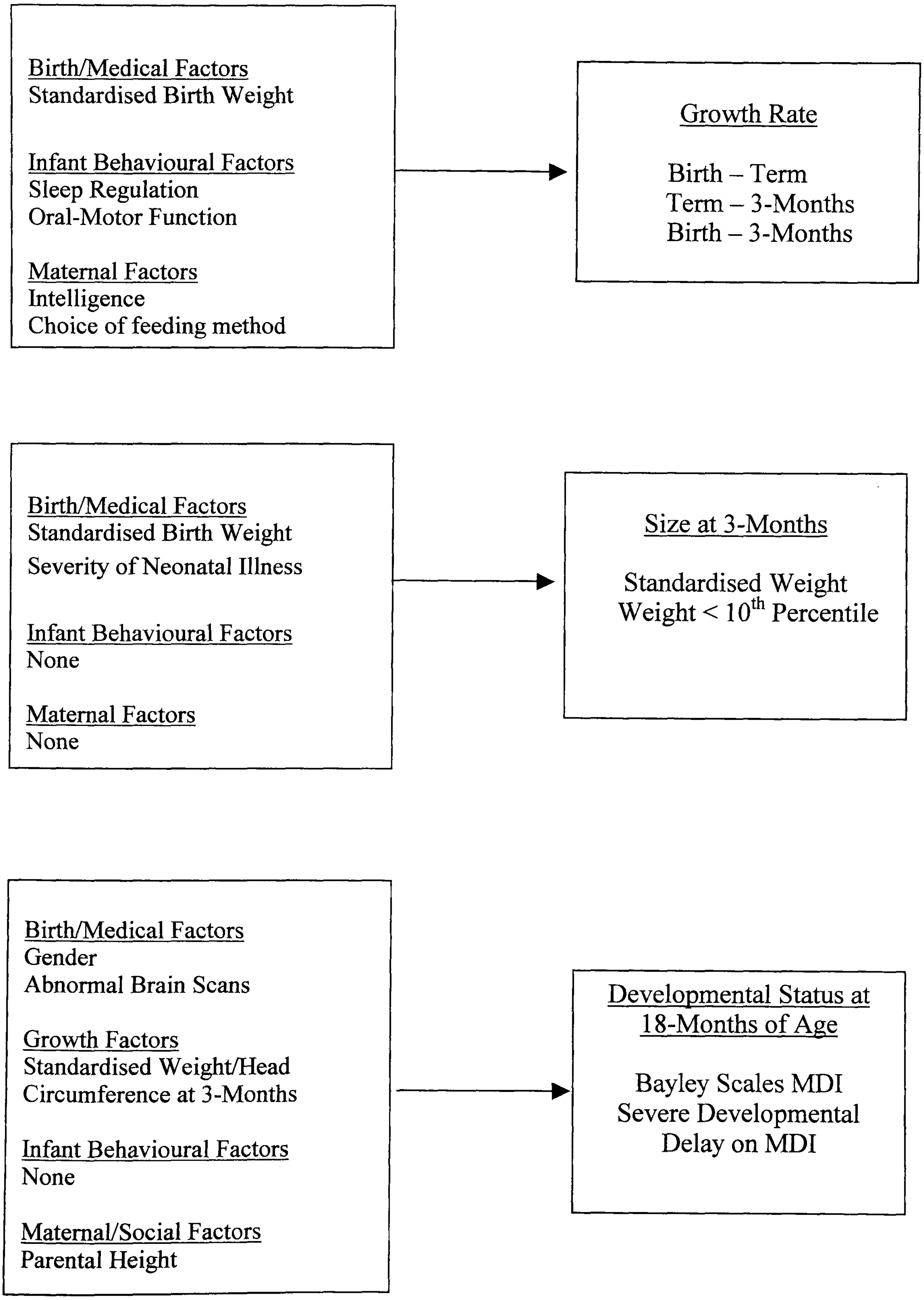
Neither maternal IQ nor socio-economic status was related to developmental status at 18 months of age. Again these findings contrasted with previous research that suggests infants from low SES backgrounds are at increased risk of requiring special education (Campbell, 1997; Leonard & Piecuch, 1997). One possible explanation is that the assessment tool used at 18 months of age (i.e. the Bayley MDI) does not identify the cognitive deficits that will necessitate special educational input.

As a group these infants were at a significant risk of being developmentally delayed at 18 months of age, using the Bayley Scales MDI. There were no infants performing above the "normal" range, and a disproportionately large number performing at a severely delayed level. These findings are consistent with previous research that shows that very preterm infants are at increased risk of cognitive problems (in addition to problems in many other areas) (e.g. Campbell, 1997).

The group of 81 very pre-term infants who were followed up at 18 months corrected age remained, on average, smaller than a normative sample, in terms of weight, height and head circumference. Some catch-up growth had occurred in terms of weight during the preceding fifteen months, but in terms of both height and head circumference these infants had fallen even further behind their term peers.

SECTION V: CONCLUSIONS

Figure 8: Variables shown to be Related to Growth & Developmental Outcomes



Chapter 12: Discussion of Findings and Their Implications

12.0. Introduction

In this final chapter the relative contribution of infant, maternal/social and birth/medical factors to the prediction models constructed for growth and developmental outcomes are briefly discussed in relation to previously published findings. The possible implications of the presented findings are then considered in respect of the current and future clinical care of very preterm infants. The diagram on page 282 shows an overview of the findings (Figure 8).

12.1. The Relative Contribution of Infant, Maternal and Medical Factors to Growth and Development

12.1.1. Growth During the Early Months of Life

During the first few weeks of life (a period during which the majority of infants remained in the neonatal unit), the mean growth rate for all the infants in the study was poor, with a larger proportion of the sample having a weight below the 10^{th} percentile at term and 3-months corrected age than at birth. This finding is in accordance with previous research (e.g. Alexander et al, 1996; Embleton et al, 2001), and is due to expected initial postnatal weight loss combined with under-nutrition (due to delayed commencement of intravenous feeds etc). Failure to catch-up after this initial period has been attributed to the general practice of calculating feed volumes on an infant's actual weight rather than the expected weight (Griffin, 2002). In the present study growth was examined for three different periods, birth to term, term to 3-months, and birth to 3-months. Not surprisingly different combinations of antecedent factors were related to growth rates during each of these periods. Although statistically significant prediction models were produced for the three growth periods, in each case the majority of the variance in growth rates remained unexplained. This was despite the earnest attempt to use a comprehensive range of early variables in the analyses.

The variables that were analysed in relation to growth during the first few months of life included those relating to the infants themselves (e.g. irritability, sleeping and oral-motor function - gender was not included in these analyses because the standardised weights (z-scores) already take into account gender differences); those relating to the mothers (e.g. type of milk given to the infant, maternal age and IQ, and socio-economic status); and those relating to early medical factors (e.g. gestational age, birth weight, severity of neonatal illness etc). However, it must be remembered that all of the infants recruited into this study were, by definition, at-risk of poor growth due to their prematurity, and it is reasonable to assume that there is a complex interaction between factors such as gestation and birth weight, and other more specific medical risk factors. A composite neonatal risk score that included individual risk items such as serious infections, surgical procedures etc. was computed but this failed to have any predictive value. Unfortunately, due to the small number of infants for whom each risk factor included in the composite score applied, it was not possible to examine these factors individually in relation to the outcome measures. In a much larger sample, where such analyses could be undertaken, it might be possible to increase the predictive value of the regression models.

12.1.1.1. Infant Factors in Relation to Early Growth

For the initial period between birth and term, none of the infant factors proved predictive of growth rate. One explanation for this finding may be that for most of this early period the infants were hospitalised and therefore were being fed prescribed amounts at regular intervals intravenously, by naso-gastric tube or latterly by mouth (with top-ups by naso-gastric tube if inadequate quantities were ingested voluntarily). Therefore individual differences in terms of temperament (sleeping and crying) or oral-motor function would have been compensated for by the hospital regime.

For the period between term and 3-months corrected age only one infant factor was a significant predictor of growth, this being the number of hours slept per day, with infants who slept for longer growing faster. One possible mechanism for this finding would be that infants who slept for more hours in every 24-hour period were expending less energy and therefore, calorific intake being equal, would grow faster. In addition, or alternatively it may be that, because they were well rested, they actually ingested more calories per day, thereby enhancing rate of growth. Certainly sleeping for more hours per day did not diminish the overall number of feeds being given during the 24-hour period.

Measures of irritability were included in the analyses, partly on the basis of a study published by Carey (1985) suggesting that a sub-group of infants who showed good weight gain had a higher proportion of infants classified as "difficult" than the slower-growing group. Consequently an a priori hypothesis of the present study had been that perhaps mothers of irritable infants would feed them more frequently as a practical way of pacifying them, which would result in faster growth rates. The results indicated, however, that there was no relationship between measures of irritability and growth rates, nor indeed between measures of irritability and number of feeds given per day. Interestingly, none of the measures of infant feeding technique were related to growth during this period. This finding contrasts with those of previous studies (e.g. Heptinstall et al, 1987; Ramsay et al, 1993). Both those studies suggested that early feeding difficulties, e.g. those caused by abnormal oral-motor function, had a detrimental effect on growth rates. There are two possible explanations of the failure in the present study to replicate these findings. The first is that the mothers in this study may have compensated for their infants poor feeding technique by adapting their own behaviour, thus ensuring that the infants received adequate quantities of milk. That is, although some maternal behaviours were examined (e.g. waking of infants who failed to self-wake) other aspects of care were not taken into account (e.g. frequency of "winding", size of teat hole, supporting jaw during feed etc.). Secondly, it may be that the measures of feeding technique were inappropriate for use on a sample of very preterm infants. As already discussed, the data obtained using the mercury strain gauge was very disappointing, however, the other measures of feeding behaviour (i.e. the feeding problem index and intake per minute) were also unrelated to growth rates.

For the overall period from birth to 3-months of age, which was very highly correlated with the initial period from birth to term, the significant predictors were different again. For this period the only infant factor that predicted growth rate was feeding efficiency (i.e. intake per minute at term) with, not surprisingly, faster feeders showing better rates of growth. None of the infant temperament factors (which included sleeping and crying variables) contributed to the prediction model. Possible reasons for these anomalous findings have been discussed above.

Because weight status at 3-months of age proved predictive of developmental status at 18-months of age, a prediction model was also computed for this outcome measure. Interestingly none of the infant factors proved predictive of 3-month weight status.

In summary then, infant factors such as irritability, sleep regulation and feeding technique had little, if any, relation to early growth or weight outcome.

12.1.1.2. Maternal/Social Factors in Relation to Early Growth

The type of milk that the infants were receiving, both at term and 3-months of age, has been included under the heading of "maternal/social factors", since primarily it is the mother's decision what type of milk her infant will receive. This applies to whether or not the infant receives breast milk at all, and if so, when the change is made to formula milk. It also, of course, applies to when the formula is changed from a preterm one, to a standard infant formula. Other maternal/social factors included maternal age and intelligence, and socio-economic status as measured using the Osborn Index.

For the initial period between birth and term, the only maternal/social factor that was predictive of growth rate was the type of milk being given at term, with those who were still predominantly receiving breast milk showing poorer growth rates during the preceding weeks. At each of the neonatal units mothers were encouraged to express breast-milk, which was then mixed with commercial fortifiers before being fed to the infants via naso-gastric tubes. The constituents of the fortifiers that were used in each of the neonatal units is not known, but studies by Wauben (1998, 1999) have suggested that the specific type of fortifier used has little impact on observed growth rates. Once oral feeds were commenced, however, no additional nutrients could be added to the breast milk, which may have resulted in lower calorific intake for these infants compared to infants being fed preterm formula. Most of the previously published research has investigated the effects of nutrition on growth after the initial hospitalisation period (e.g. Lucas et al, 2001; Cooke, 1998, 2001; Carver et al, 2001) so it is unclear whether the findings from the present study are representative or not.

For the period between term and 3-months of age, when the majority of the infants were at home in the care of their mothers, the pattern of predictors was rather different. For

this period, two maternal factors proved predictive of growth rate, the first one being the type of milk being given at term, with the infant receiving breast milk now growing better. Again this finding is in contrast to other well-known studies (e.g. Lucas et al, 2001; Schanler et al, 1999), which suggested an advantage, in growth terms, of preterm formula over breast milk. One possible explanation for this finding is that data was only available on the type of milk being given at the actual assessment points, and some of the previously breast-fed infants who were not growing very well may have been changed onto formula milk just prior to the assessment, which could influence the outcome of the analyses.
The second maternal factor that was predictive of growth between term and 3-months of age was maternal IQ, with infants whose mothers had IQs below 85 growing less well. This factor remained predictive of growth rate even when the type of milk being given was held constant, although the mechanism for this effect was not immediately clear. Although, of course, the relationship between type of milk given to infants and socio-economic background is very well-documented, specific effects of maternal factors over and above the choice of milk given have not been highlighted in other studies. However, one possibility is that the sub-group of mothers who were of low intelligence were less sensitive to their infant's needs (e.g. showing less compensatory behaviour for infant feeding difficulties), or alternatively perhaps that they were less precise about the making up of formula feeds and therefore the infants received fewer calories. Unfortunately, however, it was not possible to explore these avenues of investigation within this thesis.

For the overall period between birth and 3-months corrected age none of the maternal factors were predictive of growth. This is presumably due to the opposing effects of type of milk during the two individual time periods, and to the fact that growth for this overall period was so highly correlated with growth during the initial few weeks when maternal input was so limited due to hospitalisation.

12.1.1.3. Birth & Medical Factors in Relation to Early Growth

A variety of birth and medical factors were included in the analyses in relation to growth rate. These included gestational age, birth weight, standardised birth weight (z-score), and several variables relating to the severity of the infant's condition during initial hospitalisation (e.g. level of care during first 10 days of life, days of mechanical ventilation etc). Interestingly, the only birth factor that was predictive of growth during any of the three periods examined was birth weight z-score, with the smaller-for-gestation infants showing more rapid growth than larger infants. This finding might represent regression to the mean, as predicted by Cole (1995). Although gestational age appeared to be correlated with growth between term and 3-months and for the overall period between birth and 3-months, it failed to add significantly to the prediction models when included in the regression analyses. This is in contrast to the findings reported by Alexander et al (1996), which suggested that, at least during the period of hospitalisation, the lower gestational-age infants showed slower growth compared to in utero standards than the more mature infants.

Although some of the variables reflecting how sick the infants had been during the neonatal period initially appeared to be related to growth rates (i.e. between birth and term and for the overall period from birth to 3-months) these variables failed to add significantly to the prediction models which were devised. For the period between term and 3-months, when the majority of infants had been discharged home into the care of their mothers, there was no relationship between early neonatal condition and growth rate. There has been research published that specifically addresses the relationship between neonatal illness and growth among very preterm infants, although one study reported by Johnson et al (1998) had suggested that infants who were sicker neonatally and subsequently developed bronchopulmonary dysplasia (BPD - chronic lung damage, often as a result of prolonged mechanical ventilation) were at increased risk of poor growth once discharged from the neonatal unit. Those findings may, however, have been due to the inter-correlation between BPD and oral-motor dysfunction that has been reported by other researchers (e.g. Mickerson, 1985).

For the fourth outcome measure, i.e. being classified as small-for-age at 3-months, the only birth factor that contributed significantly to the prediction model was birth weight status, with the infants who were classified as small-for-gestation at birth being at a seven-fold increased risk of being small-for-age at 3-months. Indeed, this factor was the strongest predictor of weight status at 3-months, despite the fact that the infants whose standardised weights were lower actually showed more rapid growth during the first few months of life than the larger-for-dates infants. Furthermore, unlike for the actual growth rate measures, the level of medical care required during the first 10 days of life also proved to be a significant predictor (with the sicker infants being at an increased risk of being small-for-age at 3-months).

12.1.2. Developmental Status at 18 Months of Age

We have seen in the previous sections that the variables that predicted growth during the first few months of life included the amount the infant slept; how efficient a feeder the infant was; the type of milk received; maternal IQ; and standardised birth weight. We now turn to a consideration of the factors that predicted developmental outcome at 18-months.

As expected based on previous research (e.g. reviews by Escobar et al, 1991; Campbell, 1997), this sample of very pre-term infants was at an increased risk of being developmentally delayed compared to a normative sample, with three infants presenting with such severe cerebral palsy that it was not possible to assess their cognitive function with standardised developmental assessments. Over half of the infants were developmentally delayed, with approximately one quarter of the whole sample falling into the severely developmentally delayed category. Although the predictive value of developmental assessment at 18 months is notoriously low, what is generally accepted is that infants who perform very badly at this age are likely to remain at the bottom end of the ability spectrum at later follow-up, i.e. low remains low (Largo et al, 1990; Liaw et al, 1993). Furthermore, many of the subjects who were not classified as severely developmentally delayed may well present with educational difficulties once they reach school age due to the more complex demands made upon them.

Many of the same antecedent factors were examined in relation to developmental outcome at 18-months as were used in relation to early growth (i.e. infant factors including gender, temperament and oral-motor function; maternal/social factors including age, IQ, socio-economic status and type of milk given to infant; and birth/medical factors including gestational age, birth weight and severity of neonatal illness). Early growth itself was also examined in relation to developmental outcome. The majority of the variables were included in the analyses because previously published research suggested that they were related to developmental outcome. As with the section on factors influencing growth rates, these factors are grouped according to whether they are classified as infant, maternal/social, or birth/medical factors.

12.1.2.1. Infant Factors in Relation to Developmental Outcome

In the present study, gender was one of the most powerful predictors of developmental outcome at 18-months and this finding was in accordance with previous studies of infants, both term and very preterm, which almost universally indicate that girls outperform boys at this age (e.g. Dezoete et al, 2003; Ornstein et al, 1991; Meio et al, 2003; Stoelhorst et al, 2003). These findings might reflect a true difference in developmental progress between boys and girls or, alternatively be due to a lower level of co-operation among the boys. As previously discussed, among children born very preterm boys are more likely to exhibit behavioural and attentional problems than girls (e.g. Hille et al, 2001; Schothorst et al, 1996) and in the present study most of the children who failed to co-operate (to the extent of being allocated the lowest score possible) in the assessment were boys. Whatever the underlying cause, the results showed that the girls had a mean IQ over 9 points higher than the boys, and the boys were at a significantly higher risk of being classified as severely developmentally delayed.

None of the other factors relating to the infant's individual characteristics, i.e. crying and sleeping patterns, or oral-motor function, were predictive of developmental outcome. The lack of relationship between oral-motor function and later developmental outcome is particularly surprising, since previous research has associated oral-motor dysfunction with intraventricular haemorrhage and birth asphyxia, both of which have been identified risk factors for later neuro-developmental morbidity (e.g. Nelson & Ellenberg, 1979; Hill & Volpe, 1981; Casaer et al, 1982).

12.1.2.2. Maternal/Social Factors in Relation to Developmental Outcome

In the present study there appeared to be no direct relationship between infant's developmental performance at 18-months of age and factors such as maternal age, maternal IQ or the Osborn Index (which is a measure of socio-economic status). This is consistent with other research examining the development of very preterm infants. Among children aged 2 years, who are born at term, maternal IQ is a strong predictor of the child's developmental quotient (e.g. Yeates et al, 1979). This is not the case, however, among children who are born very preterm, with research suggesting that genetic effects are completely obscured by external factors relating to the preterm birth (e.g. Koeppen-Schomerus et al, 2000).

Parental height variables were included in some of the analyses primarily to control for genetic factors in infant size. Somewhat surprisingly, however, it was found that paternal (and consequently mean parental) height remained predictive of developmental outcome even when other variables were held constant. The reason for this association between infant developmental outcome and parental height was not clear, particularly in view of the fact that, as mentioned in the paragraph above, among very preterm infants genetic influences on developmental/intellectual outcome are slight. Further examination of the data revealed no outliers, or other explanations for this finding.

The type of milk that was given to the infants at term and 3-months was also classified as a maternal/social factor (see sub-section 12.2.1.2.) in relation to developmental outcome. The results of the present study indicated very little difference in developmental scores between the infants who were breast-fed, given preterm formula or even standard formula, at either term or 3-months corrected age. Although there has been previous research into the relative benefits of breast milk or preterm formulae for the use of very preterm infants, the results have been inconsistent, with some suggesting a developmental advantage for those infants who were breast-fed (e.g. Lucas, 1992; Horwood, 2001), but others suggesting that any such apparent differences are due to confounding variables (e.g. Jacobson et al, 1999). A review of the research (Drane, 2000) did differentiate between exclusive and partial breast-feeding, which could explain some of the discrepancies in the various study results. As previously mentioned, in the present study the infants were categorised as breast-feeding if that was the predominant milk that they received. Furthermore, data was only analysed using the type of milk being given at specific time points and therefore infants classified as formula-fed might have been being breast-fed up until just before that date which would have affected the results.

12.1.2.3. Birth/Medical Factors in Relation to Developmental Outcome

A comprehensive array of birth and early medical factors were examined in relation to developmental outcome, including the obvious ones of gestational age and birth weight. However, neither gestational age, nor birth weight were predictive of developmental outcome, and nor were any of the variables reflecting severity of neonatal illness in the present study. Some previous research has indicated a negative correlation between birth weight and later IQ among low birth weight groups (Lagercrantz, 1997), although this finding is not universal.

Among the various medical variables that were examined in relation to developmental outcome, the only one that was predictive was the presence of an abnormal ultrasound scan of the brain during initial hospitalisation, with the small sub-group of children who had such abnormal scans, not surprisingly, performing less well than those whose scans were normal. None of the other medical variables (i.e. level of care during first 10 days of life, duration of intensive care, days of mechanical ventilation) proved predictive of developmental outcome.

12.1.2.4. Early Growth in Relation to Developmental Outcome

When the relationship between growth during the first few months of life and developmental outcome at 18-months was examined, what became apparent was the importance of infant size at 3-months of age. Both weight and head circumference at 3-months of age were predictive of developmental outcome when continuous variables were used. When dichotomised variables were used 3-month head circumference was no longer predictive, but 3-month weight was (i.e. weight below the 10^{th} percentile predicted later classification of severe developmental delay). Previous studies have frequently shown that being born small-for-gestation leads to an increased risk of developmental problems, but in the reported study this was not found to be the case. Although there was a correlation between standardised birth weight and standardised 3-month weight, being born small-for-gestation was not in itself a risk factor for developmental delay. Furthermore, in-depth analysis revealed that the use of the 10^{th} percentile for classification was not arbitrary – movement across this cut-off criterion did represent real differences in growth rates, and this rate of growth during the first few months of life was predictive of developmental outcome. Further analyses also showed that, although there was also a correlation between weight at 3-months and at 18-months, the former variable contributed significantly to the prediction model for developmental outcome even when the 18-month (i.e. concurrent) weight had already been incorporated in the model.

These results support the hypothesis that there is a "sensitive period" for brain growth and development, at least in very pre-term infants, which extends beyond intrauterine life until at least three months corrected age (i.e. for a period of at least 5-7 months). Thus sub-optimal growth at any point up until 3 months corrected age (i.e. either in utero or after birth), which results in a weight below the 10^{th} percentile at that time point, may lead to an increased risk of developmental delay at 18 months of age. The data also suggested that good catch-up growth of infants born small-for-gestation in the following few months might alleviate the adverse effects on developmental outcome, at least at 18-months of age.

12.2. The Main Findings from the Study

12.2.1. The Difficulty in Predicting Variance in Outcome Measures in Very Preterm Infants

Within a sample of infants born very preterm it continues to be difficult to predict the outcome of individual infants, both in terms of early growth and of developmental progress. Despite the construction of statistically significant prediction models, a considerable proportion of the variance, both for early growth and for developmental outcome at 18-months, remained unexplained.

Interestingly infant characteristics (i.e. temperament and regulatory patterns) do not appear to relate to either outcome measure, and the influence of maternal factors (in terms of intelligence and via feeding choices) was rather limited and only had an effect after discharge from the neonatal unit. Both actual birth weight and standardised weight-for-gestation at birth proved more important, in terms of growth outcome (and therefore indirectly on developmental outcome) than gestational age. Although some of the medical variables (e.g. intensity of care) were related to early growth, they did not actually relate directly to developmental outcome. In fact, the only early medical variable that had a direct relationship with developmental outcome was the identification of abnormality on brain scan.

There are several possible explanations for the failure to explain a greater proportion of the variance, both for early growth rate, and for later developmental outcome. One such explanation could be that in some instances there were problems with reliability and or validity of the instruments that were selected. In most cases, however, more than one instrument was used to assess a particular factor (e.g. oral-motor function, or severity of neonatal illness), and it is unlikely that each of those variables would have failed to identify potential risk factors. A second, perhaps more likely explanation for the unexplained variance is that, even when environmental conditions are appropriate for normal growth and or development of term infants, these very preterm, at-risk individuals may not be able to fully utilise these resources. Each infant born very preterm faces a different and complex range of adversities, both biological and environmental, and thus the outcome in terms of both growth and development is difficult to predict with certainty.

12.2.2. The Importance of the Relationship between Growth and Development

The results of this study suggest that there is an important relationship between growth during the early months of life and later developmental outcome among very preterm infants. Indeed, apart from gender effects, which have frequently been reported in the existing literature, the rate of growth between birth and 3-months corrected age (and actual size at 3-months) was shown to be the strongest predictor of developmental outcome among this group of infants. Even after taking other variables (e.g. maternal/caretaking differences) into account, those infants who showed poor growth during the first few months of life had a poorer outcome, in terms of development, at 18-months of age.

12.3. Implications for Clinical Care

Unfortunately many of the independent variables that were related to either early growth or directly to developmental status at 18 months of age are not open to manipulation. For example, the intensity of care given during initial hospitalisation is entirely dependent on the severity of the infant's condition. There were, nonetheless, some variables that it would be possible to manipulate, for example the variables relating to nutrition, particularly during the period from birth to term, when the majority of very preterm infants were hospitalised for several weeks. The overall growth rate for the 90 infants included in the study up to 3 months corrected age was very poor. The possible reasons for this have already been discussed, but two issues are worth emphasising.

The first is that, in most cases, the infants in the study were being fed, initially intravenously and subsequently orally, according to their actual weight. It has been suggested (Alexander, 1996) that it would be more appropriate, and beneficial to improved weight gain, for these infants to be fed according to their <u>expected</u> weight instead of actual weight. This should result in increased catch-up growth, enabling the infants to regain the weight that is invariably lost in the immediate post-delivery period.

Secondly, during the period from birth to term, the infants who were still receiving breast milk at term grew particularly poorly. If it were possible to improve the fortification of expressed breast milk during the first few weeks of life, and/or to prolong this fortification beyond the establishment of oral breast-feeding, then the advantages of breast-milk in terms of growth might well be considerably greater. Even without a growth benefit, however, breast-feeding has previously been shown to offer the very preterm infant valuable protection against serious infection (e.g. Schanler, 1995; Lucas, 1990), and it is therefore important to encourage mothers of pre-term infants both to express breast-milk for their infants, and subsequently to establish successful breast-feeding.

On the basis of preliminary analyses, prediction models were formulated to predict developmental outcome at 18 months of age in very preterm infants, and specifically to identify independent risk factors for severe developmental delay at that age. As previously discussed, the two strongest predictors of severe delay within this at risk sample were male gender, and weight below the 10^{th} percentile at 3-months of age (regardless of weight status at birth). The first of these risk factors has been repeatedly identified in previously published research. However, the second major risk factor has not been specifically identified within a very preterm sample before, although it has previously been proposed that early growth rate (in a normal sample) may influence later development.

As previously discussed, there are few early predictors available that can identify those very preterm infants who are particularly at risk of developmental delay. The recognition that weight status at 3-months of age is a strong predictor of severe developmental delay among such infants could therefore be extremely important. In the present study, being born small-for-gestation increased the risk of being small-for-age at 3-months, and growth between term and 3-months was negatively associated with both formula feeding and low maternal IQ. Efforts to promote improved weight gain post-discharge, especially among infants with these identified risk factors, could be of significant value. For example, at present it is not possible to obtain the high-calorie, preterm formulae using the milk tokens available to low-income families. As these may well be the infants particularly at risk of poor growth, free provision of this type of infant formula could be extremely beneficial. Furthermore, although infants, especially those born very preterm, are generally weighed on a regular basis during the first few months post-discharge from hospital, this is often at the discretion of the individual mother. Again, the mothers who fail to attend the clinic for weighing regularly should be identified early and encouraged to comply, if necessary by having the infants weighed by a health worker in the home, in order to ensure that a good growth rate is being maintained. A dropping-off of weight in terms of percentile place, or even a failure to show catch-up growth in infants who had previously been identified as small-for-age, could then be quickly recognised and addressed.

In cases where such intervention was unsuccessful in promoting improved growth, a weight below the 10^{th} percentile at 3-months corrected age could be valuable in terms of "flagging-up" infants at particular risk of severe developmental delay, which would in turn facilitate the provision of targeted early, pre-school interventions and/or planning of later schooling requirements.

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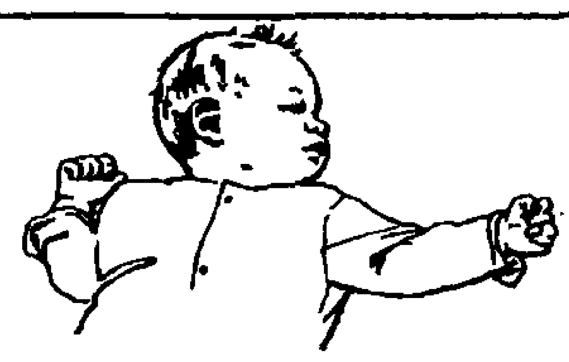
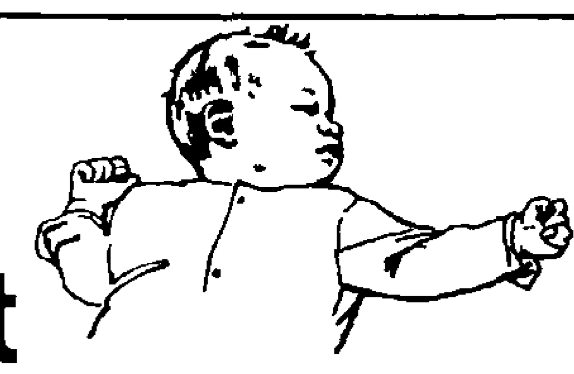
Appendix 1: Parent Information Sheet

GAIN-STUDY



Information Sheet



The Psychology Department at the University of Hertfordshire, in association with this and other Neonatal Units, is undertaking a research project to look at the progress and development of very premature babies after they leave the Special Care Baby Unit. The Research Team comprises **Professor Dieter Wolke**, who has studied premature babies for many years; **Tina Gutbrod** and **Libi Rust**, who are developmental psychologists.

The Study

The study will include babies treated in several Neonatal Intensive Care Units (NICUs)/ Special Care Baby Units (SCBUs). To be included in the study, babies need to have been born weighing less than 1500g or to have been born before 32 weeks gestation. Increasing numbers of these very premature babies are being treated and survive, but little is known about the specific development needs they or their families may have once they leave hospital. The aim of the study is to find out what factors contribute to the growth and development of these infants and the infant-parent relationships over the first year of life. We hope that the findings will help to provide even better care for families in the future.

How could this study benefit you and your baby?

Over the first 18 months of your baby's life, you will have the opportunity to:

* receive additional information about your baby's progress over the first year
* contribute to vital research into the care and development of very premature babies
* keep a videotape as a permanent reminder of your baby's first year

What does it involve?

Mothers and babies who are included in the study will be seen on several occasions. The first occasion will be just before discharge from the Neonatal Unit. At this time, a standard baby examination will be carried out which gives us information about the baby's individual characteristics. In addition, the mother will be interviewed, and asked questions about her pregnancy, the birth, her expectations for her baby's future and current care, and a member of nursing staff will complete a short questionnaire about the baby. The next session will be around the time that the baby was due to be born, when a feeding session will be observed (and a measurement obtained of how effectively the baby sucks). On this and subsequent occasions, the baby will be accurately weighed and measured. The third session will be three months later, when we would like to visit the family at home. At that time we will again observe a feed and interview the mother about their baby's feeding, sleeping and crying habits. Mothers will be asked to complete a questionnaire regarding childhood recollections and to complete a short diary of their baby's crying and sleeping habits.

The next contact time will be when the baby would have been 18 months old (if born at the expected time). On this occasion we will observe how the baby behaves in different play situations, accepts short separations and reunions, and will assess his/her general development. Again we would like to interview mothers about their infants' behaviour. The assessment will take place at a local clinic, or at the University of Hertfordshire. Your travel costs will, of course, be reimbursed.

All the information obtained during the study will be treated in the **strictest confidence** and will not be passed on to other health professionals unless specifically asked to do so by the parents. All our copies of the videotapes will be destroyed at the end of the study and will not be used, or made available, for any purpose other than the research itself.

Please understand that these examinations are in addition to the routine follow-ups arranged by the hospital, and do not replace them.

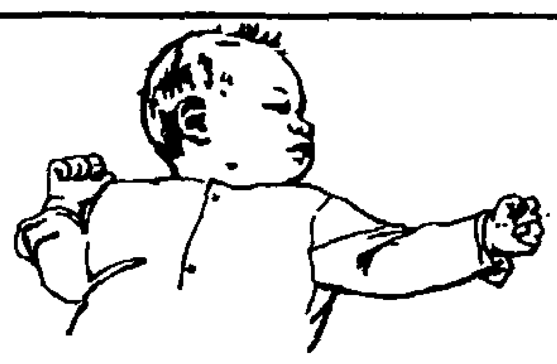
If your baby was born weighing less than 1500g, or was born before 32 weeks gestation, we would very much like you to consider participating in our study. If you would like the opportuni to discuss the study with your family in more detail, we are happy to arrange a meeting. You car contact us via phone (01707 / 285261) or ask any member of the SCBU staff to leave a message for us. If, for any reason, you decide that you do not want to participate, this will in no way affec the treatment your baby receives. Furthermore, if once you have decided to participate you change your mind, you can at any stage withdraw your consent without having to give a reason.

We very much hope that you will agree to participate in this study, which will increase the current knowledge about the development of these very small babies. **Thank you for taking the time to read this information sheet.**

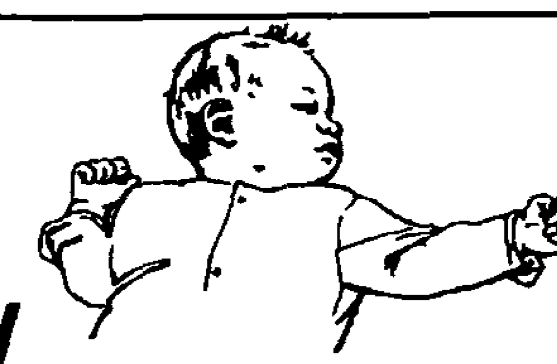
Prof Dieter Wolke Tina Gutbrod Libi Rust

Appendix 2: Consent Form

GAIN-STUDY



Consent to Participation in Study



I ....

of ....

being the legal
guardian of ....

(subsequently referred to as child) hereby give my permission fully and freely for the child and me to participate in the study entitled:

G A I N - Growth, Feeding and Development in Preterm Infants

I understand and acknowledge that the study is designed to promote medical knowledge.
I understand that non-participation will not affect the treatment which my baby receives.
I note that I may withdraw my consent at any stage in the study, without giving a reason.

The nature and purpose of the assessment procedures to be used have been explained to me

by: ....Tina Gutbrod / Libi Rust..

and I have had an opportunity to discuss these matters with him/her. I have received a written explanation of these procedures, a copy of which is attached to this form.

Signed .... Date ....

WITNESS to guardian's signature and to fact that he/she has read the document and freely given his/her consent.

Signed .... Date ....

(Witness **must not** be a member of the project team)

I confirm that I have explained to the legal guardian of the child the nature of these procedures.

Signed .... Date ....

(member of the project team acting on behalf of individual responsible for the study)

Appendix 3: Respiratory Support Summary

GAIN-STUDY

Baby's name: ....

Mother's name: ....

SSNO □□□□

Ventilation/Respiration Summary

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Date																									
IPPV/SIMV																									
HFOV																									
CPAP																									
O2 - n/c																									
O2 - headbox																									
AIR																									
O2 - %																									

Day	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
Date																									
IPPV/SIMV																									
HFOV																									
CPAP																									
O2 - n/c																									
O2 - headbox																									
AIR																									
O2 - %																									

Appendix 4: Feeding Support Summary

GAIN-STUDY

Baby's name: ....

Mother's name: ....

SSNO ☐☐☐☐

Feeding Summary

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Date																									
TPN																									
TPN/tube																									
n/g tube																									
tube/oral																									
oral																									
EBM/ptf/ftf																									
WEIGHT																									

Day	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
Date																									
TPN																									
TPN/tube																									
n/g tube																									
tube/oral																									
oral																									
EBM/ptf/ftf																									
WEIGHT																									

Appendix 5: Intensity of Care Summary

GAIN

Date of Birth: ☐☐☐☐☐☐

Date of Discharge: ☐☐☐☐☐☐

Total days of care: ☐☐☐

Baby's name: ....

Mother's name: ....

SSNO ☐☐☐☐

Intensity of Care Summary

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Date																									
Intensive care																									
High dep'cy																									
Special care																									

Day	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
Date																									
Intensive care																									
High dep'cy																									
Special care																									

Appendix 6: Crying Patterns Questionnaire (CPQ)

Now I would like to ask you a few questions about your baby's fussing and crying.

For how long does your baby fuss or cry during an average day (e.g. yesterday)?

a) ...during the morning (6am - noon)	.....hrs	......mins
b) ...during the afternoon (noon - 6pm)	.....hrs	......mins
c) ...during the evenings (6pm-midnight)	.....hrs	......mins
d) ...during the night (midnight - 6am)	.....hrs	......mins

How many separate bouts of fussing and crying are there typically in an average day (e.g. remember yesterday)? (If there is no crying at all, please record "0"). *(A "bout" is defined as a period of time in which you could not put your baby down without him/her starting to cry or fuss again).*

	number of bouts
a) ...during the morning (6am - noon)	☐
b) ...during the afternoon (noon - 6pm)	☐
c) ...during the evenings (6pm-midnight)	☐
d) ...during the night (midnight - 6am)	☐

Appendix 7: Coding of Strain Gauge Printout

Procedure for Coding Feeding Print-outs

1. Enter subject identity number in top right corner of coding sheet.

2. Identify beginning of feed and end point of coding period (five minutes from beginning of feed + time to end of sucking burst in progress at 5 minutes). Record at bottom of coding sheet and mark on printout.

3. Identify largest suck during the period to be coded, from the baseline existing at the beginning of the suck, or at the end of the suck, whichever is higher (in mm). Record at bottom of coding sheet, together with 10% of that measurement which will be the cut-off criterion for what constitutes a suck for that individual feed. Check WSG cover sheet for artefacts, winding etc, and ensure that largest suck is not an artefact.

4. Go through each sheet on printout, marking beginning and end of bursts and pauses. On coding sheet record:

   a) duration of each sucking burst - in mm
   b) number of sucks in each burst
   c) duration of each pause (which may incorporate single sucks) - in mm. 5mm is cut-off criterion for a pause
   d) note any single sucks occurring at bottom of coding sheet (to be totalled up at end of coding)

ROUND ALL MEASUREMENTS DOWN TO NEAREST MILLIMETRE

Criteria for identifying behaviours

During any one feed, the baseline can move arbitrarily, and therefore referring to baseline as a static point is inappropriate. For this reason the current baseline is taken as the starting point of the preceding suck. The variable baseline does not present insurmountable difficulties since the amplitude of the sucks in not being analysed, but rather the frequency of them.

Suck Acute deflection from and at least 50% return to starting point of that suck. The shortest side of deflection must be at least 10% size of largest suck in the coding period. Occasionally a suck may have a double peak. A deflection is not counted as a suck if it is > 5mm from leaving baseline to returning to it.

Pause	Period of at least five millimetres on baseline between end of one identified burst and beginning of next one (not counting single sucks) OR a period of at least 5 mm above baseline before returning at least 50% of way to baseline (may include several small deflections which are < 10% of largest suck and therefore not true sucks).
Burst	2 or more sucks between pauses
Beginning of feed	When baby first begins a sucking burst after latching on to teat/nipple. If the recording commences during a sucking burst, the feeding analysis should begin at the beginning of the next sucking burst.
End of feed	Identified by the mother

N.B. Measurements to be in millimetres rather than seconds. All measurements should be rounded down to nearest millimetre. As all graphs using same scale, then let computer convert to seconds (less chance of error). Ditto for beginning and end of feed.

Appendix 8: Strain Gauge Coding Sheet

SSNO □□□□ □

sgb1	sgsb1	sgp1	**sgb2**	sgsb2	sgp2	**sgb3**	sgsb3	sgp3	**sgb4**	sgsb4	sgp4	**sgb5**	sgsb5	sgp5
sgb6	sgsb6	sgp6	**sgb7**	sgsb7	sgp7	**sgb8**	sgsb8	sgp8	**sgb9**	sgsb9	sgp9	**sgb10**	sgsb10	sgp10
sgb11	sgsb11	sgp11	**sgb12**	sgsb12	sgp12	**sgb13**	sgsb13	sgp13	**sgb14**	sgsb14	sgp14	**sgb15**	sgsb15	sgp15
sgb16	sgsb16	sgp16	**sgb17**	sgsb17	sgp17	**sgb18**	sgsb18	sgp18	**sgb19**	sgsb19	sgp19	**sgb20**	sgsb20	sgp20
sgb21	sgsb21	sgp21	**gb22**	sgsb22	sgp22	**sgb23**	sgsb23	sgp23	**sgb24**	sgsb24	Sgp24	**sgb25**	sgsb25	sgp25
sgb26	sgsb26	sgp26	**sgb27**	sgsb27	sgp27	**sgb28**	sgsb28	sgp28	**sgb29**	sgsb29	sgp29	**sgb30**	sgsb30	sgp30
sgb31	sgsb31	sgp31	**sgb32**	sgsb32	sgp32	**sgb33**	sgsb33	sgp33	**sgb34**	sgsb34	sgp34	**sgb35**	sgsb35	sgp35
sgb36	sgsb36	sgp36	**sgb37**	sgsb37	sgp37	**sgb38**	sgsb38	sgp38	**sgb39**	sgsb39	sgp39	**sgb40**	sgsb40	sgp40
sgb41	sgsb41	sgp41	**sgb42**	sgsb42	sgp42	**sgb43**	sgsb43	sgp43	**sgb44**	sgsb44	sgp44	**sgb45**	sgsb45	sgp45
sgb46	sgsb46	sgp46	**sgb47**	sgsb47	sgp47	**sgb48**	sgsb48	sgp48	**sgb49**	sgsb49	sgp49	**sgb50**	sgsb50	sgp50

largest suck (mm) =

smallest suck - 10% of largest (mm) =

single sucks □□□□□□□□□□□□□□□□□□□
□□□□□□□□□□□□□□□□□□□

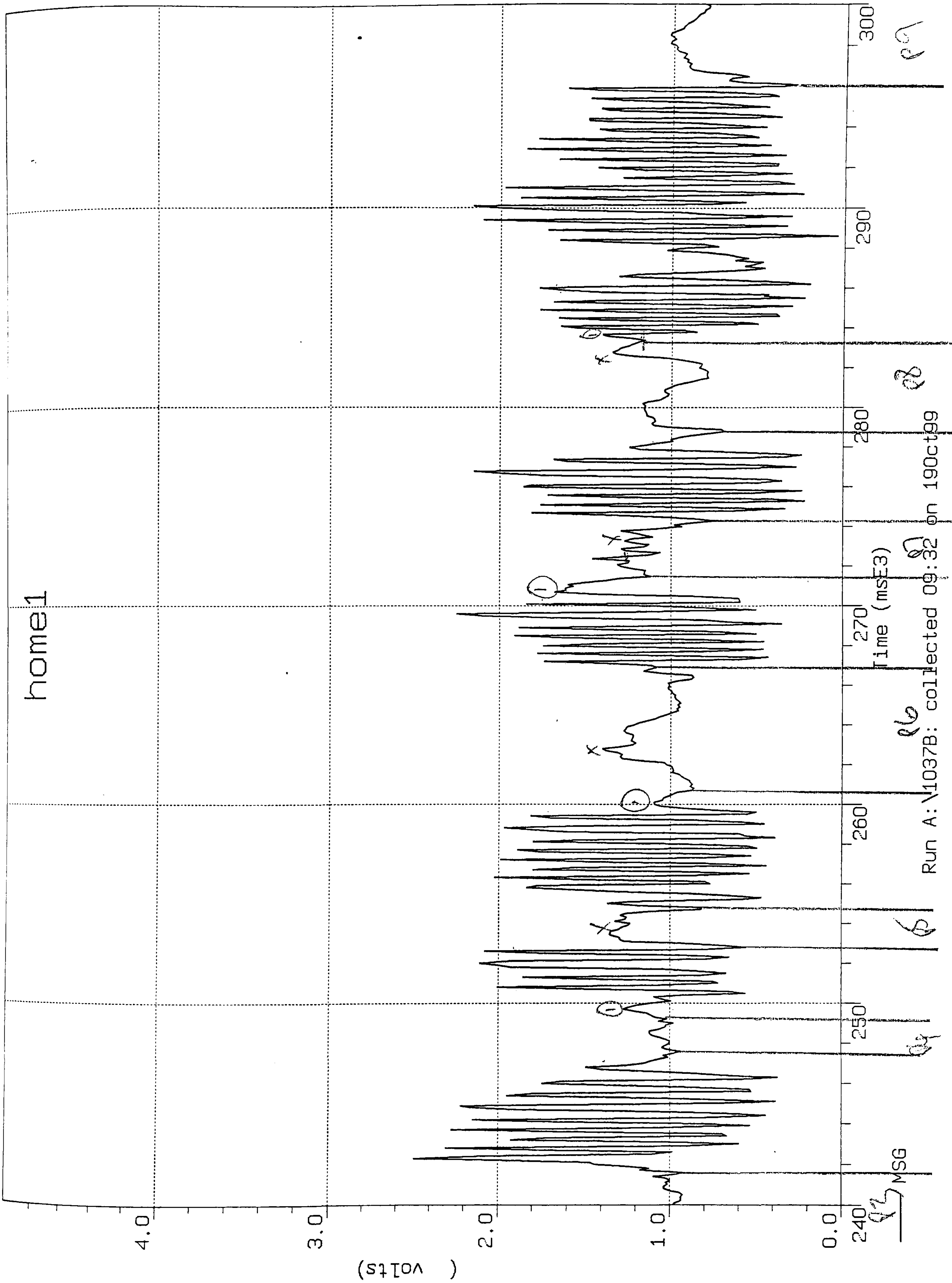
coding starts (mm) =

coding ends (mm) =

coding total (mm) =

total single sucks = □□

Appendix 9: Example of Strain Gauge Print-Out



Appendix 10: Infant Irritability Measures that were Discarded

The decision was made to remove some of the irritability measures from the main body of the thesis, primarily to reduce the quantity of non-significant data that was obtained. However, the background information, descriptive statistics and inter-correlations with the other irritability measures that were used concurrently, is included below.

Additional Irritability Measure at Term

Mother and Baby Scale (MABS)

Description

The Mother and Baby Scale (neonatal version, St. James-Roberts & Wolke, 1988) is a 43-item questionnaire completed by the mother, which rates her perceptions of unsettled and irregular infant behaviour, responsiveness and maternal confidence which are noted on a 6-point (Likert-type) scale, and then her overall impressions of infant difficulty, alertness, responsiveness and general maternal self-confidence on a 7-point semantic differential scale.

One of the authors of the MABS (Wolke, 1995) has reported the following psychometric indices for the Irritability sub-scale in a normative study: mean = 31.8, sd = 15.6, internal consistency (alpha) = 0.92. The defined clinically relevant cut-off point for the scale was set at 48 (1 sd above the mean), which means that all scores over 47 indicate high irritability.

Procedure

The questionnaire was given to the mother to complete, usually at the second assessment.

Missing data

Data was missing on the six infants who were still hospitalised at the time of the term assessment, and also on a set of triplets, for whom the MABS questionnaires had been left with the mother for completion and return by post, but were not received despite follow-up telephone calls. Consequently scores were only available on 81 of the 90 infants in the study.

Infant Irritability Composite

The Irritability subscale (MABS dimension "Unsettled-Irregular") is the only subscale used in this thesis.

Psychometric Evaluation

As can be seen, the mean and standard deviation were similar to those reported by Wolke (1995), and are relatively normally distributed.

Descriptive Statistics of MABS Irritability Scores at Term (N = 84)

Variable	Mean	Std Dev	Min-Max	Skewness	Kurtosis
MABS Unsettled-Irregular Dimension	37.3	12.6	4 - 67	-.30	-.06

Data Reduction

For comparison purposes the cut-off criterion (>47) used by Wolke to define the highly irritable infants was used in this study. This resulted in 17 (21%) of the 81 infants being classified as highly irritable.

Inter-instrument correlations at Term

It can be seen that the three variables described above, all believed to measure irritability at term, varied in the extent to which they inter-correlated. Two of the three measures were maternally-assessed, the only one which was not was the NBAS which was examiner-assessed. As can be seen, there was no significant correlation between the NBAS Irritability and the MABS unsettled-irregular (irritability) measures, but the correlation between the NBAS and the CPQ was significant ($r=.24, p< .05$) as was that between the MABS Irritability and the CPQ ($r=.35, p< .01$).

Inter-instrument Correlations at Term

Instrument	NBAS Irritability	MABS Irritability	CPQ Cry duration
NBAS Irritability	1.00		
MABS Irritability	.05	1.00	
CPQ Cry duration	**.24***	**.35****	1.00

* correlation is significant at .05 level
** correlation is significant at .01 level

Additional Irritability Measure at 3-Months

Behavioural Diary

Background

Behavioural diaries have frequently been used in studies of infant behaviour (Wolke, Gray & Meyer, 1994; Wolke et al 1994; Barr et al 1988) and provide a more objective measure of the individual behaviour patterns than merely asking the mothers general questions. There is reportedly good convergence between maternal diaries and audio-recordings (Barr et al 1988).

Procedure

At the end of the 3-month assessment, each mother was asked to take and complete a diary recording her infant's behaviour in 15 minute intervals, preferably over three consecutive days (the form only needed to be filled in every few hours). A stamped, addressed envelope was left with the forms, and the mother requested to return it within two weeks. A follow-up telephone reminder was made if the form was not returned.

Missing Data

Unfortunately, despite considerable follow-up efforts, not all the mothers returned the completed diaries. One-day diaries were returned by the mothers of 67 infants, but only 60 of the diaries were completed for the full three days.

Psychometric Evaluation

The table below gives the descriptive statistics of the crying data obtained from both the 3-day and 1-day diaries.

Descriptive Statistics of Cry Diaries at 3 months

Variable	N	Mean	Std Dev	Min-Max	Skewness	Kurtosis
3-day cry diary	60	112.92	61.16	15 – 320	.74	.77
1-day cry diary	67	111.27	59.21	0 – 300	.62	.45

Data Reduction

It was decided to dichotomise the infants into normal and excessive criers using the same classification criterion as used in the CPQ (ie >180 minutes per day), in order that the instruments could be compared. Of the 60 infants for whom 3-day diary data was available, 8 (13%) of them were classified as excessive criers, with the remaining 52 (87%) being classified as normal criers. From the 1-day diary data, which was available on 67 infants, 9 (13%) of them were classified as excessive criers, with the remaining 58 (87%) being classified as normal criers.

Since the correlation between the two diaries was r = .82 (significant at the p< .00 level), and the classification percentages were identical for the two diaries, it was decided that for further analyses the one day diary data would be used, since this was available on a large number of infants.

Inter-instrument correlations at 3-Months

As the table below shows, the inter-instrument correlations were somewhat higher at the 3-month assessment point than at Term, although the fact that all of these are mother-assessed should be taken into consideration.

Inter-instrument Correlations at 3 months

Instrument	CPQ Cry duration	1-day diary	3-day diary
CPQ Cry duration	1.00		
1-day diary	.51**	1.00	
3-day diary	.50**	.85**	1.00

** correlation is significant at the .01 level