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Exploring the fat mass and fat free mass of term and moderate to late preterm infants: an observational study

A thesis presented in partial fulfilment of the requirements for the degree of

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Abstract

Background:

Moderate to late preterm infants (32-36^{+6} weeks' gestation) make up 83% of preterm births in New Zealand. Preterm birth is associated with having a higher risk of obesity, diabetes and cardiovascular disease in later life. Preterm infants demonstrate postnatal growth restriction followed by a period of accelerated growth. When compared to term infants at equivalent ages, preterm infants have been found to have a higher % fat mass. Nutrition is a modifiable factor contributing to the growth of preterm infants. While the goal is for these infants to be breast-fed, this is often not possible in early postnatal life due to delayed maternal milk supply and immaturity of the infant. Evidence is limited for the optimal feeding strategy for these infants until full breast-feeds can be established and there is great variability in practice.

Aims:

To measure the % fat mass and fat free mass of moderate to late preterm infants and term infants after birth at Auckland City Hospital; to explore the relationship between feeding strategies currently used within Auckland City Hospital and the acquisition of fat and fat free mass in moderate to late preterm infants after birth.

Methods:

Moderate to late preterm infants and term infants were recruited from Auckland City Hospital. Air displacement plethysmography (ADP) was used to measure the fat mass and fat free mass of the infants. Preterm infants were measured once they were medically stable and term infants were measured within 72 hr of birth. Eleven preterm infants were measured a second time prior to discharge from hospital. Information regarding what the preterm infants were fed within the first five days after birth was collected from their medical notes and the infants were prospectively grouped according to which feeding strategy they predominantly received, either: breast-milk, infant formula, 10% dextrose, or parenteral nutrition. Statistical analysis was performed using independent t-tests, Pearson's Chi square tests, Mann-Whitney tests, paired sample t-tests, one-way ANOVA, and Kruskal-Wallis tests.

Results:

Forty seven preterm moderate to late preterm infants and sixty nine term infants were recruited. Term infants had a mean ± SD % FM of 10.9 ± 4.2%, when broken down by sex males had 9.4 ± 3.5% and females had 12.2 ± 4.8% (P = 0.018). Preterm infants measured within the first week of birth (n = 25) had a mean ± SD % FM of 8.7 ± 4.4% and those measured within the second week of birth (n = 19) had a mean ± SD % FM of 8.1 ± 2.9% (P = 0.6). Twenty two

preterm infants were measured at ≥ 36 weeks' postmenstrual age and had a mean ± SD % FM of 10.9 ± 5.0%, which did not differ from the % FM of term infants measured after birth (*P* = 0.98). Eleven preterm infants were measured twice during their hospital admission and their mean ± SD % FM increased from 8.5 ± 3.5% to 15.0 ± 4.2% (*P* <0.001). The median [25th-75th quartiles] % increase in FM for infants with two measurements was 98.9 [70.1, 114.9] %. One-way ANOVA revealed significant differences in FFM (*P* = 0.004), weight (*P* = 0.013), and length (*P* = 0.036) between the feeding groups. Post hoc analysis showed that infants in the parenteral nutrition group had significantly less FFM than infants in the formula group (*P* = 0.008) and were lighter and shorter than the breast-milk group (*P* = 0.013, *P* = 0.036).

Conclusions:

Moderate to late preterm infants experience a rapid increase in FM during hospital admission and reach the % FM of a term infant before term corrected age. Moderate to late preterm infants in the parenteral nutrition group were the lightest, shortest and had the least FFM. This study also highlights considerations to be made for future research using ADP in the Newborn Intensive Care Unit at Auckland City Hospital.

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Abbreviations

ACH	Auckland City Hospital
ADP	Air displacement plethysmography
AGA	Appropriate for gestational age
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CA	Corrected age
CVD	Cardiovascular disease
DXA	Dual-energy X-ray absorptiometry
ELBW	Extremely low birth weight
FFM	Fat free mass
FM	Fat mass
GA	Gestational age
GI	Gastrointestinal
HDL	High density lipoprotein
IUGR	Intrauterine growth restriction
LBW	Low birth weight
LDL	Low density lipoprotein
LGA	Large for gestational age
MRI	Magnetic resonance imaging
NICU	Newborn Intensive Care Unit
PIS	Participant information sheet
SGA	Small for gestational age
SAA	Surface area artefact
TBW	Total body water
TCA	Term corrected age
USA	United States of America
QC	Quality control
VLBW	Very low birth weight

WLR	Waist length ratio

Chapter 1: Introduction

1.1 Background and Justification

Preterm birth is a significant global issue with a rising incidence (World Health Organisation, 2012). An estimated 15 million preterm infants are born world-wide annually (World Health Organisation, 2012). A birth is defined as preterm if it occurs prior to 37 weeks' gestation. The World Health Organisation has three classifications for preterm birth: extremely preterm (<28 weeks' gestation), very preterm (28 – 31^{+6} weeks' gestation) and moderate to late preterm (32-36^{+6} weeks' gestation) (World Health Organisation, 2012). In 2013, 7.4% of all births in New Zealand were preterm, which is an increase from 7.1% in 2004 (Ministry of Health, 2007, 2015b). Moderate to late preterm infants make up the largest proportion, contributing to 83% of preterm births in 2013 (Ministry of Health, 2015b). This greater incidence results in moderate to late preterm infants having a larger economic burden on the health system than very preterm and extremely infants (Petrou & Khan, 2012).

Shortened gestational duration means less time *in utero* to grow and develop and is therefore associated with many health complications and increased mortality. The degree of prematurity greatly influences both the short- and long-term health consequences (Boyle et al., 2012). With better survival rates than those born at more preterm gestations, the vulnerability of the moderate to late preterm group is often underestimated. However, compared to full term infants, they are at increased risk of respiratory distress, hypoglycaemia, thermal instability, jaundice, infection, apnoea, and feeding difficulties, resulting in longer hospital admissions (Boyle & Boyle, 2013). Moderate to late preterm birth is also associated with impaired neurodevelopment resulting in lower intelligence quotient and higher rates of special education needs at school age than those born full term (Chyi, Lee, Hintz, Gould, & Sutcliffe, 2008; Talge et al., 2010).

Further long-term health consequences of preterm birth are adverse cardiovascular and metabolic outcomes. Research has shown that those born preterm have an increased risk of being obese and developing diabetes, hypertension and dyslipidaemia during young adulthood (Crump, Winkleby, Sundquist, & Sundquist, 2011a, 2011b; Parkinson, Hyde, Gale, Santhakumaran, & Modi, 2013; Sipola-Leppanen et al., 2015). The World Health Organisation recognises that in countries with low mortality rates from preterm birth, the focus should be on optimising care to prevent long-term complications (World Health Organisation, 2012).

Despite nutrition being a modifiable factor for the short- and long-term health outcomes of these moderate to late preterm infants, there is a lack of evidence to inform feeding strategies that will lead to the best outcomes, with the inevitable consequence of a wide variation in approach amongst newborn nurseries.

A goal for the growth of preterm infants is that it matches that of a fetus *in utero* (American Academy of Paediatrics Committee on Nutrition, 1985). Up until recently, measures for the adequacy of postnatal growth have been focused largely on weight gain as a proxy for growth (de Onis et al., 2012), rather than true measures of growth including body composition. With new technology using air displacement plethysmography (ADP), it is now possible to assess the composition of growth by accurately measuring fat mass (FM) and fat free mass (FFM) in a non-invasive manner (Ellis et al., 2007; Roggero, Giannì, Amato, et al., 2012). Studies have shown that when compared at equivalent post-menstrual ages, the body composition of preterm and term infants is different, with preterm infants having a lower percentage of fat (Giannì et al., 2012; Olhager & Törnqvist, 2014; Ramel, Gray, Davern, & Demerath, 2014; Roggero et al., 2009; Simon et al., 2013). However, during the initial time after birth they demonstrate a rapid increase in FM (Giannì et al., 2012) such that by term-corrected age, when compared to term-born infants, preterm infants have a significantly higher percentage of FM and less FFM (Johnson, Wootton, Leaf, & Jackson, 2012).

With interest rising in the research area of early growth and its later health outcomes, it has been proposed that this rapid fat deposition and FFM deficit may be linked to the observed adverse cardiovascular and metabolic outcomes (Lucas, 2005). However, early rapid weight gain is associated with improved brain growth and neurodevelopment. Preterm infants that have experienced rapid growth through enhanced nutrition in early life have favourable cognitive outcomes during childhood, yet these same children present with a higher risk of becoming overweight or obese (Belfort, Gillman, Buka, Casey, & McCormick, 2013; Belfort et al., 2011). This apparent compromise of metabolic health for improved cognition leads to the necessity of finding nutritional strategies that will maximise brain growth whilst producing an optimal body composition.

The third trimester of pregnancy is vital for fetal nutrient accretion, and being born even mildly preterm causes an infant to have decreased energy and nutrient stores (Rigo & Senterre, 2006). This point alone highlights the importance of promptly establishing a sufficient nutrient supply, in order to minimise the use of their limited stores as energy for survival as well as providing enough for optimal growth (De Boo & Harding, 2007). However, this period after

birth is a time when feeding moderate to late preterm infants has proven to be difficult. The suckling reflex of these infants is often too immature to support full breast-feeding and maternal supply of breast-milk may take several days to become adequate (Butler & Behrman, 2007). Furthermore, with an immature gut, preterm infants can have difficulty tolerating enteral feeds (Sangild, 2006). The gut of a preterm infant can have immature villi, resulting in decreased surface area and ability to absorb nutrients, and insufficient motility to move fluids through the gut (Neu, 2007). Consequently, there may be a period of delay before a full nutrient supply is established. During this period of under-nutrition, faltering growth can occur and the observed rapid growth rate only occurs once an adequate nutrient supply is commenced (Corpeleijn, Kouwenhoven, & van Goudoever, 2013). Therefore, minimising the delay in nutrient supply could prove to be beneficial for the growth pattern of moderate to late preterm infants (Su, 2014).

While it is now known that commencing feeding with minimal delay is important, there is a lack of evidence to know what the optimal feeding strategy for moderate to late preterm infants is. Consequently, there is great variability in the practice and guidelines between different Newborn Intensive Care Units (NICU) for the feeding of preterm infants (Cormack, Sinn, Lui, & Tudehope, 2013; McCormick, Escobar, Zheng, & Richardson, 2006). Currently, at the Auckland City Hospital (ACH) NICU, moderate-late preterm infants are fed with one of the following strategies for the first 1-5 days after birth: breast-milk; term or preterm infant formula; parenteral nutrition, or intravenous dextrose. The method of feeding depends on the maturity of the infant, breast-milk supply, and maternal and medical preferences. Ultimately, the aim for these infants is for them to be exclusively breast-fed. However, when breast-milk supply is inadequate, decisions need to be made about whether to supplement the infant with formula until breast-milk supply meets demand or to provide intravenous fluids. These decisions are often made through a combination of medical opinion and parental wishes, as some parents have very strong views about their child receiving formula. If, however, breast-milk supply lags behind demand for a significant period of time, medical staff may become increasingly uncomfortable about medicalising an otherwise well infant by providing intravenous nutrition when an enteral alternative exists. The lack of any studies investigating which approach may be best means that decisions are not evidence-based.

This observational, exploratory, study will explore the relationships between early feeding strategies and the FM and FFM of moderate-late preterm infants and will enable comparisons to determine if one or more of the strategies is associated with a favourable body

composition. It will also be the first study in New Zealand to utilise ADP to measure the FM and FFM of term and moderate-late preterm infants. The results will inform future studies on the direction of research regarding infant body composition and early feeding practises of moderate-late preterm infants as well as practical considerations to be taken into account for conducting research using ADP at the ACH NICU

1.2 Aims, Objectives, and Hypotheses

Aims:

1. To measure the % fat mass and fat free mass of moderate to late preterm infants and term infants after birth at Auckland City Hospital.
2. To explore the relationship between feeding strategies currently used within Auckland City Hospital on the acquisition of fat and fat free mass in moderate to late preterm infants at after birth.

Objectives:

1. To describe the fat mass and fat free mass of moderate to late preterm infants and term infants after birth.
2. To compare the % fat mass and fat free mass of moderate to late preterm infants measured at ≥ 36 weeks' postmenstrual age with that of healthy term infants after birth.
3. To measure the change in % fat mass and fat free mass in moderate to late preterm infants during hospital admission.
4. To compare the % fat mass and fat free mass of moderate to late preterm infants after birth according to the feeding strategy received in the first 5 days after birth.

Hypotheses:

1. Moderate to late preterm infants will have differing % fat mass and fat free mass at ≥ 36 weeks' postmenstrual age compared to healthy term infants at birth.
2. Moderate to late preterm infants will experience an increase in % fat mass during their hospital admission.
3. Moderate to late preterm infants will have differing fat mass and fat free mass after birth depending on the degree of prematurity and mode of feeding.

1.3 Structure of Thesis

The first chapter of this thesis has highlighted the importance of the study area and puts it into context. Chapter 2 contains an extensive review of the literature regarding the long-term health outcomes of preterm infants, growth and body composition of term and preterm infants, and feeding of moderate-late preterm infants. A detailed explanation of the study design and methods are found in Chapter 3. The results of the study are presented in Chapter 4. This is followed by a discussion of these findings in Chapter 5, including strengths and weaknesses of the study along with conclusions and recommendations for future research.

1.4 Researchers' Contributions

Table 1.1: Researchers' Contributions

Louise van Dorp	Prepared ethics applications, developed participant information sheet and data collection forms, recruited the majority of participants, performed the majority of measurements, collected all the medical and feeding data, performed statistical analysis and interpreted the results, main author of the thesis.
Dr Cath Conlon	Academic supervisor, consulted on conceptualisation of the study, designed research, revised ethics applications, assisted with recruitment of participants, assisted with measurements, revised and approved the thesis.
Professor Frank Bloomfield	Conceptualised the study, principal investigator, designed research, revised and submitted ethics applications, advised on statistical analysis of results, revised thesis chapters.
Barbara Cormack	Consulted on conceptualisation of the study, contributed to designing research, study advisor.
Owen Mugridge	Assisted with recruitment and measurement of participants.
Sabine Huth	Research nurse, assisted with recruitment and measurement of preterm infants.

Chapter 2: Literature Review

The following electronic databases were used to identify the studies that are included in this literature review: PubMed; Google Scholar, and Web of Science. The publication dates of the studies ranged from 1951 to 2015. Searches were done using the key terms: preterm infant, moderate preterm infant; late preterm infant; term infant; obesity; cardiovascular disease; diabetes; body composition; fat mass; fat free mass; air displacement plethysmography; growth; development; feeding; feeding difficulties; breast-milk; infant formula; enteral nutrition; parenteral nutrition; New Zealand.

2.1 Preterm Birth

2.1.1 Definitions and Classifications

A birth is classed as preterm if it occurs before 37 weeks' gestation (Ministry of Health, 2015a; World Health Organisation, 2012). This is further broken down into three sub-categories: extremely preterm (birth before 28 weeks' gestation); very preterm (birth between 28 and 31^{+6} weeks' gestation), and moderate to late preterm (birth between 32 and 36^{+6} weeks' gestation) (World Health Organisation, 2012).

As well as gestational age, infants can be categorised according to their birthweight. These categories are: low birthweight (LBW; < 2500 g at birth): very low birthweight (VLBW; < 1500 g at birth), and extremely low birthweight (ELBW; < 1000 g at birth) (World Health Organisation, 2011). Birthweight can be put into context of the infant's gestational age by classifying their weight as either appropriate for gestational age (AGA), large for gestational age (LGA), and small for gestational age (SGA). Infants will be classed as AGA if their birthweight lies between the 10th and 90th percentiles on a standardised growth curve, LGA if birthweight is above the 90th percentile, and SGA if birthweight is below the 10th percentile (Battaglia & Lubchenco, 1967). However, the infant's percentile will depend upon the growth curve on which birthweight has been plotted.

2.1.2 Rates of Preterm Birth

Globally, the rates of preterm birth are rising with approximately 15 million infants being born early every year (World Health Organisation, 2012). There are disparities between different regions of the world in the rates of preterm birth, with rates ranging from 5% - 18% of all

births. Generally, it is the lower income African countries that have the highest rates, with northern European countries having the lowest (Blencowe et al., 2012).

In 2014, 7.4% of births in New Zealand were preterm, with 1.2% being born <32 weeks' gestation and 6.2% being born from 32 to 36 weeks' gestation (Ministry of Health, 2015b). Of the infants cared for at Auckland City Hospital in 2014, 10.2% were born preterm (Auckland District Health Board, 2015a). This is higher than national rates due to the specialised facilities of the establishment and reflects clinical decision-making on the location of birth for women in preterm labour (Ministry of Health, 2015a). When births at ACH are sub-categorised, 2.7% were born <32 weeks' gestation and a considerable 7.5% were born from 32 to 36 weeks' gestation (Auckland District Health Board, 2015a). Throughout New Zealand, rates of late preterm births are thought to be increasing (National Maternity Monitoring Group, 2014). This is thought to be due to an increased number of elective early caesarean births (National Maternity Monitoring Group, 2014).

2.1.3 Causes of Preterm Birth

Preterm births are either spontaneous or medically induced. While the mechanisms which cause spontaneous preterm birth are not all known, there are many identified risk factors (Goldenberg, Culhane, Iams, & Romero, 2008). These include: previous preterm birth; short intervals between successive pregnancies; low maternal body mass index (BMI) during pregnancy; maternal nutrient deficiencies; intrauterine infection; a multiple pregnancy; psychological or social stress; smoking; young maternal age; advanced maternal age; pre-eclampsia, and genetic factors (Blencowe et al., 2012; Goldenberg et al., 2008; Muglia & Katz, 2010).

Medical induction of labour is the cause for 30 - 35% of preterm births (Goldenberg et al., 2008) and is performed when either the mother or fetus is at risk. Indications to induce labour before 37 weeks' gestation include: intrauterine growth restriction (IGUR); fetal distress; fetal anomaly; multiple pregnancies; pre-eclampsia, and ante partum bleeding (Ananth & Vintzileos, 2006; Mozurkewich, Chilimigras, Koepke, Keeton, & King, 2009).

2.1.4 Complications and Consequences of Preterm Birth

The third trimester (28 - 40 week' gestation) of pregnancy provides an important time for fetal growth and development. Consequently, an early birth results in the infant having underdeveloped organ systems which can cause many health complications (Behrman & Butler, 2007). Well recognised acute problems for preterm infants include respiratory distress

syndrome, chronic lung disease, apnoea, necrotising enterocolitis, gastro-oesophageal reflux, hypotension, bradycardia, anaemia, jaundice and seizures (Behrman & Butler, 2007; Escobar et al., 2006; Galson, 2008; Raju, 2006; Saigal & Doyle, 2008). Additionally, they are more susceptible to infections, have feeding difficulties, and can have trouble with hearing and sight (Behrman & Butler, 2007).

A long-term consequence of preterm birth is neurodevelopmental impairment. This can result in numerous disabilities including cerebral palsy, attention deficit-hyperactivity disorder, impaired cognitive ability, and behavioural problems (Behrman & Butler, 2007; Stephens & Vohr, 2009). Preterm infants are also known to have a higher risk of adverse cardiometabolic outcomes in later life such as obesity, diabetes, and high blood pressure (Crump et al., 2011a, 2011b; Lucas, 2005; Parkinson et al., 2013; Sipola-Leppanen et al., 2015). Developmental plasticity or programming refers to physiological changes in response to environmental factors at critical times of development (Langley-Evans, 2006; McMillen & Robinson, 2005). It has been hypothesised that these adverse cardiometabolic outcomes experienced by preterm infants later in life are a result of developmental programming in response to conditions experienced early in life (Bayman, Drake, & Piyasena, 2014).

The extent of these health consequences is affected by the degree of prematurity: the earlier the birth, the more complications the infant is likely to experience (Galson, 2008). Despite this, moderate-late preterm births should not be over-looked. Due to the significantly higher proportion of infants born moderately to late preterm than extremely or very preterm, this group has a much greater contribution to the health care burden (Boyle et al., 2012). When compared to full term infants, moderate-late preterm infants have higher rates of mortality and morbidity and are more at risk of neonatal complications such as feeding difficulties, hypoglycaemia, respiratory problems, and problems with temperature regulation than full term infants (Boyle & Boyle, 2013; Kramer et al., 2000; Shapiro-Mendoza et al., 2006).

2.2 Long-Term Consequences

2.2.1 Developmental Origins of Health and Disease

There is growing evidence that the environment and conditions experienced early in life can have lifelong consequences. Links have been drawn between nutrition and growth from as early as the embryonic stage and the risk of cardiovascular and metabolic diseases as an adult (Barker, 2004; Law et al., 2002; Phillips, Barker, Hales, Hirst, & Osmond, 1994; Stein et al., 1996). The developmental model was first hypothesised by Barker when epidemiological

studies revealed that geographical areas which had high rates of death from coronary heart disease in adults also had high past infant mortality rates (Barker & Osmond, 1986). It was hypothesised that the infant mortality rates represented poor living standards of the geographical area and therefore adverse conditions experienced *in utero* (Barker, 2007). This research was followed by investigating, more specifically, the relationship between birthweight and the cause of death in men born between 1911 and 1930 in selected parts of England. The findings showed that the men with the lowest birthweights had the highest rates of death from ischaemic heart disease (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). Since then, many studies have demonstrated similar trends, with poor living standards during infancy and childhood, slow growth *in utero* and slow growth during infancy followed by accelerated catch-up growth all being linked to increased risk of coronary heart disease and stroke (Barker, 2007; Barker, Osmond, Forsen, Kajantie, & Eriksson, 2005; Eriksson, Forsen, Tuomilehto, Osmond, & Barker, 2000; Martyn, Barker, & Osmond, 1996; Osmond, Kajantie, Forsen, Eriksson, & Barker, 2007).

This evidence sheds light onto the aetiology of coronary heart disease and related conditions, and provides rationale for research relating to early growth patterns and how they can be optimised.

2.2.2 Long-Term Health Outcomes for Preterm Infants

There is epidemiological evidence that preterm birth is associated with adverse cardiometabolic outcomes such as obesity, decreased insulin sensitivity, diabetes, cardiovascular disease, and hypertension in adulthood (Bayman et al., 2014).

2.2.2.1 Obesity and Adiposity

There is evidence that obesity in adulthood, a key feature of metabolic syndrome, is associated with preterm birth (Sipola-Leppanen et al., 2015). A cohort study determined that preterm birth was associated with twice the risk of becoming obese as an adult compared with term birth (Sipola-Leppanen et al., 2015). Mathai et al. (2013) found that, when assessed at the age of 30, adults who were born preterm had higher adiposity than those born at term, with this difference being greater in men. The distribution of body fat showed that the difference was largely due to increased intra-abdominal fat in the preterm group, a body shape that is characteristic of metabolic syndrome (Mathai et al., 2013). However, the meta-analysis conducted by Parkinson et al. (2013) does not support these findings. They report that being born preterm is associated with being shorter, lighter and having a lower BMI up until

adolescence, with no differences in BMI during adulthood (Parkinson et al., 2013). As pointed out by the authors of the meta-analysis, there was substantial heterogeneity regarding the quality and recruitment methods of the studies included, which could have affected the results (Parkinson et al., 2013).

2.2.2.2 Insulin Sensitivity and Diabetes

A recent systematic review found there is an association between preterm birth and insulin resistance in childhood (Tinnion, Gillone, Cheetham, & Embleton, 2014). Hofman et al. (2004) found that preterm born children aged 4- 10 years had lower insulin sensitivity compared to term-born children, regardless of whether they were AGA or SGA. The effect of postnatal weight gain and nutrient intake has been investigated and results indicate that higher nutrient intake and faster postnatal weight gain increase the chances of preterm born children having lower insulin sensitivity (Regan, Cutfield, Jefferies, Robinson, & Hofman, 2006; Singhal, Fewtrell, Cole, & Lucas, 2003). A large study that measured random insulin concentrations in young children aged 0.5-6.5 years found an inverse association between gestational age and insulin concentrations, demonstrating that this difference begins in early childhood (Wang, Divall, Radovick, & et al., 2014).

While there is evidence that these associations are also seen in adults who were born preterm, the research is conflicting and it is apparent that other factors also contribute (Tinnion et al., 2014). Epidemiological evidence has shown that young adults who were born preterm have higher rates of use of diabetes medications than those born at term (Crump et al., 2011a). As the study was using medication prescriptions as the outcome, the results do not distinguish between type 1 and type 2 diabetes; however, the authors suggest that based on the types of medications prescribed, it is likely that type 1 diabetes was more prevalent (Crump et al., 2011a). Dalziel, Parag, Rodgers, and Harding (2007) found that insulin resistance, as measured by insulin response to a glucose load, was associated with both lower gestational age and preterm birth.

2.2.2.3 Cardiovascular Disease and Lipid Profile

Suboptimal vascular endothelial function is a marker for the development of cardiovascular disease (CVD) (Parkinson et al., 2013). Evidence for the association between endothelial dysfunction and preterm birth is equivocal with the meta-analysis by Parkinson et al. (2013) concluding that there is not a significant association. A study that measured the aortic dimensions of 15 year old adolescents who were born very preterm found that they had

significant narrowing of the aorta compared to term-born counterparts (Edstedt Bonamy, Bengtsson, Nagy, De Keyzer, & Norman, 2008). However, other research suggests endothelial function is only compromised in those born preterm that experienced IUGR (Cheung, Wong, Lam, & Tsoi, 2004; Singhal, Kattenhorn, Cole, Deanfield, & Lucas, 2001; Skilton et al., 2011).

Another key risk factor for CVD is dyslipidaemia (M. J. J. Finken et al., 2006). A New Zealand study found that preterm-born adults had lower circulating concentrations of the favourable high density lipoprotein (HDL) cholesterol and a higher ratio of total cholesterol to HDL-cholesterol than term-born adults (Mathai et al., 2013). Sipola-Leppanen et al. (2015) found similar results, with preterm females having lower HDL cholesterol and apolipoprotein-A1 concentrations during early adulthood. Additionally, when preterm infants were followed up by Lewandowski et al. (2012) between the ages of 20 and 39 they were found to have higher concentrations of low density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides. These results have not been replicated in other studies, with some finding no difference in the lipid profiles of adults born at different gestational ages (M. J. Finken et al., 2006; Hovi et al., 2007).

2.2.2.4 Hypertension

Hypertension is the outcome with the most evidence for the association with preterm birth (Bayman et al., 2014). A meta-analysis of 27 studies that measured markers of metabolic syndrome in adults who were born preterm, found that those born preterm had higher rates of high blood pressure than those born at term (Parkinson et al., 2013). The mean difference that was found was 4.2 mmHg for diastolic blood pressure and 3.1 mmHg for systolic blood pressure, with this difference being greater in females than males (Parkinson et al., 2013). While these are seemingly small differences, it is known that a 2 mmHg reduction of blood pressure can reduce risk for myocardial infarction and stroke by 15% (Bayman et al., 2014; Cook, Cohen, Hebert, Taylor, & Hennekens, 1995; Sipola-Leppanen et al., 2015).

A large Swedish study used data on the use of anti-hypertensive medication amongst adults aged between 25 and 37 years. The results showed that as gestational age decreased, the percentage of the population using anti-hypertensive medications increased (Crump et al., 2011b). Sipola-Leppanen et al. (2015) found from a cohort study of 376 participants of varying prematurity, that those who were born early preterm were up to three times more likely to have hypertension than the control group. However, those born late preterm did not have statistically different rates of hypertension to those born at term (Sipola-Leppanen et al., 2015).

2.3 Infant Growth

The first two years after birth is a period of rapid growth, and monitoring this growth is an important aspect of assessing health status (de Onis et al., 2012; Ruffin, 2009).

2.3.1 Postnatal Growth Patterns of Term Infants

The typical growth pattern of an infant includes a period of weight loss after birth, largely due to fluid loss (Wright & Parkinson, 2004). Weight loss of up to 10% is considered normal and most infants will begin to regain this between three and five days after birth, and will reach their birthweight again within two weeks after birth (Shaw & McCarthy, 2014; Wright & Parkinson, 2004). The expected weight gain for a full term infant during the first three months after birth is 201 g/week for females and 240 g/week for males (Shaw & McCarthy, 2014). During their first year, infants are expected to grow 24 - 25 cm in length and their head circumference is expected to grow 10.5 cm (Shaw & McCarthy, 2014).

2.3.2 Postnatal Growth Patterns of Preterm Infants

Preterm infants exhibit a similar postnatal growth pattern to term infants and also experience early weight loss (Preedy, 2011). The initial percentage weight loss is often greater in preterm infants, with a weight loss of 15% being common (Preedy, 2011). The desired growth rate is to gain 15 – 20 g/kg/day until they reach a corrected age of 40 weeks' gestation (Cole, Statnikov, Santhakumaran, Pan, & Modi, 2011). The typical growth rate will subsequently decrease to 200 g per week (Cole et al., 2011).

The aim for growth in this early postnatal period is that it would meet that of a healthy fetus *in utero* (Preedy, 2011). However, despite advances in medical care, preterm infants still experience postnatal growth restriction to varying extents (Embleton, Pang, & Cooke, 2001). The period of postnatal growth restriction is followed by a period of accelerated growth (Ong & Loos, 2006). Studies have found that rapid weight gain during the first two years after birth is associated with a higher risk of obesity later in life (Baird et al., 2005; Monteiro & Victora, 2005; Ong & Loos, 2006).However, accelerated weight gain is also known to benefit the infants in other aspects. Rapid weight gain from birth to term-corrected age and from term until four months corrected age have both been associated with favourable neurodevelopmental outcomes during childhood (Belfort et al., 2011). So while rapid growth in preterm infants is associated with improved cognitive outcomes, it is also associated with adverse metabolic outcomes. This poses the challenge to optimise the growth of preterm infants in a way that

will not compromise either short-term health, cognitive development, or long-term metabolic health.

2.3.3 Anthropometric Measurements

Key anthropometric measurements routinely used to assess growth of infants in a clinical setting are weight, length and head circumference (Moyer-Mileur, 2007). These measurements are important for monitoring the nutritional adequacy of an infant's diet as well as being useful for calculating nutritional requirements (Shaw & McCarthy, 2014).

Body weight has long been used as a measure of neonatal health and to assess the adequacy of an infant's diet (World Health Organisation, 1995). Birthweight is an important measure of fetal growth (World Health Organisation, 1995). Weight is relatively simple to measure in a healthy infant; however, consideration needs to be taken for infants who are reliant on un-removable medical equipment such as ventilators for preterm or unwell infants (Roche & Sun, 2005). As weight is a measurement of the total body mass, it is affected by daily fluid fluctuations and is best measured at the same time of day to minimise this variance (Moyer-Mileur, 2007).

Crown to heel length is another growth parameter that is measured at birth. It is more reflective of lean body mass as it is not affected by fluid fluctuations (Roche & Sun, 2005). The application of length is useful for the assessment of long-term growth (Moyer-Mileur, 2007). The most reliable method for measuring infant length is to use a neonatometer, which requires two trained persons to hold and stretch the infant out (Davies & Holding, 1972; Moyer-Mileur, 2007). This measurement is more difficult than weight and requires the infant to be still. It is also harder to obtain accurate measures due to differences in posture and muscle tone, and it is therefore necessary that standardised procedures are followed (Doull, McCaughey, Bailey, & Betts, 1995; World Health Organisation, 1995)

Head circumference is a useful measurement of the overall growth of an infant (Moyer-Mileur, 2007). This measure is important as it is indicative of brain growth (King & Tavener, 2014; World Health Organisation, 1995). Waist circumference is commonly used as a measure of visceral fat in adults and children (Fredriks, van Buuren, Fekkes, Verloove-Vanhorick, & Wit, 2005). Waist-length ratio is also used and has been found to be have higher sensitivity in evaluating components of metabolic syndrome (Hsieh & Muto, 2005). These measures are less commonly used for measuring the growth of infants; however, recent studies have suggested

that waist-length ratio can be used as a simple measure of adiposity for infants (Holston et al., 2013; Stokes et al., 2012).

2.3.4 Growth Charts

As mentioned previously, the birthweights of infants can be classified as either SGA, AGA, or LGA. However, the percentile that an infant's weight is on and therefore whether it is considered appropriate for gestational age depends on which growth chart is used. There have been several different growth charts developed for both term and preterm infants (Fenton & Kim, 2013; Kuczmarski et al., 2000; Ogden et al., 2002; Olsen, Groveman, Lawson, Clark, & Zemel, 2010; Villar et al., 2013).

2.4 Measuring Infant Body Composition

The composition of the human body can be classified at different levels: atomic; molecular; cellular, or tissue (Wang, Pierson, & Heymsfield, 1992). Of most relevance to human health and chronic disease are the molecular and tissue categorisations. On a molecular level the body is broken down to lipids, water, proteins, carbohydrate, and minerals. When divided into tissues the categories are adipose tissue, skeletal muscle, skeleton and visceral organs and residual (Heymsfield, Wang, Baumgartner, & Ross, 1997). The method of measuring body composition determines what level the body components are examined at (Heymsfield et al., 1997). A common model used in the assessment of body composition is to break it down to two compartments: fat mass (FM) and fat free mass (FFM), with FFM containing water, proteins, glycogen, and minerals.

The only direct measure of body composition is cadaver analysis; therefore, any methods used for *in vivo* measurement must be indirect (Wells & Fewtrell, 2006). Development in technology over the past century has resulted in there being numerous ways to measure fat mass and fat free mass, with each method varying in accuracy, difficulty, and cost. However, each method, being indirect, involves some assumptions. Because preterm infants are a heterogeneous population that experience rapid growth, assumptions relating to body components can limit the accuracy of results and make body composition assessment in this group difficult (Koo, 2000).

2.4.1 Multi-Component Models

A gold standard for the measurement of body composition is one that minimises assumptions. Multi-component models reduce assumptions by obtaining measurements of more than two

body components (Demerath & Fields, 2014). To measure FM using a two component model, such as densitometry, FM is determined with the assumption that the density of FFM is constant and does not vary between individuals (Fields, Goran, & McCrory, 2002; Wells et al., 1999). A multi-component model employs different methods of body composition analysis to produce values for the constituents of FFM (Wells et al., 1999). In doing this, the values are individualised and do not have to be assumed for the calculation for FM percentage (Wells et al., 1999). While the chance of measurement error increases, the overall error is decreased due to reduced assumptions (Demerath & Fields, 2014).

Multi-component models have a high participant burden due to the time consuming nature requiring several measurement and they are, therefore, not always practical for an infant population, especially when serial measurements are required (Demerath & Fields, 2014). The best use of this process is for the validation of other techniques that are more practical for research and for the development of reference values for body components (Butte, Hopkinson, Wong, Smith, & Ellis, 2000; Demerath & Fields, 2014; Fomon & Nelson, 2002).

2.4.2 Isotope Dilution

A method used to determine FFM is to measure the amount of total body water (TBW), which can be done using nonradioactive isotopically labelled water. This water is ingested by the infant and given time (two-four hours) to equilibrate with body water (Demerath & Fields, 2014; Salazar, Infante, & Vio, 1994). Samples of urine, saliva, or blood are then taken and are analysed using either spectrophotometry or spectrometry (Wells & Fewtrell, 2006). Total body weight estimation is calculated by dividing the amount of labelled water given to the infant by its concentration in the analysed sample (Demerath & Fields, 2014).

Benefits for using isotope dilution to measure FFM are that it is safe, easily conducted in the field, and it has been shown to produce precise and accurate results (Demerath & Fields, 2014). However, there are limitations for using this method to measure FFM in infants. There is potential for spillage of the solution during administration with infant subjects, which can make it hard to know the actual amount given, a value that is required for the final calculation (Nielsen, Wells, Slater, Fewtrell, & Reilly, 2011). Roggero, Giannì, Amato, et al. (2012) highlight that isotope dilution is not practical for every day clinical use in preterm infants due to difficulties with solution administration and sample collection. The equation also assumes constant hydration of FFM; however, it is known that this is not the case during disease states (Wells & Fewtrell, 2006). Hydration levels also decrease with age, especially during infancy

(Demerath & Fields, 2014). It is suggested by Demerath and Fields (2014) that for these reasons this may not be the most appropriate method to measure during infancy.

2.4.3 Bioelectrical Impedance Analysis (BIA)

Bioelectrical impedance analysis is a method used to predict body composition with the use of a weak electrical current passing through the body from electrodes placed on either hands or wrists and feet or ankles (Wells & Fewtrell, 2006). The amount of resistance encountered by the current indicates the amount of TBW (Kyle, Earthman, Pichard, & Coss-Bu, 2015). Using age and sex specific predictive equations, and adjusting for height, FFM is then calculated. It has been found that in preterm infants BIA has little accuracy at predicting FFM and that basic anthropometry measures such as weight are more useful (Dung, Fusch, Armbrust, Jochum, & Fusch, 2007).

2.4.4 Dual-Energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) uses low dose ionising radiation to produce multiple two dimensional images that form three dimensional images (Wells & Fewtrell, 2006). Originally developed to measure bone density, this method is also able to calculate values for FM and FFM (Wells & Fewtrell, 2006). Images produced by DXA show regional distribution of body components and distinguish muscle from FFM which many methods are unable determine (Demerath & Fields, 2014). While some studies have found DXA to be a valid method for assessing the FM and FFM of infants, it is also known to over-predict FM in low birth weight infants (Fields, Demerath, Pietrobelli, & Chandler-Laney, 2012; Lapillonne et al., 1997). Despite radiation levels being low and at safe levels, the exposure does impact upon the possibility of conducting serial measures (Demerath & Fields, 2014). The DXA measurement requires subjects to remain still, and non-compliance with this is common amongst infants (Demerath & Fields, 2014).

2.4.5 Magnetic Resonance Imaging (MRI)

Another method to measure regional body composition distribution is MRI. Images are produced by pulses of radio frequencies passing through the body. From the images, the volumes of tissues and organs are determined and with the application of known density values mass can then be calculated. This method has some limitations for reporting FM as the value does not include lipids that are not contained in adipose and the amount of fat in adipose needs to be assumed (Wells & Fewtrell, 2006). Unlike DXA, MRI does not cause radiation exposure, resulting in greater acceptability amongst participants. However, there is a

requirement for subjects to remain still which is often hard to achieve with an infant population. Additionally, the images can be time consuming to analyse and require trained researchers (Demerath & Fields, 2014).

2.4.6 Skinfold Thickness

Measuring skinfold thickness is a quick, non-invasive method that can either be used to indicate regional fatness, or to predict total body fatness with the use of equations (Wells & Fewtrell, 2006). This measurement involves the use of callipers to measure the thickness of subcutaneous fat at different regions of the body (biceps, triceps, subscapular, supra-iliac, abdomen, thighs, and calves) (Durnin & Rahaman, 1967). While the ease and low cost of this method is appealing, it has been found that there are limitations that question its reliability and usefulness. Due to the narrow range of the measurements in an infant population, this method requires accurate and precise readings; however, it has been found that there is high inter-examiner variance when taking the measurements (Branson et al., 1982). More variability can arise from the use of different predictive equations which have been shown to produce varying results (Reilly, Wilson, & Durnin, 1995). Another limitation to using this method is that it works on the assumption that the abundance of subcutaneous fat is proportional to the abundance of visceral fat, which in many cases it is not. Skin fold thickness cannot give any indication to lean body mass which limits results to only being descriptive of body fatness (Wells & Fewtrell, 2006). Additionally, skinfold thickness can be difficult to measure in infancy, particularly when there are very small amounts of subcutaneous fat, as seen in preterm infants (Koo, 2000).

2.4.7 Air Displacement Plethysmography

The PeaPod Infant Body Composition System utilises the method of air displacement plethysmography (ADP) to measure infant body composition. This non-invasive method uses the principals of densitometry to obtain values of FM and FFM (Urlando, Dempster, & Aitkens, 2003).

2.4.7.1 Description of System and Principles

The PeaPod employs laws describing the relationship between pressure and volume to obtain the volume of the infant's body. The air pressure inside the test chamber is measured twice, once before the infant is measured and a second time with the infant inside. Applying the pressure to Poisson's Law, the volume of the chamber is able to be derived. Poisson's Law describes the relationship between pressure and volume under adiabatic conditions. This

refers to conditions when the temperature of the air does not remain constant in response to changing volume. The equation is expressed as $\frac{P_1}{P_2} = \left(\frac{V_2}{V_1}\right)^{\gamma}$ where P_1 and V_1 refer to the pressure and volume of the test chamber when it is empty, P_2 and V_2 refer to the pressure and volume measured with the infant inside, and γ is a constant. The difference in volume between the two measurements is attributed to the volume of the infant (Urlando et al., 2003). There are two additional factors that need to be taken into consideration when calculating body volume using ADP: the volume of air in contact with the surface of the body, and the volume of air in the infant's lungs. The air in close proximity to the infant's body and in the lungs is isothermal (constant temperature), which is 40% more compressible than air in adiabatic conditions, causing the volume of the isothermal air to be 40% overestimated. To control for this, the surface area artefact (SAA) has been developed (Urlando et al., 2003). This is an equation that uses the infant's length and weight to calculate the volume of air surrounding the body. Additionally, thoracic gas volume is estimated, also using the infant's length and weight with reference tidal volumes of infants from previous studies (Urlando et al., 2003). The final volume is calculated by subtracting the SAA and adding 40% of the thoracic gas volume to the raw volume.

Once the volume is known, the infant's density is calculated using the formula:

$$Density = \frac{Mass}{Volume}$$

Known densities of FM and FFM are applied to equations to work out the % FM (Urlando et al., 2003). The generic formula for calculating % FM is:

$$\%\, fat = \left[\frac{D_F D_{FFM}}{D_B(D_{FFM} - D_F)} - \frac{D_F}{D_{FFM} - D_F}\right] * 100\%$$

where D_F is the density of fat, D_{FFM} is the density of fat free mass and D_B is the body density (Sainz & Urlando, 2003). All calculations are performed systematically by the computer programme within the PeaPod.

The density of fat is constant throughout life; however, the density of FFM changes with age and differs between sexes. The value used for the density of fat is 0.9007 g/mL and age- and sex-specific values for the density of FFM are used (Butte et al., 2000; Fomon, Haschke, Ziegler, & Nelson, 1982). Water fluctuations in the first six days after birth in full term infants have been measured by Rodriguez et al. (2000) using BIA, and these values are included in calculations used by the PeaPod (COSMED, 2004).

2.4.7.2 Evaluation of ADP

ADP has been evaluated and validated against other assessment methods and has been found to be a reliable and accurate method to measure FM and FFM. Sainz and Urlando (2003) compared ADP results to the cadaver analysis of bovine tissue phantoms and found high precision and accuracy for calculating % FM from ADP. Similar conclusions were drawn by Ellis et al. (2007) when the % FM of healthy full term infants was measured in the PeaPod and using a four compartment model. The results report an insignificant mean difference of 0.6% FM between the two models and a mean difference of only 0.4% FM between repeated measures in the PeaPod. The PeaPod has also been evaluated for specific use in preterm infants. A study compared the % FM of preterm and term infants produced from ADP to results from isotope dilution and found that there was little difference between the two methods (Roggero, Giannì, Amato, et al., 2012). Findings from another validation study suggest that infant behaviour and activity levels during the measurement do not affect the results (Ma et al., 2004). The study found no significant differences between the infants being quiet and alert, awake and active, or crying intensely. Urinating during the measurement also did not affect results (Ma et al., 2004).

However, using ADP does have limitations. Infants are not able to be measured until they no longer require respiratory support and intravenous lines. As these are common medical interventions required for preterm infants in the period after birth, measurements may be delayed, thereby preventing assessment at birth. The PeaPod has limited portability. While it is able to be moved between sites, it is not easily done and requires re-calibration each time after movement (COSMED, 2004).There is also a limitation on the size of the infants that can be measured, with the maximum weight being 8 kg (COSMED, 2004). This means that serial measures cannot be conducted after the infant reaches 8 kg. Referring to the World Health Organisation growth charts, 8 kg is the 50th percentile for males at six months old and for females at eight months old (Ogden et al., 2002). Using the Paediatric Option, children from two years of age can be measured using ADP in the BOD POD, an adult ADP system, but this leaves the period from the age they reach eight kg to two years where measurements using ADP cannot be done (Demerath & Fields, 2014; Fields & Allison, 2012). This limits the use of ADP when the aim is to assess FM and FFM changes longitudinally.

Like all two compartment models, ADP works on the assumption that the density and proportions of the components of FFM do not differ between individuals (Fields et al., 2002). Other assumptions including the hydration levels of FFM and the thoracic gas volumes come

from values produced in studies on full term infants, which could limit the reliability of the results in preterm infants. However despite this, Roggero, Giannì, Amato, et al. (2012) have found that ADP produced reliable and accurate results for preterm infants.

Because of the non-invasive nature of ADP and the low requirements of the infants, studies have concluded that it is a suitable method of assessing body composition both in the clinical and research setting (Ellis et al., 2007; Ma et al., 2004; Roggero, Giannì, Amato, et al., 2012).

2.5 Fat Mass and Fat Free Mass of Infants

The rise in new technology and methods to measure infant body composition is accompanied with a growth in the research regarding different aspects of infant body composition. Several studies have endeavoured to establish reference values for body fat percentage of both full term and preterm infants (Butte et al., 2000; Fields et al., 2011; Fomon & Nelson, 2002; Hawkes et al., 2011). Early studies used chemical analysis of stillborn infants; however, it is unknown whether the values produced would be representative of healthy infant (Ellis, Shypailo, & Schanler, 1994; Widdowson & Spray, 1951; Ziegler, O'Donnell, Nelson, & Fomon, 1976). Additionally, TBW is reduced during the time between birth and the analysis of cadavers, thereby reducing the accuracy of the results (Fomon & Nelson, 2002).

Fomon and Nelson (2002) and Butte et al. (2000) have produced the most recognised reference dataset using multi component models on healthy term infants for the first year after birth. Current research on infant body composition has shown high inter-population variability and there is therefore no universal reference data.

(Wells, 2014). While this is the case, the practical nature of ADP has resulted in more research and has therefore allowed the growth of knowledge in the area and there is now a better picture of the normative values and the factors affecting FM and FFM (Wells, 2014).

2.5.1 Fat Mass and Fat Free Mass of Full Term Infants Using ADP

Table 2.1 summarises studies that have measured the % FM, FM and FFM of full term infants at birth using ADP. From the present literature review, values for % FM ranged from 7.3-13.4% for males and 7.8-13.2% for females. The results are somewhat equivocal and appear to be affected by a number of factors including sex, ethnicity, maternal BMI, gestational age, and age at time of measurement.

The lowest values of % FM, which come from a cohort of Ethiopian infants, are 7.3% and 7.8% for males and females respectively (Andersen et al., 2013). In an earlier study, Andersen et al.

(2011) suggest that this difference may is due to the lower birthweights of infants in low-income countries, causing the findings to have limited applicability to populations in higher income countries. The rest of the studies were conducted in high income countries in Europe, America, and Australia and therefore have more relevance for the present study.

Hawkes et al. (2011) measured a large sample of 743 infants and stratified the results based on gestational age into the following groups: infants born between 36^{+0} and 37^{+6} weeks' gestation; infants born between 38^{+0} and 39^{+6} weeks' gestation, and infants born between 40^{+0} and 41^{+6} weeks' gestation. The first of these age groups (36^{+0}-37^{+6}) includes both term and preterm infants and therefore cannot be used to describe the body composition of term infants. The results do, however, demonstrate a trend that % FM increases with gestational age, with the % FM of the groups being significantly different and multiple regression analysis showing a significant association between % FM and gestational age. The population in this study, while large, was a relatively homogenous group of Irish infants from low risk, primiparous pregnancies. This limits the applicability of the results to other, more ethnically diverse populations. Carberry, Colditz, and Lingwood (2010) also found a positive correlation between gestational age and % FM in full term infants; however, it was a relatively small study (n = 77) with little ethnic diversity, having 90% Caucasian participants.

As well as gestational age, the postnatal age of the infant at the time of measurement appears to affect the % FM (Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010). An Italian study that used both cross sectional and longitudinal study designs has demonstrated the changes in % FM in the first four – five days after birth. In the cross sectional study (n = 262) they found that the % FM of infants measured on the first day was significantly higher than the % FM of infants measured on the third day. The longitudinal study (n = 28) showed that the % FM of infants decreased significantly between the first and fourth day after birth. The % FM on the fifth day after birth was not significantly different to the % FM on the first day, suggesting that the loss in % FM is regained by the fifth day. While the longitudinal design requires fewer participants, the sample was still relatively small and demographic results are not reported (Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010).

It is known that throughout the lifespan, males have more FFM and lower % FM than females (Geer & Shen, 2009). There is some evidence to suggest that this difference is present throughout infancy (Hawkes et al., 2011; Simon et al., 2013). While all of the studies reviewed reported that female infants had a higher % FM than males at birth this difference was only statistically significant in two (Hawkes et al., 2011; Simon et al., 2013). Other studies have

found that body composition does not differ until later on in infancy. Carberry et al. (2010) found that the difference in % FM between males and females did not become significant until 4.5 months of age.

Maternal BMI and weight gain during pregnancy have been shown to be factors contributing to the amount of fat that newborn infants have, both having a positive relationship with % FM (Hawkes et al., 2011; Starling et al., 2015). A large American study (n = 856) found that both maternal BMI and gestational weight gain had positive, independent relationships with infant % FM at birth (Starling et al., 2015). While the study sample is multi-ethnic and applicable to the American population, it is not as diverse as the population in New Zealand. Hawkes et al. (2011) found that maternal BMI at 16 weeks' gestation was positively correlated with % FM at birth.

Table 2.1: Studies that have Used ADP to Determine % FM of Full Term Infants at Birth

Author(s)	Participants	Time of measurement (s)	% FM	FM (g)	FFM (g)	Factors affecting % FM
Hawkes et al. (2011) Ireland	*n* = 743 GA: 36^{+0}-41^{+6} weeks	Within 4 days of birth	Male: 36^{+0}-37^{+6} weeks' gestation: **8.8%** 38^{+0}-39^{+7} weeks' gestation: **9.8%** 40^{+0}-41^{+6} weeks' gestation: **10%**	Male: 36^{+0}-37^{+6} weeks' gestation: **253** 38^{+0}-39^{+7} weeks' gestation: **322** 40^{+0}-41^{+6} weeks' gestation: **358**	Male: 36^{+0}-37^{+6} weeks' gestation: **2,588** 38^{+0}-39^{+7} weeks' gestation: **2,879** 40^{+0}-41^{+6} weeks' gestation: **437**	-**Gestational age:** positive correlation with % FM -**Maternal BMI at 16 weeks' gestation:** high maternal BMI associated with higher % FM **Sex:** males had lower % FM from 38 weeks' gestation
			Female: 36^{+0}-37^{+6} weeks' gestation: **8.9%** 38^{+0}-39^{+7} weeks' gestation: **11.1%** 40^{+0}-41^{+6} weeks' gestation: **12.5%**	Female: 36^{+0}-37^{+6} weeks' gestation: **245** 38^{+0}-39^{+7} weeks' gestation: **351** 40^{+0}-41^{+6} weeks' gestation: **437**	Female: 36^{+0}-37^{+6} weeks' gestation: **2,485** 38^{+0}-39^{+7} weeks' gestation: **2,757** 40^{+0}-41^{+6} weeks' gestation: **2,962**	
Eriksson, Löf, and Forsum (2010) Sweden	*n* = 108 GA: ≥37^{+0} weeks	1 week after birth	Male: **12.5%**	Male: **484**	Male: **3,285**	
			Female: **13.4%**	Female: **484**	Female: **3,036**	
Fields et al. (2011) United States of	*n* = 35 GA: 37^{+0}-41^{+6} weeks	Measure 1 : 0-3 days old Measure 2: 1 week old	Male: Measure 1: **10.7%**	Male: Measure 1: **370**	Male: Measure 1: **3,050**	

America (USA)			Measure 2: **11.1%**	Measure 2: **390**	Measure 2: **3,050**	
			Female: Measure 1: **13.2%** Measure 2: **12.5%**	Female: Measure 1: **400** Measure 2: **420**	Female: Measure 1: **2,630** Measure 2: **2,900**	
Carberry et al. (2010) Australia	*n* = 77 GA: $\geq 37^{+0}$ weeks	Within 4 days of birth	Male: **9.4%**	Male: **341**	Male: **3,197**	**Gestational age:** Positive correlation with % FM
			Female: **10.1%**	Female: **331**	Female: **2,865**	
Andersen et al. (2013) Ethiopia	*n* = 348 GA: $\geq 37^{+0}$ weeks Birthweight: ≥ 1500g	Within 48 hr of birth	Male: **7.3 %**			
			Female: **7.8%**			
Roggero et al. (2009) Italy	*n* = 87	3 days after birth	**8.6%**			
Simon et al. (2013) France	*n* = 46	3 days after birth	Male: **9.0%**	**355**	**2,937**	**Sex:** males had significantly lower % FM than females
			Female: **11.1%**			
Olhager and Törnqvist (2014) Sweden	*n* = 29	4-8 days after birth	**8.1%**	**287**	**2,794**	
Roggero, Gianni, Orsi,	*n* = 40 GA: 37^{+0}-41^{+6}	3 days after birth	Male: **8.9%**	Male: **290**	Male: **2,910**	

Piemontese, Amato, Liotto, et al. (2010) Italy			Female: **8.7%**	Female: **260**	Female: **2,710**	
Lee et al. (2009) USA	*n* = 87	Within 48 hr of birth	**10.6%**			Positive association with fetal thigh volume measured by three-dimensional ultrasound.
Starling et al. (2015) USA	*n* = 856 GA: ≥37 weeks	Within 3 days of birth	**9.1%**	**294**	**2,851**	**Maternal BMI and gestational weight gain:** positive relationship with % FM
Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al. (2010) Italy	*n* = 262 GA: ≥37 weeks **Cross sectional sample**	Either 1,2,3, **or** 4 days after birth	Day 1: **10.5%** Day 2: **9.3%** Day 3: **8.6%** Day 4: **9.8%**	Day 1: **343** Day 2: **293** Day 3: **264** Day 4: **288**	Day 1: **2,914** Day 2: **2,826** Day 3: **2,757** Day 4: **2,652**	
(Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010) Italy	*n* = 28 GA: ≥37 weeks **Longitudinal sample**	1,2,3,4 **and** 5 days after birth	Day 1: **9.3%** Day 2: **8.8%** Day 3: **8.6%** Day 4: **8.1%** Day 5: **9.3%**	Day 1: **290** Day 2: **265** Day 3: **249** Day 4: **238** Day 5: **276**	Day 1: **2,778** Day 2: **2,662** Day 3: **2,611** Day 4: **2,626** Day 5: **2,660**	
Carberry, Raynes-	*n* = 581	Within 48 hr of birth	**9.2%**	-	-	

Greenow, Turner, Askie, and Jeffery (2013) Australia	GA: 37 – 40 weeks					
Paley et al. (2015) USA	*n = 332* GA: ≥37 weeks	1 – 3 days after birth	Male: African-American: **11.6%** Asian: **12.2%** Caucasian: **12.7%** Hispanic: **14.5%**	-	-	**Ethnicity:** Caucasian males had less FM than Asian and Hispanic (adjusted for infant age, birth weight, gestational age and mother's pre-pregnant weight).
			Female: African-American: **15.4%** Asian: **11.7%** Caucasian: **14.3%** Hispanic: **14.0%**	-	-	

GA= gestational age, FM = fat mass, FFM = fat free mass

2.5.2 Preterm Infant Body Composition

Table 2.2 summarises studies that have measured the body composition of preterm infants using ADP at birth or throughout early infancy. Only three of these studies measured the infants within the first week after birth and have reported values ranging from 4.4% FM to 8.4% FM (Giannì et al., 2012; Olhager & Törnqvist, 2014; Ramel et al., 2014). The majority of studies have measured the infants at, or close to, term-corrected age (TCA) and the values for % FM obtained at these time points range from 12.3% FM to 18.7% FM (Giannì et al., 2012; Olhager & Törnqvist, 2014; Ramel et al., 2011; Roggero et al., 2008; Roggero et al., 2009; Simon et al., 2013; Simon et al., 2014). As with full term infants, values vary between the studies and there are several influencing factors to consider.

It has been established that when compared to full term infants of equivalent ages, preterm infants have a higher % FM (Giannì et al., 2012; Olhager & Törnqvist, 2014; Ramel et al., 2011; Roggero et al., 2009; Simon et al., 2013). The cause of this difference remains unknown and could be due to either growth deficit of FFM, preferential accretion of FM over FFM, or a combination of both (Johnson et al., 2012). In an explorative study, Giannì et al. (2012) measured the body composition of late preterm (*n* = 49) infants 5 days after birth and again at TCA and found that FM increased by 182% during that period. This considerable increase in fat mass resulted in the late preterm infants having 16.1% FM at TCA compared to full term infants having 8.9% FM. A study that measured moderate-late preterm infants (*n* = 24) three times within the first 10 days after birth and again at TCA found that weight gain between days four and nine was largely due to FFM accretion, but by the time they reached TCA, the preterm infants had more FM and less FFM than full term infants (Olhager & Törnqvist, 2014). Both these studies have reasonably small numbers with European participants, making it difficult to draw conclusions that would apply to all preterm infants.

Simon et al. (2013) investigated a larger group of infants (*n* = 180) born earlier (<35 weeks' gestation) and found similar results, with the preterm infants having higher % FM when they reached 37 weeks' postmenstrual age. The authors highlight that the preterm infants had a younger postmenstrual age than the term infants at the time of the comparison and therefore the difference in % FM between the two groups could be underestimated, and propose that this gap would widen as the preterm infants get older (Simon et al., 2013). The highest % FM reported for preterm infants at term corrected age is 18.7% (Ramel et al., 2011). However, the study population was small (*n* = 26) and infants were measured between 40 and 42 weeks' gestation, which is at a more mature gestational age than the other studies.

As seen in term infants, gestational age also appears to affect the body composition of preterm infants. Ramel et al. (2014) found a positive relationship between gestational age and % FM, FM, and FFM in infants born between 30 and 36 weeks' gestation that were measured within the first three days after birth. However, when measured at TCA, studies have found that GA has a negative relationship with % FM and positive relationship with FFM (Gianni et al., 2009; Ramel et al., 2011; Roggero et al., 2008; Roggero et al., 2009; Simon et al., 2014). This suggests that those born younger deposit more fat mass during postnatal growth between birth and term-corrected age.

Only one study found a significant difference in the body composition between males and females (Ramel et al., 2014). An American study of 98 preterm infants found that at birth female preterm infants had higher % FM, FM, and lower FFM than preterm males (Ramel et al., 2014). Conversely, Simon et al. (2013) recruited both a term and preterm group and found that term males had significantly less % FM and more FFM than term females. This difference was not seen in the preterm group (Simon et al., 2013). Similarly, Hawkes et al. (2011) found that term female infants had higher % FM than males from 38 weeks' gestation, but this was not true in a group of infants aged 36^{+0} to 37^{+6} weeks' gestation. It has been suggested that growth of males is affected by prematurity more than females (Simon et al., 2013).

Table 2.2: Studies that have Used ADP to Determine % FM of Preterm Infants at Birth and/or During the Period until Term-Corrected Age (TCA)

Author(s)	**Preterm participants**	**Time of measurement (s)**	**% FM**	**FM**	**FFM**	**Nutritional Factors**	**Non- nutritional factors affecting body composition and comparison to term infants**
Giannì et al. (2012) Italy	*n* = 49 GA: 34^{+0}-36^{+6}	-5 days after birth -TCA (corrected to 40 weeks)	Measurement 1: **5.7%** Measurement 2: **16.1%**				-Significantly higher % FM than term infants at TCA
Roggero et al. (2009) Italy	*n* = 110 Birthweight: <1500g	-TCA (corrected to 40 weeks)	**14.8%**				-Significantly higher % FM than term infants at TCA -Negative association between GA at birth and FM at TCA
Simon et al. (2013) France	*n* = 180 GA: <35 weeks'	-1 week prior to discharge (average age was 37.9 and 37.7 weeks' CA for females and males respectively).	**13.4%**				-Significantly higher % FM at 37 weeks' CA than term infants at time of hospital discharge
Simon et al. (2014) France	*n* = 141 GA: <35 weeks	-Between 36 and 38 weeks' GA (mean 37.3 weeks)	**12.9%**	**308**	**2,059**	Increased protein: energy ratio at days 10 & 21 associated with reduced risk of FFM deficit.	-GA and postnatal days had positive relationship with FFM
(Ramel et al., 2014) USA	*n* = 98 GA: 30^{+0}-36^{+6} weeks	-Within 72 hrs of birth	**8.33%**	**192**	**1,975**		-Maternal diabetes -GA had positive association with % FM -Females had lower FFM and higher FM and % FM

Olhager and Törnqvist (2014) Sweden	*n* = 24 GA: 32^{+0}-36^{+6} weeks	-4 days after birth -6 days after birth -9 days after birth -Term-corrected age	4 days: **4.9%** 6 days: **4.4%** 9 days: **4.9%** TCA: **12.3%**	4 days: **150** 6 days: **135** 9 days: **159** TCA: **384**	4 days: **2,176** 6 days: **2,216** 9 days: **2,237** TCA: **2,631**		-Significantly less FFM, more FM and higher % FM than term infants at TCA
Ramel et al. (2011) USA	*n* = 26 GA: <35 weeks	40-42 weeks' CA	**18.7%**	**680**	**2,970**	Cumulative protein deficit had a negative association with weight and FFM at TCA. Energy deficit had a negative association with FFM.	-Significantly less FFM, more FM and more % FM than term infants at TCA -GA had a positive relationship with FFM
Roggero et al. (2008) Italy	*n* = 48 GA: ≤ 34 weeks	40 weeks' CA	**14.8%**				-GA had a negative relationship with % FM at TCA
Gianni et al. (2009) Italy	*n* = 67 GA: ≤34 weeks Small for gestational age (SGA)	40 weeks' CA	**14.3%**	**353**	**2,050**		-GA had a negative relationship with % FM at TCA
Roggero, Giannì, Orsi, et al. (2012) Italy	*n* = 102 Birthweight: <1500g	TCA	Group 1: **15.8%** Group 2: **16.2%**				

GA= gestational age, FM = fat mass, FFM = fat free mass, TCA = term corrected age, CA = corrected age

2.6 Early Feeding of Preterm Infants

2.6.1 Feeding Difficulties

The majority of fetal growth and nutrient accretion occurs in the third trimester of pregnancy and consequently preterm infants are born with limited nutrient stores (Shaw & McCarthy, 2014). They are therefore unprepared for even short periods with no or limited nutrient supply (Shaw & McCarthy, 2014). While there is a need to establish an adequate nutrient supply promptly after birth, preterm infants often experience feeding difficulties due to the immaturity of their gastrointestinal tracts (Neu, 2007).

2.6.1.1 Immaturity of the Gastrointestinal Tract

With immature gastrointestinal tracts, preterm infants often have difficulty with co-ordinating sucking , swallowing and breathing and with absorbing and tolerating oral or enteral feeds (Koletzko et al., 2005). The degree of development of their gastrointestinal (GI) tracts will contribute to the determination of the method of feeding.

The capacity to digest and absorb nutrients through the intestines is reduced in preterm infants. They may be born deficient in the digestive enzymes lactase, pepsin, and lipase required to digest carbohydrates, protein, and fat (Commare & Tappenden, 2007; Hamosh et al., 1981; Heyman, 2006). With a reduced ability to digest the components of breast-milk and infant formulas, malabsorption is likely to occur, potentially resulting in the infant not meeting nutrient requirements (Commare & Tappenden, 2007). In addition, the GI motility of preterm infants can also be reduced. Preterm infants have slower gastric emptying than term infants and intestinal motility does not fully mature until 36 weeks' gestation (Blackburn, 2014; Commare & Tappenden, 2007). This can result in undigested nutrients remaining in the GI tract for an extended period, increasing the risk of inflammation and necrotising enterocolitis (Commare & Tappenden, 2007).

For successful oral feeding, the suckling reflex requires coordinated sucking, swallowing, and breathing (Cleaveland, 2010). It is common amongst preterm infants for this coordination to be deficient as the sucking reflex is not developed until about 34 weeks' gestation (Arvedson, 2006; Blackburn, 2014). Yet even with the ability to suck and swallow, the efficiency and synchronisation of this process is not matured until 36-38 weeks' gestation (Blackburn, 2014). Preterm infants often demonstrate a non-nutritive pattern of sucking, which involves a fast sucking rate with a high suck: swallow ratio (Blackburn, 2014). A sucking pattern that is not

synchronised with breathing can be a tiresome process for the infant and puts them at risk of aspiration (Duggan, Watkins, & Walker, 2008; Ludwig, 2007).

2.6.1.2 Fatigue

Preterm infants have lower levels of alertness than full term infants and will spend more time asleep (Cleaveland, 2010). Additionally, other medical complications such as jaundice, hypoglycaemia and problems with temperature regulation can contribute to low levels of arousal and fatigue whilst feeding (Ludwig, 2007). This presents another problem for establishing adequate oral feeds as the infants may not be awake long enough to drink a sufficient volume (Cleaveland, 2010; Ludwig, 2007). Infants may falsely appear to have had sufficient; however, they may in fact be too tired to continue feeding (Cleaveland, 2010).

2.6.1.3 Maternal Breast-Milk Supply

After a preterm birth it is common for mothers to experience a period where insufficient breast-milk is produced to meet the infant's requirements (Geddes, Hartmann, & Jones, 2013). This delay is due to a shortened period for mammary growth and preparation (Jones & Spencer, 2007). Furthermore, preterm birth can cause stress and anxiety for the mother which can inhibit the production of breast-milk (Jones & Spencer, 2007). Frequent expressing of breast-milk initiated soon after birth, has been found to increase breast-milk production (Jones & Spencer, 2007; Maastrup et al., 2014).

2.6.2 Breast-Milk

The American Academy of Paediatrics recommend that breast-milk should be the primary source of nutrients for preterm infants (Gartner et al., 2005). There is a wealth of evidence of the benefits for preterm infants who receive breast-milk (Donovan, 2006; Field, 2005; Gartner et al., 2005; Hanson et al., 2003; Heinig, 2001; Underwood, 2013). These benefits include better short-term health outcomes, lower rates of readmission to hospital, and fewer markers of adverse cardio-metabolic outcomes in later life (Underwood, 2013).

Breast-milk produced by mothers after a preterm birth differs in nutritional composition to the breast-milk produced after a term birth. Preterm breast-milk tends to be higher in protein and fat than term breast-milk (Gidrewicz & Fenton, 2014). However, it is hard to generalise the composition of breast-milk as it is variable between individuals and is influenced by many factors including gestational age, postnatal age, time of day, time since the last feed, maternal

age and maternal diet, as well as the method used to analyse the milk (Andreas, Kampmann, & Mehring Le-Doare, 2015; Gidrewicz & Fenton, 2014).

2.6.2.1 Benefits of Breast-feeding

Breast-milk provides an infant with further benefits than simply being a source of nutrients source. One of the most recognised non-nutritional benefits of breast-milk is the positive effect on the infant's immune system (Field, 2005). Breast-milk has antimicrobial and anti-inflammatory properties, and contains immune factors to stimulate the development of the infant's immature immune system (Field, 2005; Hanson et al., 2003). As summarised by Underwood (2013), there is evidence that the provision of breast-milk is associated with a lower risk of developing necrotising enterocolitis, retinopathy of prematurity, late- onset sepsis, and being readmitted to hospital for preterm infants (Meinzen-Derr et al., 2009; Okamoto et al., 2007; Schanler, Shulman, & Lau, 1999; Vohr et al., 2006). Components of breast-milk are known to positively influence the colonisation of beneficial intestinal microbiota (Adlerberth & Wold, 2009; Donovan, 2006). A healthy gut microbiome is important for the development of the mucosal immune system (Donovan, 2006).

Breast-milk also helps with the maturation of the underdeveloped gastrointestinal tract (Donovan, 2006). It both promotes intestinal growth and development and stimulates the maturation of mucosal barriers, providing additional protection to the infant (Tudehope, 2013). Breast-milk has been found to increase the rate of gut motility, particularly gastric emptying (Donovan, 2006; Tudehope, 2013). The nutrients in breast-milk are very bioavailable, and breast-milk also contains some digestive enzymes which preterm infants lack, therefore aiding in digestion and absorption (Tudehope, 2013). There is some evidence to suggest that breast-milk positively affects neurodevelopment and cognitive function, however the research is not clear (Tudehope, 2013).

2.6.2.2 Fortification of Breast-Milk

The composition of breast-milk alone cannot always provide enough nutrients to meet the high requirements of a preterm infant and the sole use of breast-milk can result in poor growth or nutritional deficiencies (Bhatia, 2013; Tudehope, 2013). Breast-milk may therefore need to be fortified with extra energy, protein, minerals, and vitamins (Bhatia, 2013; Harding et al., 2013). Studies have indicated that fortifying breast-milk improves early weight gain, and growth of length and head circumference amongst preterm infants (Kuschel & Harding, 2004). Su (2014) found that many preterm infants fed with unfortified breast-milk had a low body

weight when discharged from hospital. Fortification of breast-milk means the infant still receives the benefits associated with breast-milk without compromising the nutritional adequacy of their feed. Standard protocol at Auckland City Hospital is that infants born at < 32 weeks' gestation or infants who weigh < 1800 g at birth will receive breast-milk fortified with a powered commercial human milk fortifier (Auckland District Health Board, 2014b).

2.6.3 Infant Formula

In cases where breast-milk is unavailable in adequate amounts, the use of an infant formula is required to meet nutritional requirements (King & Tavener, 2014). Evidence suggests that preterm infants fed with formula, either preterm or term formula, experience accelerated growth compared to infants fed with unfortified breast-milk. O'Connor et al. (2003) found a dose dependant effect between weight at term-corrected age and the amount of energy provided from preterm infant formula. When compared to unfortified donor breast-milk, infant formula has been associated with faster postnatal growth (Boyd, Quigley, & Brocklehurst, 2007). However, as mentioned previously, breast-milk provides added benefits for the development of the GI tracts and the infant's immune system (Tudehope, 2013).

Either standard infant formula or specialised preterm infant formula can be used. Preterm infant formulas are higher in energy, protein, vitamins and minerals and have been developed to meet the increased requirements of preterm infants and prevent postnatal growth restriction (Klein, 2002). There is variation in practice and recommendations as to when and for how long a preterm formula should be used instead of a standard infant formula. Agostoni et al. (2010) recommended that preterm formula should be used up until the infant has achieved a weight of 1800 g. However, other sources have concluded that the decision should not be made based on weight or gestational age, but rather on an individual basis (King & Tavener, 2014; Klein, 2002). At Auckland City Hospital, preterm formulas are used for infants who are born < 32 weeks' gestation or who weigh < 1800 g at birth.

2.6.3 Parenteral Nutrition

Parenteral nutrition is the provision of nutrients directly into the blood stream, bypassing the gastro-intestinal tract (National Collaborating Centre for Acute Care, 2006). This method of feeding is required when the oral or enteral routes are unsafe or are providing inadequate nutrients to meet the infant's requirements (Koletzko et al., 2005). Therefore parenteral nutrition can either be supplemental or, in cases when the GI tract is not functional, the sole source of nutrition. As parenteral nutrition solutions bypass the digestive system, nutrients

need to be in the form that they are found in the blood stream. Carbohydrates are provided in the form of dextrose, protein in the form of amino acids, and fat in the form of lipids (Hay, 2008). In a meta-analysis looking at early parenteral nutrition in preterm infants, Moyses, Johnson, Leaf, and Cornelius (2013) found that it was associated with positive growth outcomes including reduced postnatal weight loss and reduced time to regain birthweight. It also reported that in observational studies, early parenteral nutrition was associated with higher weight and length at discharge; however, this was not seen in randomised controlled trials (Moyses et al., 2013). The meta-analysis concluded that early parenteral nutrition is safe, and is not associated with increased risk of mortality, morbidity, sepsis, or cholestasis. However, other studies have concluded that total parenteral nutrition is a risk factor for hospital acquired infections and blood stream infections, and promote the transition to enteral feeding as soon as possible (Zingg, Tomaske, & Martin, 2012).

2.6.4 Early Enteral Feeding

Early enteral feeding or minimal enteral feeding is when small amounts of feed, preferably breast-milk, are given enterally from as early as possible (McClure, 2001). The presence of even a small amount of milk helps stimulate the development of the GI tract. There is evidence that feeding an infant with total parenteral nutrition with the absence of any enteral feeding can cause atrophy of villi and the mucosal layer and a reduction in the production of digestive enzymes (Hay, 2008; Neu, 2007). It has been demonstrated that infants who receive early enteral feeding progress to full enteral feeds faster and tolerate feeds better than infants who do not (Hay, 2008).

2.6.5 Variability in Practice

The lack of evidence to guide the feeding practices of moderate to late preterm infants means practices are highly variable amongst NICUs (McCormick et al., 2006). A study looking at the practices for infants aged between 30^{+0} to 34^{+6} at 15 American NICUs found that rates of parenteral nutrition ranged from 5 – 66% (McCormick et al., 2006). Results from a survey completed by 24 NICUs in Australasia found that enteral feeding guidelines and practices varied greatly (Cormack et al., 2013).

2.7 Summary

In summary, moderate to late preterm infants make up the largest proportion of preterm infants and are more at risk, both in the short- and long-term, than full term infants. There is evidence that preterm birth is associated with having a higher risk of obesity, diabetes and

cardiovascular disease in later life. While it is the aim that preterm infants should experience growth rates similar to that of a fetus *in utero,* preterm infants continue to demonstrate postnatal growth restriction followed by a period of accelerated growth. It is thought that this growth pattern contributes to permanent physiological changes that result in the increase risk of the adverse cardiometabolic outcomes. However, accelerated growth is also associated with improved cognitive and neurodevelopmental outcomes. Measuring body composition can be difficult, and while there are numerous methods available, they all have limitations and involve assumptions. Air displacement plethysmography has been found to be an accurate and feasible method to assess the FM and FFM of both term and preterm infants. It has been found, using ADP, that during this period of accelerated growth, the amount of FM increases dramatically, resulting in preterm infants have higher % FM than full term infants at TCA.

Nutrition is a modifiable factor contributing to the growth of preterm infants, and therefore should be optimised to ensure favourable growth patterns are achieved. Ultimately, the goal for moderate-late preterm infant is that they would be breast-fed. However, there is often a delay in establishing this due to inadequate maternal supply of breast-milk and the immature gastrointestinal tract of the infant. There is limited evidence for the optimal feeding of these infants in the period before full breast-feeds are established, and great variability in the early feeding practices for moderate-late preterm infants amongst different NICUs. This highlights a need for evidence to inform standardised feeding guidelines that will promote optimal growth in moderate-late preterm infants.

Chapter 3: Methods

3.1 Study Design

An explorative, prospective, observational study design (**Figure 3.1**) was used to explore the relationship between different early feeding strategies and the development of fat mass and fat free mass in moderate to late preterm infants.

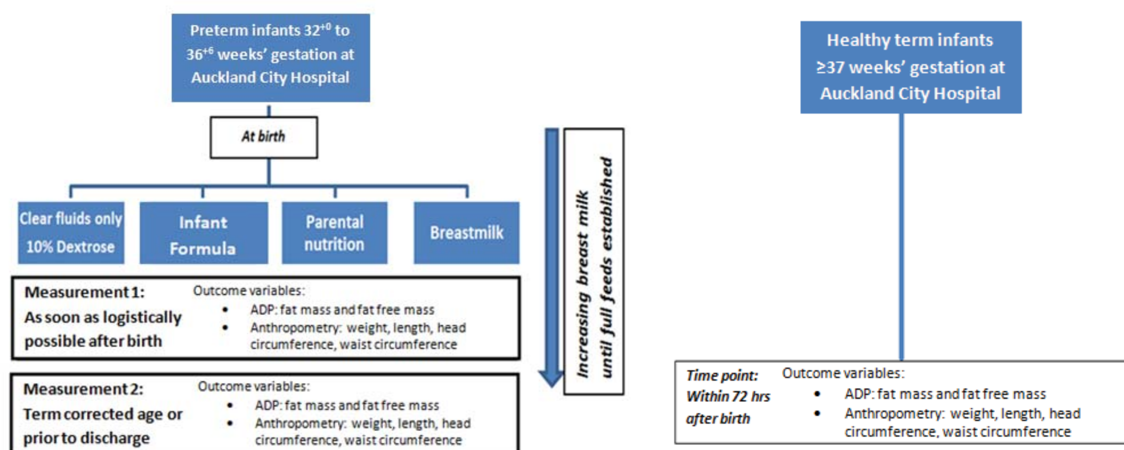

Figure 3.1: Study Design
ADP = air displacement plethysmography

3.1.1 Comparators

Preterm infants were allocated retrospectively into one of four groups, depending on what they were fed for the first 1-5 days after birth. The four comparators were: intravenous 10% dextrose; intravenous parenteral nutrition; infant formula, or breast-milk. This allocation was not random as the feeding strategy was decided by the neonatologist and the infant's parents, as per normal practice. Comparators were defined by assessing which feed type the infant predominantly received in the first 5 days.

3.1.2 Control Group

An ethnically diverse group of healthy, full term infants were used as a comparison for the desired body composition.

3.1.3 Outcome Measurements

The primary outcome measurements were % fat mass (FM), and absolute FM and fat free mass (FFM). Secondary outcome measures were other growth parameters including crown-heel length, weight, head circumference, and waist circumference.

3.1.4 Time Points

Preterm infants were measured as soon as possible after birth once their medical status was stable and they no longer required respiratory support or intravenous infusion of fluids. Infants were measured again at term-corrected age (TCA), or close to TCA, if they were still in hospital at the time. Participants were then categorised by postnatal and postmenstrual age for analysis.

Term infants were measured within 72 hours of birth.

3.2 Ethical Approval

Ethical approval was granted from the Southern Health and Disability Ethics Committee (reference: 15/STH/52, Appendix 1). Permission was given from the Auckland District Health Board Research Review Committee (reference: A+6691, Appendix 2) for recruitment and data collection to be done on the Newborn Intensive Care Unit (NICU) and maternity wards of Auckland City Hospital.
Consultation was undertaken during the development of the research protocol by a Māori Research Advisor from He Kamaka Waiora.

3.3 Setting

Infants were recruited from Auckland City Hospital (ACH). The population serviced by ADHB is made up of 52% European, 29% Asian, 11% Pacific, 8% Māori, and 2% other (Auckland District Health Board, 2014a). Each year at ACH approximately 7,500 infants are delivered. Newborn services include three postnatal wards and a NICU.

The ACH NICU is the largest in the region with 46 cots providing a range of intensive, high dependency, and low dependency care (Auckland District Health Board, 2015b). Due to the facilities and level of care offered, the unit sees a higher proportion of preterm infants than the national average and each year 500-600 of these are moderate-late preterm (Auckland District Health Board, 2013).

3.4 Participants

The study population was preterm infants that were born between 32^{+0} and 36^{+6} weeks' gestation, with a control group of healthy full term infants born at ≥ 37 weeks' gestation.

The gestational age of the infants was obtained from the medical notes.

Preterm exclusion criteria:

- Infants with a known chromosomal, genetic, or congenital disorder affecting growth; inborn error of metabolism or in danger of imminent death
- Infants who would not tolerate Air Displacement Plethysmography (ADP) (for reasons such as intubation)

Term exclusion criteria:

- Infants with a known chromosomal, genetic, or congenital disorder affecting growth; inborn error of metabolism or in danger of imminent death
- Maternal gestational diabetes
- Infants who would not tolerate ADP (for reasons such as intubation)

3.5 Consultation with Health Professionals at ACH

Meetings were held with the medical and nursing teams of the wards that recruitment took place in prior to commencement of the study. They were informed of what the study aimed to achieve, which infants would be eligible, and what participation would involve. Feedback from staff was considered and processes for the recruitment of infants were established for each ward.

3.6 Recruitment

Participants were recruited between June 2015 and October 2015.

3.6.1 Recruitment of Preterm Infants

Recruitment of the preterm infants took place in the NICU and the post-natal maternity wards. The ward lists were used to see the current admissions to the ward and the gestational ages of the infants. When the infants were in NICU, a research nurse assessed the medical status of the infant for eligibility. Once it was established that the infant met the eligibility criteria, the parents were approached by either the research nurse or a member of the research team. The parents were given an explanation of the study and a copy of the participant information sheet (PIS, Appendix 3) and were allowed time to read the PIS and consult with family members.

They were then given the opportunity to have any questions answered by the researcher. If parents agreed to take part, they were asked to provide written consent (Appendix 4). The researcher organised a time for the measurement to take place by consulting with the parents and nursing staff to fit in around feeding and other medical procedures or assessments. Measurements were taken prior to infants receiving breast-milk or formula whenever feasible.

3.6.2 Recruitment of Term Infants

The term infants were recruited solely from the post-natal maternity wards. The ward lists were used to identify any potentially eligible participants. The nurses or midwives caring for these infants were consulted to find out the suitability of approaching the parents. Mothers of infants who were deemed as being unsuitable to participate in research were not approached. Reasons included mothers who were experiencing trauma or stress associated with giving birth, or medical complications involving the mother or the infant. Those who were appropriate to approach were given an explanation of the study and a copy of participant information sheet (Appendix 3). They were then allowed time to read the PIS, consult with family members and given the opportunity to have any questions answered by the researcher. If parents agreed to take part, they were asked to provide written consent (Appendix 4). The researcher organised a time for the measurement to take place by consulting with the parents to fit in around feeding and other medical procedures or assessments. Measurements were taken prior to infants receiving breast-milk or formula whenever feasible.

3.7 Data Management

3.7.1 Confidentiality

To ensure confidentiality, each participant was given a numbered code upon recruitment. This code was used for the recording of all measurements and data collection.

3.7.2 Data Storage

All data collected were kept securely at Massey University, and only members of the research team had access. Data will be held there for 26 years after conclusion of the study and subsequently destroyed.

3.8 Data Collection

3.8.1 Demographic Data

Data were collected on demographic information (Appendix 6) from the infants' and mothers' medical notes by a member of the research team. Gestational age, birth date, maternal date of birth and ethnicity were recorded.

3.8.2 Medical Background Data

Information regarding the pregnancy and birth was gathered from the infant's and mother's medical notes (Appendix 6). Data surrounding the pregnancy included: whether intrauterine growth restriction (IUGR) occurred; use of any prenatal steroids, and any medical complications. Information collected about the birth was the type of delivery, the reason for preterm birth, and whether the infant was a singleton or multiple. Anthropometric measurements of the infant at birth that were recorded were weight, length, and head circumference. This was done by the medical staff at birth using digital scales for weight, and tape measure for length and head circumference.

3.8.3 Feeding Data

Data regarding feeding practices of preterm infants in the first 5 day after birth were collected by a member of the research team from the infants' medical notes (Appendix 5). In the NICU, this information was found in observation charts kept by the nurse caring for the infant. The charts detailed information on the number of breast-feeds, and the type, quantity and method used of any other fluids given. These data were used to determine which comparator the infant fell into.

3.9 Body Composition Measurements

3.9.1 Description of PEA POD

The PEA POD (**Figure 3.2**), which uses air displacement plethysmography, was used to measure FM and FFM (Cosmed, 2003). This system measures body density to calculate FM and FFM. Body volume is measured by the amount of air displaced once the infant is inside the test chamber. Density is calculated using the formula $Body\ density = \frac{Body\ mass}{Body\ volume}$. The density of FM is assumed to be 0.9007 kg/L and age-specific assumptions as stated by Fomon et al. (1982) were used for the density of FFM. Body density and these assumed densities are applied to formulae that are used to produce values for %FM, %FFM, total FM, and total FFM.

3.9.2 PEA POD quality control

The PEA POD was located in a quiet room with no windows that had a constant temperature of approximately 26°C. The door of the room was kept shut during any calibration or measurement processes. Prior to any measurements, the PEA POD was switched on and left to warm up for at least two hours, until the test chamber had reached a temperature of 31°C. The warm up period was followed by quality control (QC) procedures, using the standardised protocols. This process began with hardware analysis and scale calibration using the provided weight. The autorun setting was used to assess the stability of the PEA POD with the provided volume phantom. Finally, the volume performance was assessed also using the phantom volume. At any stage of QC, tests were redone if they failed.

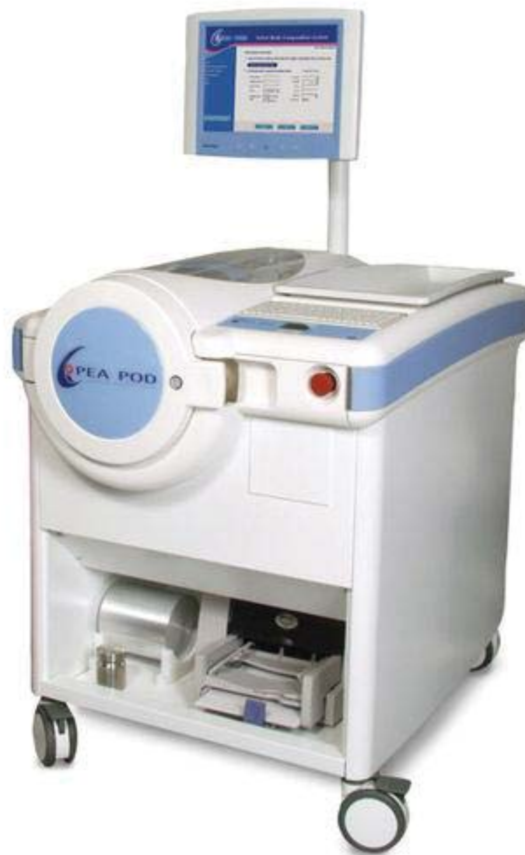

Figure 3.2: PEA POD (Cosmed, 2003) .

3.9.3 Measurement Accuracy

Processes were in place to ensure the volume measurements of the infants were controlled and accurate. All infants were measured nude, and only wore a head cap to flatten their hair to prevent it from contributing to the volume reading. If the infant had any un-removable objects such as feeding tubes and identification bracelets, duplicates were placed into the test chamber as the automatic volume calibration was under way. Duplicates were also placed on the scales, which were tared. The duplicates were removed from both the test chamber and scales before the infant was measured and allowed the volumes of these objects to be discounted when the infant was measured.

3.9.4 Measurement Procedures

The Fomon Body Density Model, Boyd Body Surface Area Model and Stocks Thoracic Gas Volume Model were used for all infants (Boyd, 1929; Fomon et al., 1982; Stocks et al., 1996). To keep infants calm for the procedures, they were undressed just prior to measurements began and kept on a surface with an overhead heated lamp. Length was measured using a Holtain Limited Harpenden Neonatometer. Infants were weighed by being placed in supine position on the calibrated and tared PEA POD scales. Infants were then transferred to the test chamber where they remained for approximately two minutes for the measurement to take place.

3.10 Other Outcome Measurements

3.10.1 Length

Crown-heel length measurements were done by a trained researcher with the assistance from the infant’s parents or nurse. The same neonatometer was used for all infants and was always positioned on a firm flat surface. The infant was placed on the board in a supine position. The head of the infant was gently held in place so that it was touching the headpiece. The infant’s legs were then straightened out to as far as possible without causing injury. While the legs were straight, the footboard was pulled towards the infant’s feet until the soles of their feet were flat against it. The length was recorded to the last completed millimetre. The measurement was taken three times and the average value was used (World Health Organisation, 2008) .

3.10.2 Head Circumference

Head circumference was measured by a trained researcher using a disposable measuring tape marked with cm and mm. The infant was placed in the supine position. The end of the tape was placed above the eyebrows of the infant and wrapped around the largest part of the head. When positioning was correct, the tape was pulled just tight enough to get a reading, which was recorded as the last completed millimetre. The measurement was taken three times and the average value was used (Intergrowth-21st Anthropometry Group, 2012).

3.10.3 Waist Circumference

Waist circumference was measured by a trained researcher using a disposable measuring tape marked with cm and mm. The infant was placed in the supine position and the tape placed around the largest portion of their waist. When positioning was correct, the tape was pulled just tight enough to get a reading, and was recorded as the last completed millimetre. The measurement was taken three times and the average value was used.

3.10.4 Z-Scores

Z-scores for the preterm infants were calculated using the z-score calculator provided by the University of Calgary which used data from the Fenton Growth Charts (Fenton & Kim, 2013; University of Calgary, 2015). The Fenton growth charts were chosen as they use a large, recent data set from several countries. The calculator also allows actual ages (weeks + days) to be used, rather than rounding to the nearest week, resulting in more accurate results (Fenton & Kim, 2013; University of Calgary, 2015).

3.11 Data Analysis

The data were entered into Microsoft Excel and the demographic and medical background data were coded. Statistical analysis was done on IBM SPSS Statistics Version 22 (IBM Corp., 2013).

Variables were tested for normality, using Shapiro-Wilk and Kolmogorov-Smirnov tests.

If a variable maintained a distribution that was not normal after logarithmic transformation, it was treated as non-parametric. Parametric data were described using means and standard deviation, while non-parametric data were described using medians and the 25th and 75th percentiles. To compare two independent groups, independent t-tests were used for parametric data and Mann-Whitney tests were used for non-parametric. Paired sample t-tests were used to compare dependent parametric data. To compare several independent groups, one-way ANOVA was used, with Hochberg’s GT2 post-hoc analysis for parametric data. When data were non-

parametric, Kruskal-Wallis tests were used to compare several independent groups. Post-hoc analysis was done using Mann-Whitney tests, after applying the Bonferroni correction to the significance level of the *P*-value. Pearson's Chi Square was used to test differences between two categorical variables.

Chapter 4: Results

4.1 Description of Participants

The characteristics of the participants are displayed in **Table 4.1**. There were 47 preterm infants and 69 term infants. Preterm infants were born at a significantly younger gestational age than term infants (mean ± SD: 34.3 ± 1.1 weeks vs 39.4 ± 1.2 weeks; $P < 0.001$, large effect size r = 0.9). All of the infants in the term group were from singleton births. In the preterm group, 32 infants were from singleton births, 11 from twin births and four from triplet births. The mean birth weight for the preterm infants was significantly lower than the term infants (2,212 ± 460 g vs 3,484 ± 543 g; $P < 0.001$, large effect size r = 0.8). Preterm infants were significantly shorter (45.4 ± 3.4 cm vs 51.7 ± 2.5; $P < 0.001$, large effect size r = 111) and had significantly smaller head circumferences at birth than term infants (31.6 ± 1.8 cm vs 34.9 ± 1.7 cm; $P < 0.001$, large effect size r = 0.7).

Table 4.1: Characteristics of Infants

Characteristics		**Preterm infants** (*n* = 47)	**Term infants** (*n* = 69)	***P****
Sex‡	Male	29 (62)	38 (55)	0.6
	Female	18 (38)	31 (45)	
Ethnicity‡	European	25 (54)	25 (36)	0.1
	Māori	7 (15)	4 (6)	
	Pacific	2 (4)	11 (16)	
	Asian	3 (7)	20 (29)	
	South Asian/ Indian	7 (15)	8 (12)	
	Other e.g. Middle Eastern, Latin American	2 (4)	1 (1)	
Gestational age (weeks)†		34.3 ± 1.1	39.4 ± 1.2	< 0.001*
Birth weight (g)†		2,212 ± 460	3,484 ± 543	< 0.001*
Birth length (cm)†		45.4 ± 3.4	51.7 ± 2.5	< 0.001*
Birth head circumference (cm)†		31.6 ± 1.8	34.9 ± 1.7	< 0.001*
Birth plurality‡	Singleton	32 (68)	69 (100)	<0.001*
	Twins	11 (23)	0	
	Triplets	4 (9)	0	

‡ *n,* (%)
†Mean ± SD
*Significant differences ($P < 0.05$) (Peason's Chi-Square Test, Independent T-Test)

4.2 Anthropometric Outcomes of Term Infants

Some of the anthropometric measurements of the term infants differed between males and females (**Table 4.2**). Term males had a significantly lower % FM than term females (9.4 ± 3.5% vs 12.2 ± 4.8; *P* = 0.018, medium effect size r = 0.3). Body weight and absolute FM did not differ between the two groups whereas males had significantly more FFM (3,038 ± 401 g vs 2,788 ± 344 g; *P* = 0.07, medium effect size r = 0.3). Males were significantly longer than females (median [25th, 75th quartiles]: 52.0 [51.0, 54.0] cm vs 51.0 [48.5, 53.0] cm; *P* = 0.031, small effect size r = 0.2) and had significantly larger head circumferences (35.5 [34.0, 36.5] cm vs 34.5 [33.7, 35.5] cm; *P* = 0.038, medium effect size r = 0.3).

Table 4.2: Anthropometric Outcomes of Male and Female Term Infants

	Total (*n = 69*)	**Male infants** (*n* = 38)	**Female infants** (*n* = 31)	***P****
Gestational age (weeks)†	39.5 ± 1.2	39.5 ± 1.2	39.4 ± 1.2	0.8
Postnatal age at measurement (days)‡	39.7 [38.9, 40.6]	2 [1, 3]	2 [1, 3]	0.7
Postmenstrual age at measurement (weeks)†	2 [1, 3]	39.8 ± 1.1	39.7 ± 1.2	0.7
% FM†	10.9 ± 4.2	9.4 ± 3.5	12.2 ± 4.8	0.018*
FM (g)†	370 ± 179	341 ± 149	407 ± 209	0.1
FFM (g)†	2,926 ± 394	3,039 ± 401	2,788 ± 344	0.07*
Weight (g)†	3,309 ± 659	3,367 ± 502	3,195 ± 493	0.2
Length (cm)‡	51.8 ± 2.5	52.0 [51.0, 54.0]	51.0 [48.5, 53.0]	0.031*
Head circumference (cm)‡	34.9 ± 1.8	35.5 [34.0, 36.5]	34.5 [33.7, 35.5]	0.038*
Waist circumference (cm)†	32.8 [32.0, 34.5]	33.2 ± 2.4	32.7 ± 2.0	0.5
Waist: length ratio†	0.64 ± 0.04	0.63 ± 0.05	0.64 ± 0.02	0.2

†Mean ± SD
‡Median [25th, 75th quartiles]
*Significant differences between males and females (P < 0.05) (Independent T-Test)

4.3 Growth Outcomes of Preterm Infants Measured in the First Two Weeks after Birth

Of the 47 preterm infants, 25 were measured for the first time within the first week (≤ 7 days) after birth and 19 within the second week (8-14 days after birth). Three preterm infants were measured for the first time during the third week or later (days 16, 17, and 29 after birth) and were excluded from the following analysis. **Table 4.3** displays the characteristics at birth of the infants grouped according to whether they were measured within the first or second week after birth. The mean ± SD birth weight of the preterm infants measured at ≤ 7 days was significantly higher than the preterm infants measured between 8-14 days (2,386 ± 440 g vs 2,046 ± 357 g; *P* = 0.009, medium effect size r = 0.4). Preterm infants measured at ≤ 7 days were longer (46.6 ± 3.3 cm vs 44.6 ± 2.8 cm; *P* = 0.049, medium effect size r = 0.3) and had larger head circumferences (32.2 ± 1.8 cm vs 30.8 ± 1.3 cm; *P* = 0.04, medium effect size r = 0.4) at birth than those measured between 8-14 days.

Table 4.3: Characteristics at Birth of Preterm Infants Measured For the First Time within the First and Second Weeks after Birth

	Measured at ≤ 7 days (*n* = 25)	**Measured at 8-14 days** (*n* = 19)	***P****
Gestational age (weeks)†	34.6 ± 1.1	34.1 ± 1.1	0.1
Postmenstrual age at measurement (weeks) †	35.2 ± 1.1	35.5 ± 1.1	0.3
Birth weight (g)	2,386 ± 440	2,046 ± 357	0.009*
Birth weight z-score‡	0.3 [-0.5, 0.8]	-0.2 [-0.7, 0.2]	0.055
Birth length (g)	46.6 ± 3.3	44.6 ± 2.8	0.049*
Birth length z-score†	0.5 ± 1.2	0.1 ± 1.0	0.2
Birth head circumference (cm)	32.2 ± 1.8	30.8 ± 1.3	0.04*
Birth head circumference z-score†	0.56 ± 1.19	-0.13 ± 0.80	0.7

†Values are means ± SD
‡Median [25th, 75th quartiles]
*Significant differences (*P* < 0.05) (Mann-Whitney Test, Independent T-Test)

The anthropometric measurements of preterm infants at the time of measurement within the first week after birth and between the first and second weeks after birth are displayed in **Table 4.4.** Preterm infants measured within the first week after birth had a significiantly higher mean weight z-score than those measured in the second week after birth (-0.46 ± 0.95 vs -1.08 ± 0.69; *P* = 0.019, medium effect size r = 0.4). The mean ± SD head circumference z-score was

signficiantly higher for infants measured in the first week after birth than those measured in the second week after birth (0.14 ± 1.34 vs -0.76 ± 0.67; $P = 0.013$, medium effect size r = 0.4).

Table 4.4: Anthropometric Outcomes of Preterm Infants Measured for the First Time within the First and Second Weeks after Birth

	Measured at ≤ 7 days (*n* = 25)	**Measured at 8-14 days** (*n* = 19)	***P****
% FM†	8.7 ± 4.4	8.1 ± 2.9	0.6
FM (g)†	208 ± 132	170 ± 64	0.3
FFM (g)†	2,084 ± 324	1,936 ± 298	0.1
Weight (g)†	2,301 ± 478	2,107 ± 311	0.1
Weight z-score†	-0.46 ± 0.95	-1.08 ± 0.69	0.019*
Δ Weight z-score from birth‡	-0.6 [-0.4, -0.8]	-0.7 [-0.8, -0.5]	0.5
Length (cm)†	46.4 ± 3.3	45.6 ± 2.3	0.4
Length z-score†	0.17 ± 1.27	-0.28 ± 0.74	0.2
Δ Length z-score from birth‡	-0.2 [-0.3, -0.1]	-0.3 [-0.9, -0.1]	0.9
Head Circumference (cm) †	32.0 ± 2.0	30.9 ± 1.3	0.066
Head Circumference z-score†	0.14 ± 1.34	-0.76 ± 0.67	0.013*
Δ Head Circumference z-score from birth‡	-0.3 [-0.5, 0.0]	-0.5 [-1.1, -0.3]	0.1
Waist Circumference (cm)†	30.1 ± 3.0	30.3 ± 2.1	0.8
Waist: length ratio†	0.67 ± 0.06	0.66 ± 0.05	0.5

†Mean ± SD
‡Median [25th, 75th quartiles]
*Significant differences ($P < 0.05$) (Independent T-Test, Mann-Whitney Test)

4.4 Anthropometric Outcomes of Preterm Infants at ≥ 36 weeks' Postmenstrual Age

Of all the preterm infants, 22 were measured at a postmenstrual age of 36 weeks or older at their first or second measurement. This group was compared to the term group and the characteristics of the two groups are displayed in **Table 4.5.** The gestational age at birth (34.8 ± 1.3 weeks vs 39.5 ± 1.2 weeks; $P < 0.001$, large effect size r = 0.09) and postmenstrual age at measurement (37.4 [36.3, 37.7] weeks vs 39.7 [38.9, 40.6] weeks; $P < 0.001$, large effect size r = 0.7) of the preterm infants was significantly less than the term infants. The term infants were measured at a younger postnatal age than the preterm infants (2 [1, 3] days vs 14 [7, 12] days; $P < 0.001$, large effect size r = 0.7). Preterm infants weighed significantly less (2,115 [1,888, 2,368] g vs 3,441 [3,111, 3,576] g; $P < 0.001$, large effect size r = 0.7), were significantly shorter (44.8 ± 3.4 cm vs 51.7 ± 2.5 cm; $P < 0.001$, large effect size r = 0.7) and had a significantly smaller head circumference (34.1 ± 1.8 cm vs 34.9 ± 1.7 cm; $P < 0.001$, large effect size r = 0.7) than term infants.

Table 4.5: Characteristics at Birth of Preterm Infants Measured at ≥ 36 weeks' Postmenstrual Age and Term Infants

	Preterm measured at ≥ 36 weeks postmenstrual age (*n* = 22)	**Term** (*n* = 69)	***P****
Gestational age (weeks)†	34.8 ± 1.3	39.5 ± 1.2	< 0.001*
Postmenstrual age at measurement (weeks)‡	37.4 [36.3, 37.7]	39.7 [38.9, 40.6]	< 0.001*
Postnatal age at measurement (days)‡	14 [7, 21]	2 [1, 3]	< 0.001*
Birth weight (g)§	2,115 [1,888, 2,368]	3,441 [3,111, 3,576]	< 0.001*
Birth length (g)†	44.8 ± 3.4	51.7 ± 2.5	< 0.001*
Birth head circumference (cm)†	31.4 ± 1.8	34.9 ± 1.7	< 0.001*

†Mean ± SD
‡Median [25th-75th quartiles]
§Mean (95% CI) for the log transformed data values, back transformed to the original scale
*Significant differences ($P < 0.05$) (Independent T-Test, Mann-Whitney Test)

Table 4.6 displays the anthropometric measurements of two groups. The % FM was not significantly different between preterm infants measured at ≥ 36 weeks' postmenstrual age and term infants, yet all the other anthropometric measurements were. Preterm infants weighed less (2,432 ± 378 g vs 3,309 ± 659 g; *P* < 0.001, large effect size r = 0.5) and had less FM (273 ± 141 g vs 370 ± 179 g; *P* = 0.022, small effect size 0.2) and FFM (2,160 ± 300 g vs 2,926 ± 394 g; *P* < 0.001, large effect size r = 0.7) than term infants. The preterm infants had significantly smaller head circumferences (32.6 ± 1.5 cm vs 34.9 ± 1.8 cm; *P* < 0.001, large effect size r = 0.5) and waist circumferences (31.6 [30.0, 32.9] cm vs 32.8 [32.0, 34.5] cm; *P* = 0.01, medium effect size r = 0.3) than the term infants. The waist: length ratio was significantly higher in the preterm group (0.68 ± 0.38 vs 0.64 ± 0.04; *P* < 0.001, medium effect size r = 0.4).

Table 4.6: Anthropometric Outcomes of Preterm Infants at ≥ 36 weeks' Postmenstrual Age Compared to Term Infants after Birth

	Preterm measured at ≥ 36 weeks' postmenstrual age (*n* = 22)	**Term** (*n* = 69)	***P****
% FM†	10.9 ± 5.0	10.9 ± 4.2	0.98
FM (g)†	273 ± 141	370 ± 179	0.022*
FFM (g)†	2,160 ± 300	2,926 ± 394	< 0.001*
Weight (g)†	2,432 ± 378	3,309 ± 659	< 0.001*
Length (cm)†	46.4 ± 2.0	51.8 ± 2.5	< 0.001*
Head circumference (cm)†	32.6 ± 1.5	34.9 ± 1.8	< 0.001*
Waist circumference (cm)‡	31.6 [30.0, 32.9]	32.8 [32.0, 34.5]	0.01*
Waist: length ratio†	0.68 ± 0.38	0.64 ± 0.04	< 0.001*

†Mean ± SD
‡Median [25th-75th quartiles]
*Significant differences (*P* < 0.05) (Independent T-Test, Mann-Whitney Test)

4.5 Growth of Preterm Infants between their First and Second Measurements

Eleven preterm infants were measured twice before they were discharged from hospital (**Table 4.7**). The % FM increased significantly between the first and second measurements (8.5 ± 3.5 vs 15 ± 4.2; $P < 0.001$, large effect size r = 0.9). Absolute FM (178 ± 85 g vs 368 ± 119 g; $P < 0.001$, large effects size r = 0.9), FFM (1,872 ± 119 g vs 2,061 ± 151 g; $P = 0.002$, large effect size r = 0.8), weight (2,050 ± 329 g vs 2,429 ± 151 cm; $P < 0.001$, large effect size r = 0.9), length (45.0 ± 2.7 cm vs 47.0 ± 2.0 cm; $P = 0.003$, large effect size r = 0.8), head circumference (30.5 ± 2.7 cm vs 32.6 ± 1.1 cm; $P = 0.031$, large effect size r = 0.7) and waist circumference (29.6 ± 2.3 cm vs 32.0 ± 1.4 cm; $P = 0.014$, large effect size r = 0.7) also increased significantly between first and second measurements. The median [25th-75th quartiles] % increase in FM between the two measurements was 98.9 [70.1, 114.9] %.

Table 4.7: Change in Anthropometric Parameters between First and Second Measurements

	Measurement 1 (*n* = 11)	**Measurement 2** (*n* = 11)	***P****
Gestational age†	33.8 ± 0.9		
Postmenstrual age at measurement (weeks)†	34.9 ± 1.0	36.5 ± 0.8	< 0.001*
Postnatal age (days)†	8 ± 4	19 ± 6	< 0.001*
% FM†	8.5 ± 3.5	15.0 ± 4.2	< 0.001*
FM (g)†	178 ± 85	368 ± 119	< 0.001*
FFM (g)†	1,872 ± 119	2,061 ± 151	0.002*
Weight (g)†	2,050 ± 329	2,429 ± 208	< 0.001*
Length (cm)†	45.0 ± 2.7	47.0 ± 2.0	0.03*
Head circumference (cm)†	30.5 ± 2.7	32.6 ± 1.1	0.031*
Waist circumference (cm)†	29.6 ± 2.3	32.0 ± 1.4	0.014*
Waist: length ratio†	0.65 ± 0.05	0.68 ± 0.01	0.2

†Means ± SD
*Significant differences ($P < 0.05$) (Paired Sample T-test)

4.6 Early Feeding Practices of Preterm Infants

Table 4.8 displays the characteristics of the infants at birth in each of the feeding groups. One-way ANOVA shows that differences exist in the gestational age of the infants in the different groups (P = 0.05, large effect size r = 0.5). Post hoc analysis shows that infants in the formula group were significantly more mature than those in the parenteral nutrition group (P = 0.005). The difference between the formula and dextrose groups was of borderline significance (P = 0.052), with infants in the formula group tending to be more mature than infants in the dextrose group. The One-way ANOVA also revealed significant differences in the mean birth weight of groups (P < 0.001, large effect size r = 0.6). Post hoc analysis shows that infants in the parenteral nutrition group were significantly lighter and shorter at birth than those in the formula (P < 0.01) and breast-milk groups (P = 0.02) and tended to be lighter than infants in the dextrose group (P = 0.054). There were significant differences in the head circumferences at birth between the feeding groups (P = 0.005, large effect size r = 0.05). The mean head circumference of infants in the parenteral nutrition group was significantly smaller than infants in the breast-milk group (P = 0.014) and tended to be less those in the formula group (P = 0.052).

Table 4.8: Description of Preterm Infants at Birth According to Feeding Group

	Dextrose (*n* = 17)	**Parenteral nutrition** (*n* = 7)	**Formula** (*n* = 13)	**Breast-Milk** (*n* = 8)	***P****
Gestational age (weeks) †	34.1 ± 0.9	33.4 ± 1.3	35.1 ± 0.8	34.5 ± 1.0	0.05*
Birth weight (g) †	2,155 ± 291	1,704 ± 319	2,483 ± 455	2,464 ± 400	< 0.001*
Birth weight z-score‡	-0.2 [-0.7, 0.3]	-0.7 [-1.6, -0.2]	0.2 [-0.5, 0.9]	0.8 [-0.5, 0.9]	0.097
Birth length (cm)†	45.9 ± 2.7	43.9 ± 1.3	46.3 ± 3.1	47.7 ± 2.6	0.009*
Birth length z-score†	0.46 ± 0.96	-0.57 ± 1.06	0.29 ± 1.23	0.74 ± 1.25	0.084
Birth head circumference (cm)†	31.1 ± 1.2	30.3 ± 1.7	32.3 ± 1.9	32.9 ± 1.5	0.005*
Birth head crimcumference z-score†	0.06 ± 0.82	0.0 ± 1.14	0.33 ± 1.34	1.0 ± 1.14	0.2

†Mean ± SD
‡Median [25th-75th quartiles]
*Significant differences (P < 0.05) (One-Way ANOVA, Kruskal-Wallis Test)
Feeding groups are defined as the feeding method predominantly recieved by the infants in the first five days after birth.

The anthropometric measurements of the preterm infants at their first measurement according to their feeding group are displayed in **Table 4.9**. Kruskal-Wallis test shows that the postnatal age at which the infants were measured differed amongst the feeding groups ($P < 0.001$). One-way ANOVA reveals significant differences in FFM ($P = 0.004$, large effect size r = 0.05), weight ($P = 0.013$, large effect size r = 0.5), and length ($P = 0.036$, medium effect size r = 0.04) amongst the feeding groups. Post hoc analysis shows that the mean weight and length of the parenteral nutrition group was lower than the mean weight and length of the breast-milk group ($P = 0.013$, $P = 0.036$). Infants in the parenteral nutrition group had significantly less FFM than the formula group ($P = 0.008$).

Table 4.9: Anthropometric Measurements of Preterm Infants at the First Measurement According to Feeding Group

	Dextrose (*n* = 17)	**Parenteral Nutrition** (*n* = 7)	**Formula** (*n* = 13)	**Breast-Milk** (*n* = 8)	***P****
Postnatal age (days)‡	9 [7, 9]	12 [12, 17]	4 [3, 7]	5.5 [4, 7]	< 0.001*
Post menstrual age at measurement (weeks)‡	35.6 [34.6, 35.9]	35.1 [34.1, 36.9]	35.6 [35.1, 35.7]	35.6 [34.5, 36.1]	0.9
FM%†	7.4 ± 3.2	10.2 ± 4.3	9.1 ± 4.5	9.9 ± 3.7	0.3
FM (g)†	158 ± 80	200 ± 82	225 ± 141	243 ± 112	0.2
FFM (g)†	1,947 ± 268	1,773 ± 193	2,209 ± 301	2,147 ± 266	0.004*
Weight (g)†	2,105 ± 306	1,974 ± 177	2,376 ± 412	2,516 ± 508	0.013*
Length (cm)†	45.9 ± 2.6	43.9 ± 1.3	46.3 ± 3.1	48.0 ± 2.5	0.036*
Head circumference (cm)†	31.0 ± 1.8	31.0 ± 1.5	32.5 ± 1.7	32.8 ± 1.9	0.069
Waist circumference (cm)†	29.5 ± 1.7	29.9 ± 2.5	30.6 ± 2.3	30.9 ± 3.1	0.5

†Mean ± SD
‡Median (25th-75th quartiles)
*Significant differences ($P < 0.05$) (One-Way ANOVA, Kruskal-Wallis Test)
Feeding groups are defined as the feeding method predominantly recieved by the inafants in the first five days after birth.

Chapter 5: Discussion

This explorative, prospective observational study is the first in New Zealand to utilise air displacement plethysmography (ADP) to measure the body composition of term and preterm infants. The results provide insight into the fat mass (FM) and fat free mass (FFM) of term and moderate to late preterm infants born at Auckland City Hospital. Additionally, this study has explored the strategies used to feed moderate to late preterm infants in the first five days after birth at Auckland City Hospital. This research has highlighted issues that will inform further research questions, as well as practical considerations to be made in developing study designs to suit the setting of the Newborn Intensive Care Unit (NICU) at Auckland City Hospital.

5.1 Characteristics of Participants

The study population included 47 preterm infants and 69 full term infants. The mean gestational age of the preterm infants was 34.3 weeks' gestation and for the term infants it was 39.4 weeks' gestation. The mean birth weight of the preterm infants was 2,212 g and for full term infants it was 3,484 g. In 2011 the average birth weight of all births in New Zealand was 3,420 g (Ministry of Health, 2014). Predictably, the preterm infants weighed less than this whereas the weight of the term infants was very similar.

The ethnicity of the mothers who gave birth in 2014 at Auckland City Hospital has been broken down to 6.5% Māori, 11.9% Pacific, 8.7% Indian, 24.9% Asian, 32.7% New Zealand European, 11.5% other European, and 3.7% other (Auckland District Health Board, 2015a). While the ethnic groups in the study population have similar proportions to those seen at Auckland City Hospital, numbers in this study are too small to be a representative sample of each group. The ethnicity of the infants was taken from their medical notes, which is self-reported by the parents. However, defining the infants as having just one ethnicity does not account for mixed ancestry, and does not reflect the ethnicity of both parents if maternal and paternal ethnicities differ. This would be a limiting factor in achieving an ethnically representative group of infants.

5.2 Anthropometric Outcomes of Term Infants

Full term infants in this study had on average 10.9% FM at birth. When broken down by sex, males had 9.4% FM and females had 12.2% FM. These results are within the ranges of values published in international research of term infant body composition after birth measured using ADP, with values ranging from 7.3-14.5% FM for males and 7.8-15.4% for females (Andersen et

al., 2013; Carberry et al., 2010; Carberry et al., 2013; Eriksson et al., 2010; Fields et al., 2011; Hawkes et al., 2011; Lee et al., 2009; Olhager & Törnqvist, 2014; Paley et al., 2015; Roggero et al., 2009; Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010; Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010; Simon et al., 2013; Simon et al., 2014; Starling et al., 2015). However, these ranges are fairly wide and the applicability of these studies to the multi-ethnic population of New Zealand is questionable due to the majority of studies including predominantly European participants (Carberry et al., 2010; Carberry et al., 2013; Eriksson et al., 2010; Lee et al., 2009; Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010; Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010; Starling et al., 2015).

Term male infants had significantly lower % FM than term females. The difference in % FM can be attributed to the male infants having significantly more FFM than the females, as the absolute FM and body weight did not differ significantly between the sexes. This difference in body composition is present throughout the lifespan; however, not all studies investigating infant body composition have found that this trend begins in infancy (Carberry et al., 2010; Eriksson et al., 2010; Fields et al., 2012; Geer & Shen, 2009). Hawkes et al. (2011) and Simon et al. (2013) also found that term male infants had a lower % FM and higher absolute FFM than female infants at birth. Hawkes et al. (2011) found that this difference was only significant in infants aged over 38 weeks' gestation, and that there was no difference between the sexes in infants aged between 36^{+0} and 37^{+6}. Likewise, Simon et al. (2013) also found that term male infants had lower % FM than term female infants, but observed no difference amongst preterm infants. This suggests that the difference between sexes emerges once infants reach full term. The difference in the body composition between preterm males and females in the present study were unable to be compared due to the small numbers after participants were categorised by postmenstrual age.

Conversely, other studies looking at the body composition of term infants have found that there is no difference in the body composition between males and females at birth (Andersen et al., 2013; Carberry et al., 2010; Eriksson et al., 2010; Fields et al., 2011; Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010). However, some of these studies have relatively small sample sizes (Fields et al., 2012; Roggero, Gianni, Orsi, Piemontese, Amato, Moioli, et al., 2010).

For the present study, it was not recorded what the term infants were fed in the time between birth and their body composition measurement. This is a limitation to the study as it limits the comparability of the results to other studies that have specified all infants were exclusively

breast-fed (Fields et al., 2011; Roggero et al., 2009; Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010). However, it is known that in 2014 78% of infants were exclusively breast-fed when discharged from ACH (Auckland District Health Board, 2015a). Additionally, Eriksson et al. (2010), point out that body composition in the first week after birth is more reflective of the environment *in utero* and is less affected by postnatal nutrition. The median postnatal age that the term infants were measured at in this study was two days. Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al. (2010) hypothesise that because the small amount of feed consumed in the first days after birth, it is not sufficient to contribute to body mass.

Maternal body mass index (BMI) and gestational weight gain have both been found from two large studies to be factors contributing to term infant body composition (Hawkes et al., 2011; Starling et al., 2015). This information was not collected in the present study which could be a limitation as they could be confounding factors to the results. Additionally, the body composition of term infants was used as a comparison for the desirable body composition for preterm infants to be meeting at term corrected age (TCA). Including infants of mothers with high BMIs could result in the values not representing an optimal body composition, as higher maternal BMI is associated with higher infant % FM (Hawkes et al., 2011; Starling et al., 2015).

5.3 Anthropometric Outcomes Preterm Infants

5.3.1 Anthropometric Outcomes of Preterm Infants in the First Two Weeks after Birth

Of the preterm infants in the study, 25 were measured within the first week after birth and 19 were measured within the second week. This is because preterm infants were measured for the first time once they were medically stable and no longer required interventions such as respiratory support or intravenous fluids. The average % FM of infants measured within the first week (mean gestational age 34.6 weeks) was 8.7%. There have been three previous studies that have measured the body composition of preterm infants using ADP within the first week. Ramel et al. (2014) found a similar result when they measured preterm infants with a mean gestational age of 31.2 weeks' within 72 hours after birth and found they had 8.3% FM. Giannì et al. (2012) found that late preterm infants with a mean gestational age of 35.2 weeks' had 5.2% FM when measured on the fifth day after birth. Olhager and Törnqvist (2014) measured preterm infants with a mean gestational age of 35 weeks' on the fourth and sixth days after birth and found they had 4.9% FM and 4.4% FM respectively. The latter two had comparatively smaller sample sizes to Ramel et al. (2014) and the present study. They were also both conducted in Europe, whereas Ramel et al. (2014) was an American study with greater ethnic diversity, which could have contributed to the difference. The present study

also has greater ethnic diversity. It has been hypothesised by (Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010) that different genetic backgrounds of populations affect the % FM of infants. This has been demonstrated to an extent in an American study by Paley et al. (2015) who found that Caucasian male infants had less FM than Asian and Hispanic males. Differences in infant body composition between ethnicities and whether these differences are due to the environment or genetics are areas that require more research.

Infants measured for the first time within the second week (8-14 days) after birth had 8.1% FM. Only one other study has published results for the body composition of preterm infants using ADP in the second week (Olhager & Törnqvist, 2014). Olhager and Törnqvist (2014), as discussed above, also measured the infants on day nine after birth and found they had 4.9% FM. While these results are quite different to the present study, both of them had very small study populations, and as mentioned previously are not of similar ethnic backgrounds, which limits the comparability of the two (Olhager & Törnqvist, 2014).

There was no significant difference in the % FM between preterm infants measured in the first week after birth and preterm infants measured in the second weeks after birth. It is unclear whether infants measured in the second week after birth would be expected to have a higher % FM than those in the first week. Studies have documented a rapid increase in FM between birth and TCA; however, it is unknown when this fat deposition occurs (Giannì et al., 2012; Olhager & Törnqvist, 2014). Olhager and Törnqvist (2014) reported that they found no difference in % FM between day four and day nine, in moderate-late preterm infants. This suggests that the % FM does not increase until after the period of postnatal weight loss. As preterm infants have been found to experience a greater percentage of postnatal weight loss and take longer to regain birth weight than term infants (Preedy, 2011), % FM may not begin to increase until after the second week after birth.

As mentioned previously, preterm infants were only measured for the first time once they were medically stable. Infants measured within the first week after birth were heavier, longer and had larger head circumferences at birth than infants measured within the second week. As birthweight is an indicator of neonatal health, it is likely that these smaller infants required longer medical interventions, and therefore were unable to be measured in the first week after birth (World Health Organisation, 1995).

5.3.2 Anthropometric Outcomes of Preterm Infants at ≥ 36 weeks' Postmenstrual Age

Preterm infants measured at ≥ 36 weeks' postmenstrual age had a younger postmenstrual age at the time of measurement than the full term infants. This difference was caused by the preterm infants being discharged from hospital before reaching term correct age. It was not the scope of this study to bring the infants back into hospital for subsequent measures. The PeaPod was situated in the NICU and was not able to be moved. As the NICU is a restricted access area due to infection control, infants were not able to return to the unit for subsequent measures after being discharged. This limits the comparability of the two groups as measurements were taken at different postmenstrual ages.

Preterm infants measured at ≥ 36 weeks' postmenstrual age had 10.9% FM. There have been two previous studies that have used ADP to measure preterm infants at similar postmenstrual ages (Simon et al., 2013; Simon et al., 2014). Both studies measured preterm infants born before 35 weeks' gestation. Simon et al. (2013) found that when measured at 37.8 weeks' postmenstrual age, the infants had 13.4% FM and Simon et al. (2014) found that their participants had 12.9% FM when measured at 37.3 weeks' postmenstrual age. These results are higher than the findings from the present study, and could be due to lower the gestational age of the infants included by Simon et al. (2014) and Simon et al. (2013). The preterm infants in this study had a mean gestational age of 34.8 weeks', whereas infants recruited by Simon et al. (2014) and Simon et al. (2013) had a mean gestational age of 31.5 weeks. This could have contributed to the infants in these studies having higher % FM at the time of measurement as gestational age has been found to have a negative relationship with % FM at TCA (Gianni et al., 2009; Ramel et al., 2011; Roggero et al., 2008; Roggero et al., 2009; Simon et al., 2014).

Term infants in the present study had 10.9% FM. This was not significantly different from the preterm infants when measured at ≥ 36 weeks' postmenstrual age, despite the postmenstrual ages of the two groups being significantly different (37.4 weeks' vs 39.7 weeks'). Preterm infants in the present study were also found to have a significantly higher waist: length ratio than the term infants. As waist: length ratio is another measure of fatness, this further suggests that the infants in this study had higher amounts of fat in proportion to their size. It has been hypothesised that preterm infants preferentially deposit FM as an adaptive mechanism to postnatal life (Giannì et al., 2012). Alternatively, Simon et al. (2013) suggest that rather than an increased deposition of FM, it could be the result of preterm infants having lower FFM. Findings from Olhager and Törnqvist (2014) support this when they found that late preterm infants measured at TCA had significantly less FFM than full term infants.

Simon et al. (2013) measured preterm infants at a similar postmenstrual age to the present study (37.8 weeks' postmenstrual age) and found that preterm infants measured at 37.8 weeks' postmenstrual age had significantly higher % FM than full term infants at birth. Again, the difference between results from Simon et al. (2013) and the present study is likely to be due to the inclusion of infants with younger gestational ages, causing the % FM of the preterm infants to be higher. Research has demonstrated that % FM increases steadily in the first six months after birth (Fields et al., 2011; Fomon & Nelson, 2002; Roggero, Gianni, Orsi, Piemontese, Amato, Liotto, et al., 2010). This suggests that by the time equivalent postmenstrual ages are met, preterm infants in this study will have a higher % FM than term infants. This has been observed in numerous studies that have measured the body composition of preterm infants using term corrected age and compared to a group of full term infants. A recurrent finding in these studies is that the % FM of preterm infants is higher than the % FM of full term infants at equivalent ages (Giannì et al., 2012; Olhager & Törnqvist, 2014; Ramel et al., 2011; Roggero et al., 2009). However, three of these studies have relatively small sample sizes (Gianni et al., 2009; Olhager & Törnqvist, 2014; Ramel et al., 2011). Additionally, Ramel et al. (2011) and Roggero et al. (2009) included infants of a younger gestational age than the present study.

5.3.3 Growth of Preterm Infants between their First and Second Measurements

Eleven preterm infants were measured twice before they were discharged from hospital. Between the two measurements the % FM increased from 8.5% to 15.0%. The average % increase in FM amongst these infants was 98.9%. It appears that during this period, FM increased more than FFM. Two other studies have also demonstrated a rapid increase in FM in early postnatal life (Giannì et al., 2012; Olhager & Törnqvist, 2014). In an explorative study, Giannì et al. (2012) found that late preterm infants experienced a 182% increase in FM from the fifth day after birth and term corrected age.

The group of infants that were measured twice had a younger gestational age than the overall group of preterm infants. This may be due to the infants with younger gestational ages requiring longer hospital stays, and therefore allowing more time for subsequent measurements. The average % FM of this group at the second measurement was higher than the % FM of the 22 infants measured at ≥ 36 weeks' postmenstrual as age discussed above (10.9% FM). This is likely due to both the younger gestational age and higher postmenstrual age at measurement of the group, as these are factors that have been associated with

increased % FM at term corrected age in preterm infants (Gianni et al., 2009; Roggero et al., 2008; Simon et al., 2014).

The small sample of infants with serial measurements limits the use of these data. Numbers were not large enough to compare the changes in body composition amongst the different feeding groups. However, being an exploratory study, the purpose is not to draw definitive conclusions but to identify trends to be researched further. These results demonstrate that the preterm infants in this sample experienced a rapid increase in % FM during their hospital admission, identifying that further research is required to determine factors contributing to this.

5.4 Early Feeding Practices of Preterm Infants

This study describes the characteristics of the infants receiving different early feeding strategies at Auckland City Hospital. Infants were grouped according to which feeding strategy they predominantly received within the first five days after birth. Of the preterm infants in the study, 38% were in the dextrose group, 16% in the parenteral nutrition group, 29% in the formula group, and 18% in the breast-milk group. A limitation in grouping the infants this way is that very rarely did they receive just one method of feeding in the first five days. This made defining the groups difficult. One way that this could have been improved would have been to define the groups based on the percentage of energy received from the different feeding strategies. The energy content and composition of the feeds could also have been a factor contributing to the outcome measurements and therefore would have been useful in determining if comparisons between the groups were appropriate.

The preterm infants in this study were a heterogeneous group including infants of a range of gestational ages measured at differing postmenstrual ages. As discussed previously, the time of measurement was dependant on the infants' medical status and suitability to tolerate ADP. Due to the small sample size, it was not possible to stratify the infants according to either gestational age or postmenstrual age when comparing the feeding groups. Being able to do this may have reduced confounding factors which could have made the results more meaningful. The results, do however, describe the characteristics of infants receiving the different feeding strategies. As this study is observational, these results are useful as they give a picture of current practise in the unit.

Overall, it appears that infants receiving parenteral nutrition were the youngest and smallest at birth. This is expected, as the criteria for receiving parenteral nutrition at Auckland City

Hospital is infants that are born < 37 weeks' gestation who are delayed in receiving full enteral feeds or who have a birthweight of < 1,500 g.

At the time of measurement, the infants in the parenteral nutrition group weighed less and were shorter than the breast-milk group, and had less FFM than the formula group. It is unclear from this study whether these outcomes are a result of the feeding strategy or rather related to their growth in utero.

5.5 Study Design

The participants in this study were recruited as a convenience sample. While the majority of the parents of eligible infants were approached, not all consented.

One reason for this could be parents feeling overwhelmed from the experience of having a preterm infant and having too much else going on in the NICU. Some eligible infants may have been missed due to being admitted to the NICU during the weekend and subsequently being discharged or transferred to another unit before their parents could be approached.

A research nurse was required to assess the suitability of preterm infants for ADP measurements and was also required, for safety purposes, to be present when measurements on the preterm infants were conducted. Limited availability of the research nurse could also have meant that some infants were unable to be assessed or measured during their admission to the NICU.

5.5.1 Air Displacement Plethysmography

A strength of this study is the use of ADP to measure FM and FFM, as this method has been shown to be a reliable and accurate in both term and preterm infants (Ma et al., 2004; Roggero, Giannì, Amato, et al., 2012).

However, as discussed in the literature review, two compartment models for measuring body composition involve assumptions. ADP uses the assumption that the density and proportions of the components of FFM do not differ between individuals (Fields et al., 2002). To reduce the effect of potential variation between individuals, multi-compartment models can be used to measure the different compartments of FFM, such as total body water using isotope dilution (Wells et al., 1999). However, this adds to participant burden, something that should be minimised in a NICU setting. Another factor that could contribute to variation between individuals is the time since the last feed. While the majority of infants were measured prior to being fed, this was not feasible for all the infants. This was due to having to fit measurements

in around the structured days of the infants, with medical procedures and assessments taking precedence over research. Measuring an infant using ADP soon after they have been fed can result in the weight of the feed contributing to their body weight and therefore reducing the accuracy of the results.

Another limitation of using ADP for this study is that measurements cannot be done until the infants are medically stable, meaning there may be a period after birth when measurements cannot be conducted. As seen in this study, this resulted in infants being measured at varying postmenstrual ages, limiting the comparability of the results.

5.6 Conclusions

The aims for this study were to measure the FM and FFM of moderate to late preterm and term infants and to explore the relationship between feeding strategies and FM and FFM in moderate to late preterm infants after birth at Auckland City Hospital.

The study is the first to describe the body composition of term and preterm infants in New Zealand using ADP. While the sample is not representative of the general population, they provide preliminary results of the body composition of infants born in Auckland, New Zealand.

Moderate to late preterm infants at Auckland City Hospital had similar % FM as term infants before they reached term-corrected age (37.4 weeks' postmenstrual age).

The moderate to late preterm infants who were measured twice during their hospital admission, experienced a rapid increase in FM.

Infants who received parenteral nutrition as their predominant feeding method for the first five days after birth were born at younger gestational ages and weighed the least at birth. At the time of measurement the parenteral nutrition group remained the lightest, shortest group, and also had the least FFM.

This study has highlighted that there are practical limitations to be considered when conducting research using ADP in the NICU at Auckland City Hospital. These include: not being able to measure the infants immediately after birth if they require respiratory support or intravenous lines, and not being able bring infants back into NICU for measurements after they have been discharged.

5.7 Recommendations for Future Research

1. Develop normative reference values for % FM, FM and FFM of term infants in New Zealand using a robust, ethnically representative sample.
2. Compare the body composition of moderate to late preterm infants at term-corrected age to that of healthy term infants.
3. Conduct a clinical trial to determine the effects of different feeding practices on the body composition of moderate to late preterm infants.
4. Identify non-nutritional factors (gestational age, postmenstrual age, postnatal age, ethnicity, maternal factors, medical conditions) affecting the FM and FFM of term and preterm infants in New Zealand.
5. Practical considerations for future studies:
    a. Have protocols in place for bringing infants back to NICU for subsequent ADP measurements after discharge to obtain measurements at older postmenstrual ages.
    b. Integrate ADP measurements with clinical care to allow for more structured timings of measurements and greater acceptability with parents.

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Appendices

Appendix 1: Ethics Approval Letter

Health and Disability Ethics Committees
Ministry of Health
Freyberg Building
20 Aitken Street
PO Box 5013
Wellington
6011

hdecs@moh.govt.nz

28 April 2015

Professor Frank Bloomfield
Liggins Institute
University of Auckland
Private Bag 92019
Auckland 1142

Dear Professor Bloomfield

Re:	**Ethics ref:**	**15/STH/52**
	Study title:	An observational study exploring the relationship between different feeding strategies and the development of fat mass and fat free mass in moderate to late preterm babies

I am pleased to advise that this application has been *approved* by the Southern Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

Summary of Study

- Professor Bloomfield explained that this is an observational study with the aim of getting the first set of data in New Zealand on body composition of healthy term and babies born at moderate to late preterm gestations of all ethnicities. This is necessary as there is increasing evidence that babies born pre-term will have increased fat mass at term and at later ages, which may result in metabolic disease in adulthood.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the researcher were as follows.

- Professor Bloomfield advised that the results will be given to parents immediately and that they will not be given any advice based on the fat mass reading. He said that the researchers will tell parents that they want to design a study in the future to find the optimal nutrition for babies born pre-term.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

- Please begin the PIS with "you and your baby are invited"
- Please include a footer with page numbers and version number.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Southern Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

Non-standard conditions:

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

- Please amend the participant information sheet and consent form, taking into account the suggestions by the Committee *(Ethical Guidelines for Observational Studies, para 6.10)*.

Please submit your non-standard conditions by email to HDECS@moh.govt.nz

Please note HDEC review is not required for non-standard conditions however they must be completed prior to commencing your study. Do not submit non-standard conditions as a post approval form (PAF).

For information on non-standard conditions please see section 128 and 129 of the Standard Operating Procedures at http://ethics.health.govt.nz/home.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 28 April 2016.

Participant access to ACC

The Southern Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Ms Raewyn Idoine
Chairperson
Southern Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix 2: ADHB Approval Letter

Research Office
Level 14, Support Bldg
Auckland City Hospital
PB 92024, Grafton, Auckland
Phone: 64 9 307 4949 Extn. 23854
Fax: 64 9 307 8913
Email: mwoodnorth@adhb.govt.nz
Website: www.adhb.govt.nz/ResearchOffice

Date 28 April 2015

Institutional Approval

Professor Frank Bloomfield
Newborn Services
National Women's Health
Auckland City Hospital

Dear Frank

RE: Research project 15/STH/52, A+ 6691: Fat mass in term and preterm New Zealand born babies and factors that influence fat mass at term-corrected age in preterm babies.

The Auckland DHB Research Review Committee (ADHB-RRC) would like to thank you for the opportunity to review your study and has given approval for your research project.

Your Institutional approval is dependant on the Research Office having up-to-date information and documentation relating to your research and being kept informed of any changes to your study. It is your responsibility to ensure you have kept Ethics and the Research Office up to date and have the appropriate approvals. ADHB approval may be withdrawn for your study if you do not keep the Research Office informed of the following:

- Any communication from Ethics Committees, including confirmation of annual ethics renewal
- Any amendment to study documentation
- Study completion, suspension or cancellation

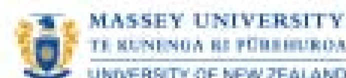
More detailed information is included on the following page. If you have any questions please do not hesitate to contact the Research Office.

Yours sincerely

On behalf of the ADHB Research Review Committee
Dr Mary-Anne Woodnorth
Manager, Research
ADHB

c.c. Malcolm Battin

..../continued next page



Participant Information Sheet

Early nutrition and body composition in babies

You and your baby are invited to take part in a research study looking at nutrition and growth in preterm and term babies.

Please take your time to think about and decide whether you wish to take part in the project. You are encouraged to discuss your baby's participation in the project with family / whanau.

Taking part is a completely voluntary (your choice) and if you decide you do not wish for your baby to take part, it will not affect you or your baby's current or future healthcare in any way. You may withdraw your baby's participation at any time.

Purpose of this study

How babies feed and grow is important for health. Although all babies are weighed after birth, we know very little about the amount of fat in their body relative to muscle (often referred to as body composition). Knowing more about babies' body composition will help us to understand how nutrition can support optimal growth. This study will measure the body composition of babies born both at term and preterm. This will help us to understand the relationships between preterm birth, how preterm babies are fed between birth and discharge from hospital, and body composition and how body composition of preterm babies compares with that of healthy term babies. In the future, this study may help us guide parents of preterm and term babies on the best advice for feeding and growth of their baby.

We are aiming to recruit moderate to late preterm babies (born between 32 and 36 weeks' gestation) and term babies (37 to 42 weeks' gestation). We are able to measure body composition using a technique called air displacement plethysomography in a PeaPod. This non-invasive and completely safe technique is routinely used in the care of many babies worldwide.

Project procedures

All measurements and data collection will be done while your baby is in hospital. For preterm babies we will measure their body composition weekly whilst they are in hospital. For term babies we will measure their body composition once before going home. Babies will be measured in the PeaPod (see picture below), as well as having their length, waist and

head circumference measured. Measuring your baby in the PeaPod is very quick and takes about 5 minutes.

As well as this we will collect data on how your baby has been fed and relevant medical information about your baby from their medical notes.

Data management

Each baby will be issued with a participant code that will be used for all data collection and measurements to ensure all information remains anonymous. Data will be confidential and only members of the research team will have access to it.

All data collected will only be used for the purpose of this study and will be stored securely.

You will be provided with a summary of the findings of the study when it is finished. Results will also be published in a scientific journal and may be presented at a conference to help guide future feeding practices of babies.

What is the PeaPod?

This equipment measures body composition- so it tells us how much fat your baby has. The technique measures the amount of air your baby pushes out of the machine, so it is completely safe, non-invasive and is used routinely in health services around the world.

Participant rights

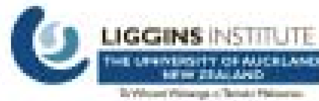
You are under no obligation to accept this invitation. If you decide to participate, you have the right to:

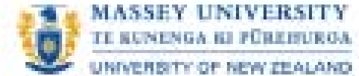
- *decline to answer any particular question;*
- *decline any measurements of your baby;*
- *withdraw from the study at any time;*
- *ask any questions about the study at any time during participation, and*
- *be given access to a summary of the project findings when it is concluded*

General Information

An interpreter will be provided if required.

You may have a friend, family or whanau support to help you this study and any other explanation you may require prior to deciding whether to participate or not. You,





and/or a friend, family or whanau support can accompany your baby during any measurements.

This study has received ethical approval from the Southern Health and Disability Ethics Regional Ethics Committee (15/STH/32) and locality approval from ADHB Research Review Committee (A+6691).

Project contacts

If you have any questions or concerns about the study at any stage you can contact:

Professor Frank Bloomfield	Dr Cath Conlon:
f.bloomfield@auckland.ac.nz	c.conlon@massey.ac.nz
(09) 923 6107	(09) 414 0800 ext 43658
021 497598	021 1730428
Liggins Institute University of Auckland Private Bag 92019	Massey University Private Bag 102904 North Shore City
Auckland 1142	Auckland

If you have any queries or concerns regarding your rights as a participant in this project you can contact an Independent Health and Disability Advocate. This is a free service provided under the Health & Disability Commissioner:

Telephone (NZ Wide): **0800 555 050**

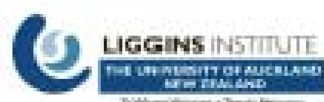
Free Fax (NZ Wide): **0800 2787 7678 (0800 2 SUPPORT)**

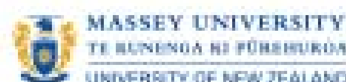
Email: advocacy@hdc.org.nz

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

Thank you, tēnā koe, for making the time to read about, and for considering taking part in this project.

Appendix 4: Consent Form





Consent Form

Early nutrition and body composition in babies

English	I wish to have an interpreter	Yes	No
English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori / kaiwhaka pakeha korero	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

- I have read and I understand the information sheet dated [Final version 6/3/2015] for volunteers taking part in the project called *Early nutrition and body composition in babies*. I have had the opportunity to discuss this project. I am satisfied with the answers I have been given.
- I have had the opportunity to use family / whanau support or a friend to help me ask questions and understand the project.
- I have had time to consider whether to take part in this project.
- I understand that taking part in this project is voluntary (my choice) and that I can stop taking part at any time and this will in no way affect my continuing or future health care.
- I understand that my participation in this project is confidential and that no material which could identify me will be used in any reports.
- I know who to contact if I have questions about the project in general or if I experience any ill effects resulting from my involvement in the project.
- I consent to my baby being measured using the PeaPod and other growth measurements (length, head circumference, waist circumference) being taken from my baby for the purpose of this study.
- I consent to medical information being collected from the medical records made during my baby's hospital admission.
- I consent to being contacted in the future regarding my baby's progress

I ____ (*full name*) hereby consent to my baby ____ (*name*) taking part in this study.

Signature: ____

Date: ______________ Time: ______________

Interpreter:

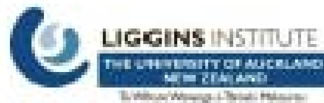
I ____________________________________ translated the project to the participant.

Signature: ____

Date: ______________

Early nutrition and body composition in babies Consent Form v1.2 23/04/15 1

Appendix 5: Feeding Data Collection Form



Participant ID: ______________

Feeding Data Collection

Date					
Age (days)					
Weight used (g)					

Feed Type (fill out all relevant tables)

Breast Milk

Breast milk fortifiers:

Nutricia Breast Milk Fortifier	g	g	g	g	g
Nestle PreNAN FM 85	g	g	g	g	g
Wyeth S-26 HMF	g	g	g	g	g
Other	g	g	g	g	g

If breastfed:

Number of feeds					
Length of feeds:	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min
	min	min	min	min	min

If bottle or enteral fed:

Amount given:	ml	ml	ml	ml	ml

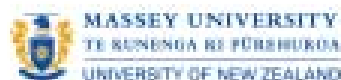
Formula

Name of formula:					
	ml	ml	ml	ml	ml
	ml	ml	ml	ml	ml
	ml	ml	ml	ml	ml

Parenteral Nutrition

Name of fluid:					
	ml	ml	ml	ml	ml
	ml	ml	ml	ml	ml
	ml	ml	ml	ml	ml
	ml	ml	ml	ml	ml

Appendix 6: Demographic and Medical Background Data Collection Form



Date: ___________

Participant ID: _____________

Demographic Information

Mother's date of birth: ______________________________________

Mother's ethnicity:

- New Zealand/European
- Other European
- New Zealand Māori
- Cook Island Māori
- Fijian
- Niuean
- Samoan
- Other
- Tongan
- Tokelauan
- Other Pacific Island
- Chinese
- Other Asian
- Indian
- South East Asian

Baby's gender: ______________________________________

Baby's ethnicity:

- New Zealand/European
- Other European
- New Zealand Māori
- Cook Island Māori
- Fijian
- Niuean
- Samoan
- Other
- Tongan
- Tokelauan
- Other Pacific Island
- Chinese
- Other Asian
- Indian
- South East Asian

Medical Background

Birth

1. Date of birth: ____________________
2. Gestational age: ____________________
3. Birth weight: ______________________ kg
4. Birth length: ______________________ cm
5. Head circumference at birth: ____________________ cm
6. Was the birth single or multiple? *(Circle one)*
   - Single
   - Twins
   - Triplets
   - Other
7. Type of delivery:
   - Vaginal birth
   - Caesarean

Infant medical details

1. Infant medical complications:
   - Respiratory distress syndrome
   - Pneumonia
   - Jaundice
   - Sepsis
   - Necrotizing enterolitis
   - Anaemia
   - No complications
   - Other:

____

____

____

____

____

2. Did the infant suffer from IUGR?
   - Yes
   - No

Maternal medical details

1. Reason for premature birth:

   - Spontaneous preterm labour
   - Severe infant growth restriction
   - Pre-eclampsia
   - Foetal distress
   - Placental abruption
   - Gestational diabetes
   - Infection
   - Other____
   ____
   ____

2. Was the mother treated with steroids prior to giving birth?
   - Yes
   - No
3. Other maternal medical complications:
   ____
   ____
   ____
   ____
   ____