Body Composition in Childhood Obesity

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Abstract

Childhood obesity has been increasing rapidly. Previous work investigating body composition in obese children and adolescents has relied primarily on body mass index (BMI), or on measures that assume constant properties of fat-free mass (FFM). This limits our understanding of the effect of treatment.

My PhD is divided into three aims. First, I explored differences in body composition between obese and non-obese children using multi-component models. Second, I investigated the effectiveness of two weight-loss programmes (a randomised controlled trial adopting the traffic-light program (TLP), and a pilot study evaluating treatment using Metformin). Third, I evaluated a bio-electrical impedance analysis (BIA) machine (TANITA BC-418 MA) as a clinical tool for assessing body composition in obese children.

Aim 1: obese children had greater hydration of FFM; this limits the accuracy of using techniques that assume constant FFM properties. Taking this into account, obese children had increased fat mass (FM) and FFM, particularly FM in the abdomen region

Aim 2: analyses from the TLP revealed that treatment and control groups significantly lost 0.1 BMI SDS during the trial; but did not significantly differ for any of the body composition outcomes. A further analysis revealed that there was a significant reduction in BMI SDS and FM but an increase in FFM in the period when obese children were treated versus an increase in BMI SDS and FM in the period when they were left. Results from the Metformin programme revealed no significant change in body composition following 6 months or 1 year treatment.

Aim 3: Using a manufacturer's equations, TANITA was not accurate at assessing body composition or its change over time. My new equations had no systematic bias in relation to body fatness, although an error of the FFM estimate of 2.2 kg, and may be used to guide management in clinical practice.

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Abbreviations

2C	two-component
3C	three-component
4C	four-component
ADP	air displacement plethysmography
APPLES	The Active Programming Promoting Lifestyle Education in Schools
AN	acanthosis nigricans
BIA	bio-electrical impedance analysis
BMC	bone mineral content
BMI	body mass index
C	circumference
CDC	centre from disease control
CT	computerized tomography
D	difference
D_2O	deuterium oxide dilution
D_{FFM}	density of fat-free mass
DXA	dual x-ray absorptiometry
ECW	extra-cellular water
FDA	Food and Drug Administration
FM	fat mass
FMI	fat mass index
FFM	fat-free mass
FFMI	fat-free mass index
GOSH	Great Ormond Street Hospital
GP	general practitioner
H_{ffm}	hydration of fat-free mass
HbA1c	glycosylated haemoglobin
HDL	high density lipo-protein
HT	height
ICH	Institute of Child Health
ICW	intra-cellular water
IOTF	International Obesity Task Force
IRS	insulin resistance syndrome
LDL	low density lipo-protein

LEAF	Lifestyle, Eating, Activity and Fitness
LEAP	live, eat and play
MRI	magnetic resonance imaging
mSv	milli sieverts
μSv	micro sieverts
N	number per group
NIH	National Institute for Health
NICE	National Institute for Clinical Excellence
R	resistance
RCT	randomized controlled trial
SD	standard deviation
SDS	standard deviation score
SE	standard error
SEE	standard error of estimate
SES	socio-economic status
TBW	total body water
TLP	traffic-light program
UCH	University College Hospital
WC	waist circumference
WHO	World Health Organisation
WHTR	waist to height ratio
WT	weight

Chapter 1: Introduction

The prevalence of childhood obesity in the UK has been increasing at a very rapid rate over the past few decades; most recent estimates report that approximately 16% of children are obese as defined by National UK cut-offs (Health Survey for England, 2008). This is a concern because childhood obesity is associated with a number of different consequences such as health risks during childhood (Figueroa-Colon *et al.* 1997; Lauer *et al.* 1997) and adulthood (Reilly *et al.* 2003), psychosocial problems (Strauss, 2000) and huge economic costs (House of Commons, 2004).

There is growing interest in the need to measure body composition in children. Assessing body composition is important in understanding the aetiology of childhood obesity, and in evaluating the success of different treatment programmes.

It has proven difficult to estimate body composition accurately in children for three main reasons. First we cannot use body composition techniques that are considered reliable in adults because children's body composition has not yet reached maturity, and equations used to estimate body composition in adults would not be suitable to use in children. Second, simple, rapid and non-invasive techniques that are suitable to use in children such as body mass index (BMI) do not give information on where fat is distributed in the body, or on the different body components such as fat and lean mass. Third, there are several methods that estimate the amount of fat and lean tissue, such as imaging techniques and deuterium oxide dilution (D_20); but most of these techniques are expensive, require a great degree of subject compliance and are usually only available in special research centres.

There has been surprisingly limited research looking both at body composition differences between obese and non-obese children, and the effectiveness of different treatment strategies in children and adolescents. In addition, most of the research conducted has relied primarily on surrogate measures such as BMI to assess body fatness. However, BMI has been previously shown to be an inaccurate measure of obesity; individuals with the same BMI levels may have very different percentage body fat levels (Wells, 2000).

The aim of this thesis is to investigate the effects of obesity on body composition in obese children and adolescents, to evaluate the effect of two different weight-loss treatment programmes on body composition, and to validate a simple technique to measure body composition in obese children and adolescents.

This thesis is divided into 8 chapters, and the following topics are discussed in each chapter: Chapter 2 includes background information on my research outlining the definition and classification of childhood obesity, the prevalence of obesity in the UK, the various effects obesity has, how obesity develops, and the different treatments attempted. The chapter also considers previous findings concerning body composition in obese children and adolescents. Chapter 3 is a review of the different available techniques used to measure obesity, outlining their advantages and disadvantages in assessing body composition in children, particularly the overweight and obese. Chapter 4 states the three hypotheses for the research and the methodology used to test them. Chapters 5, 6 & 7 describe each aim separately stating the research question, giving information on the sample size and recruitment, statistical analyses used, reporting the results obtained, followed by discussion and study limitations. Finally chapter 8 outlines the conclusion of the research giving a summary of all the findings, as well as possible implications for future research and clinical practice.

Chapter 2: Background information on childhood obesity

This chapter will include a review of the different aspects of obesity, giving a brief description of the definition and classification of obesity, followed by discussion of the prevalence of obesity in the UK and the aetiology of obesity. A description of some of the consequences of obesity and the different ways proposed to treat it are also discussed.

2.1 Growth and body composition in obese children

Growth is a dynamic process that is characterised by physiological changes occurring during life; it is genetically predetermined and significantly affected by hormonal, nutritional, and environmental factors (Bechard and Puig, 2003). Assessment of growth is essential for defining health and nutritional status, and for preventing and detecting diseases by recognising deviations from the normal pattern. Growth monitoring is also useful to assess response to interventions such as weight-loss programmes.

The process of growth occurs during four different stages of human life: gestation, infancy, childhood and adolescence. For the purpose of this thesis, it is most relevant to focus on the process of growth in childhood and adolescence, looking in more detail at obese children and adolescents.

During the first year of life, percentage body fat is increased largely by means of increased volume of the fat cells. Body fat percentage then decreases slowly as the child gets older until puberty. During the pubertal period, body fat increases again largely through an increase in the number of fat cells without significant change in the volume of fat cells; females showing a bigger increase than males (Baumgartner and Roche, 1988; Poissonnet *et al.* 1988) (refer to Figure 2-1). In addition, gender differences in the regional distribution of fat become more apparent after puberty where boys tend to accumulate more fat around their abdomen, and girls around their hips. This tendency can be attributed to hormonal changes that occur during puberty; oestrogen and progesterone increase the number and volume of fat cells around the hips for girls whereas androgens reduce them (Poissonnet *et al.* 1988). Before describing and

assessing growth and body composition in obese children, one needs to define and classify obesity.

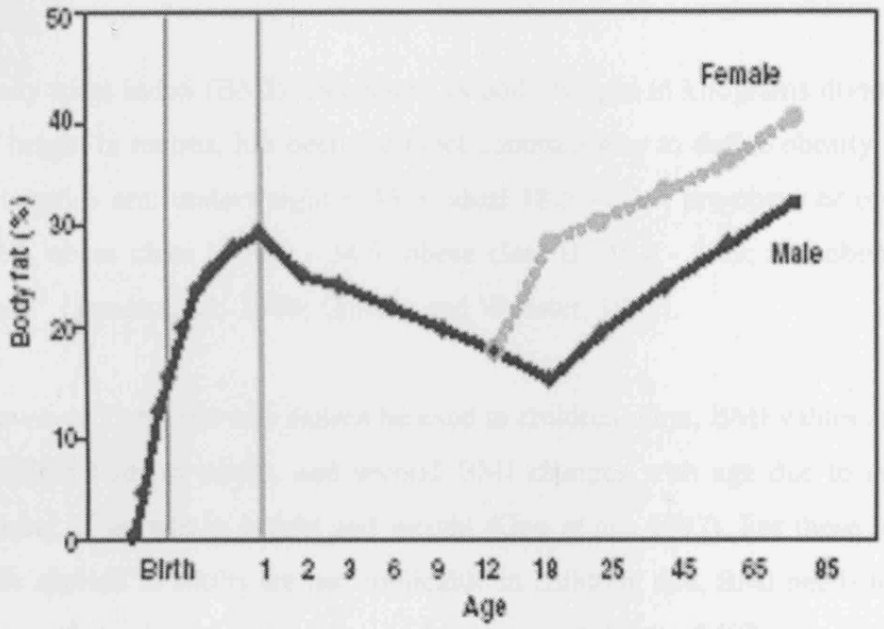


Figure 2-1 Percentage body fat against age of children and adults
Source: (Lobstein *et al.* 2004)

2.2 Definition of obesity

A typical medical dictionary defines obesity as an increase in body weight beyond the limitation of skeletal and physical requirements, as the result of excessive accumulation of body fat (Dorland's Medical Dictionary, 2007).

Similarly, the World Health Organisation (WHO) defines obesity as an increase in body weight beyond skeletal and physical standards as the result of an excessive accumulation of fat in the body (World Health Organization, 2008). They also state that overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

According to the UK Public Health Association and Faculty of Public Health, obesity is defined as an excess of body fat frequently resulting in a significant impairment of health and longevity (United Kingdom public health association and faculty of public health, 2003).

2.3 Classification of obesity

For many years, obesity has been classified using charts or cut-offs based on measurements from weight and height.

Body mass index (BMI), calculated as body weight in kilograms divided by the square of height in metres, has been the most common way to define obesity. For adults, BMI categories are: underweight < 18.5, ideal 18.5 - 24.9, pre-obese or over-weight 25.0 - 29.9, obese class I 30.0 - 34.9, obese class II 35.0 - 39.9; and obese class III > 40 kg/m^2 (James *et al.* 1988; Garrow and Webster, 1985).

However, these cut-offs cannot be used in children. First, BMI values are much lower in children than in adults, and second BMI changes with age due to differences in the timing of growth in height and weight (Guo *et al.* 1997). For these reasons BMI cut-offs applied in adults are not applicable in children, and, BMI needs to be adjusted for age so that comparisons can be made between children of different ages.

The Child Growth Foundation published BMI growth charts for girls and boys that can be used from birth to 20 years (Cole *et al.* 1995). These charts include nine percentile curves based on divisions of two thirds of a standard deviation (ranging from 0.4^{th} – 99.6^{th} percentile), where the two extremes identify the heaviest and lightest four per 1000 of the population. The charts were created by combining several UK surveys conducted in 1980 - 1990 and covering almost 15,000 children (Cole *et al.* 1995). The charts were derived using Cole's LMS method, which summarises data in terms of three smooth age-specific curves called L (lambda), M (mu), and S (sigma) (Cole and Green, 1992). The M curve corresponds to the median and the S curve corresponds to the coefficient of variation of BMI at each age and gender. The L curve, based on the Box-Cox power, allows for the substantial age-dependent skewness in the distribution of BMI. Hence the LMS method adjusts the BMI distribution for differing degrees of skewness at different ages, and allows BMI in individual subjects to be expressed as an exact centile or standard deviation score (SDS) (Cole *et al.* 1995). The formula used to calculate SD score for BMI is:

$$\text{Z-score} = \frac{[\text{BMI} / \text{M}]^{L} - 1}{\text{LS}} \qquad \textbf{Equation 2-1}$$

Where BMI is calculated as weight/height^2, and L, M and S are values specific to the child's age and gender (Cole *et al.* 1995).

These charts are currently widely used in clinical practice, and they are less affected by differences in the timing of puberty than simple height and weight charts. Figure 2-2 shows BMI percentiles of the UK population.

However, degree of overweight reported as percentage BMI (% BMI) is another common way to diagnose overweight and obesity in many weight management clinics in the UK. % BMI is calculated as (BMI - median BMI)/median BMI * 100 (median BMI = BMI at 50th percentile). % BMI is the percentage above the 50th percentile BMI for the appropriate age and gender; 50th percentile is ideal, 85th percentile is overweight and 95th percentile is obese (Paluch *et al.* 2007; Jelliffe, 1966)

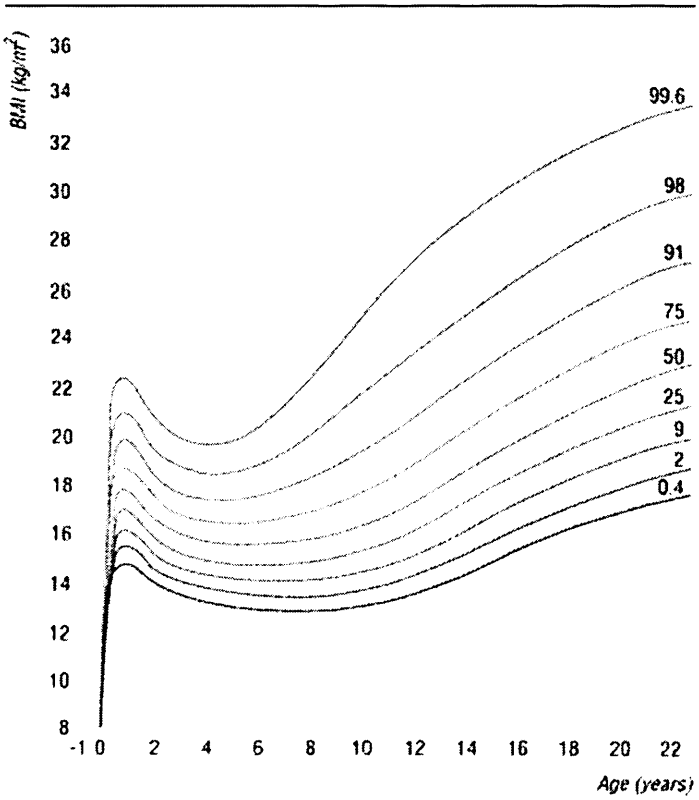


Figure 2-2 BMI percentiles of the UK population
Source: Child Growth Foundation; (Cole *et al.* 1995)

More recently in April 2006, the WHO produced BMI-for-age growth charts for boys and girls spanning from birth to five years (WHO, 2006). A total of 1,737 children were measured between 1997 and 2003 from the following countries: Brazil, Oman, Ghana, India, Norway and the US. These charts were generated for assessing the growth and development of young children all over the world. Figure 2-3 shows BMI-for age growth charts for boys and girls.

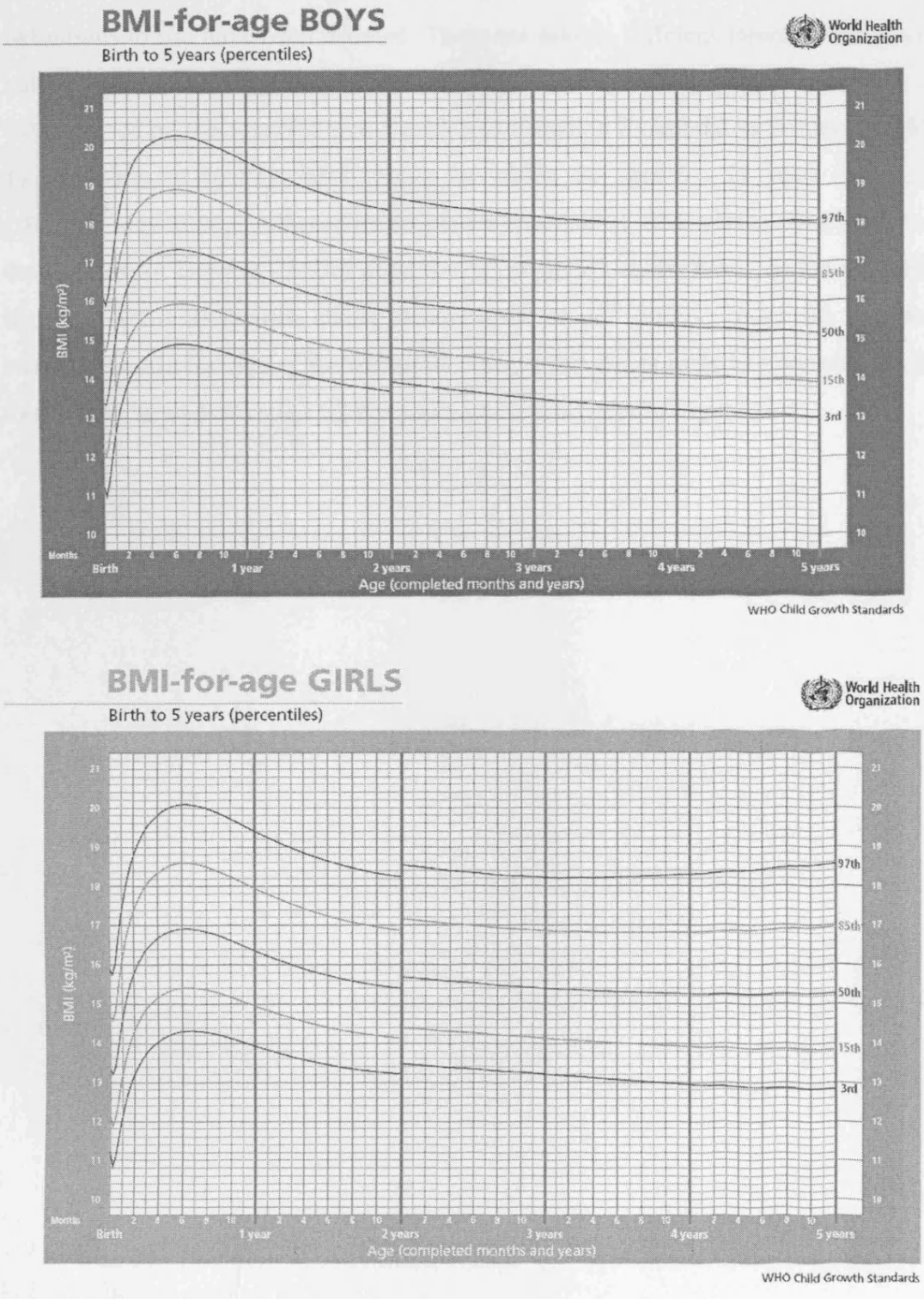


Figure 2-3 BMI-for age growth charts for boys (top) and girls (bottom)
Source: The WHO Growth Standards, 2006 (WHO, 2006)

The cut-off levels of overweight and obesity in childhood and adolescence and the best definitions to use have been debated. There are several different reference BMI cut-off values that are currently used. Must et al (1991) developed a set of reference BMI values based on the first National Health and Nutrition Examination Survey (NHANES 1) providing sex-specific BMI values for within the ages 6 - 19 years (Must *et al.* 1991). In May 2000, another more recent set of reference BMI values were produces by the Centres for Disease Control and Prevention growth charts based on the US national survey (CDC-US) growth charts (Kuczmarski *et al.* 2000). These are the revised National Centre for Health Statistics (NCHS) growth charts including ages 2 - 20 years, intended to be used for US children and adolescents (refer to Figure 2-4).

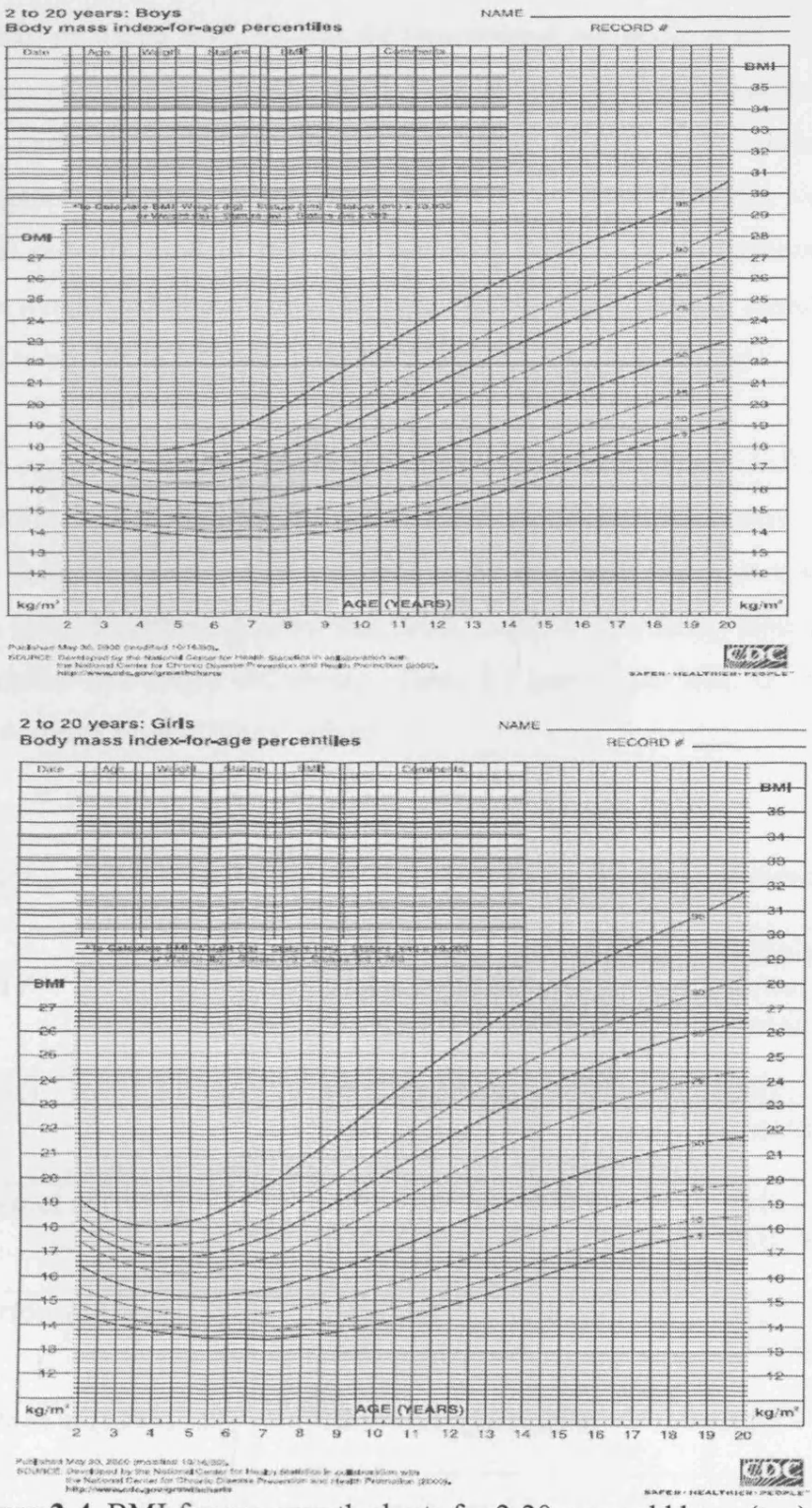


Figure 2-4 BMI-for age growth charts for 2-20 years old boys (top) and girls (bottom) Source: (National Centre for Health Statistics, 2000)

More recently, the International Obesity Task Force (IOTF) led by Cole and colleagues (2000) produced BMI cut-offs for international use (Cole *et al.* 2000). The data were produced by averaging BMI percentiles of large national cross sectional surveys from six countries including: Brazil, US, Great Britain, Netherlands, Hong Kong and Singapore covering the age range 2 - 18 years. The percentiles were chosen to match BMI cut-offs used in the adult reference population. An international definition of overweight and obesity in children is desirable to be able to monitor trends over time and to be able to compare levels between different populations.

The current recommended cut-offs to diagnose clinical obesity in the UK are as follows: children and adolescents with BMI > 85th percentile (equivalent to BMI-SDS > 1.04) are defined as overweight and BMI > 95th percentile (equivalent to BMI-SDS > 1.64) are defined as obese (Barlow and Dietz, 1998). In this thesis, these are the cut-offs used to define overweight and obesity. Table 2-1 summarises BMI cut-offs for children and adolescents from different references.

Table 2-1 BMI cut-offs for males and females from various references

	Definition of overweight	**Definition of obese**
IOTF	Males: BMI-SDS > 1.3 Females BMI-SDS > 1.19	Males: BMI-SDS > 2.37 Females BMI-SDS >2.25
WHO	BMI > 85th percentile BMI SDS > 1.04	BMI > 95th percentile BMI SDS > 1.64
Must et al (1991)	BMI > 85th percentile BMI SDS > 1.04	BMI > 95th percentile BMI SDS > 1.64
Barlow & Dietz (1998)	BMI > 85th percentile BMI SDS >1.04	BMI > 95th percentile BMI SDS > 1.64
Cole et al (1995)	BMI > 91st percentile	BMI > 98th percentile

Abbreviations: BMI= body mass index; SDS= standard deviation score; IOTF= International Obesity Taskforce; WHO= World Health Organisation
International age and sex specific BMI percentile curves that at age 18 years pass through BMI cut-offs for adult overweight and obesity of 25 and 30kg/m^2 respectively

2.4 Prevalence of obesity in children in the UK

There is a need to estimate the prevalence of obesity among children and adolescents in order to assess different preventive measures, monitor secular trends and identify high risk population groups.

A survey in the UK studying a total of 15,000 children aged 4 - 11 years found that there was little overall change in the prevalence of overweight or obesity (defined by IOTF) between 1974 and 1984 (Cole *et al.* 2000). Nevertheless from 1984 to 1994 overweight substantially increased from 5.4% to 9% in boys, and 9.3% to 13.5% in girls; and obesity increased from 0.6% to 1.7% in boys and 1.3% to 2.6% in girls (data from White, English 4-11 year old children; overweight and obesity defined by IOTF) (Chinn and Rona, 2001). The Department of Health reported that between 1995 and 2004 the frequency of obesity (defined using national UK cut-offs) in children aged 2-15 years increased from 11% to 19% in boys and from 12% to 18% in girls (Health Survey for England, 2005). More recent data from the Health Survey for England in 2006 suggest that obesity rates (defined using national UK cut-offs) in 2-15 year olds were 17% in boys and 15% in girls; a slight decrease from obesity rates reported in 2005 (Health Survey for England, 2008).
Figure **2-5** shows the prevalence of obesity amongst 2 -15 year old children in the UK, between 1995 and 2006.

A representative cross-sectional survey measuring children aged 2 – 5 years, and 11-16 years in 1977, 1987 and 1997 reported that waist circumference (WC) has increased over that period; particularly in girls (McCarthy *et al.* 2003; McCarthy *et al.* 2005). Trends in increased WC exceeded those in BMI.

These findings show that there has been a remarkable trend towards increased obesity, especially central obesity, in the UK. Even though the prevalence of obesity in children is still high, recent data suggest that these rates, especially in girls, are now slightly lower than five years ago but still much higher than a few decades ago.

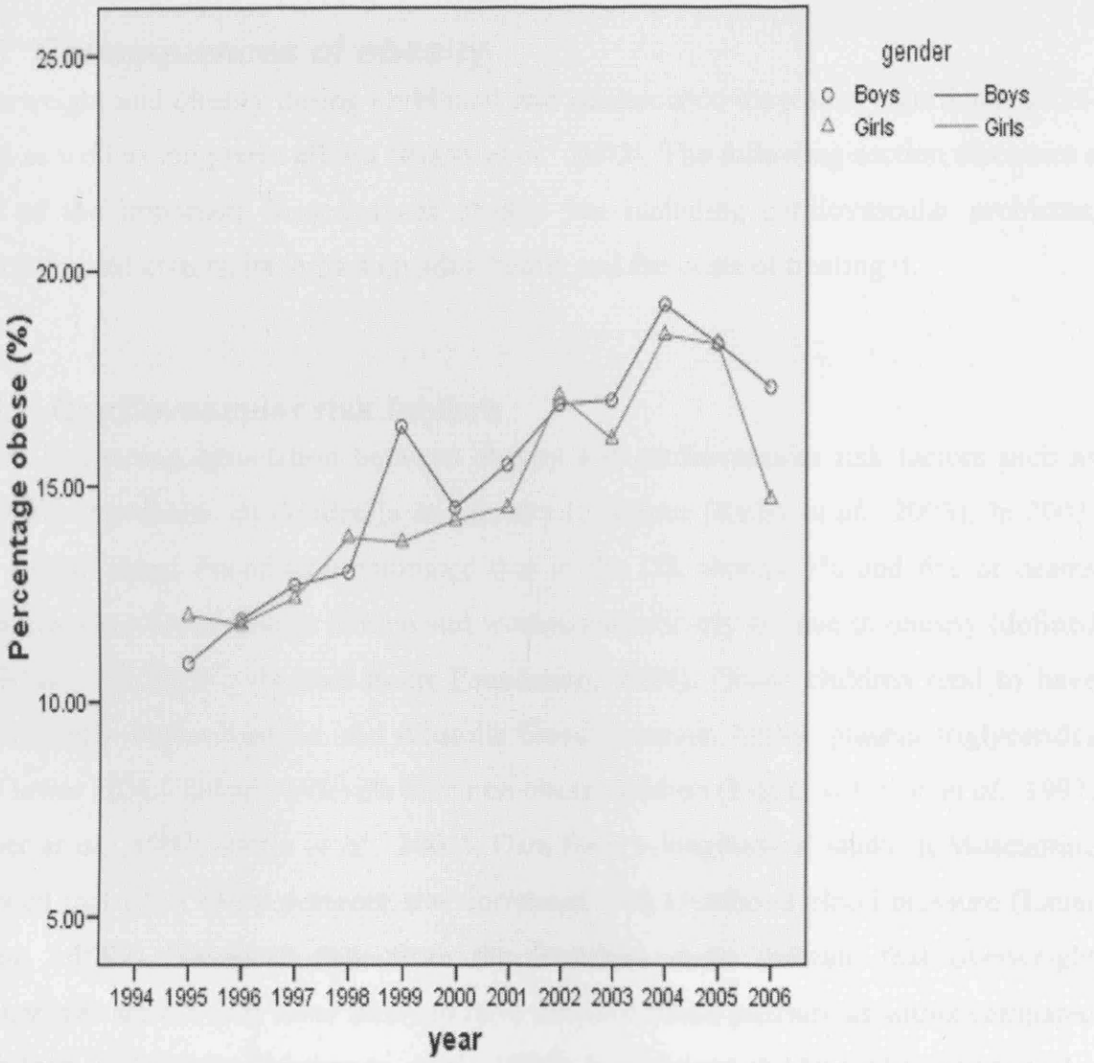


Figure 2-5 Prevalence of obesity among 2 - 15 year old children in England, 1984 to 2006

Source: (Health Survey for England, 2005; Health Survey for England, 2008)

2.5 Consequences of obesity

Overweight and obesity during childhood and adolescence may have significant short-term as well as long-term effects (Reilly *et al.* 2003). The following section discusses a few of the important consequences obesity has including cardiovascular problems, psychological effects, its impact on adult health and the costs of treating it.

2.5.1 Cardiovascular risk factors

There is a strong association between obesity and cardiovascular risk factors such as high blood pressure, dyslipidemia and insulin resistance (Reilly *et al.* 2003). In 2003, the British Heart Foundation estimated that in the UK around 5% and 6% of deaths from coronary heart disease in men and women respectively are due to obesity (defined as BMI > 30 kg/m^2) (British Heart Foundation, 2004). Obese children tend to have significantly higher systolic and diastolic blood pressure, higher plasma triglycerides and lower HDL-cholesterol levels than non-obese children (Figueroa-Colon *et al.* 1997; Lauer *et al.* 1997; Reilly *et al.* 2003). Data from a longitudinal study in Muscantine showed that adult blood pressure was correlated with childhood blood pressure (Lauer *et al.* 1997). Similarly data from the Bogalusa study indicate that overweight adolescents are 8.5-fold more likely to have elevated blood pressure as adults compared with lean adolescents (Srinivasan *et al.* 1996). In addition, children who maintained a high blood pressure into adulthood were found to be taller, heavier and more obese compared to those who had lower blood pressure; indicating that the level at which blood pressure tracks during childhood is related to growth and obesity (Lauer *et al.* 1984). One study found that over half of the subjects with persistent blood pressure elevations were obese (defined as BMI > 95^{th} percentile) during childhood (Rames *et al.* 1978).

Insulin-resistance syndrome is developing in growing numbers of obese children. Acanthosis nigricans (AN), a skin disorder characterized by hyper-pigmentation or darkening of the skin, is a clinical marker that has been linked to surrogate markers of insulin resistance not only in adults but also in children and adolescents (Sinha and Schwartz, 2007). AN is most common in areas with body folds such as the neck and armpits (refer to Figure 2-6). Obese children with insulin resistance during childhood are at a greater risk of developing health problems during adulthood; indicating that obesity in childhood may cause complications in adulthood and is a risk factor for both

child and adult diseases such as type II diabetes (Aggoun, 2007). Therefore there is a need for primary prevention early in life in order to avoid such complications in future.

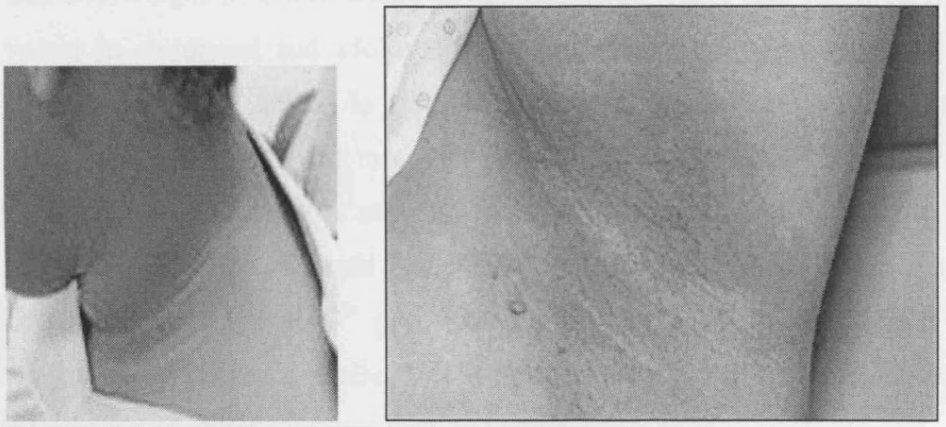


Figure 2-6 Examples of acanthosis nigricans in the neck and armpits
Source: (McMahon *et al.* 2004)

2.5.2 Psychological effects

Not only does obesity impact on physical health, it also impacts on mental health. Obese children are more likely to experience psychological or psychiatric problems, low self esteem and behavioural problems compared to non-obese children (Reilly *et al.* 2003). For example, Strauss found that 34% of obese girls and 14% of obese boys had low self-esteem compared to only 8% and 9% of those who were not obese respectively (obesity defined as BMI > 95^{th} percentile) (Strauss, 2000). Furthermore, gender differences in general self esteem have been reported where overweight and obese girls have lower self-esteem than overweight and obese boys (Israel and Ivanova, 2002; Reilly *et al.* 2003). In addition, age was found to be associated with risk of psychological morbidity in those obese children; the risk increasing from childhood through adolescence (Reilly *et al.* 2003; Israel and Ivanova, 2002).

2.5.3 Impact of childhood obesity on health in adulthood

The persistence of obesity present in childhood and adolescence into adulthood represents another significant consequence of early obesity (Reilly *et al.* 2003). One study found approximately 85% of individuals who were obese in childhood, remained obese in adulthood (Must *et al.* 1992). Data from the Fels longitudinal study revealed that overweight or obese adults at the age of 35 years had significantly higher BMI values in childhood and adolescence compared to those who were not overweight or obese (Guo *et al.* 2002). In addition, childhood obesity seems to increase the risk of subsequent morbidity and mortality (Reilly *et al.* 2003; Gunnell *et al.* 1998). In a cohort from the Boyd Orr study in Britain, children who had a BMI > 75^{th} percentile had twice the risk of death from heart disease compared to those whose BMI was between the 25^{th} and 49^{th} percentiles (Gunnell *et al.* 1998). In a meta-analysis reviewing longitudinal studies that examined the risk of becoming an obese adult, the proportion of obese children who became obese adults ranged from 26 - 41% for pre-school children and 42 - 63% for school aged children (Serdula *et al.* 1993).

Most of the available evidence on the persistence of childhood obesity was based on older studies when the prevalence of obesity was much lower. Therefore the magnitude of the consequences of childhood obesity is likely to be much greater now following the epidemic of childhood obesity.

2.5.4 Cost

Because of the rise in the prevalence of obesity and the consequences obesity brings to health both physically and mentally, the costs associated with obesity have become an extremely important public health issue. In 2006, according to the WHO, obesity accounted for 2 - 6% of total health care costs in many developed countries (World Health Organization, 2006). The true costs would probably be much greater as not all obesity-related conditions were included in the calculations.

The National Audit Office estimated that the cost of treating obesity in England in 1998 was 9.5 million pounds, and in 2002 this figure increased to 45.8-49 million pounds. The estimated total costs of treating obesity and its consequences in England in 1998, including indirect costs such as loss of earnings due to sickness, was 2.1 billion pounds (British Heart Foundation, 2004). England's chief medical officer reported that the

direct cost of obesity to the NHS in 2003 was 0.5 billion pounds, while the indirect cost to the UK economy was at least 2 billion pounds (Vlad, 2003). This shows that the financial burden of obesity has increased drastically over the past decade and this trend is continuing to increase.

2.6 Aetiology of obesity

There is considerable debate around possible mechanisms underlying the increasing prevalence of overweight and obesity amongst children and adolescents. Determining the causes of obesity is important in order to find solutions for tackling it. Obesity is a multi-factorial disease; in that there is no single factor that can explain its aetiology. Many genetic, medical and environmental factors have been reported to contribute to the incidence of obesity. These will be discussed separately below.

2.6.1 Medical conditions

Obesity can develop due to a number of specific medical disorders. These include hormonal disorders such as hypothyroidism, hyper-cortisolism and hyper-insulinism and leptin deficiency (Zametkin *et al.* 2004; Montague *et al.* 1997). These disorders can increase the likelihood of the child becoming obese. However, such conditions are a relatively rare cause of childhood obesity; in that less than 10% of obese children are thought to be affected (Moran, 1999).

Other medical effects that can increase the child's likelihood of developing obesity start before the child is born i.e. during the fetal period. The quality of the environment during which the offspring is developing may lead to adverse effects on the child's health in future (Wells, 2007). This may occur when the offspring is exposed to different factors during pregnancy such as toxins (through maternal smoking) and poor metabolic control (through gestational diabetes). It has been reported that offspring of mothers with gestational diabetes are 50% more likely to become obese children (Styne, 2001).

2.6.2 Genetic factors

It is well known that genetic factors contribute to the development of obesity. However there is inconsistency between studies regarding the variability in adiposity that is inherited due to genes rather than derived from environmental factors.

There is increasing evidence that there is a relationship between the weight status of parents and their offspring. Children from families in which one or both parents are overweight or obese were found to have a substantially higher risk of becoming obese than did children whose parents are not overweight or obese (Lake *et al.* 1997). Data from the Health Survey for England showed that when both parents were classified as obese or overweight, around 20% of children aged 2 - 19 years were obese compared with just 7% of children where neither of the parents was obese or overweight (Jotangia *et al.* 2005). Similarly, in a retrospective cohort study, it was reported that parental obesity more than doubles the risk of adult obesity among both obese and non-obese children below 10 years of age (Whitaker *et al.* 1997). Some studies found a stronger correlation between child and parental BMI in mother and child compared to father and child (Wada and Ueda, 1990; Sorensen *et al.* 1992; Lake *et al.* 1997); whilst other studies found no such relationship (Ayatollahi, 1992). A possible reason for the differences in findings is the inadequacy of self-reported parental weight and height data.

The limitation in investigating the relationship between parental fatness and childhood fatness is that similarity in fatness may not only be due to genes but could also be due to inherited lifestyle behaviours. It could also be that environmental factors affect the expression of certain genes which could alter the susceptibility to obesity (Dolinoy *et al.* 2006) Therefore, adoption and twin studies are better for predicting genetic influences on fatness because they have greater capacity to differentiate between genetic and environmental effects.

Twin studies suggest that at least 25% of the tendency to become overweight or obese is inherited (Bouchard, 1991). Brook and colleagues (1975) measured skin-fold thicknesses in a group of twins aged 3 - 15 years (Brook *et al.* 1975). They found that heritability was higher in children over the age of 10 years; whereas environmental factors exerted a stronger effect on fatness in the younger group of children. A plausible reason for this stronger effect is that children over 10 years are able to make their own decisions and they are more likely to be affected by their peers and other surrounding lifestyle behaviours, which in turn may influence their responses to diet and physical activity and allow genetic effects to emerge.

Several adoption studies explored the contributions of genetic factors and family environment to human fatness by assessing adoptees, their biological mothers and fathers and their adoptive mothers and fathers (Sorensen *et al.* 1992; Stunkard *et al.* 1986; Vogler *et al.* 1995). Their results showed a strong relation between the weight and BMI of the adoptees and their biological parents. However no relation was found when the adoptee's weight and BMI were compared against those of adoptive parents. This represents strong evidence for genetic effects; whereas no apparent effect of the family environment was revealed.

2.6.3 Environmental factors

Obesity develops when a disruption to the energy balance equation occurs. Based on the law of thermodynamics, obesity develops when energy intake (amount of food and drink consumed measured in calories or kilojoules) exceeds energy expenditure (energy used for physical activity and other metabolic processes in the body) (Helmholtz, 1847). The body is said to be in an 'energy positive state' and this extra energy tends to be stored in the body as fat. There are multiple factors influencing this imbalance; however diet and physical activity seem to play a major role in the rising prevalence of obesity.

It has been hypothesized that there is an association between dietary composition and body fat percentage. Tucker and colleagues (1997) examined the relationship between diet composition and adiposity in a large sample of children (Tucker *et al.* 1997). They found that total energy intake and dietary fat intake were positively related to obesity independent of gender, physical activity and parental BMI. Similar findings were observed in Maffeis and colleague's study (1996) whereby obese children were found to have higher intakes of fat than non-obese children, and this increased fat intake was assumed to be responsible for the increased fat mass (Maffeis *et al.* 1996a).

Between 2001 and 2004, British children aged 5 - 15 years ate less than half the recommended portions of fruits and vegetables a day (Health Survey for England, 2005). The Health Survey for England showed that the proportion of adults that consumed more than five portions a day of fruits and vegetables between 2001 and 2004 has increased by around 2%; however no changes were observed in the mean number of portions of fruits and vegetables consumed by children (Health Survey for England, 2005). In addition, no significant differences in the levels of obesity were observed between children who consumed different numbers of portions of fruits and

vegetables a day (Jotangia *et al.* 2005). However, between 2005 and 2006, there was a significant increase in the consumption of fruits and vegetables among children aged 5 - 15 years; girls were more likely than boys to consume five or more portions of fruits and vegetables (Health Survey for England, 2008). At the same time, the prevalence of obesity in children between 2005 and 2006 decreased. Caution is advised when interpreting results obtained from questions involving food consumption. Since parents of obese children are more likely to be overweight or obese themselves, portion sizes may be underestimated and 'good food' consumption over-reported whilst consumption of 'bad foods' may be under-reported (Schoeller *et al.* 1990).

The rising prevalence of obesity has also been linked in part to the increased consumption of high sugar drinks (Health Survey for England, 2005). These drinks provide little or no nutritional value beyond energy, and they provide a large amount of added sugars in children's diets. There is evidence that children who consume sugar-sweetened beverages regularly between the ages of 2 and 5 are three times more likely to be overweight compared to non-consuming children (Dubois *et al.* 2007; Welsh *et al.* 2005). In a prospective analysis, Ludwig and colleagues (2001) found that for each additional serving of sugar-sweetened drink consumed in children (average age of 12 years), both BMI and the odds of becoming obese increased by approximately 0.24 kg/m^2 over the follow-up of 19 months, after adjusting for dietary and lifestyle factors (Ludwig *et al.* 2001).

Over the past two decades, there has been a remarkable increase in portion size of foods paralleling the rising obesity epidemic, which suggests that large portion sizes may play a role in the increase of body weight amongst children and adolescents. Items at fast food chains are 2 - 5 times larger now than 20 years ago. Studies have shown that when children were provided with larger portions, they ate more (McConahy *et al.* 2002).

It is widely believed that reduced physical activity and increasing sedentary behaviour is implicated in the aetiology of childhood obesity (Reilly and Dorosty, 1999; Reilly *et al.* 2003). Even though the prevalence of obesity in children increased between 2002 and 2006, physical activity levels (i.e. number of hours of activity; assessed using questionnaires) in British boys and girls did not change significantly (Health Survey for England, 2008). However, there was a tendency for obesity rates to rise inversely in association with children's level of physical activity; obesity rates in children aged 2-11

years were 14.8% versus 17.4% in highly active versus sedentary respectively (Health Survey for England, 2005).

A review by Spear and colleagues in 2007 reported inconsistent findings on the association of physical activity and BMI in children and adolescents (Spear *et al.* 2007). The lack of validated questionnaires to assess activity levels accurately makes it difficult to interpret and compare results from different studies. Also, the majority of studies used BMI to assess adiposity. BMI however does not give separate information on fat and lean mass, and physical activity promotes the growth of lean tissue (Torun and Viteri, 1994); this can therefore be overlooked when indices such as BMI are used to assess adiposity levels.

There is increasing evidence that watching television in childhood is an important contributing factor to the current cause of childhood obesity. In a longitudinal study assessing the impact of childhood television viewing on BMI, watching television was significantly associated with increased BMI (Hancox and Poulton, 2006). This association tended to be stronger in girls, particularly during adolescence, than in boys. A similar longitudinal study showed that each additional hour of television watched on weekends at five years of age increased the risk of developing obesity in adulthood by around 7% (Viner and Cole, 2005). The Framingham Children's Study showed that by age 11, children who watched 3 hours or more of television per day had increased body fat compared with those who watched less that 1.75 hours per day (Proctor *et al.* 2003).

It can be argued that the time one spends television viewing displaces the time one can be physically active instead. Moreover, those that view television are exposed to food advertising which may encourage unhealthy eating behaviours such as snacking and oversized meals. Salmon et al (2006) showed that children who watched television for more than two hours a day were more likely to have high energy drinks and snacks, and less likely to have fruit compared to those who watched less than two hours of television a day (Salmon *et al.* 2006). A potential limitation of such studies is that they rely on the parents' and children's reporting of diet and physical activity.

The obesity epidemic has also been accompanied by a parallel trend in sleep deprivation (Patel and Hu, 2008). Whereas dietary intake and level of physical activity each alter one side of the energy balance equation, recent research suggest that sleep alters both

sides of this energy equation therefore affecting energy balance more strongly (Taheri, 2006). A systematic review on sleep duration and weight gain in adults and children supported the evidence that short sleep duration is strongly associated with increased weight and obesity risk; the relationship weakened with age (Patel and Hu, 2008). In obese children, short sleep duration was also found to be associated with greater insulin resistance and impaired glucose tolerance compared to obese children with normal sleep duration (Flint *et al.* 2007). Several mechanisms linking short sleep duration with obesity have been suggested. These include increased energy intake due to altered hormone levels, reduced physical activity levels due to being tired, decreased body temperature impacting energy expenditure through thermo-regulation and altered hormones such as cortisol predisposing to insulin resistance (Flint *et al.* 2007; Patel and Hu, 2008; Taheri, 2006).

2.7 Factors associated with obesity

2.7.1 Socio-economic status (SES)

Recently, increased evidence for the influence of SES on later fatness in children has been found (Stamatakis *et al.* 2005). SES is often measured using one of three indicators: income, education or occupational status; the latter being the most commonly used marker of SES in adults. In children parental SES is used as an indicator of children's SES.

The Health Survey for England reported that the levels of obesity in children aged 2 -11 years were highest among those with lower social class (17.1%) compared to those with parents in managerial or professional occupations (12.1%) (Health Survey for England, 2005). A British birth cohort followed up from birth to 43 years showed that lower childhood social class was associated with increased BMI in adult life (Hardy *et al.* 2000). In another cohort investigating the rate of childhood obesity in 5 – 11 year old children in Plymouth, the prevalence of obesity was higher in those of lower SES (Kinra *et al.* 2000b). This was also observed in other Western countries (Wardle and Griffith, 2001; Wardle *et al.* 2002; Laitinen *et al.* 2001; Stamatakis *et al.* 2005; Kinra *et al.* 2000a). In Finland for example, data from the 1966 birth cohort showed that the family's social class during childhood had a long-term influence on BMI; where obesity was found to be most common in the lowest social class group (Laitinen *et al.* 2001).

Gender differences in the effect of social class on fatness were also observed. Higher occupational status was associated with a lower risk of obesity in women, but not in men (Wardle *et al.* 2002; Langenberg *et al.* 2003). Lower social class occupations, such as manual occupations, tend to be more physically demanding especially for men. This higher level of physical activity might be partly responsible for the prevention of overweight and obesity risk in lower SES occupations among men compared to women.

Different attitudes and practices relative to weight control might be a possible factor contributing to SES differences in fatness. It has been found that those from lower SES are less likely to feel overweight and so are less likely to try to control their weight compared to those from higher SES group who are more likely to perceive themselves as overweight (Wardle and Griffith, 2001). The role of stigma associated with overweight and obesity, and discrimination against people who are overweight or obese,

especially in the higher SES group of people, may be another reason why those from higher SES have lower risk of obesity. Higher SES individuals place greater emphasis on healthy weight and are more rejecting of overweight, particularly women, and show higher levels of dieting (Gortmaker *et al.* 1993). These differences may account for the results obtained.

2.7.2 Birth weight

A high birth weight has been associated with an increased risk of later obesity (measured by BMI) (Dietz, 1994; Parsons *et al.* 1999). However, there is evidence that a high birth weight programs lower susceptibility to cardiovascular disease (Barker *et al.* 1993; Barker, 1995). Since BMI is strongly correlated with both fat and lean mass, the high birth weight might be due to increased lean mass rather than fat mass. On the other hand, low birth weight is associated with programming of greater abdominal or central fat. Malina and colleagues (1996) reported that as birth weight decreased, more subcutaneous fat (measured using skin-fold thickness) was accumulated within the trunk than within the extremities, especially in girls (Malina *et al.* 1996). Similar observations were reported by Koziel and Jankowska (2002) who found that 14 year old girls with low birth weight accumulated increased abdominal fat (assessed using waist-hip ratio) (Koziel and Jankowska, 2002). A suggested reason for this is that babies who have low birth weight lack muscle and so will have a high ratio of fat to lean mass if they become overweight or obese in the future; thus increasing the risk of coronary heart disease. Conversely, a high BMI associated with a high birth weight may reflect increased lean tissue.

Studies have shown inconsistent relationships between birth weight and body composition in later life. Singhal and colleagues (2003) showed that a high birth weight was associated with greater FFM but not with greater FM (assessed using skin-fold measurements) in children and adolescents aged 13-16 years; an increase in 1 SD score of birth weight was significantly associated with an increase in 0.9-1.4 kg (2 -3%) of lean mass (Singhal *et al.* 2003). Similar findings were observed in the New Delhi birth cohort where birth weight was strongly correlated with adult lean mass (assessed using skin-fold thickness) (Sachdev *et al.* 2005). Their study however showed a gender difference where higher birth weight only in females was also related to increased adiposity. A similar sex difference was also observed in the Guatemalan Longitudinal Study where the effect of growth during early childhood on adult fatness (predicted

using equations from hydrostatic weighing) was much greater in women than in men (Li *et al.* 2003). Eriksson and colleagues (2001) observed a positive correlation between birth weight and later obesity (defined as BMI > 30 kg/m^2); however this association was only significant among males (Eriksson *et al.* 2001). A possible reason behind the differences in outcomes between the studies might be due to the different methods used to assess obesity; Eriksson relied only on BMI whilst the others used skin-fold measurements and circumferences as well.

2.7.3 Gastro-intestinal bacteria

Very recent research suggests that there might be a link between obesity and the type and proportion of bacteria in the digestive tract. The human gut is predominantly composed of two types of beneficial bacteria: the Bacteroidetes and the Firmicutes. A study in mice showed that the introduction of certain gut microbiota from normal mice into germ-free mice produced a rapid increase in body fat despite a reduction in food consumption (Backhed *et al.* 2004). In humans, Ley and colleagues (2006) showed that the relative proportion of the Bacteroidetes is decreased in obese compared to leaner people, and this proportion increased after weight-loss (Ley *et al.* 2006). This indicates that manipulation of bacteria in the gut could be another approach in the treatment of obesity. However, more research is needed before this can be confirmed.

2.8 The biology of obesity

Using a simplistic approach, obesity is fundamentally a result of a problem with energy balance: when energy intake is in excess of energy expenditure, the difference in input and output results in changes in fat stores (Helmholtz, 1847). However, not only does obesity encompasses mechanisms of energy balance, it is a multidimensional condition which also includes a biological basis for the development of obesity such as the contribution of genes, appetite and physiological adaptations (Trayhurn, 2005). This makes the basis of treatment strategies of obesity extremely difficult. Figure 2-7 summarises the different factors that may affect the energy balance equation, therefore affecting body composition; hence offering various targets for treatment. Even though other factors are associated with childhood obesity (as described previously), for the purpose of this thesis, I will focus on diet, activity, drugs, and behaviour.

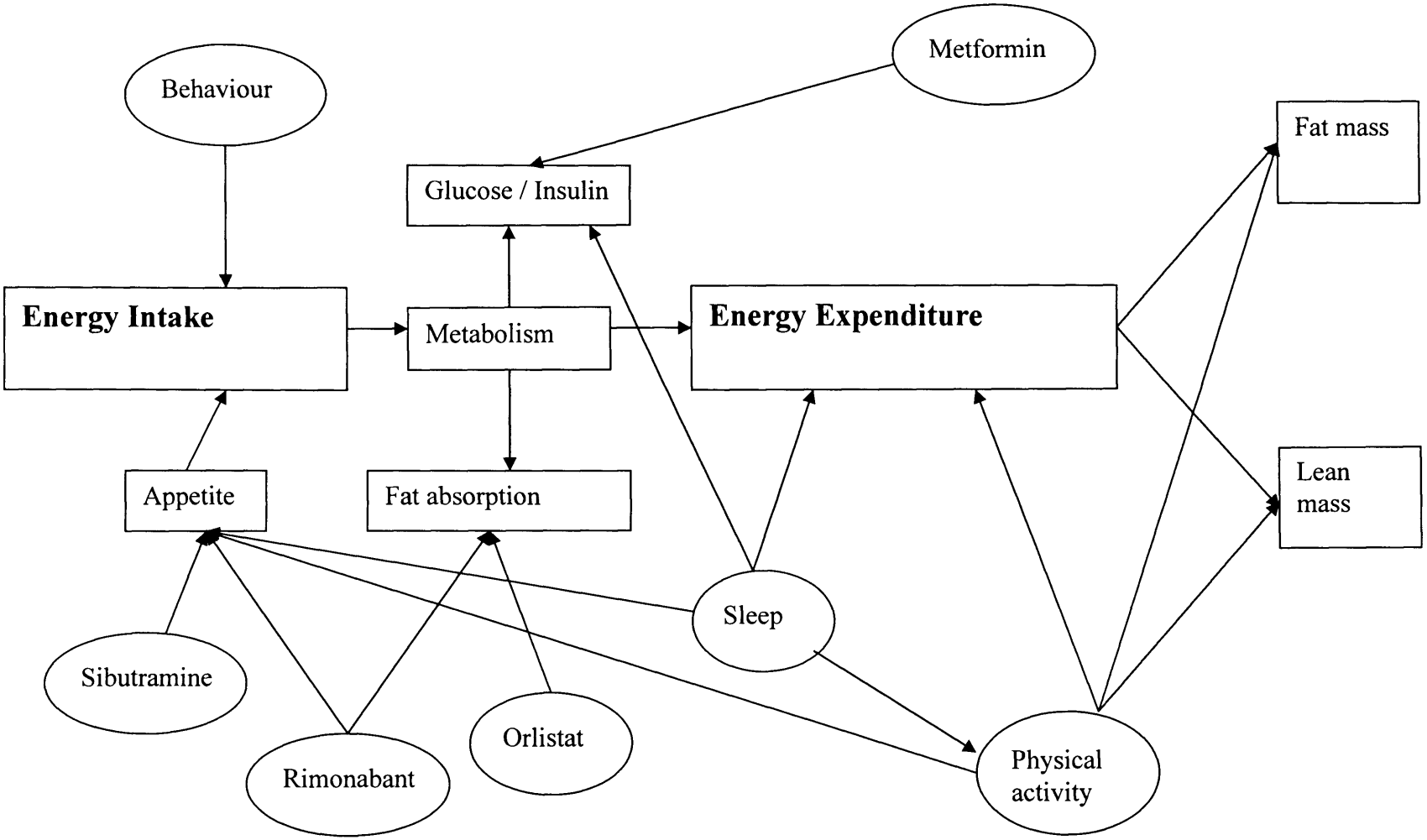


Figure 2-7 The mechanisms affecting energy intake and energy expenditure and the point of impact of different treatments.

2.9 *Treatment of obesity*

Uncertainty over the exact aetiology of obesity remains one of the chief barriers to designing effective strategies for its prevention and treatment. Because obesity is a multi-factorial condition, numerous treatment strategies have been attempted. These include weight loss programmes based on dietary restriction, exercise, behaviour modification, pharmacotherapy or a combination of these approaches.

2.9.1 Diet

It is important that a child has a healthy diet as this is a crucial period for growth and bone development. Experts do not recommend that moderately overweight or obese children are put on a restricted diet to lose weight; instead it is recommended that they maintain their weight and try to grow into it (Lobstein *et al.* 2004). Changing unhealthy eating habits is recommended, not only to the overweight and obese but to all children irrespective of their weight. However, weight loss is recommended in extremely severely obese cases such as children with congenital leptin deficiency whereby treatment with leptin results in decreased energy intake and hence weight reduction (Farooqi *et al.* 1999).

In view of the evidence on various aspects of diet in relation to the risk of overweight and obesity, it is encouraged that young children limit their intake of sugar sweetened beverages, by consuming mineral water instead. It has also been recommended by nutritionists and dieticians that parents watch the portion size they give their children during meal times, and to limit eating out. The energy density of foods is another variable that can affect food intake. Energy density simply refers to the amount of energy in food per unit weight (kilojoules per gram). Water increases the weight of food but not energy density, whereas fat increases the energy density more than carbohydrate and protein. Foods that are high in energy density have been shown to increase total energy intake while foods that are low in energy density decrease energy intake (Ello-Martin *et al.* 2005). Therefore one strategy to reduce energy intake is to provide children with low-energy dense foods such as fruits and vegetables.

2.9.2 Activity

'Lack of physical activity is a major underlying cause of death, disease and disability, and is one of the ten leading global causes of death and disability' (World Health Organization, 2002).

Physical activity is the only readily modifiable component of the energy expenditure component of the energy balance equation. Consequently, increasing physical activity has the potential to improve weight loss and maintenance. Not only does physical activity play a role in preventing or reducing weight gain, it has also been shown to improve insulin sensitivity and promote the growth of lean tissue and increase bone strength in young adolescents (Carrel *et al.* 2005).

The time and intensity of physical activity has been shown to correlate with a reduction in fat level in children and adolescents. In a large cross sectional study of 9 -10 year old European children, Ekelund and colleagues (2004) reported that those who spent less than one hour of physical activity a day were significantly fatter (measured by skin-fold thickness) than those who were active more than two hours a day (Ekelund *et al.* 2004). A systematic review of controlled trials of interventions to prevent childhood obesity and overweight concluded that trials involving compulsory rather than voluntary physical aerobic activity were more effective in reducing adiposity in children (Connelly *et al.* 2007).

Accurate measurement of physical activity is difficult, some researchers relying on self-reported data from parents or children whilst others use activity monitors. Also, studies might be limited in the methods used to assess body composition. This makes comparisons between studies difficult, and data concerning the relative and absolute contribution of sedentary behaviour to obesity are difficult to interpret.

2.9.3 Psychological management

A systematic review conducted by McLean and colleagues (2003) suggested that weight loss interventions targeting food intake and physical activity might be more effective if they incorporate a psychological and educational approach (McLean *et al.* 2003). Also, there has been substantial research on whether to involve family members in the treatment programme. Inconsistent findings were reported, however a recent meta-analysis of family based behavioural programs for children indicated that including the parents in the treatment of childhood obesity may be more beneficial than treating the child alone (Young *et al.* 2007). Such benefits may be due to parents having more control over the purchase of food and its preparation, and their lifestyle behaviour, consequently affecting the child's behavioural choices and level of physical activity.

A number of studies investigating the effectiveness of treating childhood obesity with behavioural management have been conducted. I have chosen to discuss only the recent few that were either randomised control trials (RCT) or those that used the traffic light diet (a family-based behavioural program). These are summarised in Table 2-2.

A two year family based behavioural program based on the traffic light diet was conducted on obese children (mean age 13 years) in China (obesity defined as weight-for-height > 120% of Chinese reference) (Jiang *et al.* 2005). Children were randomised to either a treatment group (n = 33) or a control group (n = 35); whereby children were assessed every six months using conventional weight and height measurements. At the end of the program, those in the treatment arm had a significant reduction in BMI and BMI SDS compared to the control arm; BMI reduction of 2.6 kg/m^2 versus 0.1 kg/m^2, and BMI-SDS reduction of approximately 1.8 versus 0.5 SDS in the treatment arm versus the control arm respectively. The programme was successful in decreasing the degree of obesity.

Similarly, a 10 week behavioural trial in the US investigated the effect of the traffic light program on obese children (obesity defined by CDC cut-offs) compared to those that had usual clinic treatment (Johnston and Steele, 2007). At the end of the trial, those on the program demonstrated significantly greater reduction in BMI SDS compared to controls.

A one year RCT compared the effects of the 'Bright Bodies' family behavioural treatment in a group of 8-16 year old obese children (obesity defined as BMI > 95th percentile based on the CDC growth chart) (Savoye *et al.* 2007). Families met biweekly the first six months, and bimonthly after; also incorporating a session of exercise in the program. At the end of the trial, Bright Bodies was found to significantly decrease BMI and % fat (assessed by a bio-electrical impedance device: TANITA TBF-300) in the treatment group whilst significantly increasing these parameters in the control group; the treatment group (n = 75) significantly lost an average of 4% body fat and 1.7 kg/m^2 BMI whereas the control group (n = 44) significantly gained an average of 2% body fat and 1.6 kg/m^2 BMI.

In a one year family behavioural treatment in Spain, obese children (% BMI > 120%) significantly lost 0.67 BMI SDS after six months and maintained this loss at one year follow-up (Bermudez de la Vega *et al.* 2007). There were no controls in this study; therefore conclusions drawn from this study may not be reliable.

A 12 week RCT LEAP (live, eat and play) behavioural trial in Australia investigated the effect of a 12 week program on overweight and obese (IOTF cut-off) children aged between 5 - 10 years (McCallum *et al.* 2007). The family attended four consultations with their GP where they were provided with information targeting healthier lifestyle goals. No significant reduction in BMI was observed between the treatment and control groups at follow-up.

Differences in outcome between the different studies may be due to the participants differing in relation to ethnicity, sample size, the criteria used to define obesity, and the method and duration of the treatment programme. The majority of the studies used conventional BMI to assess the effectiveness of the programme. BMI cannot differentiate between the fat and lean component of total body weight. For this reason, the results obtained and conclusions drawn should be interpreted with caution especially when exercise is incorporated into the programme. Therefore, there is a need to assess body composition in more detail before any judgments on the success of behavioural programmes can be concluded.

Table 2-2 A summary trials evaluating the effect of family-based interventions on treating child obesity

Author country year	Inclusion/Exclusion	Age (years)	Sample size	Duration	Follow-up	Measures	Results
Johnston & Steele US 2007	BMI > 85th percentile CDC cut-off	6 - 18	treatment n = 41 control n = 41	10 weeks	NO	WT & HT	BMI SDS decreased significantly more in treatment versus controls, but by an unspecified magnitude ($p<0.05$)
McCallum et al Australia 2007	BMI SDS > 3 excluded IOTF cut-off	5 - 10	treatment n = 82 control n= 81	12 weeks	9 months 15 months	WT & HT	**9months (BMI SDS):** Treatment changed from 2.0 to 1.96 Controls changed from 1.9 to 1.93 Treatment-control = 0.04 ($p = 0.6$) **15 months (BMI SDS):** Treatment did not change Controls changed from 1.9 to 1.92 Treatment-control = 0.08 ($p = 0.4$)
Savoye et al US 2007	BMI > 95th percentile CDC cut-off	8 - 16	treatment n = 44 control n= 75	1 year	6 months 12 months	WT & HT % fat (by TANITA-300)	**6 months (% fat):** Treatment lost 3.2% fat Controls gained 2% fat. Treatment–control= 5.2% ($p < 0.001$) ***12 months* (% fat):** Treatment lost 4% fat Controls gained 6% fat Treatment –control = 6.0% ($p < 0.001$)
Bermudez et al Spain 2007	weight-for-height > 120% (Spanish reference)	6 - 13	treatment n = 50 no control	1 year	6 months 12 months	WT & HT	***6 months:*** BMI SDS changed from 4.77 to 4.13 ($p=0.002$) *1 year:* no significant further change
Jiang et al China 2005	weight-for-height >120% (Chinese reference)	13	treatment n = 33 control n = 35	2 years	every 6 months for 2 years	WT & HT	**At 2 years BMI SDS:** Treatment: changed from 4 to 2.2 Control: changed from 4 to 3.5 Treatment –control = 1.3 ($p < 0.001$)

Abbreviations: n= number per group; BMI= body mass index; CDC= centre for disease control; SDS= standard deviation score, WT= weight; HT= height; IOTF= international obesity task force

2.9.4 Drug therapy

Some drugs are used in the management of obesity in adults, however great care should be taken when anti-obesity medications are used in children. It should not be assumed that the risks and benefits associated with drugs used in adults are the same in children and adolescents. Most of these drugs have not yet been adequately studied with respect to efficacy, safety and long-term effects in children and adolescents. At present, there are only a few drugs approved by the Food and Drug Administration (FDA) for the treatment of adult obesity; these include Orlistat (Xenical, Roche) and Sibutramine (Meridia, Abbott Laboratories). Other drugs such as Rimonobant (Acconplia) and Metformin (Glucophage) are usually recommended for obese patients with high insulin levels or at risk of developing diabetes. All drugs are usually prescribed in combination with a program of diet, exercise and behaviour modification. A summary of the drugs, the mechanisms by which they function, their side effects and evidence in obese children and adolescents is shown in Table 2-3.

2.9.4.1 Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor that works by binding to gastrointestinal lipases causing a partial inhibition of fat absorption from the gut. It has been shown to reduce the absorption of dietary fat by approximately 30% in adults (Zhi *et al.* 1994), and approximately 27% in obese adolescents (Zhi *et al.* 2003); whereby ingested fat is excreted in the faeces. Orlistat is usually given at the standard dose of 120 mg three times daily taken before meals. Major adverse side effects that have been previously reported in those taking Orlistat are predominantly gastrointestinal and include increased defecations and increased incidence of fatty or oily stools. These effects have limited their usefulness in almost one in three adolescents (Ozkan *et al.* 2004).

In adults, 6 months of Orlistat treatment was shown to produce significant weight loss: 4.2%, 5.5% 6.2% in obese patients with type II diabetes, hyper-cholesterolaemia and hypertension respectively (Guy-Grand *et al.* 2004). Similar results were also observed when obese adolescents were treated with Orlistat; mean decreases in weight, BMI and waist circumference which were highly correlated with a decrease in FM (assessed by DXA or ADP) (Chanoine *et al.* 2005; Chanoine *et al.* 2005; McDuffie *et al.* 2002b). Only one pilot study by Norgren and colleagues (2003) investigated the effects of Orlistat treatment in obese pre-pubertal children (Norgren *et al.* 2003). They found that 12 weeks of taking Orlistat caused a weight-loss of approximately 4 kg and was highly correlated with a decrease in fat mass (assessed by DXA), with no major negative side-effects reported.

Orlistat not only affects body weight and body composition, but has also been shown to have some effects on blood lipid and glucose measurements. It significantly decreases low density lipoprotein cholesterol concentrations, lowers leptin concentrations and improves indicators of glycemic control, decreasing fasting glucose and insulin levels in adults (Hsieh *et al.* 2005; Guy-Grand *et al.* 2004) and adolescents (Chanoine *et al.* 2005; McDuffie *et al.* 2002b). Therefore, Orlistat appears to have anti-diabetic and anti-atherogenic properties and may help prevent risk factors for the metabolic syndrome in people who are overweight and obese.

Since Orlistat limits fat absorption, it is necessary to determine whether deficiencies of mineral and fat soluble vitamins occur due to treatment. Previous studies showed no significant changes in serum levels of vitamins A, E and K between those on treatment compared to those on placebo; however impairments of vitamin D absorption were found in both adults and adolescents (Chanoine *et al.* 2005; McDuffie *et al.* 2002a). This can cause problems in terms of bone formation; particularly in adolescents and children who are still growing. No changes in bone mass or density were seen after one year treatment with Orlistat apart from those explained from the weight loss itself in adults (Gotfredsen *et al.* 2001) and children (Chanoine *et al.* 2005). Moreover, it has been demonstrated that no significant effects on mineral absorption or mineral balance were observed in those on Orlistat treatment (Zhi *et al.* 2003). Nevertheless, it remains unknown whether there would be any significant effects on bone formation with long-term use of Orlistat.

2.9.4.2 Sibutramine

Sibutramine is a serotonin nor-epinephrine reuptake inhibitor which causes a centrally mediated increase in satiety (feeling of fullness) and energy expenditure. It is usually given at a low dose at the start of treatment (5 mg/day) and increases gradually to 15 mg/day; taken as one single dose in the morning. Adverse effects that have been previously reported in those taking Sibutramine include increased blood pressure and heart palpitations in both adults (Wadden *et al.* 2005) and adolescents (Berkowitz *et al.* 2003).

Several studies have shown that Sibutramine used in combination with an appropriate diet and exercise program in obese adults is effective in terms of weight maintenance and reduction. Mathus-Vliegen (2005) showed that weight loss was more effectively maintained in adult obese patients using Sibutramine compared to those only on low calorie diets (Mathus-Vliegen, 2005). Similarly, Wadden and colleagues (2005) showed that those on combined therapy of Sibutramine plus diet and exercise over one year showed a weight loss of 12.1 ± 9.8 kg, whereas those treated by lifestyle modification alone lost only 6.7 ± 7.9 kg (Wadden *et al.* 2005).

Similar to studies of adults, the addition of Sibutramine with a behavioural program induced significantly greater weight loss in obese adolescents compared with those on placebo (Berkowitz *et al.* 2003). They also reported significant reductions in hunger.

Moreover, high-density lipoprotein cholesterol increased by around 8% in the Sibutramine group; which suggests a reduced risk of developing insulin resistance, heart disease and type II diabetes mellitus. In a large randomised multi-centre European study (STORM trial) of weight loss and long-term weight maintenance in a group of obese people aged 17 - 65 years, the Sibutramine-treated group continuously had significantly lower body weight compared to the placebo-treated group, and weight maintenance was positively influenced by continued Sibutramine treatment (van Baak *et al.* 2003).

2.9.4.3 Metformin

Metformin, a dimethyl biguanide, acts by suppression of endogenous glucose production in the liver, but may also have an insulin sensitising effect in peripheral tissues through an effect on the key intracellular enzyme AMP kinase (Hundal and Inzucchi, 2003). It is usually prescribed at a starting dose of 500 mg/day and then increased up to 1,000 mg/day for those weighing < 50 kg, 1,500 mg/day for those weighing 50 - 75 kg and 2,000 mg/day for those weighing > 75 kg. Metformin is generally taken with meals to minimise gastrointestinal side effects such as abdominal pain, nausea, vomiting and diarrhoea.

Metformin has been traditionally used as an anti-diabetic agent to reduce hyper-insulinaemia and hyperglycaemia in adults with type II diabetes mellitus. It has also been effective in reducing weight gain in tightly treated type II diabetes. One randomised clinical trial showed that type II diabetic patients taking Metformin for 6 weeks showed a reduction in insulin requirements and improvements in glycemic control with no weight gain (Janssen *et al.* 1991). Jones and colleagues (2002) conducted a multi-centre double-blind placebo controlled trial whereby paediatric patients with type II diabetes were randomised to take Metformin or placebo for one year (Jones *et al.* 2002). Similar to the trial by Janssen and colleagues (1991), they reported improved glycemic control in the Metformin group; mean glycosylated haemoglobin (HbA1c) was significantly lower in the Metformin group compared with placebo (7.5% versus 8.6%), indicating a reduction in blood glucose levels.

Metformin has also been used in adjunct to insulin therapy in patients with type I diabetes. In adolescents, two short-term randomised controlled trials have investigated the effectiveness of Metformin on insulin sensitivity and metabolic control in type I diabetes. Hamilton and colleagues (2003) reported that in 27 adolescents treated for

three months, Metformin in addition to insulin resulted in minimal reduction in fasting glucose but a significant reduction in BMI compared with placebo (Hamilton *et al.* 2003). Similarly, Sarnblad and colleagues (2003) reported that 26 adolescents treated with metformin for 3 months showed improved HbA1c and insulin-induced glucose uptake compared with controls; no significant changes in BMI, weight and waist circumference were observed (Sarnblad *et al.* 2003). Both trials demonstrated that Metformin improves metabolic control and Metformin was generally well tolerated in adolescents with type I diabetes.

Metformin seems to have positive effects on patients with diabetes; however it may also be used in obese non-diabetics to help lose weight. Paolisso et al (1998) found that administration of Metformin for 15 days reduced food intake, body weight and body fat in a group of obese adults (Paolisso *et al.* 1998). The weight loss effect has also been confirmed in the BIGPRO study whereby administration of Metformin for one year induced a significant weight loss and a reduction in blood glucose and plasma insulin levels in a group of obese middle-aged subjects (Fontbonne *et al.* 1996). Giving Metformin to obese adolescents with family history of type 2 diabetes caused similar effects (Freemark and Bursey, 2001; Kay *et al.* 2001). Those on Metformin showed a significant reduction in plasma leptin levels and weight loss which was primarily due to fat (assessed by using bio-electrical impedance).

2.9.4.4 Rimonabant

Rimonabant (Acomplia) is currently recommended for adult obese patients with a risk of developing diabetes or cardiovascular disease. It was first developed when scientists noticed that cannabis smokers experienced an increase in appetite, and worked on the idea of blocking cannabinoid receptors in the brain to reduce the increase in appetite. The drug was approved by the FDA in 2006, however due to its side effect of severe depression; there has been extreme caution in prescribing it. Other reported side effects include mood disorders, anxiety, nausea and dizziness (Despres *et al.* 2005; Scheen *et al.* 2006). Rimonabant is usually taken as a daily dose of 20 mg in the morning.

Rimonabant works by blocking receptors in the part of the brain that regulate food intake and the body's ability to break down sugars and fats in the blood, therefore acting on the central nervous system to decrease appetite and on the gastrointestinal tract to

diminish fat absorption. It mimics the effects of both Orlistat and Sibutramine by acting on both the central and peripheral systems.

Two randomised-controlled studies investigating the effectiveness of taking Rimonabant for one year showed promising results (Scheen *et al.* 2006; Despres *et al.* 2005). 18 - 70 year old obese adults with type II diabetes and untreated dyslipidemia were randomised to either placebo, 5 mg of Rimonabant or 20 mg of Rimonabant, in conjunction with a hypo-caloric diet. Weight loss was greater in both groups receiving Rimonabant compared to placebo with average loss of approximately 4 kg. Also, those on the larger dose lost on average 4cm from their waist and showed improvement in a number of cardiovascular and metabolic risk factors (Despres *et al.* 2005; Scheen *et al.* 2006). Those with dyslipidemia showed improvement in their lipid profiles (Despres *et al.* 2005).

To date there are no studies looking at the effectiveness of using Rimonabant in obese children and adolescents.

Table 2-3 Drugs used for treating obesity

Drug	Mechanism	Side Effects	Evidence in obese children and adolescents
Orlistat	Gastrointestinal lipase inhibitor	loose stools, oily discharge, deficiency of fat-soluble vitamins particularly vitamin D	***Decreases:*** WT, BMI, WC, LDL, leptin, glucose & insulin
Sibutramine	Appetite suppressant	High blood pressure & heart rate	***Decreases:*** WT ***Increases***: HDL
Metformin	Endogenous glucose suppressant & increases insulin sensitivity	abdominal pain, nausea, diarrhoea	***Decreases:*** WT, fat (by BIA), leptin, glucose & insulin
Rimonabant	Gastric lipase inhibitor & appetite suppressant	depression, mood disorders, anxiety, nausea, dizziness	None

Abbreviations: WT: weight; BMI: body mass index; WC: waist circumference; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; BIA: bio-electrical impedance analysis.

2.9.5 Surgery

Bariatric surgery can be divided into three main categories. Mal-absorptive surgery, the most common of the three categories, bypasses part of the gastrointestinal tract to limit the absorption of food. Restrictive surgery reduces the size of the stomach whereby the feeling of fullness is accomplished with lower food intake. Finally mixed surgery as the name implies uses a combination of the first two techniques. Costs of bariatric surgery are approximately in the range of £5,500 per procedure.

The National Institute of Health (NIH) Consensus Development Panel concluded that surgery is an appropriate treatment for adults with a BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 if co-morbid conditions were present (National Institute of Health, 1991). According to The National Institute for Clinical Excellence (NICE) criteria, bariatric surgery is not recommended for those under 18 years, and surgery should not be performed in adults unless there is sufficient evidence that all other weight-loss measures have been adequately tried but have failed to achieve long-term weight maintenance.

A recent study looking at the effects of bariatric surgery in 68 adolescents followed-up over a period of 30 years found excellent weight loss results and the long-term mortality rate was very low (4%) (Papadia *et al.* 2007). Side effects reported after bariatric surgery was performed in adolescents include: gastro-intestinal bleeding, bowel obstruction and nutrient deficiencies in addition to nausea, vomiting and constipation (Strauss *et al.* 2001).

Bariatric surgery seems to be well tolerated in adolescents; however due to the number of side effects reported, this procedure should remain the last option for treatment. Adolescents should be given the opportunity to lose weight using less invasive methods such as family-based behavioural programs and diet modifications. To date, there are no data on the use of bariatric surgery in children under 12 years old, and more extensive research is necessary for weighing the risks and benefits of surgical intervention in obese children and adolescents.

2.9.6 Available treatment in the UK

Compared to the many weight-loss programmes available for adults, there are very few weight-management programmes available for children and adolescents in the UK. These include weight-management clinics, weight-loss camps and government initiatives and plans incorporating school-based interventions. Each of these strategies is described in detail below.

2.9.6.1 Weight-management clinics

There are a few weight-management clinics available in different hospitals around London such as Great Ormond Street Hospital (GOSH), University College Hospital (UCH) and Royal Free Hospital. The clinics accept overweight and obese children and young adolescents who are referred to the specialised weight-management out-patient clinics by their GPs. They tend to include a multi-disciplinary team of dieticians, psychologists and doctors who follow up the children over time giving them advice on healthy eating, setting goals and assessing their growth to check their progress. These clinics can be quite useful as families learn about 'good foods' and 'bad foods', and setting targets and milestones is usually a good way to keep the children motivated. However, there are not enough clinics around the UK and some families may live far away and may not be able to come frequently to appointments due to time constraints and travel expenses.

2.9.6.2 Weight-loss camps

There are two main weight loss summer camps available in the UK. Wellspring UK is a 12 week residential program based in the Lake District, where 12 - 17 year old overweight adolescents are invited to register for the programme. The programme aims to teach participants about healthy eating and nutrition and incorporates various sports and outdoor activities. Carnegie International camp is another weight loss camp developed at Leeds Metropolitan University based at Woodhouse Grove Boarding school in Apperley Bridge. Similarly, it works under the same objectives as Wellspring UK whereby 11 - 17 year olds take part in different activities and are placed on a healthy eating regime. 12 weeks is the maximum duration of the programme; however participants can chose to stay for any duration during the summer holiday. In a group of 57 obese adolescents that took part in the programme, adolescents lost an average of 5.6 kg and showed a reduction in BMI SDS of 0.28, indicating that the programme is

effective in managing obese children and adolescents during their stay (average stay = 4 weeks) (Walker *et al.* 2003). However, there is not enough information on whether these changes remain after the children finish the programme, or on the long term effects of the intervention. A disadvantage of these camps is that they are very expensive; the monthly fee is in the region of £3,000. Even though these summer programmes may look promising, not many people can afford to register their children.

2.10 Government initiatives and plans

Stopping the rising trend in the prevalence of childhood obesity is now considered to be a public health priority. The NHS plan intends to tackle child obesity by promoting healthy eating and physical activity. There are now a number of government plans and initiatives specifically targeting schools and school children.

The Healthy School Programme includes the National School Fruit Scheme and Safe Active Travel to School (Department of Health, 2000). The National School Fruit Scheme aims to promote healthier eating in nurseries where every child aged 4 - 6 years will be entitled to a free piece of fruit each school day (Department of Health, 2000). Evidence from the National Diet and Nutrition Survey shows that school pupils in England consume an average of 3.4 portions of fruit and vegetables a day; with only 27% achieving the recommended intake of five a day. Safe Active Travel to School is a strategy aimed to reduce car journeys to school; hence promoting walking or cycling whenever possible. These programs tend to target all pupils instead of those who are already obese; to avoid increasing stigmatisation of overweight children at school. The Healthy Schools initiatives also aim to provide healthy tuck shops and vending machines to influence the choice of food available. Crisps, chocolate and fizzy drinks are the main items sold in tuck shops and vending machines; therefore providing healthy alternatives such as fruits may be useful especially if schools have adopted teaching the pupils about healthy eating and unhealthy foods.

The Active Programming Promoting Lifestyle Education in Schools (APPLES) programme consists of teacher training, modifications of school meals, and the development and implementation of school action plans designed to promote healthy eating and physical activity over one academic year (Sahota *et al.* 2001). APPLES is a randomised controlled trial (RCT) which included a total of 634 children aged 7 - 11 years from ten primary schools in the UK, randomised to either receive a school-based intervention or act as controls. There was no difference in change in BMI SDS between the two groups, and the programme had little effect on children's eating behaviour other than a modest increase in the consumption of vegetables. Results from APPLES were disappointing however one can argue that one year was not enough for a 'lifestyle' intervention to show any results, and it is possible that investigating a longer duration of APPLES may yield promising results.

'Eat smart, play smart' is a Food Standards Agency teaching resource developed for primary school teachers throughout the UK to use with children aged 5 - 7 years. The program was originally launched in 2004 in Australia and was developed to help children understand about the need for healthy diets and encourage them to be more active. A one year evaluation of the program reported no significant changes in overweight and obesity (assessed using BMI and skin-fold thickness); however consumption of fruit and vegetables increased significantly (Warren *et al.* 2003)

The Department of Health stated that physical activity levels in England are declining (Health Survey for England, 2005). Current recommendations suggest that adults should accumulate at least 30 minutes of moderate activity on most days of the week, and children should accumulate at least one hour of moderate activity on most days of the week. In view of the rapid increase in childhood obesity, and the declining levels of physical activity, the Prime Minister recently announced a £100 million campaign to increase school children's activity to five hours of sport every week, two hours of which are included in the curriculum; equivalent to one hour of sport every day of the school week (Department for children, 2007). The aim of introducing this campaign is not only to counteract obesity but also to increase bone strength.

Chapter 3: Body composition techniques for measuring obese children and adolescents

3.1 Introduction

There has been considerable interest in the need to measure body composition in children. Due to the rise in the prevalence of childhood obesity, assessing body composition is important in understanding the aetiology of childhood obesity, and in evaluating the success of different treatment programmes. As mentioned earlier, body composition is extremely difficult to measure in young children and adolescents for two main reasons. Firstly, accurate techniques tend to be more expensive, time consuming and are usually only available in specialized research centres. Secondly, measuring children is notoriously challenging as it can be difficult to make them comply with measurement protocols.

The body can be divided into five levels of body composition with increasing complexity: atomic I, molecular II, cellular III, tissue IV and whole body V (Wang *et al.* 1992) (refer to Figure 3-1**).** The gold standard for measuring body composition with optimum accuracy is through cadaver analysis. Therefore because this is not possible, a number of other techniques; mainly at the molecular level, have been used to estimate and predict body composition.

This chapter includes a review of the different techniques used to assess body composition in children and adolescents, giving details on the advantages and disadvantages regarding their use with children and adolescents, specifically the obese.

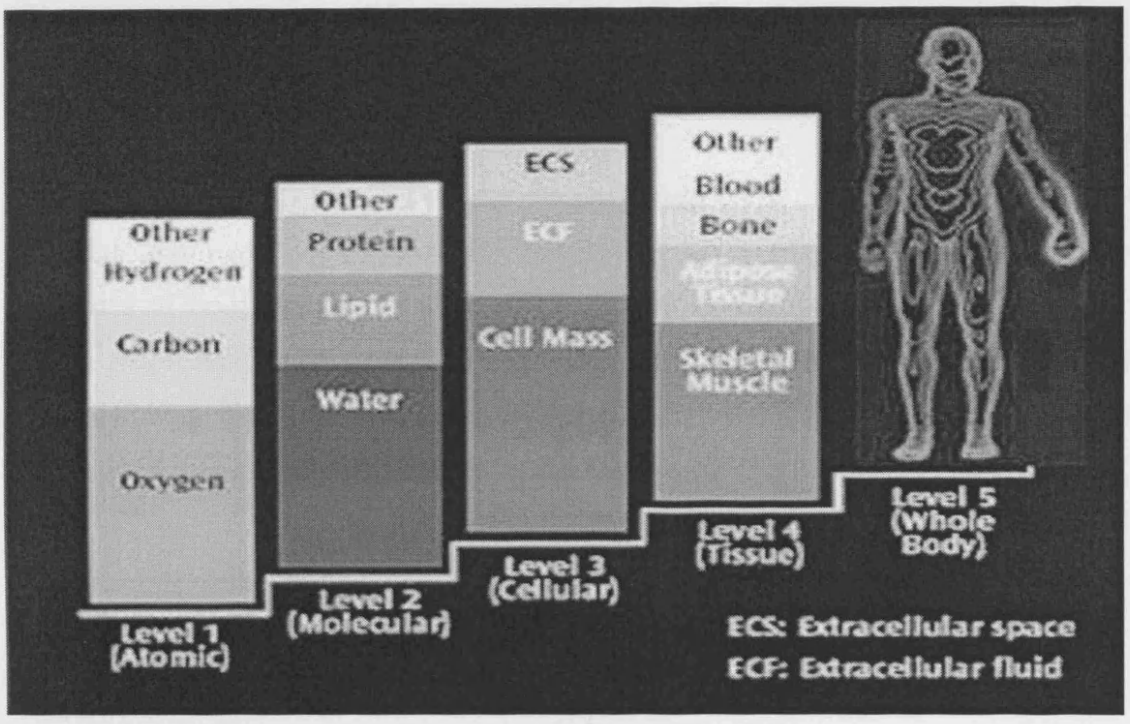


Figure 3-1 The five-level model of human body composition
Source: (Wang *et al.* 1992)

3.2 Anthropometry

3.3.1 Weight, height and body mass index

Although from a medical perspective obesity is defined as an excess of body fat and not an excess of body weight, it is usually classified on the basis of weight relative to height. At present, routine measures including weight, height and BMI are often used for monitoring growth and nutritional status. These have been used because they are very easy to calculate, quick to measure and non-invasive.

Many studies have reported a high correlation between BMI and percentage body fat in childhood (Pietrobelli *et al.* 1998; Ellis *et al.* 1999); this gives the impression that BMI is a good index of body fatness. Nevertheless, BMI has numerous limitations making it a poor index of body composition. First, compared to adults, children and adolescents vary in their growth rates and level of maturity. It has been reported that during growth, children tend to increase in the lean more than fat component of BMI (Maynard *et al.* 2001). Second, BMI correlates with both the lean and fat content of the body, and so it cannot differentiate between the two components and hence may give misleading information on body fat growth in children and adolescents (Wells, 2000). Third, BMI gives no information on where the fat is distributed in the body. Previous studies have shown that fat located around the abdomen area increases the risk of developing cardiovascular diseases in both adults and children independent of their body weight or BMI levels (Larsson *et al.* 1984).

Certain ethnic groups display a different relationship between BMI and percent body fat to that described for Caucasians. For example on average Asians tend to have a significantly greater proportion of fat mass for the same BMI value compared to Caucasians (Dudeja *et al.* 2001). The reverse is true for the average black population; a study showed that for the same level of body fat, age and gender American blacks have 1.3 kg/m^2 higher BMI compared to Caucasians (Deurenberg *et al.* 1998). These differences in fat levels have public health implications for the definition of BMI cut-offs for obesity, which would need to be population-specific. For example, the WHO suggested that obesity related diseases among Asian populations increase above a BMI of 23 kg/m^2, as opposed above 25 kg/m^2 in Caucasians (World Health Organization, 2004).

In specific population groups such as athletes, estimation of body fat from BMI is likewise problematic since they have a higher proportion of lean mass than non-athletes. Also, using BMI as a measure of body fat in various weight loss programmes may give false results. Weight loss does not equal fat loss as on average approximately 22-30% of the weight is lost as lean tissue and the remaining 70-78% is fat loss, and this may also vary between individuals (Webster *et al.* 1984). In addition, many recent weight-loss programmes are incorporating exercise as part of their regime. Physical activity may lead to increase in limb muscle mass as it has been shown to be a stimulant of muscle growth in children; therefore changing body composition but not necessarily weight (Torun and Viteri, 1994). Hence, weight maintenance or even slight weight gain may be experienced during exercise interventions, and this change may be overlooked if BMI is used as the outcome.

In addition there can be big differences in fat and lean levels within the same BMI level even within a group of children of the same age, sex and ethnicity. Wells (2000) measured a group of 64 children and estimated their FM and FFM (by D_2O) (Wells, 2000). Figure 3-2 shows a graph of FM versus FFM, both adjusted for height, indicating variability in percentage fat that can occur for a given BMI value. FFMI and FMI add up to BMI, so there are lines of constant BMI value decreasing across the graph. It is also possible to add non-parallel lines of constant percentage fat (Hattori *et al.* 1997). For example, girls A and B on the graph are both eight years old and they both have a BMI of 18 kg/m^2; however A has double the fat compared to B. This graph clearly shows that BMI is not a good indicator of fat in young children and can give misleading information on the amount of fat and lean in populations with similar BMI values.

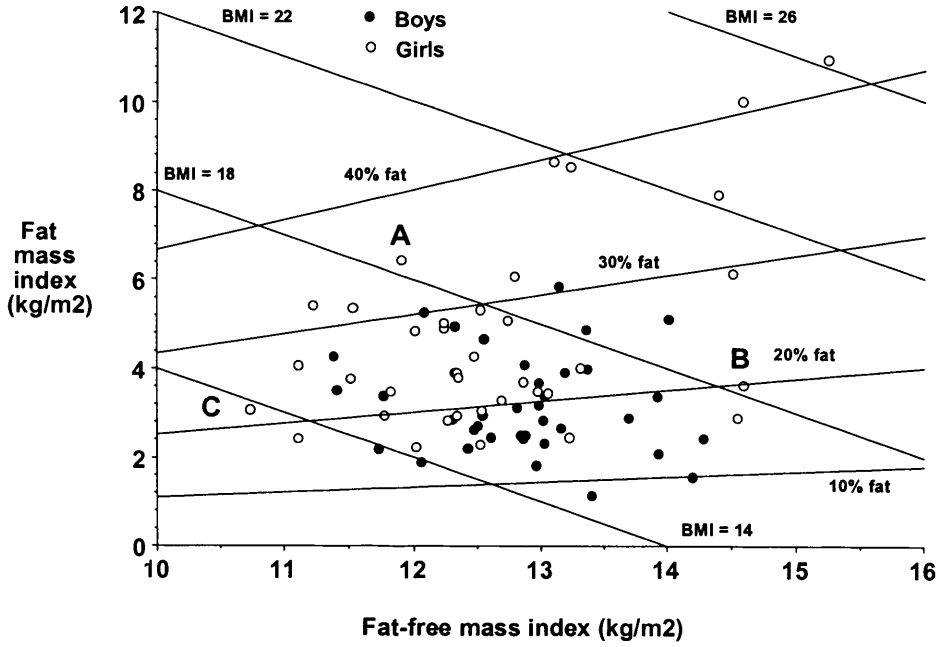


Figure 3-2 A Hattori chart of FFMI and FMI in 64 children aged 8-12 years.
Fat mass index (FMI) = FM/HT^2; fat free mass index (FFMI) = FFM/HT^2
Source: (Wells, 2000)

3.3.2 Waist circumference (WC)

Measuring WC is another common way for assessing obesity in adults and children because it is fairly simple, fast and non-invasive.

An android fat distribution with excess fat in the upper areas of the body, especially in the abdomen, has been associated with an increased risk of developing coronary artery disease compared to the gynoid pattern which relates to fat distributed in the lower parts of the body, particularly in the hips and thighs (Daniels *et al.* 1999). Measuring WC has proved to be a useful tool for assessing risk for obesity-related diseases such as cardiovascular disease (Lemieux *et al.* 2000). Inconsistent relationship on the association between WC and abdominal fat has been reported, some finding no significant relationship (De Ridder *et al.* 1992; Wells and Fewtrell, 2006) On the other hand, some studies have shown that WC correlates well with intra-abdominal adipose tissue (measured by MRI or CT) in adults and children; with correlations in the range of 0.5 to 0.8 (Taylor *et al.* 1998; Fox *et al.* 1993; Lobstein *et al.* 2004; Owens *et al.* 1999). Measuring body fat distribution may be more important than measuring total adiposity for assessing risk of developing metabolic complications.

The criteria for selection of cut-off points for waist circumference in adults are as follows: action level 1: men, > 94 cm, women, > 80 cm; and action level 2: men, > 102 cm, women, > 88 cm for diagnosis of abdominal obesity which are based on data derived from adult Caucasians (Lean *et al.* 1995). These WC cut-off points were based on high sensitivity and specificity profiles against cut-off values of BMI (25 kg/m^2 for action level 1 and 30 kg/m^2 for action level 2) and waist-to-hip circumference ratio (0.95 for men and 0.80 for women for both action levels) in adult Caucasians. A similar indicator was used in the WHO report where an increased risk of developing complications is present when WC exceeds 94 cm in men and 80 cm in women (World Health Organization, 2000). However, these cut-offs were derived from Caucasian populations, and several studies have shown that they are inappropriate in other ethnic populations (Wildman *et al.* 2004; Zhu *et al.* 2005; Wildman *et al.* 2004; Misra *et al.* 2006). For example, compared to White populations, Asians have been shown to have greater WC for the same BMI leading to a greater prevalence of cardio-vascular risk factors at lower BMI levels (Wildman *et al.* 2004). Therefore revised ethnic specific cut-off points for WC have been proposed for males and females (refer to Table 3-1).

Waist circumference to height ratio (WHTR) is another index used to assess the risk of disease related to central fatness in both adults and children; cut-off WHTR = 0.5 (McCarthy and Ashwell, 2006).

Moreover, adult WC cut-offs cannot be used for children, instead age- and gender-specific reference data are available for WC in children and adolescents. Similar to BMI measurements, raw WC measurements can also be converted to SDS using UK reference data for children aged 5 - 16.9 years collected in 1988 (McCarthy *et al.* 2001).

Table 3-1 Waist circumference cut-offs corresponding to established BMI cut-offs for adults from different ethnic groups

		WC cut-offs corresponding to BMI cut-offs (cm)				
	BMI cut-offs (kg/m^2)	**White**	**Black**	**Mexican American**	**Indian Asians**	**Chinese**
Men	25	94	86.4	88.7	78*	80§
	30	102	98.8	101.2	90**	
Women	25	80	83.5	83.1	72*	80§
	30	88	93.9	93.6	80**	

Abbreviations: WC: waist circumference; BMI: body mass index
* at BMI cut-off > 21; ** at BMI cut-off > 25; § at BMI cut-off of 24
Source: (Wildman *et al.* 2004; Misra *et al.* 2006; Zhu *et al.* 2005)

3.3.3 Skin-fold thickness

Skin-fold thickness measurements are another popular traditional technique that can be applied to infants and children. This method measures subcutaneous fat at several sites of the body by "pinching" the skin with callipers. Even though measuring skin-fold thickness is non-invasive, easily performed and inexpensive it has many disadvantages. First, it measure only subcutaneous fat, and hence assumes that subcutaneous fat is proportional to the person's total body fatness. This proportion actually varies widely and is highly dependant on gender, age and ethnicity (Deurenberg *et al.* 1990). Some people have a greater proportion of their total body fat situated internally rather than subcutaneously; hence measurements obtained using skin-fold callipers may not be representative. Second, relative skin-fold data only refer to measures of fatness but not lean mass; hence only one index on body composition is considered. Third, the equations that convert skin-fold measurements to measures of body fat are inaccurate, with a prediction error of about 3-5%; being highest in pre-pubertal children; and the data obtained cannot be considered to be reliable (Deurenberg *et al.* 1990; Reilly *et al.* 1995). Finally, skin-folds are also very difficult to measure in the obese, the callipers cannot grasp the wide fold of the skin; therefore underestimating measures of subcutaneous fat.

The best way of using skin-fold thickness data is by using the raw data because they are relatively reliable indices of regional fatness (Wells and Fewtrell, 2006). These can be converted into SDS using UK reference data for infants (Paul *et al.* 1998) and children (Davies *et al.* 1993). The children's reference data however are very old (Tanner and Whitehouse, 1975) and therefore a revised standard for skin-fold thicknesses for healthy children is needed.

BMI, WC and skin-fold measurements are the most widely used tools of assessing body composition because to date they are the only existing outcomes with reference data; but only BMI and WC are practical in those obese.

3.3 Two-component model (2C)

Various different models can be used to estimate body composition; the simplest is the 2C model which divides total body weight into the components FFM and FM. This model assumes constant properties of FFM, like constant density or hydration. In those cases, the accuracy of the results obtained by the 2C model will depend on the validity of the assumptions made about the different components of FFM. A summary of the different equations used to estimate percentage fat by the 2C model is shown in Table 3-2.

Generally, three main factors introduce variations in the properties of FFM. First, properties are not constant even between healthy subjects of a given age and sex (Wells *et al.* 1999). Second, properties change significantly during growth due to the process of chemical maturation (Fomon *et al.* 1982). Third, different diseases states may involve a variety of conditions such as: over hydration, under hydration, muscle wasting, tumour growth, mineral loss or oedema, each of which exerts effects on the properties of FFM. All these sources of errors reduce the validity of the 2C models of body composition (Wells and Fewtrell, 2006).

For the rest of this section, I have selected a number of the various techniques that use the 2C model for calculating body composition, and I will describe each method in detail separately.

3.3.1 Isotope dilution

Deuterium oxide (D_2O) dilution has been used to measure TBW because it can be safely administered in humans and because deuterium (^2H) weighs approximately twice as much as hydrogen (^1H); and can thus be detected using a mass spectrometer. D_2O is a stable, non-toxic, non-radioactive isotope of water $^2H^1H^{16}O$. It is naturally occurring but heavier than normal water $^1H_2{}^{16}O$ because the hydrogen part of the water has one extra neutron, giving its other name 'heavy water'. Hydrogen atoms in the body water pool are fully exchangeable with isotopic water by substituting the hydrogen (^1H) with deuterium (^2H) (Culebras and Moore, 1977). ^{18}O is another isotope that can be used to measure TBW. D_2O is used more than $H_2{}^{18}O$ as the latter isotope is substantially more expensive. TBW values calculated from ^{18}O and ^2H are highly correlated (Schoeller *et al.* 1980).

The principal of using isotopic tracers to calculate body water is that if a quantity of tracer is added to the body water pool, measurement of the concentration of tracer in body fluids will allow the size of the body water pool to be calculated (Culebras and Moore, 1977). The tracer isotope is assumed to have reached an equilibration with the body water pool by a specified time after administration of the dose.

There are three ways of measuring isotopic enrichment in the body: by taking samples from saliva, urine or blood. Blood is too invasive to use in healthy paediatric populations; whereas saliva samples and urine samples are preferable to use in children and infants respectively (Schoeller *et al.* 1980). The time needed for the isotope to equilibrate in the body is longer when a urine sample is taken instead of a saliva sample; 4 - 6 hours compared to 3 - 4 hours respectively (Schoeller *et al.* 1982).

The limitation of using isotope dilution to calculate TBW is that during the time taken for the isotope to equilibrate with the body water pool, some of the isotope may be lost from the body by sweating or voiding and also may be diluted by additional fluid intake. However, losses in expired air and urine are negligible because of the long half-life of isotopic hydrogen in the body. On the other hand, any fluid consumed during the equilibration period should be taken into account during TBW calculation otherwise the concentration of the isotope at the time of equilibration will be lower than predicted by the model, and TBW will be overestimated (see below).

The equation used to calculate TBW is:

$$N = \frac{TA}{a} * \frac{(Ea - Et)}{(Es - Ep)}$$ **(Halliday and Miller, 1977) Equation 3-1**

where N is the dilution space in ml, A is the dose given in grams, T is the amount of tap water in which the dose sample was diluted before analysis, a is the portion of the dose in grams diluted for spectrometer analysis, Ea is the isotopic enrichment of the dosing portion, Et is the isotopic enrichment of the tap water, Es is the post dose enrichment and Ep is the pre dose enrichment. Ea, Et, Es and Ep are measured in delta units which express isotopic enrichment relative to a standard, in this case International Standard Vienna Standard Mean Ocean Water.

Values of N are converted into values for TBW by dividing by 1.044 when using D_2O technique, but only by 1.01 when using $H_2{}^{18}O$, as there is more non-aqueous H compared to O in the body (Racette *et al.* 1994).

$$TBW = \frac{N(D_2O)}{1.044} \text{ approximately equal to } \frac{N(H_2{}^{18}O)}{1.01}$$ **Equation 3-2**

Furthermore, any fluid consumed during the equilibration period should be subtracted from the raw TBW values calculated, as they would increase the dilution space volume; thus yielding overestimated results.

FFM can be calculated from TBW by using assumed FFM hydration values. However, due to the process of chemical maturation during growth, the relative proportions of water, protein and mineral change with age and puberty; whereby there is a non-linear decrease in H_{ffm} (Fomon *et al.* 1982). Therefore a constant used for adults may not hold true for children. Also obese children were found to have a significantly increased H_{ffm} compared to non-obese children (Bray *et al.* 2001; Haroun *et al.* 2005). Therefore constants used in normal-weight children may not be applicable in the obese.

$$FFM = \frac{TBW}{H_{ffm}}$$ **Equation 3-3**

FM can then be calculated by subtracting FFM from total body weight.

FM = WT - FFM **Equation 3-4**

3.3.2 Body density and volume measurements

3.3.2.1 Under-water weighing/hydro-densitometry (UWW)

Hydro-densitometry (see **Figure 3-3**) is based on the principle of Archimedes which states that the volume of an object is equal to the object's loss of weight in water. This method measures whole body density (calculated as body mass/body volume) by measuring body weight and body volume and predicting body composition by assuming constant densities of FM and FFM (Siri, 1961). Since fat is homogenous, it is relatively reasonable to assume that the density of fat is constant (FIDANZA *et al.* 1953). However because of the heterogeneous nature of the FFM components (mainly water, mineral and protein), the validity of the constant density of FFM poses one limitation to using this method. FFM composition can be influenced by age, gender and ethnicity in addition to changes due to growth, sexual maturation and the effect of various diseases (Fomon *et al.* 1982; Bray *et al.* 2001; Haroun *et al.* 2005).

One limitation to using hydro-densitometry as a measurement tool to evaluate body composition is that the method requires the subject to be completely submerged in water (refer **to** Figure 3-3**)** (Fields and Goran, 2000). Hence this technique is generally not recommended for sick patients, those scared of water and for the majority of the paediatric population.

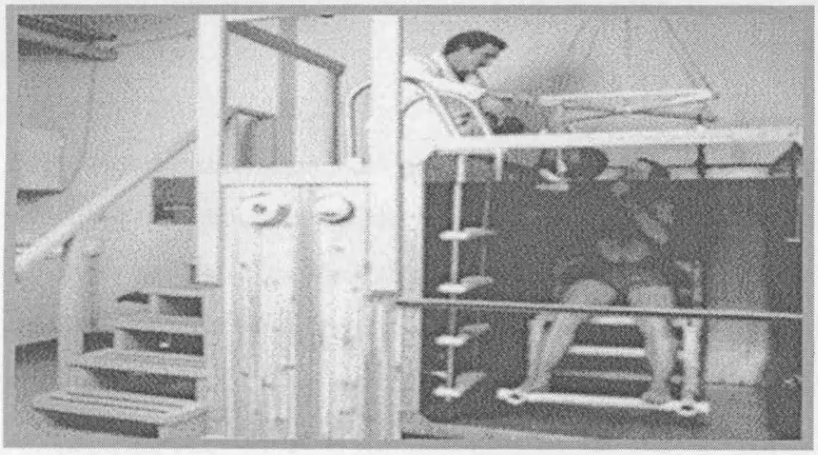


Figure 3-3 Under-water weighing machine
Source: www.mhhe.com

3.3.2.2 Air-displacement plethysmography (ADP)

This technique is based on the same principle as underwater weighing but instead of using water it uses air displacement to determine the subject's body volume. An advantage of this technique over hydro-densitometry is that the subject does not have to be submerged in water making it more favourable and feasible in many (Dewit *et al.* 2000). Also child-specific equations have been recently developed to predict lung volume for children over five years old; hence reducing the error in estimating % body fat (Fields *et al.* 2004).

ADP has been evaluated to examine the reliability of body volume measurement by BODPOD relative to UWW. Strong correlations between ADP and UWW have been reported in normal weight adults and children, and also in overweight and obese adults, with correlations in the range of 0.7 - 0.9 (Fields et al, 2001; Ginde et al, 2005) However, compared to hydro-densitometry, ADP has been shown to have a better precision in measuring body volume and calculating FM and FFM in both adults and children (Wells and Fuller, 2001; Dewit *et al.* 2000; Fields *et al.* 2002).

ADP requires the subjects to sit still in a chamber for a couple of minutes; therefore those who are claustrophobic or are very young might not be able to comply with the measurement protocol. The other disadvantage of using such a technique is the time needed to calibrate the machine (40 minutes) before the measurement is performed. Also due to the size of the equipment, ADP is not suitable for field studies and most routine clinics.

The other consideration that needs to be taken into account when estimating body volume is the amount of air left in the lungs, also called residual lung volume which can either be estimated or measured. Even though lung volume can be measured, it is usually estimated using predicted equations because the procedure involves the subject exhaling air into a tube which can be very difficult for young children.

Using Siri's equation (Siri, 1956), % fat can be calculated from density using the following equation:

$$\% \text{ fat} = (495 / D_b) - 450 \qquad \textbf{Equation 3-5}$$

where D_b is body density calculated by dividing weight by volume.

3.3.3 Dual X-ray Absorptiometry (DXA)

DXA was originally designed to assess bone mineral density as a screening and diagnostic test for osteoporosis. However over the last decade DXA has been increasingly used to measure body composition as it also provides information on FM, FFM and their distribution in the trunk and upper and lower limbs (Mazess *et al.* 1990). This is because it is fairly quick, a whole body scan lasts about 10 minutes, and it can be used in young children. The DXA scanner emits two distinct low energy x-ray beams with different energy levels, and bone mineral is then calculated from the differential absorption of the two energies after taking into account soft tissue. In current instruments the radiation dose is very low (< 3 μSv per scan), which is lower than a day's background radiation in the UK. The precision of soft tissue body composition by Lunar DPX-L was established by repeated measurements on 20 adults over four days (Kiebzak *et al.* 2000). A variation of 0.6%, 2% and 1% for BMC, FM and FFM respectively was reported; regional measurements were less precise than total body measurements. For ethical reasons, repeated measures have not been performed on children.

Caution is required when using DXA for body composition measurements. First, DXA scanner software assumes a hydration constant of 73% for FFM. This constant might be appropriate for healthy adults but would not be appropriate for children or adolescents where the hydration status changes during growth, or in disease states that might alter the hydration of FFM. Second, a recent study comparing DXA with the 4C model in a wide group of patients showed that the precision of using DXA (Lunar Prodigy) varies according to gender, size, fatness and disease (Williams *et al.* 2006). Similar findings by Wong and colleagues (2002) comparing DXA (Hologic QDR-2000W model) with the 4C model in a group of young girls reported that an individual's FM can be 28% under or over-reported relative to the 4C model (Wong *et al.* 2002). This implies that DXA is not a very reliable tool for measuring body composition in case-control studies and for longitudinal studies assessing changes in body composition such as weight loss programmes. Moreover, the DXA scanner has a weight limit of 115 kg and a limited width area. Hence, it is not suitable to use in morbidly obese children and adolescents. Another limitation of the DXA scanner is that it only estimates the proportion of fat and lean tissue in pixels containing no bone; therefore the composition of fat and lean in the trunk is less accurate than in the limbs due to the greater amount of bone in the trunk

including ribs, pelvis and spine. Even though the radiation is low, it would be unfavourable to use in short term longitudinal studies or routine clinical assessments such as weight management clinics. Finally, having a DXA scan is expensive (current costs in the range of £100 per scan), and due to its large size it is not made easily available in clinics and hence has some limitations for use as a routine body composition assessment tool.

3.3.4 Bio-electrical impedance analysis (BIA)

BIA is a simple, non-invasive, inexpensive technique that needs very little maintenance and minimal operator training. BIA machines, for example TANITA machines, work by sending a low, safe electrical signal through the body. BIA is based on the fact that lean tissue, such as muscle and blood, contains high levels of water and electrolytes and therefore acts as a conductor of an electrical signal. Fat tissue is comparatively anhydrous and acts as a resistor to the flow of an electrical signal. The machine therefore relies on the assumption that body conductivity is proportional to TBW. The only direct measurement BIA machines make is impedance; all other values such as FM, FFM and TBW are calculated using in-built equations predicting TBW from data on impedance and height and in some cases other terms such as weight, age and sex.

BIA measures resistance of a body to an electric current (refer to

Figure 3-4). Based on the theory that the body is a cylinder of a certain length, the resistance (R) of the cylinder is given by:

$$R = K * HT/A \qquad \textbf{Equation 3-6}$$

where R is resistance, K is a constant known as resistivity, HT: is the length of the cylinder, and A is the cross/sectional area. If the equation is re-arranged:

$$A = K * HT/R \qquad \textbf{Equation 3-7}$$

Multiplying both sides of the equation by length gives:

$$Ht*A = K* HT^2/R \qquad \textbf{Equation 3-8}$$

$$Ht*A = Volume\ (V) \qquad \textbf{Equation 3-9}$$

$$V = K * HT^2/R \qquad \textbf{Equation 3-10}$$

Therefore, the volume of the cylinder/body can be determined by measuring its length and resistance. The volume of the body is the volume of the conducting material i.e. TBW. Hence V can be replaced with TBW and the equation becomes:

$$TBW = K * HT^2/R \qquad \text{Equation 3-11}$$

One limitation of using BIA is that the human body is not a uniform cylinder of constant ionic properties. Therefore, BIA predicts rather than measures TBW. Another limitation of using BIA to predict TBW is that this method assumes that the hydration status of FFM is constant. However, physiological and pathological factors such as pregnancy, obesity, disease states and ethnicity may interfere with the hydration status. We have previously shown that the hydration of FFM was significantly higher in obese children compared to lean children matched for age and gender (Haroun *et al.* 2005). Therefore more research is needed in order to determine the validity of BIA in obese individuals.

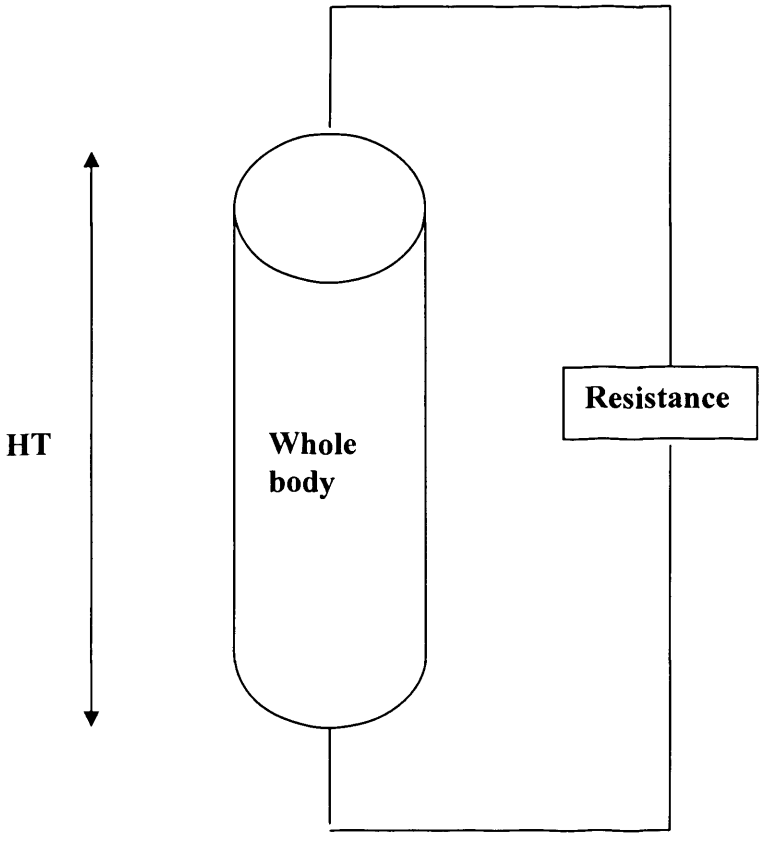


Figure 3-4 A diagram illustrating the theory behind whole body impedance

3.3.5 Magnetic resonance imaging (MRI)

MRI (see Figure 3-5) works by creating a strong magnetic field around the body causing hydrogen nuclei located either in water or fat to align with or against the magnetic field. The absorption and emission of energy by these nuclei are then analysed hence producing multiple cross-sectional images of the body which are then combined by computer software to calculate regional tissue volumes. This method therefore estimates the volume of adipose tissue.

MRI can differentiate between subcutaneous and visceral fat. Subcutaneous fat is located underneath the skin while visceral fat is located internally within the abdomen and surrounding the organs. There is growing interest in looking at visceral fat rather than total body fat as a risk factor for metabolic conditions associated with obesity in children and adolescents as it is more metabolically active (Taksali *et al.* 2007).

One problem with using MRI is the assumption made on the density of fat and the fat content of adipose tissue. As mentioned earlier the density of fat is relatively constant but the fat content of adipose tissue is not (Thomas, 1962). The other problem with using MRI is that it only estimates fat present in the adipose tissue, which is different to total fat estimated using other techniques; therefore posing a problem when converting adipose tissue to total fat.

MRI is safe because it does not use radiation. However its use is limited primarily because of the high cost of the equipment (approximately £350 per scan) and also because of the time needed for scanning and analysis – a typical whole body scan takes approximately 10 minutes. Also some subjects, particularly very young children, may not be able to keep still for the scan and so movement artefacts may result. In addition, the scan is performed in an enclosed area while lying on a bed; hence those who are claustrophobic might not be able to perform the scan.

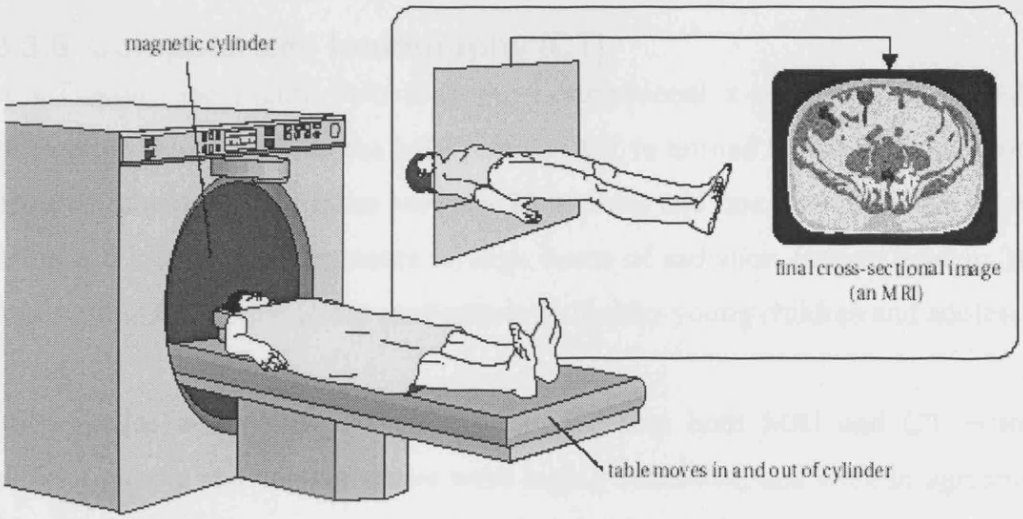


Figure 3-5 MRI scanner
Source: www.mritoday.net

3.3.6 Computerized tomography (CT)

A CT scan (see Figure 3-6) uses three-dimensional x-rays to take cross-sectional pictures of the body. Like the MRI scanner, CT is limited by the high equipment cost and time; the procedure takes between 20 minutes and one hour. Another limitation to using a CT scanner is exposure to high doses of radiation (approximately 10 mSv); making it unfavourable to use particularly in healthy young children and adolescents.

Mitsiopoulos and colleagues (1998) reported that both MRI and CT estimates of skeletal muscle and adipose tissue were highly correlated, and were in agreement with those obtained from cadaver analyses (Mitsiopoulos *et al.* 1998).

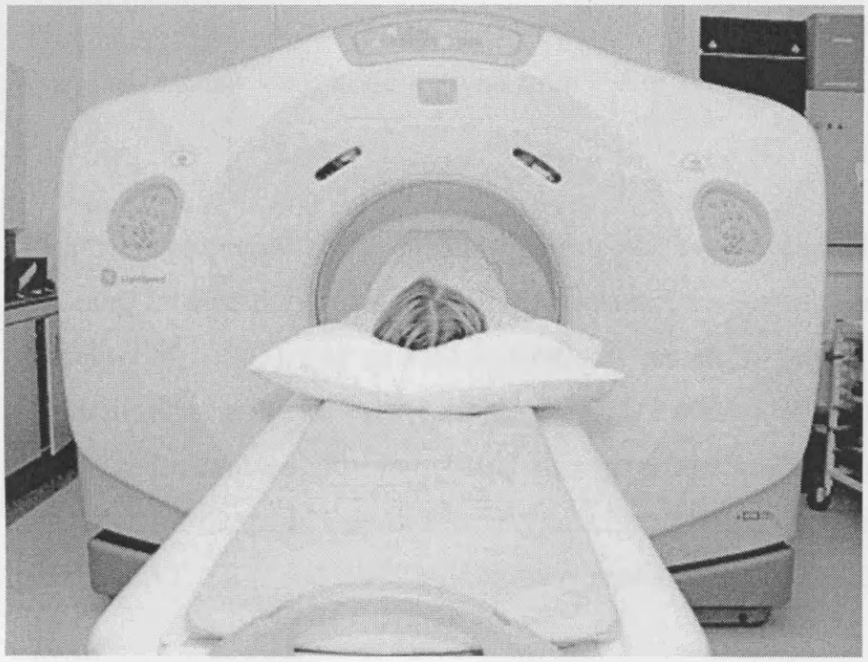


Figure 3-6 CT scanner
Source: www.cancerhelp.org

3.4 Multi-component models

Multi-component models are considered to be the most accurate method to estimate whole-body composition *in-vivo* because they minimize the assumptions made about the composition of FFM (Wells and Fewtrell, 2006). In the multi-component models the different properties of FFM such as hydration, density and bone mineral content (BMC) are actually measured rather than assumed as in the 2C models.

A summary of the different equations that can be used to calculate body composition using the 2C, 3C and 4C models of body composition is given in Table 3-2.

The equations and models differ regarding assumptions made concerning the relationships and densities of the various components of FFM. In this thesis, the equations used for calculating body composition in children and adolescents using the 3C and 4C models were those derived from Fuller and colleagues (1992) (Fuller *et al.* 1992).

The three component (3C) model divides total body weight into FM, water and remaining fat-free dry tissue, assuming constant densities of these three components (Brozek *et al.* 1963), and an assumed ratio of protein to mineral. It is advantageous compared to using the 2C model in that it avoids the assumption that the water content of FFM is constant between individuals of a given age and gender. It can also provide an estimate of the hydration and density of FFM. The measurements required for this model are WT, TBW and BV. The following equation is used to calculate FM:

FM (kg) = [2.22] BV – [0.764] TBW – [1.465] WT **Equation 3-12**

Where BV is measured in litres; TBW in litres; WT in kg (Fuller *et al.* 1992)

The four component (4C) model divides body WT into fat, water, protein and mineral, thereby avoiding the assumption that the ratio of protein to mineral in FFM is constant. However, the model assumes a constant ratio of osseous (bone mineral) to non-osseous mineral (total body mineral). This model requires the same measurements used for the 3C model in addition to BMC measurement (by DXA). The equation is as follows:

FM (kg) = (2.747) BV – (0.71) TBW + (1.46) BMC – (2.05) WT Equation 3-13

where BMC is measured in kg (Fuller *et al.* 1992)

The reliability of estimating body fat in children using the multi-component models was tested by Wells and colleagues (1999) (Wells *et al.* 1999). The propagated errors (whereby the total error is a function of the independent and additive technical errors) for calculating FM and FFM for the 2C, 3C and 4C models are shown in Table 3-3. It is clear that the precision of estimating body composition when using multi-component models is not invalidated by the sum of errors associated with performing multiple measurements. On the contrary, using multi-component models was shown to improve accuracy because assumptions made concerning the different components of FFM are minimized.

Table 3-2 Equations for estimating body composition based on 2C, 3C and 4C models

Model	Equations	Reference
2C	FM = (4.95)BV – 4.50WT for adults	(Siri, 1956)
	FM = (4.57)BV– 4.142WT for adults	(Brozek *et al.* 1963)
	FM = (5.27)BV – 4.85WT for children	(Wells *et al.* 1999)
3C	FM = (2.118)BV – (0.78TBW) – 1.354WT	(Siri, 1961)
	FM = (6.386)BV – (3.96M) – 6.09WT	(Lohman, 1986)
	FM (kg) = (2.22) BV – (0.764) TBW – (1.465) WT	(Fuller *et al.* 1992)
	FM (kg) = (2.15)BV – (0.771)TBW – (1.390)WT *	(Haroun *et al.* 2005)
	FM (kg) = (2.106)BV – (0.776)TBW – (1.339)WT **	
4C	FM = (2.747)BV – (0.714)TBW + (1.146)M – 2.0503WT	(Selinger, 1977)
	FM = (2.7474)BV – (0.7137)TBW + (1.1471)M – 2.0503WT #	(Baumgartner *et al.* 1991)
	FM = (2.559)BV – (0.734)TBW + (0.983)BMC – 1.841WT	(Friedl *et al.* 1992)
	FM (kg) = (2.747)BV– (0.71)TBW + (1.46)BMC – (2.05)WT	(Fuller *et al.* 1992)
	FM = (2.5126)BV – (0.7389)TBW + (0.947)BMC – 1.7896WT	(Heymsfield *et al.* 1996)

Abbreviations: WT= weight (kg); M= mineral (osseous and non-osseous) (kg); FM= fat mass (kg); BV= body volume (l); TBW= total body water (l); BMC= bone mineral content (kg) *Equation to be used in control children (-2 < BMI SDS < 1.64) aged 7 - 14 yeas
**Equation to be used in obese children (BMI SDS > 1.64) aged 7 - 14 years
Equation to be used in White adults aged 65 - 94 years

Table 3-3 Propagation of methodological error on FM and FFM values obtained by the different models

	Error calculating FM/FFM (kg)	**% of FFM**	**% of FM**
4C model*	0.22	0.5	3.1
3C model **	0.20	0.5	2.8
2C models:			
D_2O	0.27	1.3	3.8
UWW	1.00	3.8	13.8
BOPDPOD	0.3	1.1	5.2
DXA	0.2 - 0.4	1.5	3

* measurements involved BODPOD, D_2O and DXA
** measurements involved BODPOD and D_20

Source: (Wells *et al.* 1999) & (Wells and Fuller, 2001): error estimated from 30 children aged 5 - 16 years; average weight assumed to be 48.7 kg (41.5 kg FM and 7.2 kg FFM)

Abbreviations: FM= fat mass; FFM= fat-free mass; D_20= deuterium oxide dilution; UWW= under-water weighing; DXA= dual x-ray absorptiometry.

3.5 Summary

When assessing body composition in a cross-sectional study, it is important that the technique used to measure body composition is accurate. However when assessing body composition in a longitudinal study, the accuracy of the measurements is not the only relevant issue and the precision of the measurements will also contribute to the ability to accurately detect significant changes.

Different factors can affect the different body components such as fat and lean mass; especially during growth. Therefore adult constants and equations should not be applied to children when assessing body composition as these may yield false results. Also obesity may alter the different components on FFM such as hydration or density (Bray *et al.* 2001; Haroun *et al.* 2005); therefore this aspect should be considered when assessing body composition in obese children or adolescents.

Multi-component models are the most accurate to estimate whole body composition, especially when a disease state has an effect on the various components of lean mass. On the other hand, the best technique to use when regional body composition is required is MRI as it provides information on the regional distribution of fat and also gives separate information on subcutaneous versus visceral fat. Measuring regional fat may be more appropriate in ranking individuals according to risk of developing cardiovascular diseases.

Multi-component techniques require the use of several methods to measure body composition; and these methods tend to be expensive and are only available in big research centres. Therefore it is important to find a simple technique that can be used to detect change in body composition without bias, by validating it against the gold standard *in vivo* which is the multi-component model. This technique can then be used easily by paediatricians in clinics to look at body composition changes in different disease states such as obesity.

Chapter 4: Hypotheses, recruitment, methods used, ethical considerations and study pian

This chapter outlines the different hypotheses I proposed to test in this thesis, a brief description of where subjects were recruited from, the methodology used and finally an overview of the study plan along with the ethical considerations.

4.1 Hypotheses

This study is divided into three main hypotheses; each of these hypotheses will be described in detail in chapters 5, 6 and 7 including details on study design, sample size calculation and statistical analyses.

The first hypothesis tested:

1. Body composition differs between obese and non-obese children and adolescents

The different components of the body, such as fat-free mass (FFM) and fat mass (FM) in addition to the various components of FFM such as hydration (H_{ffm}) and density (D_{ffm}), were compared between normal weight and obese children and adolescents.

The second hypothesis tested:

2. Body composition of obese children and adolescents on different weight-loss programmes changes over a period of 6 months and 1 year.

For this part of the study, two different weight-loss programmes available at Great Ormond Street Hospital (GOSH) were investigated: the Traffic Light Program (TLP) and Metformin program. Details of the two programmes are described in detail in chapter 6. Body composition was assessed at baseline, six months and one year after taking part in the program, to investigate and evaluate the success of the programmes in changing body composition i.e. detecting a change in FM or FFM and their distribution.

Finally, the third hypothesis tested:

3. A new BIA machine, TANITA BC-418 MA, can accurately measure body composition, and change in body compositions in obese children and adolescents compared to the multi-component model.

For this part of the study, body composition measurements from the impedance machine were compared against those obtained from the 3C and 4C models. TBW or FFM (estimated from D_2O and the 3C or 4C model respectively) was compared to height^2/R (measured by TANITA BC-418 MA). Validating the TANITA machine enables the construction of equations that can be used to estimate body composition specifically for a group of obese individuals within a specific age range. These equations were then tested in a sub-group of obese children that had longitudinal measures of body composition to assess the accuracy of the machine in estimating body composition changes over time.

4.2 Recruitment

Participants were recruited over a period of four years, between January 2004 and January 2008, from four different sources:

1. Paediatric outpatient weight management clinic based at GOSH, run by Dr. Russell Viner
2. Weight management clinic based at UCH, run by Dr. Russell Viner and Dr. Terry Segal
3. Traffic light programme (TLP) based at GOSH, run by Prof. Jane Wardle, Helen Croker and Dr. Russell Viner
4. Lifestyle, Eating, Activity and Fitness (LEAF) weight management clinic in Chichester, run by Dr. David Candy
5. On-going body composition research project based at ICH/GOSH, run by Jane Williams

Obese patients presenting to the weight management clinics at GOSH and UCH were initially referred though their local hospital, General Practitioners (GPs), paediatricians, school nurses and dieticians.

Non-obese subjects (used as controls) in addition to a few obese subjects were also recruited via an on-going body composition research project. This group of subjects were recruited via the media: leaflets and posters were distributed in different places in London including hospitals, universities and sports centres, and details of the study were also published in the Metro and Evening Standard newspapers a number of times during the study period.

4.3 Methods

4.3.1 Anthropometry

Body weight was measured with minimum clothing to the nearest 0.01 kg using the electronic weighing scale integral to the BODPOD machine (described later). The accuracy of the scale was determined by using two weights, each weighing 10 kg. Standing height was measured to the nearest millimetre using a wall-mounted stadiometer (Holtain, Dyfed, UK). BMI was calculated as weight (kg)/ height (m)^2.

Circumferences of the head, mid-upper arm (MUAC), waist (WC), hips, calf and thigh were also measured using a non-stretchable flexible measuring tape and recorded to the nearest 0.1 cm. WC was measured midway between the tenth rib and the top of the iliac crest (World Health Organization, 1995), whilst hip circumference was measured at the widest girth. All measurements were done on the left hand side of the body while the subject was standing; in accordance with the Anthropometric Standardization Reference Manual (Callaway *et al.* 1988).

Height, weight, BMI and WC were converted into SDS using current 1990 UK reference data calculated using the LMS Growth program (Cole *et al.* 1995; McCarthy *et al.* 2001).

4.3.2 Deuterium oxide dilution (D_20)

Total body water (TBW) was determined by, using an oral dose equivalent to 0.05 g ^2H_2O/kg of body weight (99.9 atom % excess, Sigma Chemical Co. Chemicals, Poole, UK). Saliva samples were collected using absorbent salivettes (Starstedt, Rommelsdorf, Germany) prior to administration of the dose to determine the natural background concentrations of the isotopes in the body. Further saliva samples were collected at four hours (for non-obese subjects or controls) or five hours (for obese subjects) (unpublished data) after dosing to give enough time for the isotope to equilibrate fully with the body water pool. Subjects were asked to refrain from introducing any food or liquid at least 30 minutes before the saliva sample was collected. Saliva samples were spun using a centrifuge, frozen at -80°C and then analysed using the equilibration method (Scrimgeour *et al.* 1993). 0.5 ml of saliva sample along with a platinum-on-alumina catalyst rod was placed in a sealed vial and flushed using 2% Hydrogen in Helium gas for approximately seven minutes. The samples were then left to equilibrate at room temperature for at least eight hours before analysis. Isotopic enrichment of the dose and the saliva samples was then determined in duplicate using isotope ratio mass spectrometry (Geo 20-20; Europa Scientific, Crewe, UK or Delta Plus, XP, Thermo-Fisher, Germany). The accuracy of the analyses was checked by measuring water standards at the beginning, middle and end within each batch of samples analysed. The mean SD of deuterium analyses is less than 2.5%.

Subjects were asked to record amount of fluid consumed during the equilibration period, and were given a pre-paid padded envelope to send the second saliva sample along with the instruction sheet for taking saliva sample (refer to Appendix 7). Raw TBW was corrected for any drinks consumed during the equilibration period by subtracting the amount of fluid consumed during that period.

4.3.3 Air-displacement plethysmography (ADP)

Body volume (BV) was measured by ADP using the BODPOD instrumentation (Life Measurement Instruments, Concord, California, USA) following the manufacturer's instructions and recommendations (see Figure 4-1). Briefly, the machine was warmed up for at least 30 minutes and calibrated with and without a 50 litre metal cylinder until acceptable criteria were met (SD < 75 ml and mean volume is < 0.1 litres different from actual volume of the cylinder). The subjects were asked to wear tight fitting swimming costumes and swimming caps and to remain seated in the fibreglass chamber during the measurement. Subjects sit in the anterior chamber (450 litres) which is connected to a rear measuring chamber (300 litres) via oscillating diaphragms used to induce pressure changes in the anterior chamber. In each test, duplicate measures of body volume are performed, each lasting about 50 seconds. If the two measurements differed by more than 150 ml, the system required that a third measurement be performed. The final result reported by the BODPOD instrumentation is the average of the duplicate raw volume measurements or the average of the closest two if three measurements were performed. Two complete tests (i.e. a minimum of four raw volume measurements) were performed on each child. If the densities of the two measurements differed by more than 0.007kg/l, a third test was performed to ensure precision (Wells and Fuller, 2001). Corrections were made for lung volume (Rosenthal *et al.* 1993) and surface area artefact (Dewit *et al.* 2000) using children's equations to obtain actual body volume. This value was then used in subsequent calculations using the multi-component model to calculate FM and FFM.

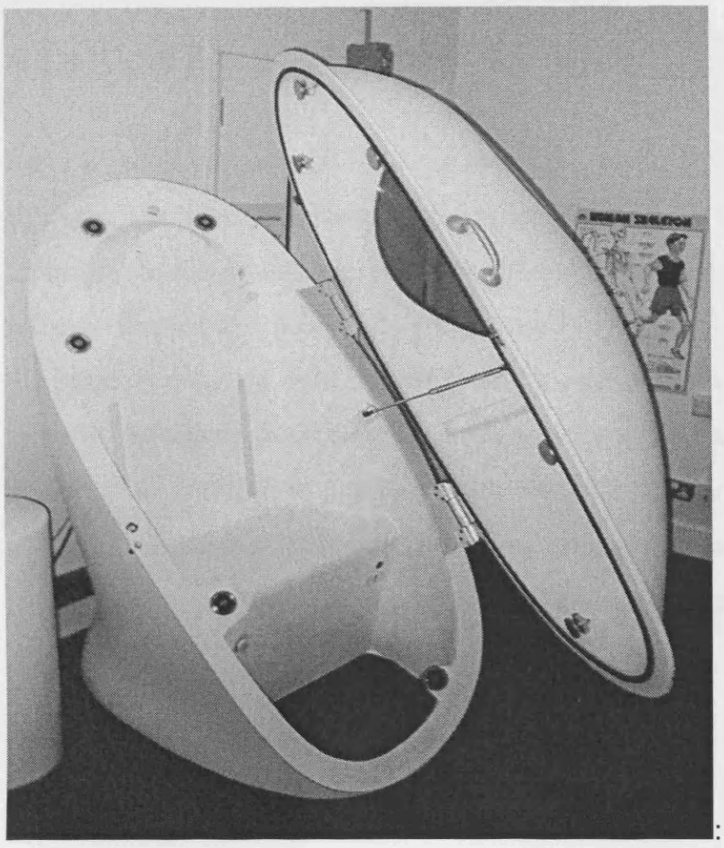
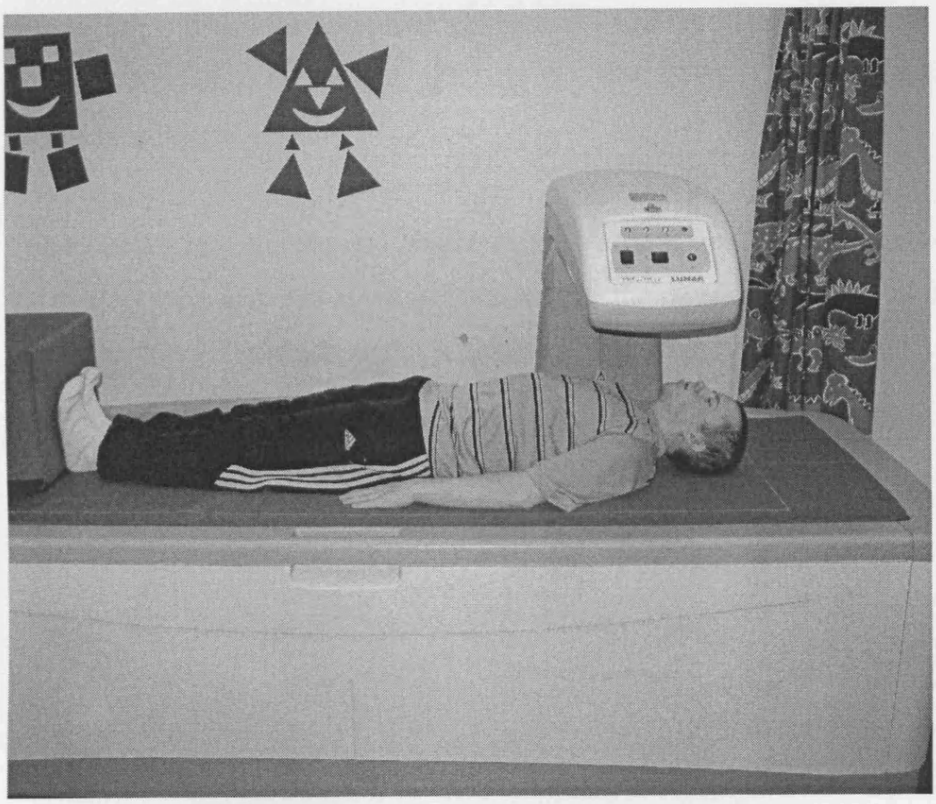


Figure 4-1 BODPOD machine
Source: Nutrition Unit, Institute of Child Health

4.3.4 Dual X-ray absorptiometry (DXA)

Bone mineral content (BMC) was measured using DXA (Lunar Progidy, GE Medical Systems, Madison, Wisconsin, USA) (see Figure 4-2). The scanner was calibrated daily according to the manufacturer's recommendations using a spine phantom, and all scans were performed and analysed by a licensed radiographer. The scan was performed with the subjects wearing light indoor clothing containing no metal, and they were required to lie in the supine position with arm and legs at their sides during the whole scan. The typical scan duration is approximately 10 - 15 minutes, depending on the weight and height of the subject. The radiation exposure per scan is estimated to be 2.2 μSv, which is lower than the total daily background radiation exposure in the UK; estimated to be 7 μSv.



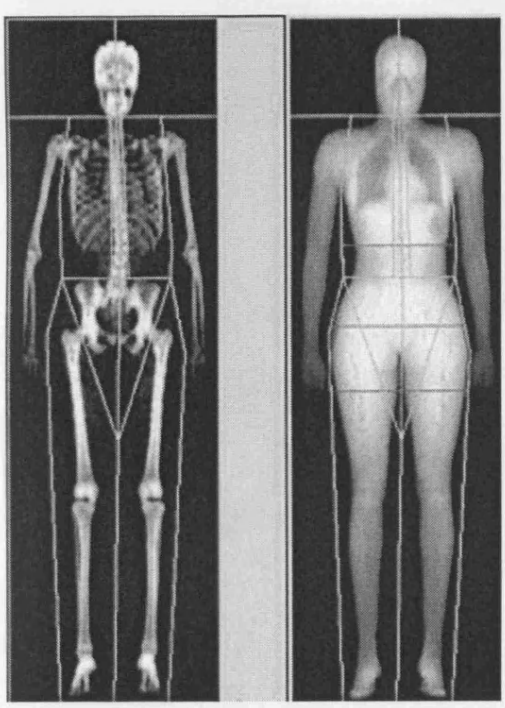


Figure 4-2 DXA machine (top); example of DXA whole body scan print-out (bottom)
Source: Radiology department, Great Ormond Street Hospital

4.3.5 TANITA body fat analyser

Whole body BIA was measured using the TANITA machine (BC-418 MA), which provides a printout for weight, BMI, % fat, FM, FFM, TBW and desirable body fat ranges (see Figure 4-3).

The subject's age, gender and height were entered manually into the machine, and then the subject was asked to stand in bare feet on the metal foot plates of the machine for approximately 30 seconds whilst holding the arm grips.

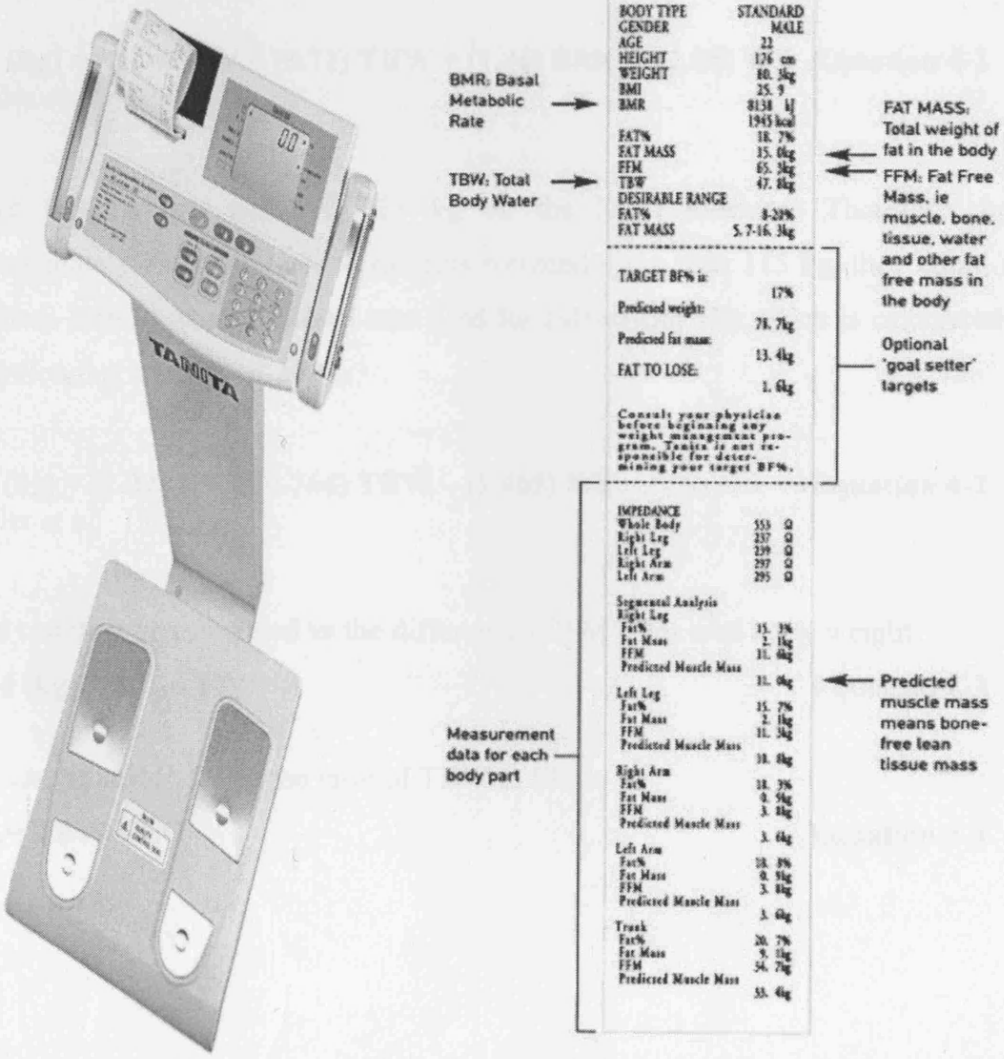


Figure 4-3 TANITA body fat analyser (left); example of TANITA print-out (right)
Source: www.tanita.co.uk

4.4 Outcome measures

The different outcome measures obtained from the measurements above include:

1. WT
2. BV from BODPOD
3. TBW from D_2O
4. BMC obtained from DEXA
5. R from TANITA (BC-418 MA)

Using the 4C model, FM was calculated using the following equation:

FM (kg) = (2.747) BV – (0.71) TBW + (1.46) BMC – (2.05) WT **Equation 4-1**
(Fuller *et al.* 1992)

There is a weight limit of 115 kg on the DXA machine. Therefore, because approximately 5% of the obese subjects weighed more than 115 kg, they could not be scanned. Instead, the 3C model was used for calculating FM which is calculated using the following formula:

FM (kg) = (2.22) BV – (0.764) TBW – (1.465) WT **Equation 4-2**
(Fuller *et al.* 1992)

FFM can then be calculated as the difference of FM from total body weight:

FFM (kg) = WT – FM **Equation 4-3**

H_{ffm} can be calculated as the ratio of TBW to FFM:

H_{ffm} = TBW/FFM **Equation 4-4**

4.5 Assessment of confounding factors

Factors that might confound results obtained from this study were assessed using questionnaires (refer to Appendix 5). These include:

4.5.1 Age

The participating subject's age was collected and was precisely calculated using the following equation:

Age = (date of birth - date of measurement)/365.25 **Equation 4-5**

4.5.2 Social data

Social data which included ethnic origin and parent's educational attainments and occupation were collected in order to establish an overview of social class of the subjects being measured. Social class was defined on the basis of the primary earner's occupation according to the registrar general's classification which consisted of six categories: I professional, II intermediate, IIINM skilled non-manual, IIIM skilled manual, IV semi-skilled, V unskilled (Office of Population Censuses and Surveys, 1991). Those with no occupation were not classified in this scheme, but for analysis were given a social code of greater than V. Socio-economic status (SES) was also expressed as an index of over-crowding based on the ratio of number of people per room of the house.

4.5.3 Medical history

For each child participating in the study a brief medical history was obtained from the parent or guardian. The information collected included:

- Details of any fractures
- Medical illnesses during childhood such as asthma, diabetes, epilepsy etc.
- Long-term medications or currently on any medications such as bronchodilators, steroids, hormones etc.
- Supplements such as multivitamins, minerals, fish oils etc.
- Family history of diseases including high cholesterol, heart disease, osteoporosis, hypertension and diabetes
- Details of any surgery during childhood
- Parent's weight and height
- Gestation and birth weight

4.5.4 Physical activity

Level of physical activity was assessed using a special questionnaire. The child was asked how many physical education (PE) lessons he or she had a week and the number of hours they spent on activities outside PE classes. The child's inactivity level was also assessed by asking how many hours they spend sitting around watching television and videos and playing on the computer. The total number of hours was reported on a usual school day and on a usual weekend day. In addition, the parent's opinion of the child's physical activity compared to their peers of the same age and gender was asked. This was answered on a five-point scale ranging from "much less active" to "much more active".

4.5.5 Pubertal status

Sexual maturation was assessed according to the Marshall and Tanner classification. Children over the age of nine years were given self assessment pictures (breast development and pubic hair in females; genitalia and pubic hair in males) (refer to Appendix 6). Each child was asked to indicate which picture mostly resembled their current appearance. The categories include: pre-pubertal boys with pubic hair stage and gonadal stage I and girls with pubic hair stage and breast stage I; pubertal boys with pubic hair and gonadal stage II to III and girls with pubic hair stage and breast stage II to III; late pubertal/post-pubertal boys with pubic hair and gonadal stage IV to V and girls with pubic hair stage and breast stage IV to V. It has been previously demonstrated that there is a good agreement between self-assessment stages of puberty and those assessed by a physician (Duke *et al.* 1980).

4.6 Ethical considerations and study plan

Ethical approval was granted by GOSH for Children NHS Trust/ Institute of Child Health Research (ICH) Ethics Committee. Ethical approval was also obtained from University College Hospital (UCH) (refer to Appendix 1)

The project was also registered with the Data Protection Act at ICH/GOSH. Only those involved in the research and a representative from the research ethics committee have access to the data collected in the study. Each participant was given a unique study number. Names and addresses along with the consent forms were not computerized; they were stored in a filing cabinet separate to the measurements data files. Data on my computer is password protected at ICH. Data storage and all other procedures are compliant with the Data Protection Act.

Children were recruited from the outpatients clinics at GOSH and UCH, and through a weight-management clinic at Chichester: lifestyle, eating, activity and fitness (LEAF) clinic, and also through the media. The study was verbally explained to both the parents and children. If they expressed interest in taking part, a parent information sheet (refer to Appendix 2a) and child information sheet (refer to Appendix 2b) was then given or sent to them. At this point their contact details including address and telephone number were collected. They were contacted after approximately one week to ensure that enough time was given to read and understand the information regarding the project. A suitable appointment was then made and an appointment letter was sent (refer to Appendix 3).

For the TLP, children were recruited through their general practitioners (GPs)

After explaining the study and before proceeding with the measurements, both written parental consent (refer to Appendix 4a) and child assent (refer to Appendix 4b) were obtained. Subjects over 16 years did not require parental consent and were given participant consent forms (refer to Appendix 4c). These forms were signed by the parents and participants first, and then by myself before commencing.

Travel expenses were reimbursed, and all subjects received a print-out copy of their whole body skeleton (obtained from the DXA scanner) in addition to a £5 voucher from WH Smith as a token of appreciation.

The study took place at GOSH in the body composition suite situated in the Radiology Department. Participating subjects were asked to report to X-ray reception on the day of the study. The suite consisted of two rooms: the first contained the DXA scanner, and the second contained the BODPOD and TANITA BC-418 MA. The study took almost one and a half hours; half an hour was spent in the DXA room and the remainder of the time was spent in the second room. The appointment was considerably shorter for follow-up visits; especially third visits where DXA scans were not performed.

Chapter 5: Body composition in obese children and adolescents

5.1 Introduction

There has been substantial research investigating body composition in obese children. However, the majority of these studies have been limited by the methods used to assess body composition with many using BMI as the main outcome. However, children's body composition development is not stable: the process of growth and maturation alters their body composition making theoretical approaches suitable for use in adults inappropriate for children. In order to estimate body composition with optimum accuracy in young children and adolescents, it is necessary to use methods that minimize assumptions made about the various body components. This study uses the most accurate technique, also known as the 'gold standard' (the 4C model) to investigate body composition differences between obese and non-obese children and adolescents.

5.2 Hypothesis

Body composition differs between obese and non-obese children and adolescents

This hypothesis can be subdivided into the following four objectives:

1. Compare differences in size between obese and non-obese children
2. Compare gross tissue masses, the fat and lean tissues, between obese and non-obese children
3. Compare the composition of FFM, specifically hydration and density, between obese and non-obese children and adolescents.
4. Compare regional distribution of fat and lean mass between obese and non-obese children and adolescents.

Furthermore, for all the main objectives above, this study will additionally test for gender differences in obese and non-obese children, and whether differences between obese and controls vary by gender. The effect of age on body composition will also be described in obese and non-obese children.

5.3 Study design

These hypotheses were investigated in a cross-sectional study looking at all the obese children, and comparing their body composition outcomes with those of non-obese children after matching them for age (to within one year) and gender. If obese children were recruited as part of a treatment programme, only their baseline data were used in this analysis.

5.4 Inclusion and exclusion criteria

To be eligible to take part in this part of the study, obese children were > 4 years old, with BMI > 95th percentile equivalent to BMI SDS > 1.64 as defined by the 1990 UK reference cut-offs (Cole *et al.* 1995). Because different ethnic groups vary in body composition, only those from White ethnic origin were included in this part of the analysis.

Controls had BMI-SDS between -1 and 1, to ensure that obese children were not compared to overweight or underweight children. They were required to be healthy i.e. not taking any kind of medication or having a condition that could affect their growth or nutritional status, and they should have been born > 37 weeks gestation.

5.5 Recruitment

Obese children were recruited from weight-managements clinics based at GOSH and UCH, and from the LEAF clinic in Chichester. Both obese and control children were also recruited from an ongoing body composition research project for healthy children and adolescents at ICH/GOSH. Thus, some obese children and adolescents were not recruited as patients.

5.6 Sample size

The conventional formula for a paired sample t-test used to determine the number of children required to detect a difference between two case-control matched groups is:

$$N = 8 (SD^2/D^2) \qquad \textbf{Equation 5-1}$$

Where N is the number per group, SD is the standard deviation, D is the difference between groups. This provides 80% power and significance cut-off of 0.05 ($p < 0.05$). This formula allows you to calculate for a given SD of a trait what magnitude and difference you can detect for a given sample size, or how many subjects you need per group to detect a given difference. Hence, very few subjects (N) are needed to detect a big effect (D) and vice versa. Most biological factors create relatively small effects and there is no consensus on the cut-off point for excess fatness of overweight or obesity in children and adolescents; hence the difference (D) is best expressed in SD score (SDS) format. This simplifies the formula to:

$$N = 8/D^2 \qquad \textbf{Equation 5-2}$$

The sample size included in the analysis is a total of 106 pairs. Based on the above equation, a difference of 0.27 SDS can be detected.

5.7 Methods

The 4C model was used to estimate body composition. This model uses a combination of measurements including volume (from BODPOD), TBW (from D_2O) and BMC (from DXA); details of each of these measurements were explained in chapter 4. Estimates of body composition were also derived using the 3C model and compared against those obtained from the 4C model in both the obese and control groups.

Different factors that might confound the results such as pubertal status, socio-economic status (SES), activity levels, parental BMI and birth weight were assessed using questionnaires; details can be found in chapter 4.

5.8 Statistical analysis

All statistical analyses were performed using the program Statistical Package for Social Science (SPSS v.15 for Windows).

Correlations were used to associate age with size (including BMI), gross tissue masses (including FM and FFM) and H_{ffm} in obese and control children and adolescents.

Paired sample t-tests were used to compare the different body composition outcomes, such as FM, FFM and H_{ffm} between matched obese and non-obese children and adolescents. Paired sample t-tests were also used to compare outcomes from the 3C model versus the 4C model in 99 children and adolescents with data from both models.

Independent sample t-tests were used to investigate gender differences in body composition for the obese and non-obese; gender being the independent variable.

Chi-Square tests were used to test for differences between obese and non-obese, and between genders in non-interval variables such as: SES, physical activity level and pubertal status.

General linear models were used to test for body composition differences between obese and controls after adjusting for potential confounding factors such as SES, birth weight, pubertal status, maternal and paternal BMI, and to investigate what proportion of the crude difference these confounders account for. In each model, the dependant variable was the outcome such as FM and FFM, the fixed factors included non-continuous factors such as sex, status (obese or control) or physical activity level, and the co-variants were confounding factors such as height or gestation. In this study, two models were generated. These will be explained in detail later on.

5.9 Results

5.9.1 Background characteristics of the sample

A total of 186 obese children and adolescents were measured although some had to be excluded from the analyses because they did not fulfil the inclusion criteria for this part of the study, or they did not have complete required measurements (see Table 5-1 for details). Therefore, the sample size consisted of 112 obese children and adolescents; 45 males and 67 females, ages ranging between 4.6 - 21.7 years. A breakdown of where the obese sample was recruited from can be seen in Table 5-2.

Of the final sample of 112 eligible obese children and adolescents, a total of 106 (45 males; 61 females) were matched with controls due to lack of available controls for some ages required. No significant differences were seen between the non-matched obese sample and the remaining obese sample for any of the background or physical characteristics. Therefore the final sample included in the analyses was 106 matched pairs of obese and control children and adolescents. The maximum age difference between matched obese and controls was 0.95 years, however 91.5% of the sample were matched to within 0.5 years.

The background characteristics of the matched obese and control children and adolescents are given for boys and girls in Table 5-3 and Table 5-4 and respectively. Data are presented as mean, standard deviation (SD) and range. There was no significant difference in age between obese and pair-matched control children and adolescents (average difference = 0.2 years; $p = 0.5$; range = 0 - 0.9 years). No significant differences were found for SES, pubertal status and birth weight in obese versus controls matched for age, gender and ethnicity. No significant difference in gestational age was found between obese and control girls, however obese boys were on average born significantly earlier than control boys (mean difference = 0.8 ± 0.3 weeks; $p = 0.01$).

Even though there were no significant differences in the number of hours of physical activity reported between obese and controls, a significant difference was apparent when the rating of physical activity compared to peers was used (this is when parents ranked their children on a scale of 1-5 of how active or inactive they perceived them to be); whereby obese were significantly less active compared to controls ($p = 0.002$ for

boys; p = 0.03 for girls). Also, obese children had significantly heavier parents compared to controls. Mothers and fathers of obese boys had on average 4.0 kg/m^2 (p = 0.003), and 3.3 kg/m^2 (p = 0.004) higher BMI values respectively, and those of obese girls were 6.5 kg/m^2 (p = 0.002), and 2.3 kg/m^2 (p = 0.03) respectively heavier.

Table 5-1 A list of the sample excluded from the analyses

Number excluded	**Reason**
1	H_{ffm} outside the normal range; defined by 68 - 84%
2	no BODPOD measurement
13	unknown ethnicity (missing)
58	non-white
21	*Black*
15	*Asian*
2	*Chinese*
20	*other ethnic backgrounds*

Table 5-2 Description of where the final sample was recruited from

Number	**Recruitment**
3	LEAF clinic in Chichester
3	UCH clinic
23	Metformin trial at UCH
25	"Traffic Light Program" at GOSH
52	Reference study

5.9.2 Effect of age

In both obese and non-obese children and adolescents, age was found to be positively associated with BMI; and this was highly significant ($p < 0.001$) (refer to Figure 5-1).

In terms of gross tissue masses, age was found to be positively and significantly associated with FM and FFM in both groups of children ($p < 0.001$). However, after adjusting FM and FFM for height, age was no longer associated with FM in obese children ($p = 0.2$), but the association with FFM remained significant. A scatter-plot demonstrating these associations are shown in Figure 5-2 and Figure 5-3.

Looking at the composition of FFM, it can be shown from Figure 5-4 that there is a negative association between age and H_{ffm} in both obese and controls. Correlations showed that this association was borderline significant in obese ($p = 0.07$), but highly significant in controls ($p < 0.001$).

These findings support my approach of matching for age when comparing obese and non-obese children and adolescents.

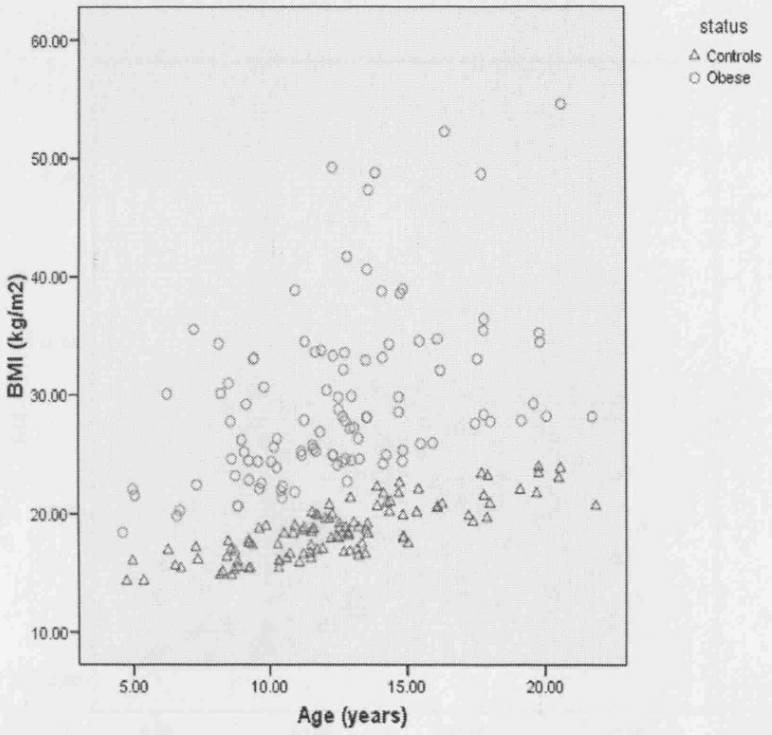


Figure 5-1 A scatter-plot demonstrating the association between age and BMI in obese and control children and adolescents

Obese: $r = 0.44$, $p < 0.001$; Controls: $r = 0.81$, $p < 0.001$

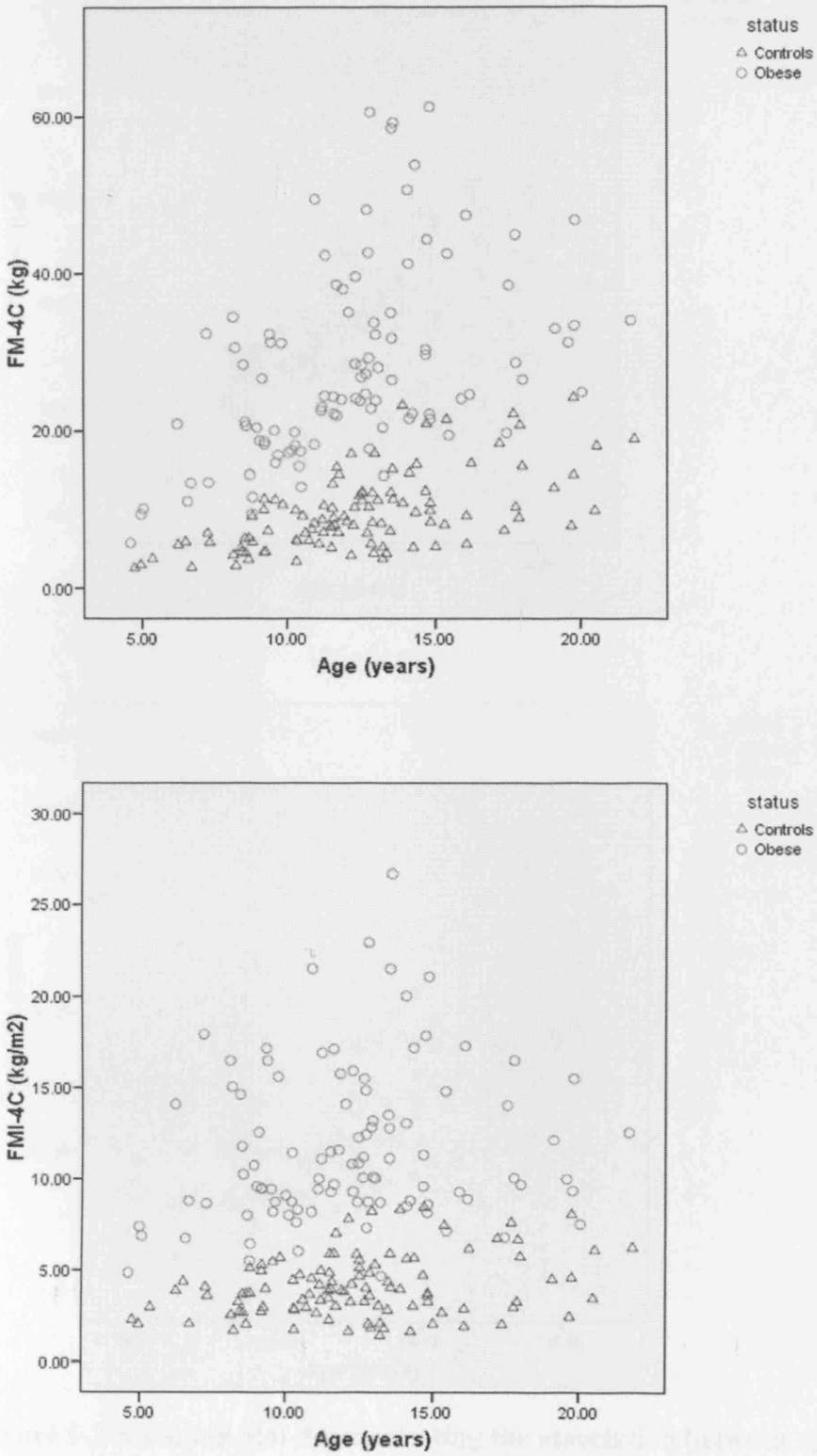


Figure 5-2 A scatter-plot demonstrating the association between age and FM (top) and FMI (bottom) in obese and control children and adolescents

FM: obese: $r = 0.46$, $p < 0.001$; controls: $r = 0.61$, $p < 0.001$

FMI: obese: $r = 0.15$, $p = 0.2$; controls: $r = 0.30$, $p = 0.002$

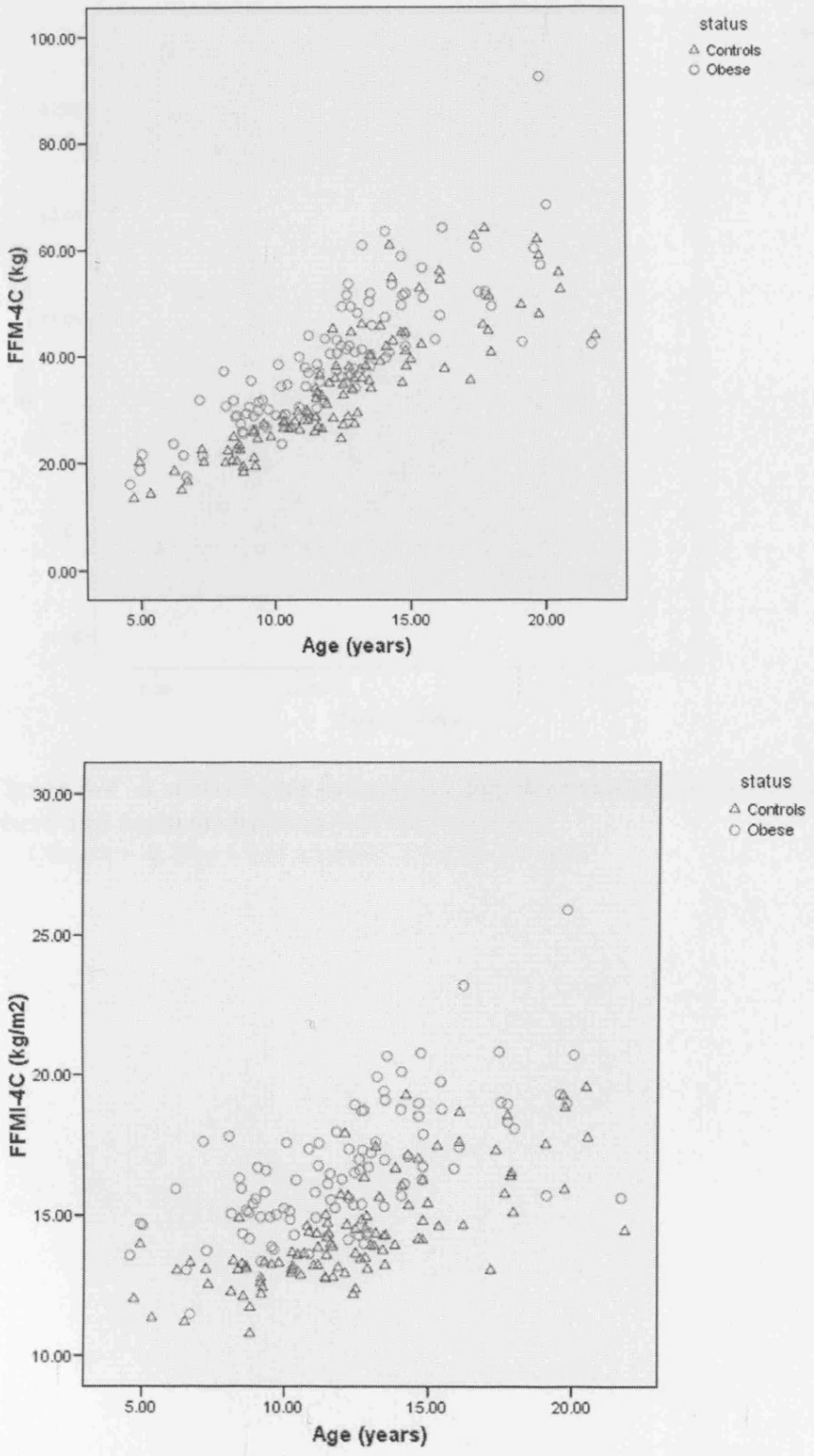


Figure 5-3 A scatter-plot demonstrating the association between age and FFM (top) and FFMI (bottom) in obese and control children and adolescents

FFM: obese: $r = 0.82$; $p < 0.001$; controls: $r = 0.87$, $p < 0.001$

FFMI: obese: $r = 0.63$, $p < 0.001$; controls: $r = 0.73$; $p < 0.001$

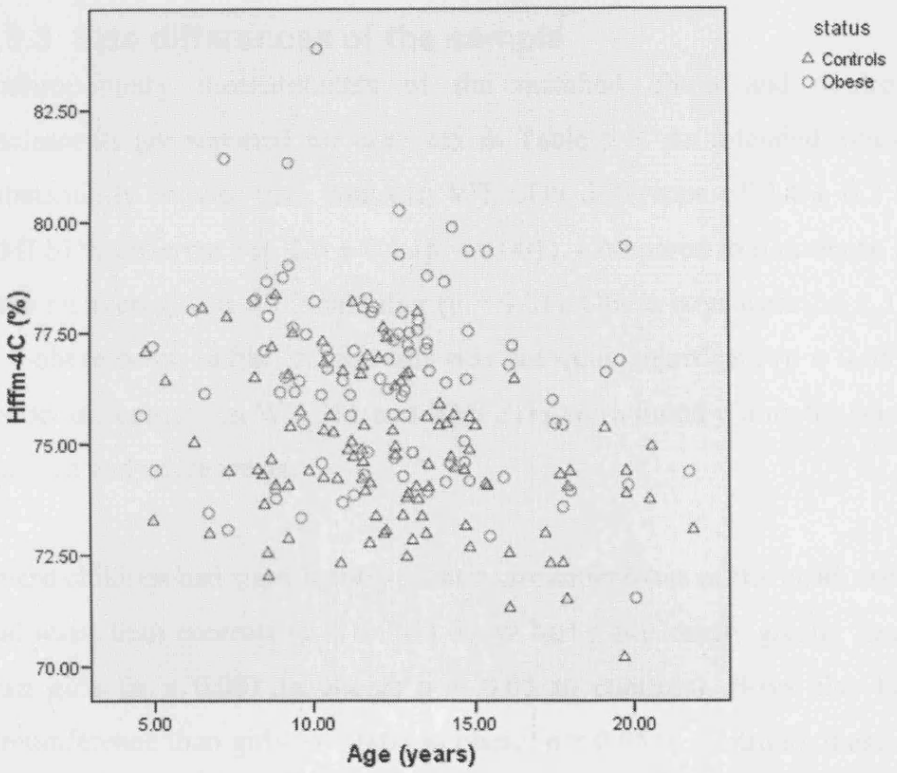


Figure 5-4 A scatter-plot demonstrating the association between age and H_{ffm} in obese and control children and adolescents.

Obese: r = -0.19, p = 0.07; controls: r =-0.34, p < 0.001

5.9.3 Size differences of the sample

Anthropometry measurements of the matched obese and control children and adolescents are reported for each sex in Table 5-5. As intended, obese children were substantially heavier than controls; WT SDS difference of 2.4 ± 0.2 ($p < 0.001$) and BMI SDS difference of 2.6 ± 0.1 ($p < 0.001$). Compared to non-obese girls, obese girls were on average 3.0 ± 1.2 cm taller ($p = 0.01$). Obese boys were 2.6 ± 1.5 cm taller than non-obese boys; unlike in girls this was not quite significant ($p = 0.08$). No significant gender differences in WT, HT and BMI SDS were found within the obese or the control children and adolescents.

Obese children had significantly greater circumferences of the head, arm, calf, thigh, hip and waist than controls ($p < 0.001$). Boys had significantly greater head circumference than girls ($p = 0.001$ in obese; $p = 0.05$ in controls). Boys also had greater waist circumference than girls ($p = 0.04$ in obese; $p = 0.05$ in controls); these differences were no longer significant when WC SDS was used. There were no significant gender differences in the arm, calf, hip and thigh circumferences in the obese or the control group.

5.9.4 Body composition differences in the sample

Raw body composition measurements and whole body composition outcomes using the 3C and 4C model for the matched obese and control sample are described in Table 5-6. A comparison of values obtained using the 3C and 4C model in the matched sample that had measurements from both models is given in Table 5-7. The latter table shows the average differences between matched pairs, whereas the former table only shows the average value of each of the measurements. Comparing raw body composition measurements between obese and control children and adolescents using paired sample t-tests, the former group had significantly higher body volume (BV), total body water (TBW) and bone mineral content (BMC) ($p < 0.001$). There were no gender differences in obese or control children and adolescents for measures of BV and BMC. However, obese and control boys had significantly greater TBW compared to girls; $p = 0.02$ and $p = 0.005$ respectively.

Measurements of FM, FFM and % fat levels obtained from both the 3C and 4C models were also significantly greater in obese versus matched controls ($p < 0.001$). Control

boys had approximately 3.2 kg more FFM ($p = 0.006$) and 6.7 kg less FM ($p < 0.001$) than control girls, using both the 3C and 4C models. These gender differences remained significant when FM index (calculated as FM/ HT^2) (FMI) and FFM index (calculated as FFM/HT^2) (FFMI) were used.

There were no gender differences in FM between obese boys and obese girls. This remained when FMI was used. On the other hand, FFM was significantly greater in obese boys compared to girls (mean difference of 6.7 kg), but only when the 3C model was used ($p = 0.03$). This difference lost its significance when FFMI was used.

The various components of FFM including water, protein and mineral were then investigated. Obese children were found to have significantly greater H_{ffm} compared to controls ($p < 0.001$); with a difference of 1.4% when using the 3C model versus 1.7% when the 4C model was used. Not surprisingly, because an increased hydration was found in obese children, a significantly lower density of FFM (D_{ffm}) was found in obese children using both the 3C (mean difference = -0.007 ± 0.002; $p<0.001$) and 4C model (mean difference = -0.005 ± 0.001; $p < 0.001$); the former model overestimating the difference by 0.002 kg/l. Because DXA was incorporated in the 4C model, only the 4C model can provide information about the protein and mineral components of FFM. Both of these components were also found to be significantly greater in obese children compared to matched controls. The protein to mineral ratio was also significantly lower in obese children ($p < 0.001$). This ratio is assumed to be constant when measurements obtained from the 3C model are estimated.

Obese boys had significantly greater H_{ffm} compared to obese girls using the 3C and 4C models. D_{ffm} was significantly greater in obese girls compared to obese boys only when the 4C model was used ($p = 0.02$). Gender differences in H_{ffm} and D_{ffm} were not observed in controls. Protein mass was found to be significantly greater in control boys compared to girls ($p = 0.005$); but not between obese boys and girls. No gender differences were found for mineral mass either in the obese or in the control groups.

5.9.5 Regional body composition differences of the sample

Regional body composition measured by DXA can be seen for obese and controls presented separately for each sex in Table 5-8. As expected DXA showed that the different body segments including the arms, legs and trunk regions had significantly greater amounts of fat, lean and bone in obese children and adolescents compared to matched controls ($p < 0.001$). Except for the significantly greater amount of arm lean in obese boys compared to girls ($p = 0.04$), there were no gender differences in bone, fat or lean in the different body components of obese children and adolescents. On the other hand, control boys had significantly greater lean mass in the trunk ($p = 0.003$), legs ($p = 0.001$) and arms ($p = 0.001$) than girls. Control girls had a significantly greater amount of fat in the trunk ($p = 0.001$), legs ($p < 0.001$) and arms ($p < 0.001$) than boys. Also, control boys had significantly greater BMC in the legs ($p = 0.03$), but the BMC in the trunk and arm region was not significantly different between control boys and girls.

5.9.6 Effects of confounding variables

After looking at absolute body composition differences between obese and control children, the next step was to confirm whether these differences persist after adjusting for potential confounding factors. Therefore, general linear models were conducted separately for each sex to check whether confounding factors had any effect on the results obtained. Table 5-9 and Table 5-10 are divided into three main sections: the first section shows the mean differences between matched obese and control children and adolescents before any factors were taken into account, the second section incorporates age, height, pubertal status and activity level (number of hours and activity level compared to peers) into the model, and the third section included everything in section two in addition to birth weight SDS, gestation, SES and parental BMI. The second model describes factors relating directly to the child, whereas the third model also includes factors relating to the family. All models had two additional variables included in the model: these were status (dummy variable 1 for being obese versus 0 for being a control), and match (where every matched pair had the same corresponding number in the match column). Because some data were missing from confounding factors such as parental BMI, the sample size after adjustments was lower than before any adjustments were made. Therefore, to be confident any differences in outcome were not due to the smaller sample size, the same test was performed on the sample that was included in the final model (data not presented in the table).

After adjusting for the different factors mentioned above, both obese girls and boys remained significantly heavier than controls; however the mean difference in weight SDS and BMI SDS decreased by 0.3 and 0.2 for girls and 0.7 and 0.4 for boys respectively. Similarly differences in waist circumference between obese and controls was also partly due to the various confounders incorporated in the model; the mean difference decreased by 6.1 cm for girls versus 7.2 cm for boys.

In terms of whole body composition, the magnitude of the difference in FM and FFM between obese and control children and adolescents was reduced after adjusting for various confounders but these differences remained significantly different. In obese boys for example, approximately 6 kg of FM and 2 kg of FFM can be accounted for the mentioned confounders, whereas the remainder of the difference (11 kg of FM and 6 kg of FFM) was due to their obesity status.

Looking at the composition of FFM, there was a significant difference in H_{ffm} between obese and controls ($p < 0.001$); and this difference remained significant for boys ($p = 0.02$) and borderline significant for girls ($p = 0.07$) even after taking confounders about the child into account (model 1). On the other hand, when all the other confounders were added into the model (model 2), this difference was borderline significant for boys ($p = 0.07$) and no longer statistically significant for girls ($p = 0.4$). In boys, the magnitude of the difference did not change whereby obese boys remained approximately 2.3% more hydrated compared to controls, however the SE increased from 0.5 to 1.2 possibly accounting for the change in significance. In girls the absolute difference in H_{ffm} decreased from 1.4% to 0.8% (in model 1) or 0.7% (in model 2). Similar to boys, the SE in H_{ffm} in girls increased from 0.3 to 0.8.

Additional analyses were performed specifically on H_{ffm} to check whether there was one particular variable confounding the results obtained. Results showed that there was not one particular variable causing an effect, and it is possible that because these factors are not causing significant changes, when incorporated into a model absolute differences or significances change in magnitude. Confounding factors also influence the components of lean mass.

Data on regional distribution of fat, bone and lean has also been presented in Table 5-9 and Table 5-10; however because of the limitations of using DXA on obese children, differences between obese and controls may be affected by the nature of the measurement and not due to the effect of the various confounders. Broadly, differences in regional fat distribution remained significantly different between obese and non-obese boys and girls even after adjusting for confounders. Differences in regional distribution of lean mass between obese and non-obese girls remained significantly different after adjusting for confounding factors. It is apparent from the model that some of the differences in lean mass in the trunk and legs were due to activity or puberty (model 1). Differences in regional distribution of lean mass between obese and non-obese boys decreased but remained significantly different after adjusting for puberty and physical activity, but were no longer significant after adjusting for factors about the family environment (model 2). This shows that some of the extra lean mass in obese children is predicted by the family environment.

Table 5-3 Background characteristics of boys (obese & controls)

	Obese				**Controls**			
	n	**mean**	**SD**	**range**	**n**	**mean**	**SD**	**range**
Age (years)	44	12.8	3.5	5.0-20.6	44	12.8	3.5	5.0-20.6
Gestation (wks)*	44	39.7	1.4	36-43	44	40.4	1.4	37-42
Birth weight (kg)	43	3.7	0.5	2.5-4.8	43	3.6	0.6	2.5-5.0
Paternal height (cm)	40	176.8	7.0	154.9-190.5	40	177.4	10.1	152.4-198.1
Paternal BMI (kg/m^2) **	36	30.2	4.6	21.5-45.4	36	27.0	3.5	18.8-35.2
Maternal height (cm)	43	164.5	6.5	152.4-175.3	43	164.2	6.4	149.9-177.8
Maternal BMI (kg/m^2) **	42	29.5	5.1	18.6-41.9	42	25.6	5.3	20.1-40.6
Physical activity (hours/wk)	42	7.1	5.1	0-28	42	7.8	5.4	0-24
Physical activity compared to peers (n, %) *								
Much less active& less active	14	32.6			2	4.7		
Same	20	46.5			18	41.9		
More active	8	18.6			15	34.9		
Much more active	1	2.3			8	18.6		
Social Class (n, %)								
Class 1	5	11.4			13	29.5		
Class 2	15	34.1			14	31.8		
Class 3	2	4.5			6	13.6		
Class 4 or more	22	50.0			11	25.0		
Pubertal status (n, %)								
Pre-pubertal	9	20.9			8	18.2		
Early pubertal	25	58.1			21	47.7		
Late pubertal	9	20.9			15	34.9		

*Significant difference between groups at $p<0.05$, **Significant difference between groups at $p<0.005$.
Abbreviations: n= number in group; SD= standard deviation; wks= weeks; BMI= body mass index

Table 5-4 Background characteristics of girls (obese & controls)

	Obese				**Controls**			
	n	**mean**	**SD**	**range**	**n**	**mean**	**SD**	**range**
Age (years)	61	12.2	3.7	4.6-21.7	61	12.2	3.6	4.7-21.9
Gestation (wks)	61	40.2	1.2	38-44	61	40.0	1.3	37-42.6
Birth weight (kg)	60	3.5	0.5	2.7-4.6	60	3.4	0.5	2.2-4.7
Paternal height (cm)	51	177.5	7.1	154.9-193.0	51	177.9	8.3	154.9-203.2
Paternal BMI (kg/m^2) **	49	28.8	6.3	18.8-56.4	49	26.4	4.0	20.1-37.1
Maternal height (cm)	52	164.9	6.5	152.4-177.8	52	162.5	6.0	152.4-175.3
Maternal BMI (kg/m^2) **	51	31.0	12.7	19.7-93.2	51	24.5	4.4	16-43.2
Physical activity (hours/wk)	60	5.6	4.8	0-25	60	6.5	4.8	0-20
Physical activity compared to peers (%) *								
Much less & less active	16	26.2			5	8.3		
Same	29	47.5			26	43.3		
More active	13	21.3			23	38.3		
Much more active	3	4.9			6	10.0		
Social Class (%)								
Class 1	4	6.5			10	16.4		
Class 2	19	30.6			26	42.6		
Class 3	9	14.5			10	16.4		
Class 4 or more	30	48.4			15	24.6		
Pubertal status (%)								
Pre-pubertal	9	14.8			20	32.8		
Early pubertal	33	54.1			25	41.0		
Late pubertal	20	32.8			16	26.2		

*Significant difference between groups at $p<0.05$, **Significant difference between groups at $p<0.005$

Abbreviations: n= number in group; SD=standard deviation; wks= weeks; BMI= body mass index

Table 5-5 Anthropometry measurements of the matched sample (obese & controls)

	Obese						**Controls**					
	Boys			**Girls**			**Boys**			**Girls**		
	n	**mean**	**SD**	**n**	**mean**	**SD**	**n**	**mean**	**SD**	**n**	**mean**	**SD**
Anthropometry												
Weight (kg) [1,2]	44	77.5	33.3	61	68.4	22.5	44	45.8	14.7	61	42.3	14.0
Height (cm) [2]	44	157.4	17.0	61	151.4	14.8	44	154.8	17.3	61	148.4	17.6
BMI (kg/m^2) [1,2]	44	30.1	8.2	61	29.0	6.4	44	18.5	2.2	61	18.5	2.5
Weight SDS [1,2]	44	2.7	1.1	61	2.6	0.9	44	0.3	0.6	61	0.13	0.7
Height SDS [2]	44	0.7	1.09	61	0.72	0.92	44	0.37	0.88	61	0.22	0.92
BMI SDS [1,2]	44	2.8	0.8	61	2.6	0.8	44	0.20	0.59	61	0.05	0.60
MUAC (cm) [1,2]	42	32.9	6.5	58	32.0	5.1	44	23.1	3.4	58	23.2	3.4
Head C (cm) [1,2,3,4]	42	57.3	2.7	60	55.7	2.0	42	55.1	2.2	60	54.2	2.1
WC (cm) [1,2,3,4]	42	94.0	19.0	60	87.0	14.5	42	66.4	7.5	60	63.6	7.2
Hip C (cm) [1,2]	42	101.6	16.9	60	100.7	16.3	42	80.4	10.8	60	80.5	12.8
Thigh C (cm) [1,2]	42	58.1	13.7	60	57.8	13.2	42	45.5	6.1	60	45.8	7.0
Calf C (cm) [1,2]	42	37.9	7.7	60	36.3	7.4	42	32.3	9.3	60	30.3	4.2
WC SDS [1,2]	36	2.5	0.8	53	3.1	0.8	36	0.5	0.6	53	0.6	0.7

Abbreviations: n= number per group; SD= standard deviation, BMI= body mass index; SDS= SD score, MUAC= mid-upper arm circumference, C= circumference, WC= waist circumference

1: significant difference between obese & control boys; $p < 0.05$

2: significant difference between obese & control girls; $p < 0.05$

3. significant difference between obese boys & obese girls; $p < 0.05$

4: significant difference between control boys & control girls; $p < 0.05$

Table 5-6 Whole body composition measurements of the matched sample (obese & controls)

	Obese						Controls					
	Boys			Girls			Boys			Girls		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
Body volume (l) [1,2]	44	77.4	34.3	61	68.4	23.2	44	43.4	13.7	61	40.8	13.7
TBW (l) [1,2,3,4]	44	35.3	13.9	61	29.5	7.9	44	28.4	9.6	61	23.4	7.1
3C data												
Weight (kg)	44	77.5	33.5	61	68.4	22.5	44	45.8	14.7	61	42.3	14.0
FM (kg) [1,2,4]	44	31.5	19.3	61	29.1	13.5	44	7.4	3.2	61	10.6	5.2
FMI (kg/m^2) [1,2,4]	44	12.2	5.8	61	12.3	4.9	44	3.1	1.2	61	4.6	1.6
FFM (kg) [1,2,3,4]	44	46.0	17.7	61	39.3	10.9	44	38.4	13.4	61	31.7	9.9
FFMI (kg/m^2) [1,2,4]	44	17.9	3.7	61	16.4	2.0	44	15.4	2.1	61	13.8	1.5
% Fat [1,2,4]	44	39.2	8.8	61	41.1	7.5	44	16.7	5.9	61	24.2	6.4
D_{ffm} (kg/l) [1,2,3]	44	1.08	0.02	61	1.08	0.02	44	1.09	0.007	61	1.09	0.006
H_{ffm} (%) [1,2,3]	44	76.4	2.1	61	75.2	1.7	44	74.2	1.6	61	74.0	1.5
4C data												
Weight (kg)	39	68.3	21.8	60	67.7	21.9	39	43.7	14.0	60	41.9	13.7
BMC (kg) [1,2]	39	2.0	0.7	60	2.0	0.7	39	1.7	0.7	60	1.6	0.6
FM (kg) [1,2,4]	39	26.3	10.7	60	29.0	13.0	39	7.5	2.9	60	10.8	5.3
FMI (kg/m^2) [1,2,4]	39	10.8	3.7	60	12.3	4.5	39	3.2	1.1	60	4.7	1.7
FFM (kg) [1,2,4]	39	42.0	15.0	60	38.6	10.6	39	36.2	12.8	60	31.1	9.5
FFMI (kg/m^2) [1,2,4]	39	16.9	2.7	60	16.7	2.1	39	15.0	2.0	60	13.9	1.5
% Fat [1,2,4]	39	38.5	7.9	60	41.6	7.3	39	17.6	5.9	60	24.8	6.6
D_{ffm} (kg/l) [1,2,3]	39	1.085	0.010	60	1.091	0.01	39	1.092	0.006	60	1.094	0.006
H_{ffm} (%) [1,2,3]	39	77.2	2.3	60	76.1	1.8	39	74.9	1.8	60	74.7	1.6
Protein mass(kg) [1,2,4]	39	7.0	2.7	60	6.7	1.9	39	7.0	2.9	60	5.9	1.8
Mineral mass (kg) [1,2]	39	2.6	0.9	60	2.5	0.9	39	2.2	0.8	60	2.0	0.8
Protein:mineral ratio	39	2.7	0.5	60	2.8	0.5	39	3.2	0.5	60	3.0	0.4

Abbreviations: n= number per group; SD= standard deviation; TBW= total body water, BMC= bone mineral content, FM= fat mass, FFM= fat-free mass, FMI= fat mass index, FFMI= fat-free mass index, D_{ffm}= density of FFM, H_{ffm}= hydration of FFM. 1: significant difference between obese & control boys 2: significant difference between obese & control girls 3.significant difference between obese boys & obese girls 4: significant difference between control boys & control girls; $p < 0.05$

Table 5-7 Differences in body composition for obese versus matched controls for the 3C and 4C models

	3C model (n = 99)			4C model (n = 99)		
	difference	**SE**	**p**	**difference**	**SE**	**p**
FM (kg)	18.3	1.1	<0.001	18.5	1.1	<0.001
FMI (kg/m^2)	7.5	0.4	<0.001	7.6	0.4	<0.001
FFM (kg)	7.0	0.8	<0.001	6.8	0.8	<0.001
FFMI (kg/m^2)	2.5	0.2	<0.001	2.4	0.2	<0.001
% fat	19.2	1.0	<0.001	18.4	0.9	<0.001
H_{ffm} (%)	1.4	0.2	<0.001	1.7	0.2	<0.001
D_{ffm} (kg/l)	-0.007	0.002	<0.001	-0.005	0.001	<0.001
Protein (kg)				0.52	0.17	0.003
Mineral (kg)				0.45	0.06	<0.001
Protein:mineral				-0.32	0.06	<0.001

Difference= mean difference, calculated as obese-control values

Abbreviations: SE= standard error, FM= fat mass, FFM= fat-free mass, FMI= fat-mass index, FFMI= fat-free mass index, H_{ffm}= hydration of FFM, D_{ffm}= density of FFM

Table 5-8 Regional body composition measurements by DXA of the matched sample (obese & controls)

	Obese (n = 99)				Controls (n = 99)			
	Boys (n = 39)		Girls (n = 60)		Boys (n = 39)		Girls (n = 60)	
	mean	SD	mean	SD	mean	SD	mean	SD
Arm bone (kg) [1,2]	0.2	0.1	0.2	0.1	0.2	0.1	0.2	0.08
Arm fat (kg) [1,2,4]	2.7	1.2	2.8	1.2	0.6	0.3	1.0	0.5
Arm lean (kg) [1,2,3,4]	4.2	1.9	3.6	1.0	3.5	1.4	2.7	0.9
Leg bone (kg) [1,2,4]	0.8	0.3	0.8	0.3	0.7	0.3	0.6	0.3
Leg fat (kg) [1,2,4]	10.6	4.3	11.9	5.6	3.6	1.5	5.0	2.4
Leg lean (kg) [1,2,4]	13.5	4.9	12.1	3.5	11.7	4.6	9.6	3.1
Trunk bone (kg) [1,2]	0.6	0.2	0.6	0.3	0.5	0.2	0.5	0.2
Trunk fat (kg) [1,2,4]	13.0	5.5	14.2	6.3	3.0	1.6	4.8	2.8
Trunk lean (kg) [1,2,4]	17.8	6.0	16.7	4.7	16.1	5.7	13.5	4.2
Trunk fat: whole body fat [1,2,4]	0.5	0.05	0.5	0.04	0.4	0.05	0.4	0.05

Abbreviations: n= number per group; SD= standard deviation

1: significant difference between obese & control boys; $p < 0.05$
2: significant difference between obese & control girls; $p < 0.05$
3: significant difference between obese boys & obese girls; $p < 0.05$
4: significant difference between control boys & control girls; $p < 0.05$

Table 5-9 Differences in size, whole body (by 4C) and regional body composition (by DXA) between obese versus controls girls

	no adjustment				Model 1: adjusted for adjusted for age, HT, pubertal stage & activity				Model 2: adjusted for age, SES, HT, pubertal stage, activity, parental BMI, birth weight SDS & gestation			
	N	**mean**	**SE**	**P**	**N**	**mean**	**SE**	**P**	**N**	**mean**	**SE**	**P**
Weight SDS	122	2.5	0.2	<0.001	120	2.0	0.2	<0.001	105	2.2	0.4	<0.001
BMI SDS	122	2.6	0.1	<0.001	120	2.2	0.2	<0.001	105	2.4	0.4	<0.001
Waist C (cm)	121	23.2	1.6	<0.001	120	17.8	2.2	<0.001	105	16.9	4.6	0.002
Body volume (l)	121	27.7	2.2	<0.001	120	20.9	2.8	<0.001	105	18.2	5.1	0.002
TBW (l)	121	6.1	0.7	<0.001	120	4.9	0.8	<0.001	105	4.2	1.7	0.02
BMC (kg)	121	0.4	0.1	<0.001	119	0.3	0.1	<0.001	104	0.2	0.1	0.1
FM (kg)	121	18.3	1.5	<0.001	119	13.6	2.0	<0.001	104	11.3	3.5	0.005
FFM (kg)	121	7.5	0.9	<0.001	119	6.3	1.0	<0.001	104	6.3	2.0	0.006
% Fat	121	16.8	1.2	<0.001	119	12.2	1.6	<0.001	104	10.8	3.1	0.003
D_{ffm} (kg/l)	121	-0.004	0.001	0.007	119	-0.002	0.002	0.3	104	0.000	0.003	0.9
H_{ffm} (%)	121	1.4	0.3	<0.001	119	0.8	0.4	0.07	104	-0.7	0.8	0.4
Protein mass(kg)	121	0.8	0.2	<0.001	119	0.8	0.2	<0.001	104	1.5	0.4	0.002
Mineral mass (kg)	121	0.5	0.1	<0.001	119	0.4	0.1	<0.001	104	0.3	0.2	0.1
Protein:mineral	121	-0.2	0.1	0.001	119	-0.1	0.1	0.4	104	0.3	0.1	0.2
Regional (DXA)												
Arm bone (kg)	121	0.04	0.01	<0.001	119	0.03	0.01	<0.001	104	0.03	0.01	0.03
Arm fat (kg)	121	1.8	0.1	<0.001	119	1.5	0.2	<0.001	104	1.3	0.3	<0.001
Arm lean (kg)	121	0.8	0.1	<0.001	119	0.8	0.1	<0.001	104	0.9	0.2	<0.001
Leg bone (kg)	121	0.2	0.0	<0.001	119	0.2	0.0	<0.001	104	0.1	0.1	0.05
Leg fat (kg)	121	6.9	0.6	<0.001	119	5.2	0.9	<0.001	104	3.8	1.4	0.02
Leg lean (kg)	121	2.5	0.3	<0.001	119	1.8	0.4	<0.001	104	1.8	0.6	0.009
Trunk bone (kg)	121	0.1	0.0	<0.001	119	0.1	0.0	<0.001	104	0.03	0.06	0.6
Trunk fat (kg)	121	9.4	0.7	<0.001	119	7.3	0.9	<0.001	104	5.6	1.7	0.005
Trunk lean (kg)	121	3.2	0.4	<0.001	119	2.5	0.5	<0.001	104	3.2	1.1	0.01

Abbreviations: N= obese + controls; HT= height; SE= standard error; VMI= body mass index; SDS= standard deviation score; SES= socio-economic status; C= circumference; TBW= total body water, FM= fat mass; FMI= FM index; FFM= fat-free mass; FFMI= FFM index; D_{ffm}= density of FFM; H_{ffm}= hydration of FFM; DXA= dual x-ray absorptiometry. Highlighted p-values refer to those that lost significance in model 2.

Table 5-10 Differences in size, whole body (by 4C) & regional body composition (by DXA) between obese versus controls boys

	no adjustment				**Model 1: adjusted for adjusted for age, HT, pubertal stage & activity**				**Model 2: adjusted for age, SES, HT, pubertal stage, activity, parental BMI, birth weight SDS & gestation**			
	N	**mean**	**SE**	**P**	**N**	**mean**	**SE**	**P**	**N**	**mean**	**SE**	**P**
Weight SDS	88	2.4	0.2	<0.001	84	1.8	0.2	<0.001	76	1.7	0.2	<0.001
BMI SDS	88	2.6	0.1	<0.001	84	2.3	0.2	<0.001	76	2.2	0.3	<0.001
Waist C (cm)	86	27.6	2.5	<0.001	82	19.6	2.9	<0.001	74	17.1	3.8	0.006
Body volume (l)	88	34.0	4.1	<0.001	84	21	3.8	<0.001	76	18.6	2.7	<0.001
TBW (l)	88	6.9	1.4	<0.001	84	4.5	1.2	0.001	76	3.8	1.9	0.08
BMC (kg)	83	0.3	0.1	<0.001	79	0.2	0.1	0.001	74	0.1	0.1	0.2
FM (kg)	83	18.9	1.7	<0.001	79	13.0	1.9	<0.001	74	14.7	3.1	0.003
FFM (kg)	83	5.8	1.5	<0.001	79	4.1	1.2	0.003	74	2.4	1.8	0.2
% Fat	83	20.9	1.4	<0.001	79	16.9	1.7	<0.001	74	19.9	3.9	0.002
D_{ffm} (kg/l)	83	-0.007	0.002	0.001	79	-0.006	0.003	0.06	74	-0.007	0.006	0.3
H_{ffm} (%)	83	2.3	0.5	<0.001	79	2.0	0.8	0.02	74	2.5	1.2	0.07
Protein mass(kg)	83	0.02	0.3	0.9	79	-0.1	0.4	0.8	74	-0.7	0.6	0.3
Mineral mass (kg)	83	0.4	0.1	<0.001	79	0.3	0.1	0.001	74	0.2	0.1	0.2
Protein:mineral	83	-0.4	0.1	<0.001	79	-0.4	0.2	0.02	74	-0.5	0.3	0.2
Regional(DXA)									74			
Arm bone (kg)	83	0.04	0.01	<0.001	79	0.03	0.01	<0.001	74	0.03	0.02	0.1
Arm fat (kg)	83	2.1	0.2	<0.001	79	1.5	0.2	<0.001	74	1.7	0.3	0.001
Arm lean (kg)	83	0.8	0.2	<0.001	79	0.7	0.2	<0.001	74	0.7	0.3	0.07
Leg bone (kg)	83	0.1	0.0	<0.001	79	0.1	0.0	0.01	74	0.07	0.06	0.3
Leg fat (kg)	83	7.1	0.7	<0.001	79	4.8	0.9	<0.001	74	6.0	1.2	0.003
Leg lean (kg)	83	1.8	0.5	0.001	79	1.4	0.5	0.007	74	1.1	0.7	0.2
Trunk bone (kg)	83	0.08	0.03	0.005	79	0.08	0.03	0.006	74	0.03	0.05	0.6
Trunk fat (kg)	83	10.0	0.8	<0.001	79	7.1	0.9	<0.001	74	7.4	1.4	0.002
Trunk lean (kg)	83	1.7	0.6	0.009	79	0.9	0.5	0.1	74	-0.008	0.7	1.0

Abbreviations: N= obese + controls; HT= height; SE= standard error; BMI= body mass index; SDS= standard deviation score; SES= socio-economic status; C= circumference; TBW= total body water, FM= fat mass; FMI= FM index; FFM= fat-free mass; FFMI= FFM index; D_{ffm}= density of FFM; H_{ffm}= hydration of FFM; DXA= dual x-ray absorptiometry. Highlighted p-values refer to those that lost significance in model 2.

5.10 Discussion

Obese children in this study were found to have heavier parents compared to those that were not obese. This is consistent with the findings of previous studies (Lake *et al.* 1997; Whitaker *et al.* 1997). This association may be due to two factors: first obesity is partly heritable; therefore obesity tracks from parents to children, and second the environment parents live in and their lifestyle behaviour may influence the children's behaviours.

In the sample population studied, obese children were on average 3 cm taller than controls after matching for age, gender and ethnicity. This is consistent with the findings of previous studies (Kain *et al.* 1998). There is not sufficient evidence to explain why obese children are taller, however two theories may explain the reason behind this common finding. First, obese children might have been exposed to a higher plane of nutrition early on in life which may have contributed to faster development and growth (Bray *et al.* 2001; Tse *et al.* 1989; Mills *et al.* 1986) Reports however have shown that even though obese children may be taller as children or young adolescents, they are usually found to be stunted when followed up later on in young adulthood (Tse *et al.* 1989). Second, reports have shown that earlier sexual maturation in girls is associated with an increase in FM whereas earlier sexual maturation in boys is associated with decreased FM (Guo *et al.* 1997; Wang, 2002). Pubertal status has been assessed in this study and obese children remained significantly taller than controls after adjusting for pubertal status.

Due to their increased size, obese children had significantly greater body circumferences compared to controls. Only about one third of the waist circumference in obese children was accounted for by factors such as parental size and activity. Regional body composition analyses using DXA confirmed that obese children had significantly greater fat and lean mass in their limbs and trunk compared to controls; the difference being greatest in trunk fat. Differences in fat remained significant after adjusting for pubertal stage and activity. This indicates that obese children are gaining weight disproportionately in the abdominal region, which is correlated with an increased risk of metabolic complications (Daniels *et al.* 1999; Taylor *et al.* 1998).

In terms of gross tissue masses, obese children had greater amounts of both fat and lean mass compared to controls. Even though gender differences in these components were

observed in controls whereby boys have less fat and more lean compared to girls, this was not observed in obese children. Also, the association of age with an increase in both fat and lean mass after adjusting for height was observed in controls, but only for lean mass in the obese. This phenomenon demonstrates that the association of body composition with age and gender is lost when a child becomes obese, and obese children show a different pattern of growth compared to those who are not obese. This aspect should be taken into account when assessing body composition in obese children.

After examining gross tissue composition differences, the next step was to look at differences in the composition of FFM, including water (H_{ffm}), mineral and protein. An increased H_{ffm} found in obese children has been previously reported in Bray's study (Bray et al, 2001) where fatter children had significantly greater H_{ffm} compared to the leaner ones (77.2% versus 74.3%; $p < 0.001$). Bray and colleagues (2001) found obese children to have approximately 3% more H_{ffm} compared to controls, whereas this study showed that obese boys and girls had only 2.3% and 1.4% more H_{ffm} respectively (Bray *et al.* 2001). The differences in the absolute percentages between Bray's finding and my finding can be attributed to the difference in methodology used to assess body composition. Bray and colleagues calculated H_{ffm} as TBW (measured by ^{18}O isotope dilution)/FFM (from DXA), whereas H_{ffm} in this study was calculated as TBW (measured by D_20)/FFM (from the 4C model). The 4C model has been previously shown to be a more reliable predictor of FFM compared to the DXA machine (Williams *et al.* 2006); making the difference in H_{ffm} between obese and controls obtained in this study more robust. Another possibility in the differences in outcome is the degree of obesity; children in Bray's study had an average BMI of 22 kg/m^2 whereas average BMI in my study was 30 kg/m^2.

One possibility explaining the increase of H_{ffm} might be an expansion of extra-cellular water (ECW) space (Battistini *et al.* 1995); however this was not measured directly in this study. Previous research has shown that in adults this over-hydration persisted even after weight reduction was achieved either by dietary modification (Marken Lichtenbelt and Fogelholm, 1999) or surgery (Leone *et al.* 2000). The reason behind an increase in ECW space remains poorly understood, and it is possible that obesity causes irreversible alterations in hemodynamics and fluid regulation (Marken Lichtenbelt and Fogelholm, 1999).

The other part of FFM that was also found to be significantly altered was the mineral mass (0.5 kg extra mineral mass in obese children), which is mainly present in bone. This is consistent with reports from previous studies where obese children were found to have greater absolute BMC (Fischer *et al.* 2000). Increased weight has been associated with earlier bone accumulation due to earlier sexual maturation (Whiting, 2002). After adjusting for factors such as pubertal status and activity, this increased mineralization remained significant. However when other factors such as parental BMI and SES were also taken into account, this increased in mineralization found in obese children was no longer significant. In relative terms obese children tend to be under mineralized for their weight, and have a higher rate of fractures compared to non-obese children, indicating that obesity is not protective for bones (Skaggs *et al.* 2001; Goulding *et al.* 1998). This may be due either to the bone growth taking time to catch up with the rapid increase in weight, causing bone fragility (Goulding *et al.* 1998), or to smaller bone dimensions in those obese (Skaggs *et al.* 2001).

Since the water and mineral components of FFM were higher in obese children, the proportion of protein was reduced resulting in lower D_{ffm} and a lower ratio of protein to mineral compared to controls. These differences in the composition of FFM are not only important health outcomes but they also need to be taken into account when assessing body composition with optimum accuracy.

After adjusting for factors that may be associated with obesity, the broad conclusion drawn is that some of the differences in body composition between obese and non-obese children were not due to obesity per se, but were due to differences in activity or puberty or they can be predicted by the family environment, illustrating that obesity tracks from parents to children. However, around two thirds of an obese child's fat can be attributed to other factors causing obesity such as their diet whereas only one third is due to factors about the child or their family such as parental size or SES.

Data from this study confirmed that when children grow, they increase in both the fat and the lean components of weight, and the rate of the growth of these separate tissues would be overlooked if simple indices like BMI were used. Also, results from using multi-compartment models show that the properties of FFM are not constant; obese children have significantly different composition of FFM compared to controls matched for age, sex and ethnicity. These differences remained significant even after adjusting

for factors such as SES, birth weight, gestation Therefore for this group of subjects, results from 2C models that assume constant properties of FFM may provide inaccurate body composition values. For example using the 2C model to estimate FFM, such as D_2O which assumes a constant hydration of FFM, is problematic if the adult constant of 73% is used. Also, the 3C model assumes a constant ratio of protein to mineral, and this ratio was found to be significantly lower in obese children. The 3C model was shown to underestimate fat and overestimate FFM, but the absolute differences did not differ substantially. Therefore in situations where DXA cannot be used, such as extreme obesity, the 3C model is considered a fairly accurate technique in estimating body composition.

5.11 Study limitations

Even though TBW was measured using D_20, ECW and intra-cellular water were not measured in this study. Therefore the reason behind the increased hydration values found in obese children can only be speculated on, based on findings from previous studies.

Due to the weight limit of 115 kg on the DXA machine, I was unable to scan very large children. Therefore I could not use the 4C model to obtain measurements of body composition in the heaviest children and only the 3C model was used on this group. Also regional analysis of body composition using the DXA should be interpreted with caution in the obese population. Due to their large size, some of the obese children were scanned with their arms partially tucked underneath their trunk, to fit in the designated scanning area. This could lead to misinterpretation of some results in terms of specific regional areas measured and analysed, specifically the arms and trunk.

Data on birth weight, physical activity and parental weight and height were estimated by the parents. Therefore, the reliability of the data recorded depends on the honesty and accuracy of the parental report. In order to minimize such limitations in future studies, it is recommended that whenever possible, data required are measured rather than estimated: parents' weight and height should be measured, the child's activity levels can be measured using activity monitors instead of estimating the number of hours they are active. This is because the child might be enrolled in an activity such as football, however he might be a goal keeper who is standing still most of the time rather than running around.

Data on the children's dietary intake was not collected in this study. Given that the quality and quantity of one's diet may be associated with differences in BMI or fat levels between populations (Tucker *et al.* 1997; Maffeis *et al.* 1996b), it would have been interesting to investigate whether differences in fat between obese and control children was confounded by what they ate and the quantity consumed. A food frequency questionnaire or a food diary could describe a person's food habits; however the reliability of such data largely depends on the honesty of the children or their families, in addition to the accuracy of determining portion sizes. Previous research has shown that dietary intake recorded may be extremely biased and not recommended for use in obesity research (Schoeller *et al.* 1990).

Chapter 6: Evaluation of the success of two treatment programmes in obese children

6.1 Introduction

There has been considerable research on the effectiveness of various weight loss programmes in adults. However weight loss programmes in adults are very different to those in children; successful treatment in adults may not be successful in children and adolescents. In addition, most of the research conducted in children has used prediction techniques to assess body composition. It is important to measure the different body components directly to be confident that the programmes were successful at reducing body fatness. For example, programmes involving physical activity may not alter body weight per se, but might change the relative proportions of the fat and lean components. This aspect can be overlooked if surrogate measures such as BMI are used.

There are limited available weight management programmes for children and adolescents in London. I have chosen the only two available programmes used in GOSH and UCH to test whether body composition in children changes after taking part in either of the two programmes. The best available technique (multi-component model) has been used to assess whole body composition.

Each of the two programmes will be discussed separately in two different sections: the first is a psychological program adopting the traffic light system, and the second is a pharmacological program using Metformin.

6.2 *Traffic light program (TLP)*

6.2.1 Rationale of the study

The first treatment programme is the TLP which is a family-based program used for the treatment of paediatric obesity. The programme is based on the 'stop light diet' developed and tested by Len Epstein and colleagues in the United States (Epstein *et al.* 1985). The program has already been tested in the US; however it still remains to be evaluated in the UK clinical setting. A pilot study looking at the effectiveness of a family based behavioural treatment in the UK confirmed that it is feasible and acceptable to be used in Britain (Edwards *et al.* 2006). Prof. Jane Wardle is conducting the first randomised controlled trial (RCT) in the UK. Therefore the aim was to recruit all children taking part in the treatment programme to measure their body composition and evaluate the efficacy of the treatment programme.

The program teaches parents and children healthy eating by adopting the 'traffic lights' system for classification of foods, depending on nutritional value and energy density. Green indicates foods which can be eaten without worrying (like vegetables), yellow indicates food the child should be cautious about eating (like meat and dairy products), and red indicates foods which the child should stop and think about before eating (like cakes and biscuits).

The programme consists of regular 1.5 hour meeting sessions over a period of six months. The first ten sessions were held weekly, the next three fortnightly and the last two monthly. These involved both the child and at least one of their parents meeting with a dietician and a psychologist. After the program ended, follow-up meetings were conducted every six months for a year. The children's body composition was measured at baseline, 6 months and 1 year.

The aims of the psychological program are as follows:

1. Halt weight gain instead of aiming at weight loss
2. Provide nutritional education such as having a healthy balanced diet rather than calorie counting
3. Provide behaviour change training for both parents and children
4. Create a healthy microenvironment by changing the whole family's unhealthy patterns
5. Encourage maintenance of change

The TLP-RCT consisted of five consecutive treatment arms labelled as: waves 1 to 5. On average each wave was six months apart. In wave 1, children were randomised to two groups: the first group would start the treatment program immediately whilst the second group waited for six months before starting the treatment programme. The latter group would then act as controls. At this point, wave 2 would commence including wave 2 treatment group and wave 2 control group. Wave 2 treatment group would commence treatment with Wave 1 controls, and wave 2 control group waited for six months before starting treatment. This process was then repeated for each consecutive wave in a similar way. When two siblings from one family participated, they were both assigned to the same treatment arm. All participating obese children received the same duration of treatment of approximately six months; whether they were part of the treatment or control group. The only difference between the groups was that the control groups waited for six months before commencing treatment, and when they did become treated, they were not counted as part of the RCT treatment program. Refer to Figure 6-1 and Figure 6-2 for a summary of the trial profile.

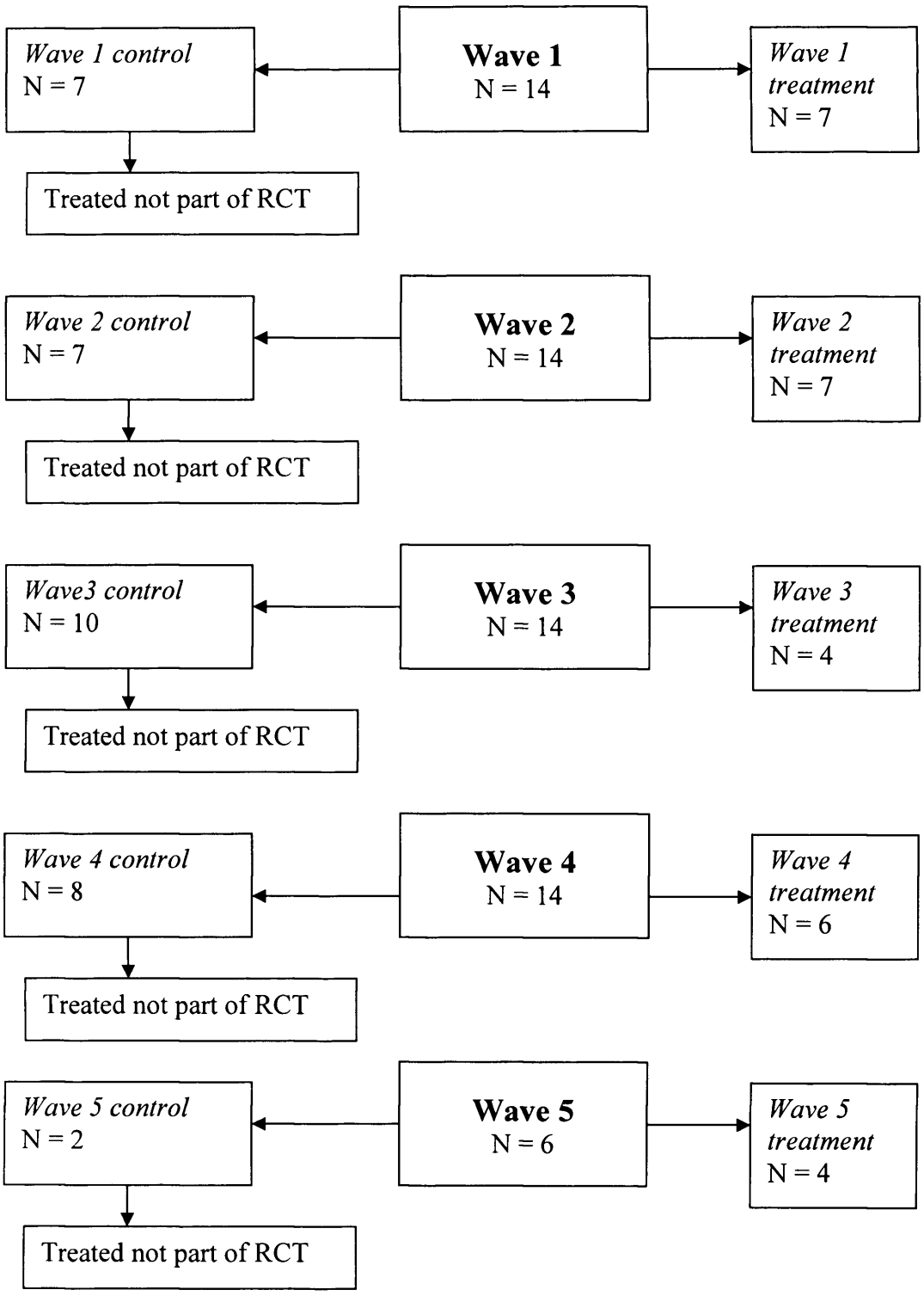


Figure 6-1 A summary of the different waves of the traffic-light program
Treatment groups started TLP immediately, whilst controls waited for 6 months before joining consecutive wave treatment group. When controls get treated after 6 months, they do not become part of the RCT treatment group

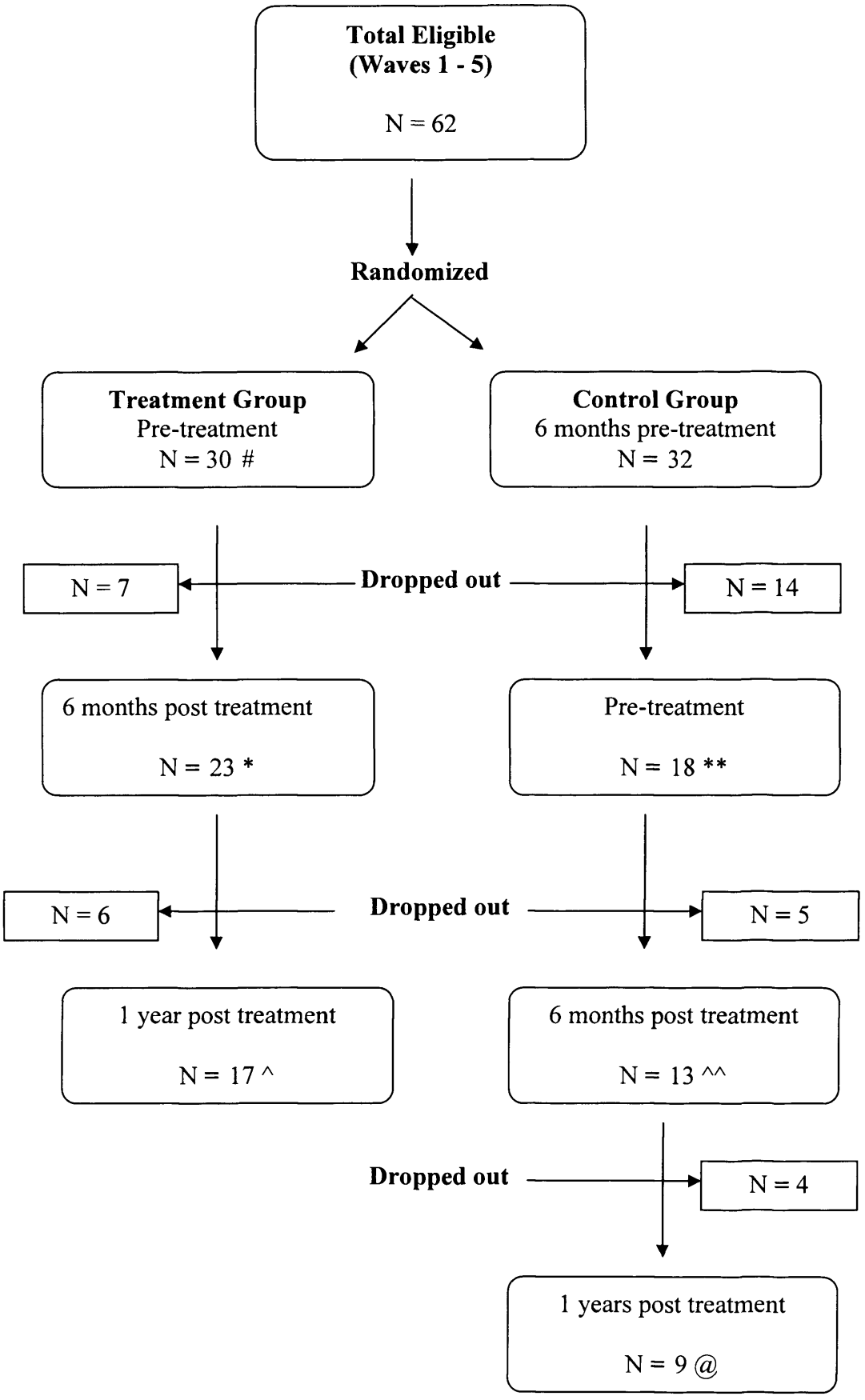


Figure 6-2: A summary of the traffic-light program
28 (3C), 27 (4C). *18 (3C), 17 (4C). **16 (3C), 16 (4C). ^ 16(3C). ^^13 (3C). @ 9 (3C).
Numbers refer to those with available data for the 3C and 4C models.

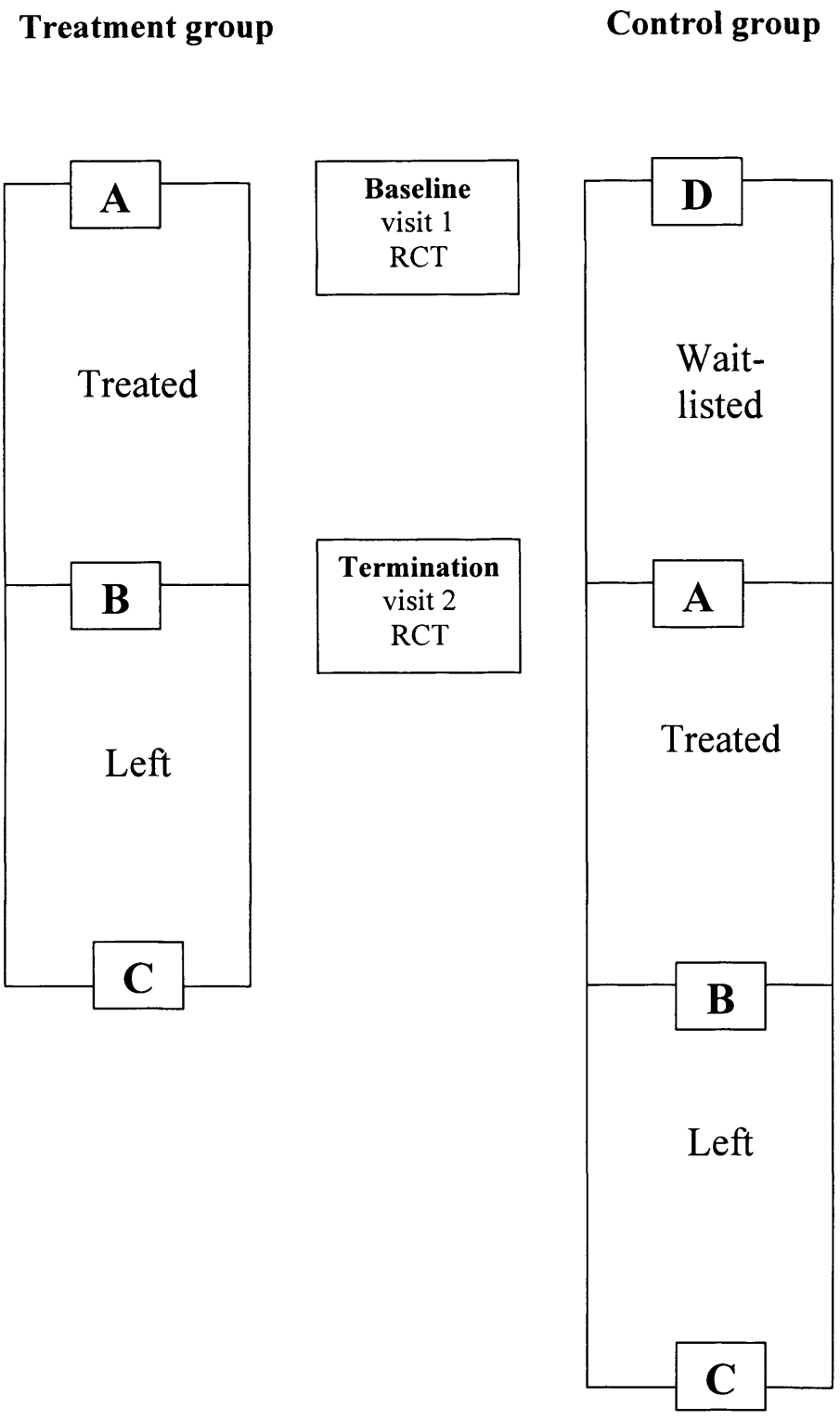


Figure 6-3 Different measurement time points (A, B, C, D) for the treatment and control groups

RCT treatment group includes time points: A, B & C
RCT control group includes time-points D, A, B & C
RCT treatment (B-A) compared with RCT control (A-D)
Treated then left compares: (C-B)-(B-A); wait-listed then treated compares: (B-A) - (A-D)

6.2.2 Hypothesis

The traffic light program significantly alters body composition in children.

6.2.3 Study design

This was a longitudinal RCT investigating the effects of the TLP on body composition in obese children. Children were randomized into two different groups: the treatment group and the control/waiting list group. The treatment group were measured before starting the treatment programme (baseline pre-treatment measurement) and measured again after six months and after one year of being on the program. The control group were measured six months before starting treatment (6-months pre-baseline measurement), then immediately before starting treatment (baseline measurement) and then again after six months and after one year of being on the program.

6.2.4 Recruitment

Children in this part of the study were recruited from the TLP programme at GOSH. Children were initially recruited through GPs, paediatricians, school nurses and dieticians in London. All referrals were made to an outpatient clinic at GOSH, and those who were potentially eligible to participate in the study were given information sheets about the study.

6.2.5 Inclusion and exclusion criteria

To be eligible to participate in the TLP, children had to be between 8 and 13 years old with a BMI > 95th percentile, equivalent to BMI SDS > 1.64, using UK 1990 reference data (Cole *et al.* 1995). The children should not be suffering from any medical or psychological condition associated with their obesity and they should not be receiving any other medical or psychological treatment. At least one parent or carer was required to attend the treatment sessions with the child, and both the child and the parent were required to read and understand English.

6.2.6 Sample size

Several factors were taken into account before calculating the appropriate sample size. First, the sample size needs to be large enough so that the research question can be answered confidently, and second the sample should be small enough to be practical to conduct. Also, there are two types of errors that need to be considered: type I error and type II error (Peat and Barton, 2005). Type I error is defined as the probability of rejecting the hypothesis when it is true, and type II error is defined as the probability of not rejecting the hypothesis when it is false. The former error occurs when a statistical significance is found but it is of no clinical importance, and the latter error occurs when a difference of clinical importance exists but does not reach statistical significance usually because the sample size is small.

Therefore, for the RCT, the conventional formula for a non-paired independent sample t-test ($n = 16\ SD^2/D^2$) was used to calculate an appropriate sample size. For example, 64 children per group would detect a difference of 0.5 SD score. If there was a 25% drop-out rate, this difference would increase to 0.8 SD score. However, this particular trial was designed to take into account cluster effects, which can occur when subjects are recruited in waves, such that those within a certain wave may show a common effect. Such cluster effects require an increased sample size in order to accommodate them. Previous applications of this obesity treatment in the US showed a 10% change in % BMI, as did the pilot study in the UK (Edwards *et al.* 2006; Epstein *et al.* 1985). The RCT was therefore powered to be able to detect a 10% difference in change in % BMI, taking into account cluster effects. The sample size needed assuming a 30% drop-out, would be 24 subjects per group; providing 90% power, and $p < 0.05$.

A total of 62 obese children were recruited to take part in the trial; 30 in the treatment group and 32 in the control group. 7 children dropped out of the treatment arm and 14 dropped out of the control arm, bringing the sample size down to 23 in the treatment group and 18 in the control group. The final sample size can therefore detect a difference in change of 0.8 SD score.

6.2.7 Methods

The 4C model was used to estimate body composition (details explained in chapter 4). Obese children only had DXA measurements for their first two visits; therefore the 3C

model was used to estimate body composition for visit 3 and visit 4 measurements. The DXA scanner has a weigh limit of 115 kg, therefore subjects beyond that weight were not scanned and the 3C model was used to estimate their body composition.

6.2.8 Statistical analysis

Independent sample t-tests were used to determine baseline and final differences in background data and various body composition outcomes between treatment and control groups, with intervention as the independent factor (dummy variable = 1 for the control group, and dummy variable = 2 for the treatment group).

Chi square tests were used to compare non-parametric data such as ethnicity, pubertal status, physical activity levels and SES between treatment and control groups.

Two different analyses were conducted using paired sample t-tests. First differences in change in body composition were investigated between the treatment group versus the waiting-list group on the RCT. For the treatment group differences between pre-treatment and 6-month follow up outcomes were analysed, and for the control group differences between 6-months pre-treatment and pre-treatment measurements were analysed. A second analysis investigated change in body composition between those that were treated first and then left versus those that were left for six months before being treated. The first group includes everyone that had complete measurements for being treated and then left (this includes those on the treatment group and the control group who were subsequently treated but not within the RCT). The second group only included those that had 6-months pre-treatment measurements (i.e. only the control group). These analyses are described in detail later.

6.2.9 Results

A total of 62 obese children were recruited for the programme. These were randomised to two groups: 30 in the treatment group (22 females; 8 males) versus 32 in the control group (22 females; 10 males). Baseline differences in background and body composition characteristics in treatment and control groups are summarised in Table 6-1. The mean age and BMI SDS for both groups was approximately 10 years and 3 SDS respectively. The treatment group had heavier mothers compared to the control group; average BMI difference of 4 kg/m^2. This difference however was not statistically significant ($p = 0.1$). There were no other significant differences in any of the baseline characteristics between the treatment and control groups.

Of the 62 subjects who were originally recruited and had baseline body composition assessments, 21 obese children (14 females; 7 males) dropped out of the trial leaving a total of 41 (30 females; 11 males) remaining in the trial. A summary of background and body composition characteristics between those that remained in the trial versus those that dropped out of the trial are summarised in Table 6-2. In terms of background characteristics compared to those who remained in the trial, drop-outs were similar in age, ethnicity, maternal and paternal BMI, physical activity, social class and pubertal status. However, drop-outs had significantly greater gestational age (mean difference = 0.9 weeks; $p = 0.02$) and significantly higher birth weight (mean difference = 0.3 kg; $p = 0.04$). Also, drop-outs were significantly shorter by 0.8 SDS which is equivalent to 7 cm ($p = 0.03$), than those who remained in the trial. In terms of body composition, drop-outs had significantly lower body volume (mean difference = 11.0 litres; $p = 0.04$) and BMC (mean difference = 0.3 kg; $p = 0.02$) compared to those included in the trial. Drop-outs also had on average 6.4 kg lower FFM (by 3C) compared to those included in the trial; this difference was statistically significant ($p = 0.02$). When adjusted for height, FFM was no longer different between both groups. No other significant differences in body composition were observed between both groups.

Even though a number of obese children dropped out of the treatment trial, some ($n = 8$) agreed to have body composition measurements at time of follow-up. The sample size however was too small for meaningful analysis.

The final sample included in the RCT included 23 (18 females; 5 males) in the treatment group and 18 (12 females; 6 males) in the control group. Their background characteristics are summarised in Table 6-3.

The mean age of the treatment and control groups was 10.7 and 10.0 years respectively. Even though there were no significant differences in any of the background characteristics between both groups, children of fatter mothers appear more likely to be included in the treatment programme. Maternal BMI was approximately 8 kg/m^2 higher in the treatment group compared to the control group, but the SD was large hence the difference did not achieve significance. In addition, the majority of the sample included in the RCT were reported to be less active than peers (assessed by using a questionnaire), they came from a lower social class (class 4 or more), and were in puberty stages II and III (as assessed by indicating pictures that resembled their status at time of measurement). The treatment and control groups were very similar in baseline body composition characteristics, with no significant differences for any of the measurements (refer to Table 6-4).

Change in body composition was then assessed for the treatment and control groups. The average time elapsed between the two measurements was 7 months; minimum difference = 5 months and maximum difference = 10 months, which was similar in both groups. For the treatment group, change in body composition was calculated as the difference between baseline and follow-up measurements (i.e. before and after being on the TLP), calculated as 6-months post treatment – pre-treatment (B – A). For the control group, change in body composition was calculated as the difference between two baseline measurements, one 6 months before treatment date and another just before they commenced the treatment, calculated as (A – D). Refer to Figure 6-3.

Table 6-5 shows differences in body composition between the treatment group versus control group. First, paired sample t-tests were used to assess change in body composition within each of the two groups separately, to investigate any change in body composition during the trial. In both groups, obese children gained significantly in weight and height. However when converted into SDS these differences were no longer significant. BMI SDS significantly reduced by an average of 0.1 SDS for both groups. Body volume, TBW and BMC were significantly greater at follow-up in the treatment and control groups. No significant differences in FM or % fat were observed, however children in both groups had significantly greater FFM (2.3 kg for treatment, 2.4 kg for control) at follow-up, changes which remained significant after adjusting for height. Second, independent sample t-tests were used to investigate whether change in body composition over time differed significantly between the groups. No significant differences were observed for any of the measurements except for FFM, whereby those in the treatment group gained 0.6 kg/m^2 more FFMI compared to those in the control group ($p = 0.02$).

A further analysis was performed to investigate differences in change in body composition between those who received treatment, and then left as opposed to those that had to wait for 6 months before they received treatment. Body composition was assessed by the 3C model because children only had a bone scan for their first two visits; hence the 4C model was not used.

Those being first treated then left underwent measurements at time points A, B and C. Change in body composition was calculated as: change in body composition when being left – change in body composition when being treated. This corresponds to (C – B) – (B – A), and would include everyone (both from treatment and control groups in the RCT) that had the corresponding measurements. These time points are shown in figure 6-3.

This group included a total of 26 children, 17 from the RCT treatment group and 9 from the RCT control group.

On the other hand, those that were being first wait-listed and then treated underwent measurements at time points D, A and B. Since only those from the control group RCT had measurement time point D, only those from the control group were included in this

calculation (n = 13). Change in body composition was calculated as: change in body composition when being treated – change in body composition when being left. This corresponds to (B – A) – (A – D).

Table 6-6 illustrates relative change in body composition for both groups. The first group (being treated then left) reveal that being left resulted in an increase in all body composition parameters except FFMI. A significant relative increase in WT SDS, BMI SDS, MUAC, thigh circumference and FM was apparent when comparing change in body composition between being left versus being treated.

Analyses from the second group (being wait-listed then treated) reveal that relative to being left with no treatment, being treated improved body composition; results include a slight relative reduction in WT SDS and FM in addition to a reduction in MUAC, hip and calf circumferences. None of these differences however achieved statistical significance. One possible reason could be that the sample size used for this analysis was smaller (n = 13) compared to the other group: treated then left (n = 26). Hence this sample does show a trend but a larger sample size may be needed to achieve significant effects.

Table 6-1 Baseline differences in background and body composition characteristics between treatment versus controls in the RCT

	Treatment			Controls		
	n	**mean**	**SD**	**n**	**mean**	**SD**
Background						
Age (years)	30	10.6	1.6	32	10.0	1.5
Gestation (weeks)	30	40.3	1.1	32	40.0	1.9
Birth weight (kg)	30	3.6	0.4	32	3.6	0.6
Paternal BMI (kg/m^2)	23	28.2	8.9	27	28.9	4.3
Maternal BMI (kg/m^2)	30	33.6	11.6	31	29.6	7.0
Physical activity (hours/wk)	30	5.1	5.6	32	5.3	4.9
Physical activity compared to peers (n, %) Much less & less active Same More active Much more active	 14 (46.7) 12 (40.0) 3 (10.0) 1 (3.3)			 12 (37.6) 15 (46.9) 4 (12.5) 1 (3.1)		
Social Class (n, %) Class 1 Class 2 Class 3 Class 4 or more	 1 (3.3) 8 (26.7) 7 (23.3) 14 (46.7)			 1 (3.1) 11 (34.4) 4 (12.5) 16 (50)		
Pubertal status (n, %) Pre-pubertal Early pubertal Late pubertal	 5 (17.2) 18 (62.1) 6 (20.7)			 4 (12.5) 23 (71.9) 5 (15.6)		
Anthropometry						
Weight SDS	30	3.0	0.9	32	3.1	0.8
Height SDS	30	1.4	1.2	32	1.3	1.1
BMI SDS	30	3.1	0.7	32	3.2	0.6
WC SDS	30	3.4	0.5	32	3.5	0.6
Body volume (l)	29	71.0	20.4	32	67.8	20.5
TBW (l)	29	29.4	7.0	32	28.8	7.8
BMC (kg)	29	1.8	0.5	32	1.8	0.6
3C data						
FM (kg)	28	32.0	11.8	32	29.7	10.8
FMI (kg/m^2)	28	13.7	4.0	32	13.8	3.8
FFM (kg)	28	39.2	9.1	32	37.9	10.4
FFMI (kg/m^2)	28	16.9	2.3	32	17.3	2.5
4C data						
FM (kg)	27	31.6	11.1	32	30.2	10.8
FMI (kg/m^2)	27	13.7	3.9	32	13.8	3.8
FFM (kg)	27	37.7	7.6	32	37.3	10.3
FFMI (kg/m^2)	27	16.4	1.8	32	17.1	2.7

Abbreviations: SD=standard deviation; SD= standard deviation; SDS= SD score; WC= waist circumference; TBW= total body water; BMC= bone mineral content; FM= fat mass; FMI= FM index; FFM= fat-free mass; FFMI= FFM index. No significant differences between groups.

Table 6-2 Baseline differences in background and body composition characteristics between drop-outs versus those included in the RCT

	Drop-outs			**Trial**		
	n	**mean**	**SD**	**n**	**mean**	**SD**
Age (years)	21	10.0	1.4	41	10.4	1.7
Gestation (weeks) *	21	40.7	1.0	41	39.9	1.7
Birth weight (kg) *	21	3.8	0.6	41	3.5	0.5
Paternal BMI (kg/m^2)	16	30.1	5.1	34	27.9	7.4
Maternal BMI (kg/m^2)	21	31.0	8.7	40	31.9	10.2
Physical activity (hours/wk)	21	5.0	3.5	41	5.3	5.9
Physical activity compared to peers (n, %)						
Much less & less active	6 (28.6)			20 (48.8)		
Same	11 (52.4)			16 (39.0)		
More active	3 (14.3)			4 (9.8)		
Much more active	1 (4.8)			1 (2.4)		
Social Class (n, %)						
Class 1	0 (0)			2 (4.9)		
Class 2	9 (42.9)			10 (24.4)		
Class 3	3 (14.3)			8 (19.5)		
Class 4 or more	9 (42.8)			21 (51.2)		
Pubertal status (n, %)						
Pre-pubertal	2 (9.5)			7 (17.5)		
Early pubertal	17 (81.0)			24 (60)		
Late pubertal	2 (9.5)			9 (22.5)		
Anthropometry						
Weight SDS	21	2.8	0.8	41	3.2	0.9
Height SDS *	21	0.8	1.1	41	1.6	1.1
BMI SDS	21	3.1	0.5	41	3.2	0.7
WC SDS	21	3.3	0.5	41	3.5	0.6
Body volume (l) *	21	62.2	18.3	40	73.1	20.5
TBW (l)	21	26.2	7.0	40	30.5	7.2
BMC (kg) *	21	1.6	0.4	40	1.9	0.5
3C data						
FM (kg)	21	27.5	9.9	39	32.5	11.6
FMI (kg/m^2)	21	13.1	3.4	39	13.9	4.0
FFM (kg) *	21	34.3	8.9	39	40.7	9.6
FFMI (kg/m^2)	21	16.5	2.2	39	17.5	2.5
4C data						
FM (kg)	21	32.4	11.2	38	28.1	9.9
FMI (kg/m^2)	21	13.4	3.6	38	13.9	3.9
FFM (kg)	21	33.8	8.7	38	39.5	8.7
FFMI (kg/m^2)	21	16.3	2.5	38	17.1	2.3

* Significant difference between groups at $p < 0.05$

Abbreviations: n= number per group; SD=standard deviation; BMI= body mass index; SDS= SD score; WC= waist circumference; TBW= total body water; BMC= bone mineral content; FM= fat mass; FMI= FM index; FFM= fat-free mass; FFMI= FFM index.

Table 6-3 Background characteristics of final RCT sample: treatment versus controls

	Treatment			**Controls**		
	n	**mean**	**SD**	**n**	**mean**	**SD**
Age (years)	23	10.7	1.7	18	10.0	1.5
Gestation (weeks)	23	40.3	1.2	18	39.3	2.0
Birth weight (kg)	23	3.6	0.4	18	3.4	0.5
Paternal BMI (kg/m^2)	18	27.2	9.2	16	28.6	4.6
Maternal BMI (kg/m^2)	23	35.1	12.1	17	27.6	4.5
Physical activity (hours/week)	23	5.1	6.0	18	5.6	5.9
Ethnicity (n, %) White Asian Black Other	 12 (52.2) 2 (8.7) 5 (21.7) 4 (17.3)			 7 (38.9) 6 (33.3) 2 (11.1) 3 (16.7)		
Physical activity compared to peers (n, %) Much less & less active Same More active Much more active	 11 (47.8) 9 (39.1) 2 (8.7) 1 (4.3)			 9 (50) 7 (38.9) 2 (11.1) 0 (0)		
Social Class (n, %) Class 1 Class 2 Class 3 Class 4 or more	 1 (4.3) 6 (26.1) 6 (26.1) 10 (43.4)			 1 (5.6) 4 (22.2) 2 (11.1) 11 (61.2)		
Pubertal status (n, %) Pre-pubertal Early pubertal Late pubertal	 3 (13.6) 13 (59.1) 6 (27.3)			 4 (22.2) 11 (61.1) 3 (16.7)		

Abbreviations: n= number per group; SD= standard deviation; BMI= body mass index.

No significant differences between groups.

Table 6-4 Baseline body composition of the final sample in RCT: treatment versus controls

	Treatment			Controls		
	n	**mean**	**SD**	**n**	**mean**	**SD**
Anthropometry						
Weight (kg)	23	73.6	20.9	18	70.7	19.3
Height (cm)	23	152.5	9.8	18	148.8	10.3
BMI (kg/m^2)	23	31.1	6.0	18	31.4	5.9
Weight SDS	23	3.2	1.0	18	3.3	0.8
Height SDS	23	1.6	1.2	18	1.6	0.9
BMI SDS	23	3.1	0.7	18	3.3	0.7
MUAC (cm)	23	34.0	4.7	18	32.8	4.2
Head C (cm)	23	56.1	2.0	18	55.5	1.9
WC (cm)	23	92.5	11.3	18	91.3	10.0
Hip C (cm)	23	103.2	12.4	18	101.6	12.5
Thigh C (cm)	23	62.2	8.0	18	61.4	8.8
Calf C (cm)	23	38.1	4.6	18	38.3	5.0
WC SDS	23	3.5	0.6	18	3.6	0.6
Body volume (l)	22	74.9	21.6	18	71.0	19.6
TBW (l)	22	31.1	7.1	18	29.8	7.5
BMC (kg)	22	2.0	0.5	18	1.9	0.6
3C data						
FM (kg)	21	33.6	12.7	18	31.3	10.4
FMI (kg/m^2)	21	13.9	4.3	18	13.9	3.9
FFM (kg)	21	41.8	9.0	18	39.3	10.4
FFMI (kg/m^2)	21	17.5	2.3	18	17.5	2.7
% fat	21	43.5	5.7	18	43.8	5.3
H_{ffm} (%)	21	75.4	1.6	18	75.9	2.0
D_{ffm} (kg/l)	21	1.09	0.01	18	1.08	0.01
4C data						
FM (kg)	20	33.0	12.0	18	31.7	10.5
FMI (kg/m^2)	20	13.8	4.1	18	14.1	3.8
FFM (kg)	20	40.1	7.3	18	38.9	10.3
FFMI (kg/m^2)	20	16.9	1.8	18	17.3	2.7
% fat	20	44.1	5.8	18	44.5	5.2
H_{ffm} (%)	20	76.6	1.8	18	76.8	2.1
D_{ffm} (kg/l)	20	1.09	0.01	18	1.09	0.01
Protein mass (kg)	20	6.8	1.3	18	6.7	2.2
Mineral mass (kg)	20	2.6	0.6	18	2.4	0.8

Abbreviations: n= number per group; SD= standard deviation; SDS= SD score; BMI= body mass index; MUAC= mid-upper arm circumference; C= circumference; WC= waist circumference; TBW= total body water; BMC= bone mineral content; FM= fat mass; FFM= fat-free mass; FMI= FM index; FFMI= FFM index; H_{ffm}= hydration of FFM; D_{ffm}= density of FFM

Table 6-5 Change in body composition: treatment versus controls

	Treatment				Controls			
	n	**D1**	**SD**	**p**	**n**	**D2**	**SD**	**p**
Age (years)	23	0.6	0.1	<0.001	18	0.6	0.2	<0.001
Anthropometry								
Weight (kg)	23	3.0	3.9	0.001	18	3.5	3.8	0.001
Height (cm)	23	2.4	1.5	<0.001	18	3.0	1.5	<0.001
BMI (kg/m2)	23	0.3	1.4	0.3	18	0.3	1.6	0.5
Weight SDS	23	-0.06	0.2	0.2	18	-0.05	0.2	0.3
Height SDS	23	-0.1	0.2	0.001	18	-0.1	0.3	0.1
BMI SDS	23	-0.1	0.2	0.02	18	-0.1	0.2	0.04
MUAC (cm)	23	0.02	1.3	0.9	18	0.7	1.5	0.06
Head C (cm)	23	0.0	1.3	0.9	18	0.1	0.9	0.5
WC (cm)	23	0.8	3.9	0.3	18	0.5	4.1	0.6
Hip C (cm)	23	1.6	4.4	0.09	18	1.8	3.1	0.03
Thigh C (cm)	23	0.0	2.1	0.9	18	-0.5	2.7	0.4
Calf C (cm)	23	0.4	1.4	0.2	18	0.7	1.3	0.04
WC SDS	23	-0.1	0.2	0.3	18	-0.1	0.3	0.2
Body volume (l)	22	3.1	4.3	0.003	18	3.3	3.9	0.003
TBW (l)	19	2.0	1.2	<0.001	16	1.8	1.7	0.001
BMC (kg)	22	0.1	0.1	0.001	18	0.2	0.1	<0.001
3C data								
FM (kg)	18	1.0	3.7	0.3	16	1.0	2.9	0.2
FMI (kg/m^2)	18	1.0	0.6	0.2	16	-0.1	1.3	0.7
FFM (kg)	18	2.3	1.3	<0.001	16	2.4	2.1	<0.001
FFMI (kg/m^2) *	18	1.0	0.6	<0.001	16	0.4	0.8	0.06
% fat	18	-0.9	2.5	0.2	16	-0.9	2.4	0.2
H_{ffm} (%)	18	0.7	1.4	0.07	16	-0.2	1.6	0.6
D_{ffm} (kg/l)	18	0.003	0.006	0.06	16	0.001	0.006	0.7
4C data								
FM (kg)	17	1.3	3.7	0.2	16	1.0	2.9	0.2
FMI (kg/m^2)	17	0.5	1.5	0.2	16	-0.1	1.3	0.7
FFM (kg)	17	2.3	1.3	<0.001	16	2.3	2.2	0.001
FFMI (kg/m^2) *	17	1.0	0.6	<0.001	16	0.4	0.8	0.09
% fat	17	-0.8	2.6	0.2	16	-0.8	2.3	0.2
H_{ffm} (%)	17	0.8	1.7	0.06	16	-0.1	1.8	0.8
D_{ffm} (kg/l)	17	-0.003	0.006	0.09	16	0.001	0.007	0.7
Protein mass (kg)	17	0.1	0.9	0.6	16	0.3	0.9	0.2
Mineral mass (kg)	17	0.1	0.2	0.004	16	0.2	0.1	<0.001

* significant difference between groups; $p < 0.05$
D1 = differences between measurements made at time points B and A (B – A)
D2 = differences between measurements made at time points A and D (A – D)
Abbreviations: n= number per group; SD= standard deviation; SDS= standard deviation score; BMI= body mass index; MUAC= mid-upper arm circumference; C= circumference; WC= waist circumference; TBW= total body water; BMC= bone mineral content; FM= fat mass; FFM= fat-free mass; FMI= FM index; FFMI= FFM index; H_{ffm}= hydration of FFM; D_{ffm}= density of FFM

Table 6-6 Differences in change in body composition between those that were treated then left versus those that were wait-listed then treated

	Treated then left				**Wait-listed then treated**			
	n	**Δ_1**	**SD**	**p**	**n**	**Δ_2**	**SD**	**p**
Anthropometry								
Weight (kg)	26	2.3	5.6	0.04	13	-1.4	5.6	0.4
Height (cm)	26	0.02	1.1	0.9	13	-0.5	1.6	0.3
BMI (kg/m^2)	26	0.9	2.2	0.04	13	-0.3	2.6	0.7
Weight SDS	26	0.2	0.4	0.02	13	-0.006	0.3	0.9
Height SDS	26	0.06	0.3	0.3	13	0.06	0.4	0.6
BMI SDS	26	0.1	0.3	0.04	13	0.01	0.3	0.9
MUAC (cm)	26	1.6	1.8	<0.001	13	-0.8	2.6	0.3
Head C (cm)	26	0.09	2.0	0.8	13	0.2	1.4	0.6
WC (cm)	26	2.2	6.1	0.08	13	0.05	7.0	1.0
Hip C (cm)	26	0.9	6.8	0.5	13	-0.6	4.9	0.7
Thigh C (cm)	26	1.8	3.9	0.03	13	1.7	3.7	0.1
Calf C (cm)	26	0.8	2.3	0.1	13	-0.3	1.6	0.5
Body volume (l)	25	2.4	6.1	0.06	13	-1.6	6.1	0.4
TBW (l)	26	0.02	3.2	1.0	13	-0.6	2.7	0.4
3C data								
FM (kg)	25	2.1	4.4	0.02	13	-1.0	4.1	0.4
FMI (kg/m^2)	25	0.06	2.1	0.9	13	0.2	1.9	0.7
FFM (kg)	25	0.07	2.9	0.9	13	- 0.4	2.7	0.6
FFMI (kg/m^2)	25	-1.1	1.3	<0.001	13	0.6	1.2	0.1

Δ_1 = differences calculated using data from the following time points: (C – B) – (B – A): left - treated

Δ_2 = differences calculated using data from the following time points: (B – A) – (A – D): wait-listed-treated

Abbreviations: n= number per group; SD=standard deviation; BMI=body mass index; SDS=SD score; MUAC=mid-upper arm circumference; C= circumference; WC=waist circumference; FM=fat mass; FMI= fat mass index; FFM=fat-free mass; FFMI= fat-free mass index

6.2.10 Discussion

Weight-loss programmes have proven to be extremely difficult not only in obese adults but also in obese children and adolescents. Most previous studies used BMI and BMI SDS to assess the efficacy of family-based treatment programmes (McCallum *et al.* 2007; Jiang *et al.* 2005; Bermudez de la Vega *et al.* 2007). BMI however does not give any indication of changes in fat or lean mass, or any information about the distribution of fat in the body. Therefore, accurate measurement of body composition is crucial when investigating the effectiveness of various treatment programs, especially those that incorporate physical activity.

The results from this study illustrate that obese children in both the treatment group and control group had a slight but significant reduction in BMI SDS at six-month follow-up (mean reduction = 0.1 SDS), but there were no significant differences in outcome between the groups. A similar finding was observed in the study of McCallum and colleagues in 2007, whereby nine months of treatment resulted in a reduction of 0.1 BMI SDS in the treatment group, with no significant difference between being part of the treatment group or the control group (McCallum *et al.* 2007).

On the other hand several other studies reported a significant decrease in BMI SDS in the treatment versus control group (Johnston and Steele, 2007; Jiang *et al.* 2005; Bermudez de la Vega *et al.* 2007). Johnston and Steele (2007) reported that 10 weeks of treatment resulted in a significantly greater decrease in BMI SDS in the treatment group versus control group (Johnston and Steele, 2007). One possible reason for the different finding is the population used in the study; Johnston and Steele included overweight in addition to obese children, whereas my study only included obese children. Those with greater adiposity may find it more difficult to adhere to the treatment programme compared to those who are less obese.

Jiang and colleagues (2005) also reported a significant reduction in BMI SDS between treatment and control groups (mean difference in BMI SDS between treatment and control group = 1.3) (Jiang *et al.* 2005). Jiang's sample consisted solely of obese Chinese children, whereas the population from my study consisted of a mix of ethnic groups (approximately 50% White and 50% other ethnic groups including Asian, Black and other). Since ethnic groups vary in their body composition and perhaps in the

factors that increase their risk of weigh gain and response to treatment, the results obtained from Jiang's study may not be comparable to those obtained from my study.

Bermundez de la Vega (2007) also showed that 6 months of treating obese children on the TLP resulted in a significant reduction in BMI SDS (average reduction = 0.6 SDS) (Bermudez de la Vega *et al.* 2007). Even though the sample size used in his study was large (n = 50), there were no controls. The effectiveness of the trial was therefore not confirmed.

This study is the first to measure body composition changes in obese children with the most accurate approach at present; using the multi-component model. No significant change in FM or % fat was observed between both the treatment and control group. There was however a significant increase in FFM (by 2.3 kg) in both the treatment and control groups at the end of the trial even after adjusting for change in height. Also, there was a significant difference between both groups whereby those in the treatment group had an average of 0.6 kg/m^2 more FFMI compared to controls ($p = 0.02$). One possible reason for this is that the treatment group became more active at the end of the trial. There were no differences in the number of hours of physical activity or level of activity compared to peers between the treatment and control group at baseline. However, at follow-up, the treatment group were on average doing 1.5 hours of physical activity a week more than the control group. Also, 6% of those on the treatment group reported that they were more or much more active compared to their peers, as opposed to none on the control group. None of these differences in physical activity achieved statistical significance.

Only one study assessed the efficacy of the TLP by measuring body composition in a group of obese children (Savoye *et al.* 2007). They found a significant decrease in % fat in the treatment versus control group (mean difference at 6 months = 5.2 %). Savoye and colleagues used a foot-foot impedance machine to assess body composition. This method however relies on using in-built equations that rely on using constant hydration values (usually 73%). I have previously reported in chapter 5 that obese children have significantly greater H_{ffm} compared to non obese children (average hydration = 77%; SD = 2). Therefore, results obtained from impedance equipment need to be interpreted with caution. Validation of BIA in obese children will be discussed in depth in the next chapter (chapter 7).

Even though results from the RCT did not reveal differences in body composition between treatment and control groups, differences in change in body composition when being treated as opposed to being left resulted in positive findings. There was a trend in relative reduction in weight, BMI and fat in the period when they were treated, versus a relative increase in weight, BMI and fat in the period when they were left. This illustrates that even though no significant differences were observed between treatment and control groups, there was a relative positive group effect in being treated versus being left.

One reason behind differences observed between the two analyses is that the groups included in each of two analyses varied in body composition, i.e. those who were part of the control group performed better when they received treatment compared to those on the treatment group. Since the RCT analysis only compares change in body composition between pre-baseline and baseline measurements for the control group, how the control group then performs on treatment is not studied. Hence the efficacy of the treatment programme may be overlooked if the control group performed better than the treatment group. On the other hand when the second analysis was performed, whereby everyone who received treatment was included such that those who were part of the RCT control group were also added, a significant positive effect was observed. Figure 6-4 and Figure 6-5 clearly illustrate that compared to those who were part of the RCT treatment group, most of those that were originally part of the RCT control group showed a greater reduction in FM (mean change = -1.5 ± 3.3 kg for the control group versus -0.6 ± 3.1 kg for the treatment group), and a greater reduction in BMI SDS (mean change = -0.08 ± 0.2 for the control group versus -0.05 ± 0.2 for the control group).

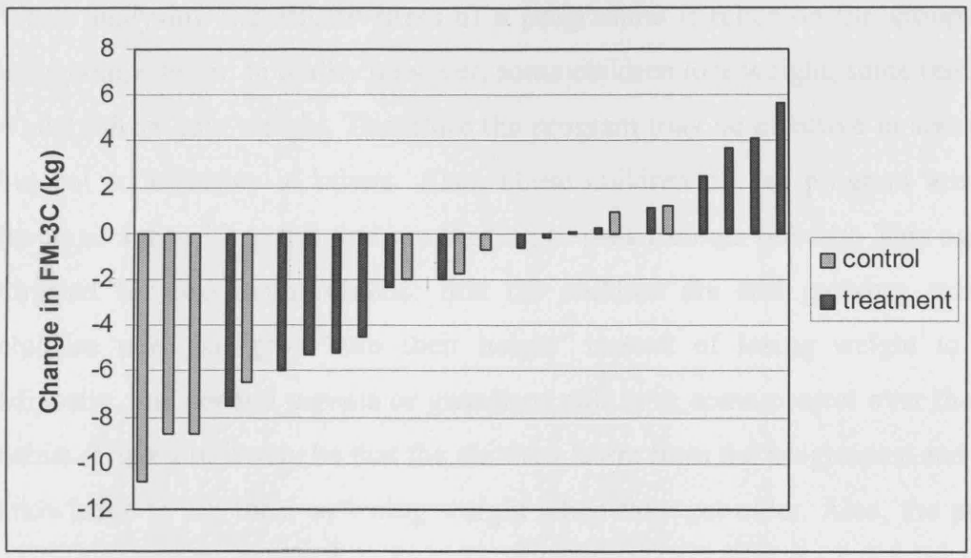


Figure 6-4 Change in FM in the control group versus the treatment group
Change in FM was calculated as: change in FM when being treated - change in FM when being left
Change in FM = (B - A) - (C - B)
Each bar represents a subject

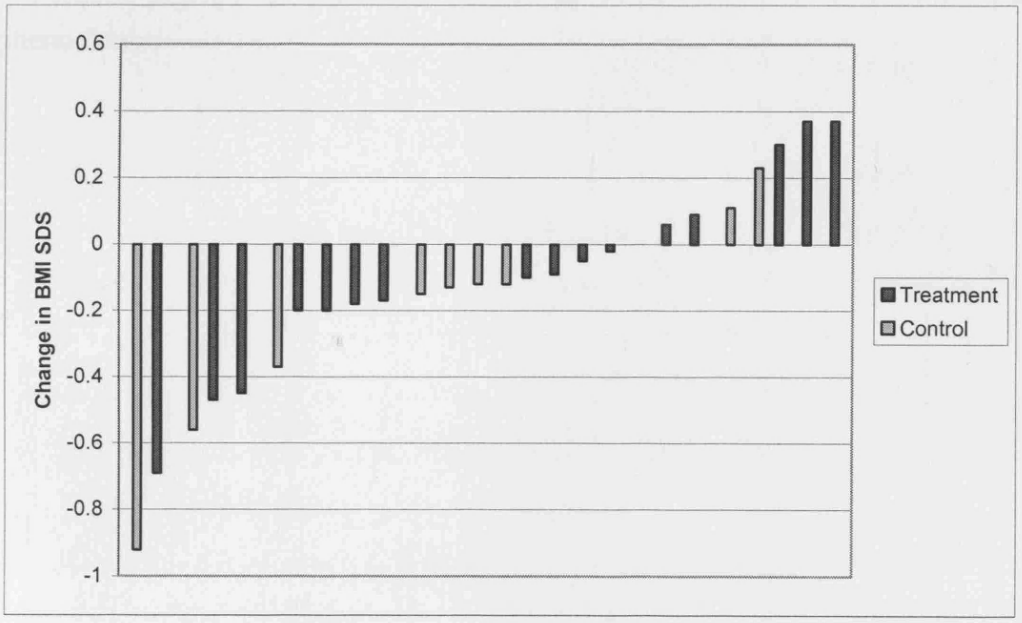


Figure 6-5 Change in BMI SDS in the control group versus the treatment group
Change in BMI SDS was calculated as: change in BMI SDS when being treated - change in BMI SDS when being left
Change in BMI SDS = (B - A) - (C - B)
Each bar represents a subject

When analysing the effectiveness of a programme it relies on the group changing in body composition. In reality however, some children lose weight, some remain the same whilst others gain weight. Therefore the program may be effective in some individuals but not so effective in others. Also, obese children on the program are very young (average age = 10 years) and are starting to pass through puberty. This age group was targeted for two main reasons: first the children are still growing, whereby obese children need to 'grow into their height' instead of losing weight to lose excess adiposity, and second parents or guardians still have some control over their children's habits. Therefore it may be that the children learnt from the programme and will use this knowledge to aid them in losing weight when they get older. Also, the programme is designed to improve parent behaviour and attitudes towards food and physical activity, this change in behaviour may require more time than 6 months, and the effectiveness of the programme may become more evident after a few years. Hence, the TLP aims to re-assess those who took part in the program after five years to investigate this phenomenon.

6.2.11 Study limitations

Maternal BMI in the treatment group was on average 8 kg/m^2 higher than those in the control group although mothers reported their weights and heights rather than being measured. Even though this was not statistically significant, this aspect may have affected results obtained from the RCT.

Even though the average time between measurements was not significantly different between the treatment and control arms (average difference = 7 months), it may be that individuals who were unable to attend the body composition appointment as soon as their treatment ended did change in BMI SDS, which may have an effect on evaluating the effectiveness of the trial. Unfortunately this issue was out of my control as families were contacted and appointments arranged at the time they agreed to be measured. Other obligations such as school exams, illnesses and holidays could not be avoided.

The trial consisted of different wave arms which started at different times of the year. Families treated in the same wave may be different to those treated in other waves. Having different waves in the TLP did not appear to have an effect on the findings of the study. This was checked by including a dummy variable for each child in the analyses depending on which wave they belonged to, and investigating if being in a specific wave influenced response to treatment. Because the sample size remaining from each wave was very small the effects this might have on the results could not be addressed properly, however no indication of any wave effect was apparent.

The treatment programme consisted of obese children from White, Asian, Black and other ethnic groups. Different ethnic groups vary in their body composition. However, this phenomenon should not have a big effect on the results as there were no significant differences in ethnicity between the treatment and control groups.

6.3 Metformin program

6.3.1 Rationale of the study

The second programme investigated was a pharmacological management programme using Metformin. A group of children and adolescents seen at the weight management clinics at GOSH and UCH have elevated levels of insulin in their blood, and they might also have a family history of type II diabetes. These children and adolescents were prescribed Metformin. Metformin, a biguanide, acts by suppression of glucose production in the liver, and therefore reducing the production of insulin from the pancreas; hence reducing appetite (Hundal and Inzucchi, 2003). It has been traditionally used for the treatment of type II diabetes in adults by improving hyper-insulinemia, hyper-glycemia and reducing weight. Similar effects have also been shown in non-diabetic adults (Fontbonne *et al.* 1996; Paolisso *et al.* 1998).

The effects of Metformin on different measures of body composition have not been adequately studied (refer to Table 6-7). In adolescents, only two RCTs have investigated the effectiveness of Metformin (Kay *et al.* 2001; Freemark and Bursey, 2001). Kay and colleagues (2001) showed that obese hyper-insulinemic adolescents who took Metformin for 8 weeks had a significant reduction in their body weight and fat levels compared to those who did not take Metformin (Kay *et al.* 2001). A similar positive finding of taking Metformin for 6 months was reported by Freemark & Bursey (2001) (Freemark and Bursey, 2001). They showed that BMI significantly decreased (-0.12 SDS) in the Metformin group but increased (+ 0.9 SDS) in the placebo group. A recent pilot study which evaluated the effects of taking Metformin for 3 months in a group of Chinese obese adolescents also reported a significant reduction in BMI in those who took the medication (Fu *et al.* 2006). Body composition was not a primary outcome in the two latter trials, so reported changes in BMI do not reveal the effects of Metformin on different body components such as body fat or lean mass. The first study did look at body composition in more detail, however bioelectrical impedance analysis (BIA) was used as the assessment tool. Hence, due to the methodology used in all three trials, results arising from the studies should be interpreted with caution.

Table 6-7 A summary of the different studies looking at the effects of Metformin in adolescents

Study reference	Study Population	Type of trial	Duration of treatment	Measures	Findings treatment *versus* controls
(Kay et al. 2001)	24 hyper-insulinaemic obese 13-17 years	RCT	8 weeks	WT (kg) FM (BIA) (kg) FFM (BIA) (kg)	-6.1 ± 0.8 *versus* -3.2 ± 0.2 kg* -6.0 ± 0.62 *versus* -2.7 ± 0.5 kg** -1.6 ± 0.6 *versus* -1.8 ± 0.3 kg
(Freemark and Bursey, 2001)	29 obese hyper-insulinaemic 12-19 years BMI > 30 kg/m^2 family history of type II diabetes	RCT	6 months	BMI SDS	-0.1 *versus* +0.2*
(Fu et al. 2006)	20 obese 10-16 years metabolic syndrome	pilot study	3 months	BMI (kg/m^2)	30.6 ± 3.6 *versus* 27.5 ± 4.1 kg/m^2†

Abbreviations: RCT= randomised controlled trial; WT= weight; BIA= bio-electrical impedance analysis; FM= fat mass; FFM= fat-free mass; BMI= body mass index; SDS= standard deviation score

*Significantly different: Metformin versus placebo group, $p < 0.02$
** Significantly different: Metformin versus placebo group, $p < 0.001$
†Significantly different: before versus after Metformin, $p < 0.001$

6.3.2 Hypothesis

Six months and one year of taking Metformin significantly alters body composition in a group of obese children and adolescents.

6.3.3 Study design

This section describes a pilot study looking at body composition changes after taking Metformin for 6 months and for 1 year in a group of children and adolescents. There were no controls at this stage and subjects acted as their own controls; their second body composition measurements were compared to their first, and their final body composition measurements at 1 year were also compared to their first. Obese children included in this study may have started taking Metformin before taking part in the study.

6.3.4 Recruitment

Children and adolescents were recruited from weight management clinics at GOSH and UCH.

6.3.5 Inclusion and exclusion criteria

To be eligible subjects had BMI-SDS > 95th percentile based on the 1990 UK reference cut-off point (Cole *et al.* 1995). Subjects also had insulin resistance tested by the paediatrician (Dr. R Viner) in clinic by an oral glucose tolerance test, or showed signs of acanthosis nigricans. Subjects on other weight loss programmes were excluded from taking part in this study.

6.3.6 Sample size

The formula used to calculate sample size for the Metformin part of the study is the same one used for aim 1 (refer to chapter 5):

$$n = 8 (SD^2/D^2) \qquad \textbf{Equation 6-1}$$

32 subjects will detect a difference of 0.5 SDS. A total of 36 obese children and adolescents were recruited to take part in the study, however only 22 completed the

trial. 12 had complete 4C measurements and 17 had completed 3C measurements; enabling detection of a difference of 0.8 and 0.7 SDS respectively.

6.3.7 Methods

Body composition was estimated using the 4C model (details described in chapter 4). For those who could not be scanned on the DXA (weight > 115 kg), the 3C model was used instead to estimate their body composition. Regional body composition was determined by DXA. DXA was assessed at baseline and at six months. Therefore the 4C model and regional body composition was not assessed at one year, and only the 3C model was used at that stage.

6.3.8 Statistical analysis

SPSS was used to analyse all the data. Paired sample t-tests were used to compare body composition differences between follow-up (6 months and 1 year) and baseline measurements.

6.3.9 Results

6.3.9.1 Characteristics of the sample

A total of 36 obese children and adolescents were recruited for the Metformin trial. The entire sample had baseline body composition measurements, however 9 did not take Metformin and 5 did not attend the 6-month follow-up appointment, bringing the sample size down to 22 (9 males, 13 females). Figure 6-6 is a flow-chart describing the Metformin trial.

Table 6-8 describes baseline characteristics of the Metformin group including those that were prescribed the drug but did not take it, those that dropped-out of the trial, and finally those that continued in the program. The three groups did not significantly differ in age, weight or BMI. The average age was 14 years and average BMI SDS was 3.5. Also, there were no significant differences in any of the circumferences, whole body composition or regional body composition measurements between the three groups. Hence, no significant physical or measured baseline differences were found between those that remained in the trial and those that did not end up in the trial.

Table 6-8 Baseline characteristics of the Metformin group including those that: did not take Metformin, dropped out, and remained in the trial

	Did not take			Dropped out at 6-months			Remained in the trial		
	n	***mean***	***sd***	***n***	***mean***	***sd***	***n***	***mean***	***sd***
Age (years)	9	13.9	2.9	5	14.4	0.9	22	14.5	3.5
weight-SDS	9	3.6	1.0	5	4.2	0.5	21	3.7	0.8
height-SDS	9	1.3	1.9	5	0.7	1.0	22	0.7	1.3
BMI SDS	9	3.4	0.7	5	3.7	0.3	21	3.5	0.6
BMI (kg/m^2)	9	37.7	7.9	5	41.5	5.5	21	38.0	7.6
Circumferences (cm)									
MUAC	9	39.3	6.3	5	40.7	2.9	22	39.2	5.5
WC	9	107.9	18.7	5	115.2	7.8	22	109.2	16.4
Hip C	9	121.0	16.0	5	125.3	7.6	21	118.4	13.7
Thigh C	9	71.7	9.4	5	74.2	7.2	21	69.3	7.8
Calf C	9	44.1	4.9	5	46.8	4.8	22	43.3	4.3
Whole body composition (kg/m^2)									
FMI-3C	9	18.1	5.8	4	20.5	5.3	21	17.6	5.4
FFMI-3C	9	19.6	2.7	4	20.6	2.2	21	20.5	3.6
FMI-4C	7	16.5	4.4	3	18.6	3.7	16	16.5	4.6
FFMI-4C	7	18.0	1.0	3	19.9	2.7	16	8.0	1.9
Regional body composition by DXA (kg/m^2)									
Trunk-FMI	7	7.6	1.8	4	10.0	1.7	16	8.1	1.8
Trunk-FFMI	7	7.8	0.5	4	8.9	0.7	16	8.7	1.7
Limbs-FMI	7	8.5	2.5	4	9.7	1.8	16	8.0	1.9
Limbs-FFMI	7	7.4	0.8	4	8.3	0.5	16	7.9	1.3

Abbreviations: n= number per group; SDS= standard deviation score, MUAC= mid upper arm circumference, WC= waist circumference, C= circumference, FMI= fat-mass index, FFMI= fat-free mass index, DXA= dual x-ray absorptiometry

No significant differences between groups

Table 6-9 Physical characteristics of Metformin group: at baseline, at 6 month follow-up and at 1-year follow-up

	Baseline			6- month follow-up			1- year follow-up		
	n	***mean***	***SD***	***n***	***mean***	***SD***	***n***	***mean***	***SD***
Age (years)	22	14.5	3.5	22	15.1	3.5	12	14.6	3.7
weight-SDS	21	3.7	0.8	21	3.7	0.8	12	3.6	1.0
height-SDS	22	0.7	1.3	22	0.6	1.4	12	0.4	1.4
BMI SDS	21	3.5	0.6	21	3.5	0.6	12	3.5	0.6
BMI (kg/m^2)	21	38.0	7.6	21	38.2	7.9	12	38.0	7.9
Circumferences (cm)	15	3.8	0.8	15	3.8	0.8	8	3.6	0.9
MUAC	22	39.2	5.5	22	39.0	5.1	12	38.1	6.0
WC	22	109.2	16.4	22	108.6	16.8	12	107.4	17.5
WC-SDS	15	3.8	0.8	15	3.8	0.8	8	3.6	0.9
Hip C	21	118.4	13.7	22	120.1	14.2	12	116.7	14.6
Thigh C	21	69.3	7.8	21	68.9	6.5	12	66.7	7.4
Calf C	22	43.3	4.3	22	43.5	4.7	12	42.6	4.7
Whole body composition (kg/m^2)									
FMI-3C	21	17.6	5.4	17	18.1	5.2	8	15.8	5.6
FFMI-3C	21	20.5	3.6	17	20.7	4.1	8	19.9	3.6
FMI-4C	16	16.5	4.6	12	17.5	4.6	-		
FFMI-4C	16	18.0	1.9	12	18.9	2.3	-		
Regional body composition by DXA (kg/m^2)									
Trunk-FMI	16	8.1	1.8	15	8.1	2.3	-		
Trunk-FFMI	16	8.7	1.7	15	8.2	0.9	-		
Limbs-FMI	16	8.0	1.9	15	7.9	1.8	-		
Limbs-FFMI	16	7.9	1.3	15	7.7	0.9	-		

Abbreviations: n= number per group; SDS= standard deviation score, MUAC= mid upper arm circumference, WC= waist circumference, C= circumference, FMI= fat-mass index, FFMI= fat-free mass index, DXA= dual x-ray absorptiometry

Figure 6-6 Flowchart of the Metformin trial

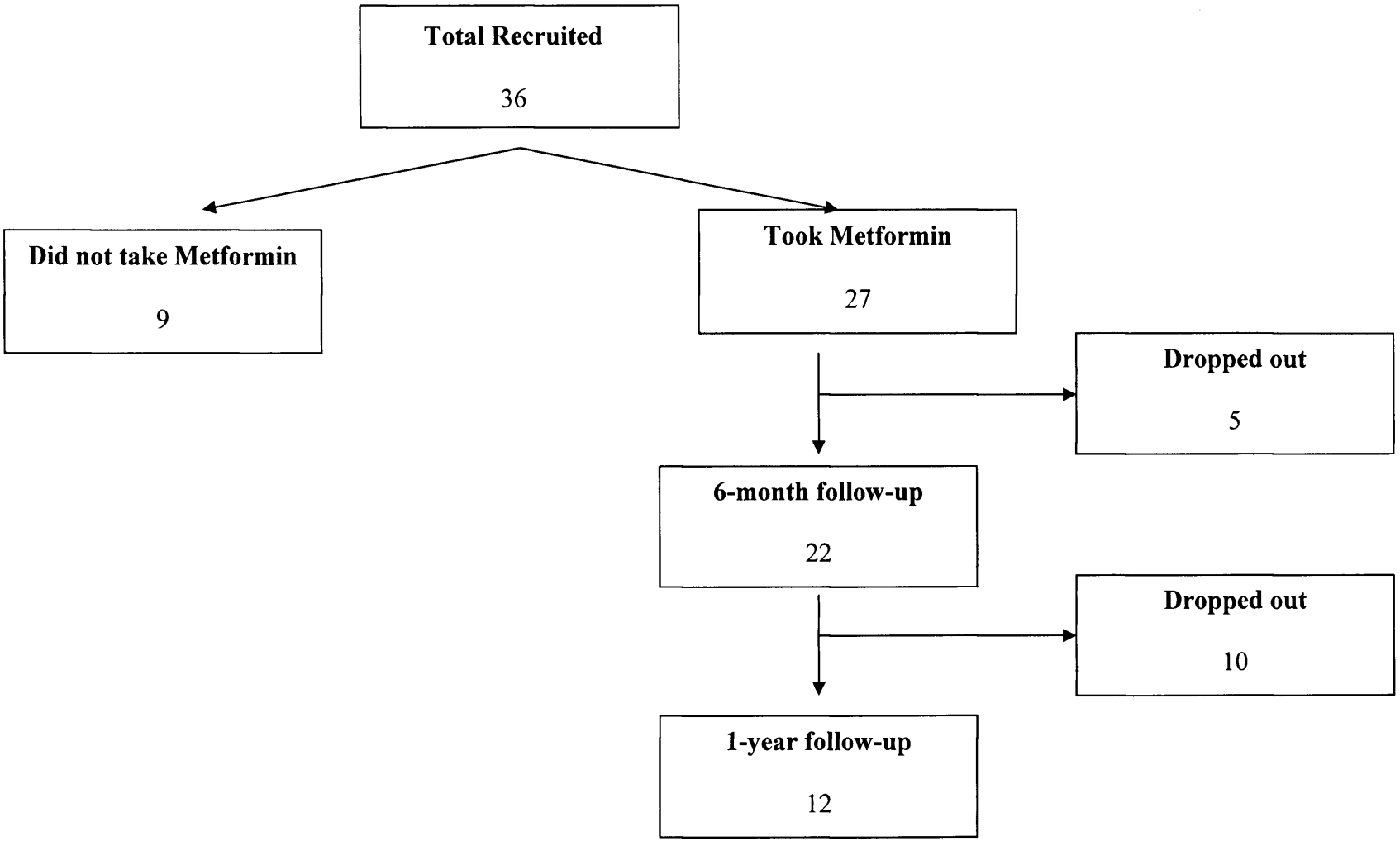


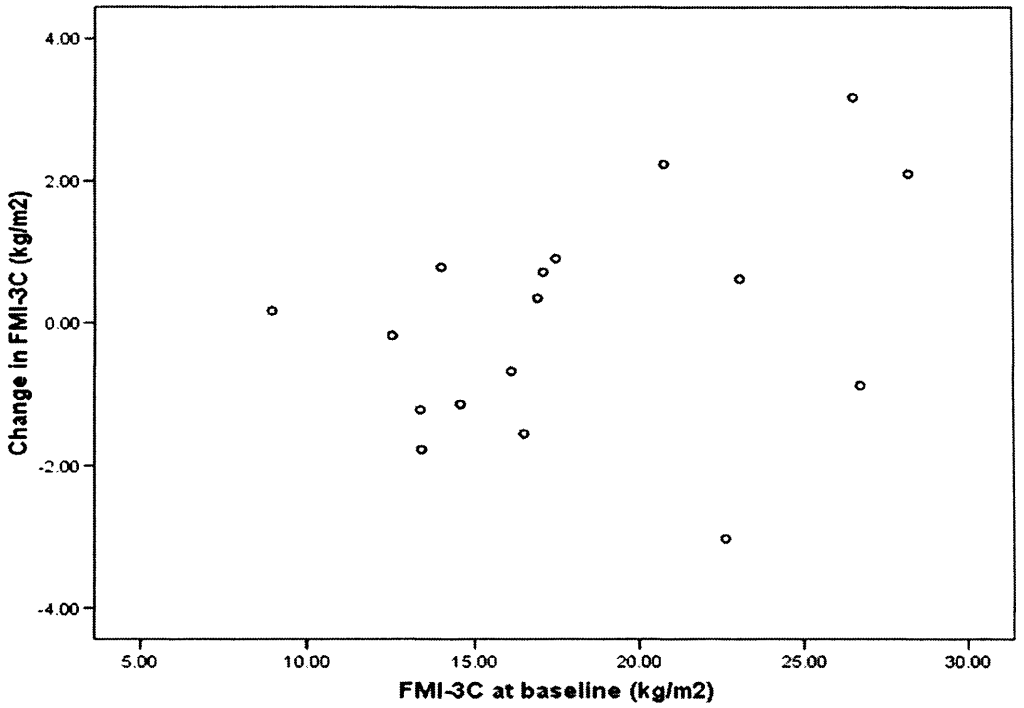
Table 6-10 Differences in body composition between baseline and 6-month follow-up, and between baseline and 1 year follow-up

	Δ 6 month follow-up - baseline				**Δ 1 year follow-up - baseline**			
	n	***mean***	***SD***	***p-value***	***n***	***mean***	***SD***	***p-value***
WT-SDS	21	-0.03	0.3	0.7	12	-0.07	0.4	0.6
HT-SDS	22	-0.03	0.4	0.7	12	-0.2	0.3	**0.03**
BMI SDS	21	-0.07	0.2	0.1	12	-0.1	0.3	0.2
BMI (kg/m^2)	21	0.07	1.8	0.9	12	-0.2	2.4	0.8
Circumferences (cm)								
MUAC	22	-0.2	1.9	0.6	12	-0.03	2.0	1.0
WC	22	-0.6	5.9	0.6	12	-0.1	4.2	0.9
WC-SDS	15	-0.07	0.3	0.4	8	-0.02	0.2	0.8
Hip C	21	1.2	4.6	0.3	12	0.1	4.9	0.9
Thigh C	21	-0.4	4.0	0.6	12	-1.3	4.3	0.3
Calf C	22	0.2	1.4	0.6	12	-0.09	1.6	0.2
Whole body composition (kg/m^2)								
FMI-3C	17	-0.04	1.6	0.9	8	3.5	5.2	0.1
FFMI-3C	17	0.46	1.1	0.1	8	-1.3	7.5	0.6
FMI-4C	12	1.3	2.0	**0.04**				
FFMI-4C	12	0.51	2.3	0.4				
Regional body composition by DXA (kg/m^2)								
Trunk-FMI	15	0.2	1.0	0.6				
Trunk-FFMI	15	-0.2	0.7	0.3				
Limbs-FMI	15	-0.01	0.8	1.0				
Limbs-FFMI	15	0.03	0.3	0.7				

Δ: differences obtained by paired sample t-test.

Difference at 6 months = 6 month follow-up visit – baseline visit, and difference at 1 year = 1 year follow-up visit – baseline visit

Abbreviations: n= number per group; SD= standard deviation; SDS= SD score; WT= weight; HT= height; BMI= body mass index; MUAC= mid upper arm circumference, WC= waist circumference, C= circumference, FMI= fat-mass index, FFMI= fat-free mass index, DXA= dual X-ray absorptiometry



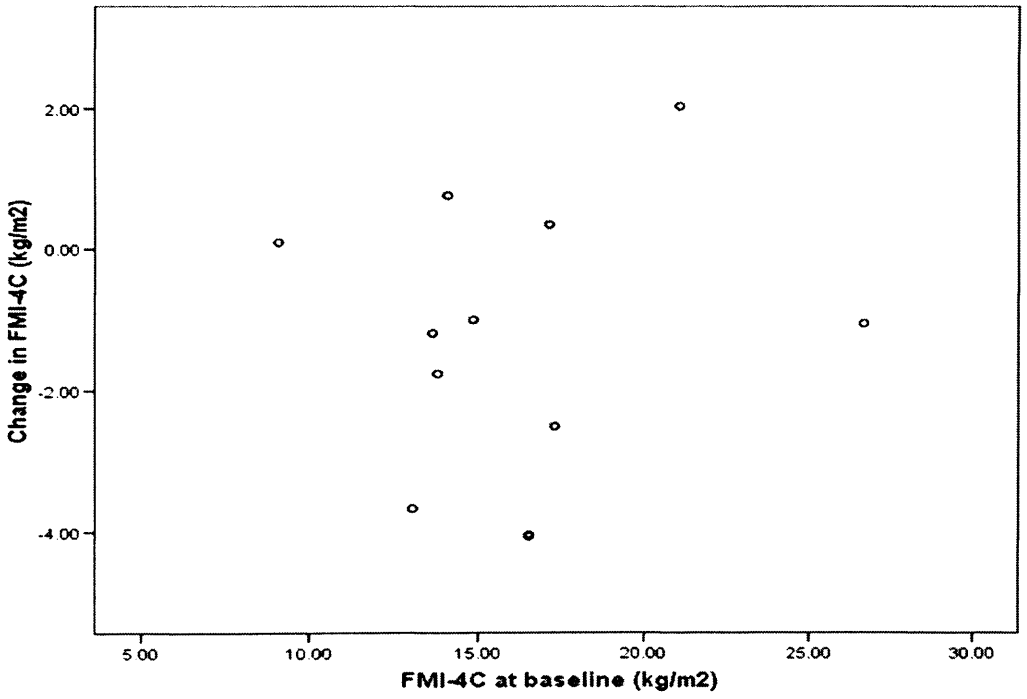
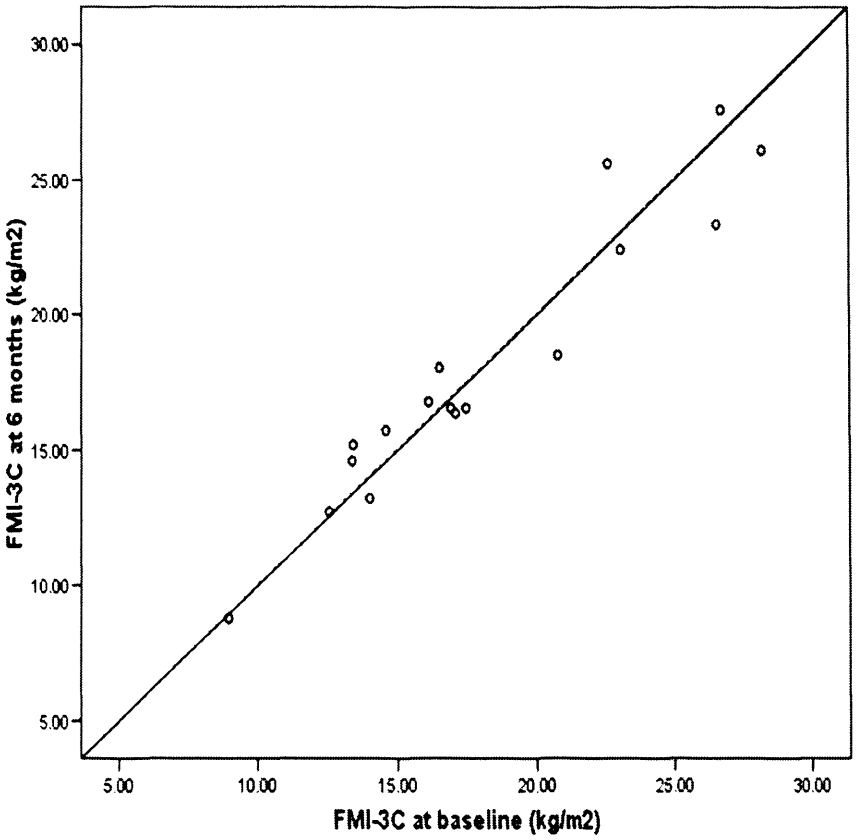


Figure 6-7 Relationship between FMI at baseline and change in FMI over 6 months by the 3C model (top) and 4C model (bottom)
FMI-3C: r = 0.37; p= 0.2
FMI-4C: r = 0.12; p = 0.7



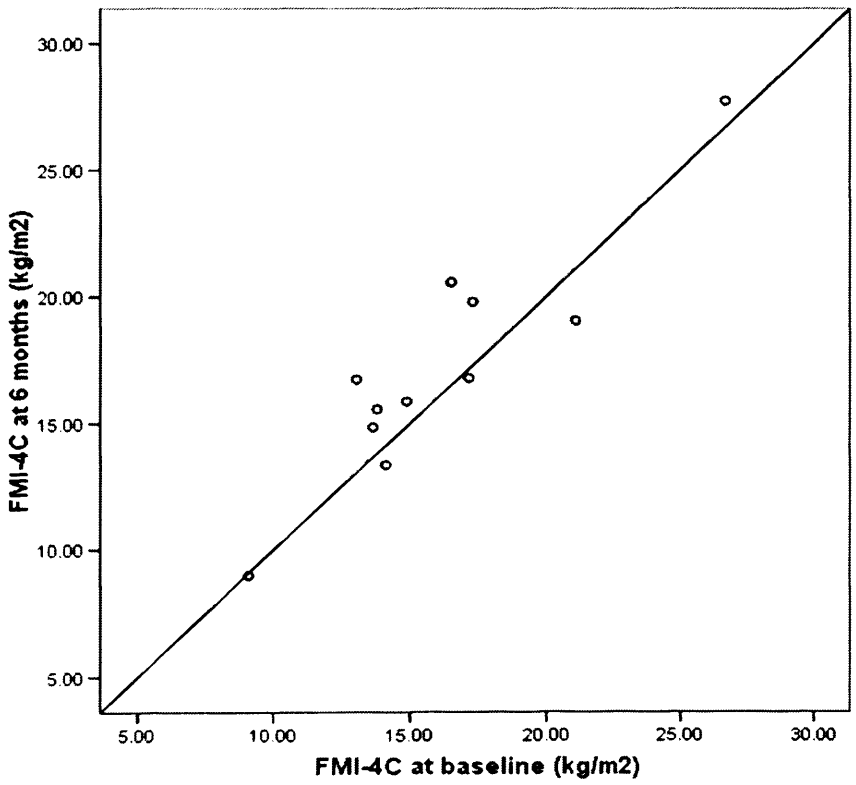


Figure 6-8 Relationship between FMI at baseline and FMI at 6 months by the 3C (top) and 4C (bottom) models. FMI-3C: r=0.96; p<0.001; FMI-4C: r=0.91; p<0.001

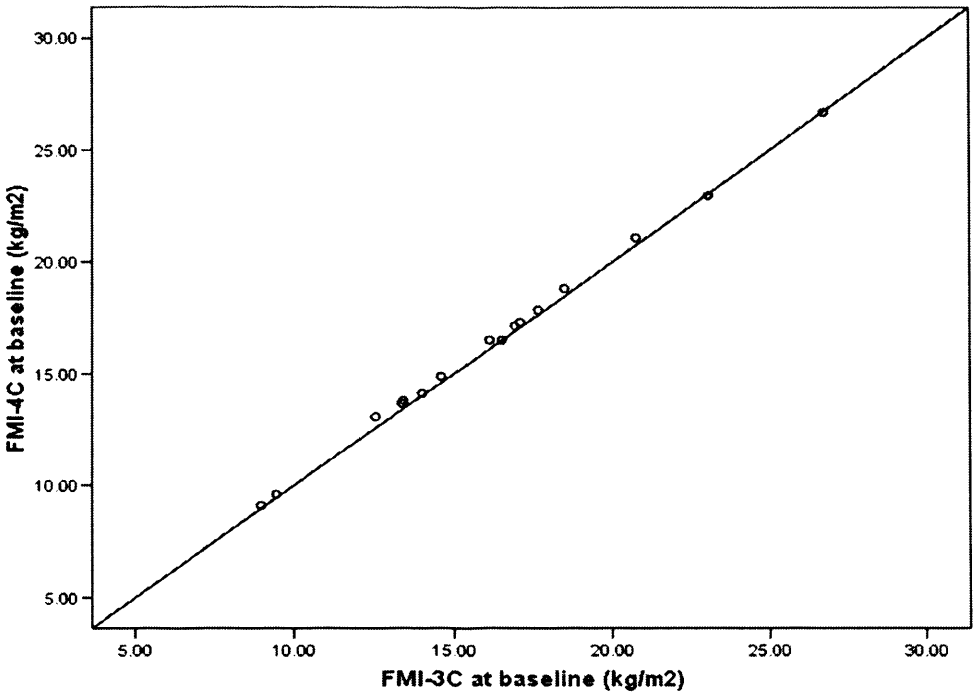


Figure 6-9 Relationship between baseline measurements of FMI calculated by the 3C model and FMI calculated by the 4C model $r = 0.99$; $p < 0.001$

Table 6-9 illustrates the characteristics of the Metformin trial at baseline, at 6-months and at 1-year. DXA measurements were only performed at baseline and at six month follow-up; therefore the one year follow-ups did not have any 4C data or regional body composition measurements.

Paired sample t-tests were used to test for body composition differences by comparing measurements at baseline and six months, or by comparing measurements at baseline and one year. The differences were calculated by subtracting data obtained from six months and baseline, or by subtracting data from one year follow-ups and baseline (refer to Table 6-10 for details).

6.3.9.2 6-month follow-up

After six months of taking Metformin, there was a 0.03 decrease in both weight and height SDS, and a 0.07 decrease in BMI SDS; however these decreases were not significant. In terms of body circumferences, following intervention the children lost an average of 0.2 cm off their arm, 0.6 cm off their waist, and 0.4 cm off their thigh, but gained an average of 1.2 cm on their hips and 0.2 cm on their calves. None of these gains or losses achieved any statistical significance. Only 17 and 12 children had baseline and follow-up whole body composition measurements for the 3C and 4C models respectively. Children lost an average of 0.04 kg/m^2 FMI and gained 0.5 kg/m^2 FFMI calculated by the 3C model; these were not significant. However, FMI calculated using the 4C model showed that children significantly gained 1.3 kg/m^2 ($p = 0.04$).

Because there were differences in outcome between the 3C and 4C models, I then did a scatter plot of FMI at baseline versus FMI at 6 months for both the 3C and 4C models (refer to Figure 6-8). The graph for the 3C model shows that most of the points lie close to the line of identity, indicating that there is no systematic trend to gain or loss of fat after six months. However, the graph for the 4C model shows that the majority of the points lie on top of the line of identity, indicating that obese children gained fat after six months of treatment.

In order to test whether there was a difference in the sample investigated between the 3C and 4C models, a paired sample t-test was used only on the 12 that had data for both the 3C and 4C models at baseline and at six months. Similar to the findings obtained when the entire sample was included, the 4C model showed that subjects significantly increased in fat after treatment ($p = 0.04$) however no significant change was observed when the 3C model was used ($p = 0.5$).

A total of 15 children had regional body composition assessed by DXA. Comparing body composition at six months to that at baseline, children gained 0.2 kg/m^2 fat mass in the trunk area and lost 0.01 kg/m^2 in the limbs area, and gained 0.03 kg/m^2 FFM in the limbs area and lost 0.2 kg/m^2 FFM in the trunks area. None of the regional data comparisons achieved statistical significance.

Because some of the sample included in the above analyses included those who were already taking Metformin before taking part in the study; baseline body composition data before starting treatment was not available. Therefore a further analysis

investigating change in BMI SDS during the first six months of taking Metformin was conducted. Weight and height measurements of the 22 obese subjects was obtained from their out-patient clinic notes at UCH and GOSH. Results reveal that six months of taking Metformin resulted in an average loss of 0.05 ± 0.04 BMI SDS; this difference however was not statistically significant ($p = 0.3$).

6.3.9.3 1 year follow-up

A total of 12 children attended one year follow-up appointments, and of those only 8 had whole body composition measurements analysed. After one year of taking Metformin, children had a reduction of 0.07 and 0.1 weight and BMI SDS respectively; these reductions were not significant. The sample had a significant reduction in height SDS of 0.2 ($p = 0.03$). In addition, the sample lost an average of 0.03 cm off the arm, 0.1 cm off the waist, 1.3 cm off the thigh and 0.09 cm off the calf, whereas they gained 0.1 cm on the hip. None of the changes in circumferences were significant. In terms of whole body composition, assessed using the 3C model, children after one year of taking Metformin had an average increase of 3.5 kg/m^2 FMI and a reduction of 1.3 kg/m^2 FFMI; neither of changes was significant.

6.3.10 Discussion

Very few studies have investigated the effect of Metformin on body composition in a group of obese children and adolescents. This is the first study to measure body composition using a multi-component model approach instead of using the conventional approach, measuring weight, height and BMI.

My study showed that six months of taking Metformin did not significantly change BMI or BMI SDS; BMI changed from 38 kg/m^2 to 38.2 kg/m^2, and BMI SDS decreased by 0.07 SDS.

A pilot study found that obese adolescents who took Metformin for three months lost an average BMI of 3.1 kg/m^2 (Fu *et al.* 2006). A possible reason behind the differences obtained between my study and Fu's study is that the obese children that were part of my trial were much larger than those on Fu's study; mean BMI = 38 kg/m^2 versus BMI = 27.5 kg/m^2 respectively. Therefore, it is possible that those fatter at baseline find it more difficult to lose weight compared to the thinner ones.

Freemark and Bursey (2001) performed a RCT investigating the effect of Metformin on a group of obese adolescents, and after six months of being on the trial, those on the medication lost an average of 0.12 BMI SDS whereas those on placebo gained 0.23 BMI SDS (Freemark and Bursey, 2001). Even though my results were not significant, it could be that this slight loss or maintenance of BMI and BMI SDS is actually a significant outcome. According to Freemark and Bursey's study, those that do not take the medication increased in BMI SDS over time. Hence, the fact that Metformin halted this gain might be viewed as a positive accomplishment.

Taking Metformin for six months and for one year did not significantly improve body composition outcomes; fat and lean did not significantly differ at the end of the trial. Contrary to my findings, Kay and colleagues (2001) found that obese adolescents on Metformin lost an average of 6 kg of fat over a period of 2 months, whilst those that took placebo only lost 2.7 kg (Kay *et al.* 2001). There are several reasons that could explain the differences between these findings. First, the duration of treatment was substantially longer in my study compared to Kay's study; six months-one year, versus two months. Second, Kay's study was an RCT whereas my study was a pilot study; therefore I had no controls to compare to. Third, body composition was assessed using

the multi-component approach in my study, whereas Kay's study used BIA to estimate fat and lean. The latter technique is less accurate in assessing body composition. BIA assumes constant properties of FFM which have been previously demonstrated not to be constant in obese children (refer to Chapter 5). Therefore, the findings obtained from Kay's study should be interpreted with caution. Hence due to the many differences between the trials, comparing results from these studies is not very robust.

In this study, both the 3C and 4C models were used to assess body composition changes in obese children. The 3C model showed that there were no significant changes in body composition after six months of taking Metformin; however the 4C model showed that children significantly increased in fat after six months of treatment. This difference in outcome observed between the two models might be due to three reasons. First the sample size used in the 3C model was larger than that used in the 4C model; 17 versus 12. Second, the difference might be due to the methodology. Third, there might be a bias in the sample investigated, whereby those that gained weight after six months of treatment were studied. Therefore, analysis from the sample that had data from both the 3C and 4C models (i.e. in the 12) were performed, and results show that the difference between models remained; indicating that the 4C model shows a bigger weight gain compared to the 3C model. Change in FMI (by 3C model) in the 17 was -0.04 ± 1.60 kg/m^2 whereas change in FMI (by 3C model) on the 12 was 0.26 ± 1.17 kg/m^2. This indicates that there was a sample bias where those analysed by the 4C model tended to be those gaining more weight.

Data from the RCT of the behavioural program illustrated that controls significantly lost approximately 0.1 BMI SDS in six months. The controls from the traffic light program however are not suitable to use as controls for the Metformin program. Those on the Metformin trial were older and were substantially larger; average age = 14.5 versus 10 years and average BMI SDS = 3.5 versus 3.0.

A previous study showed that girls with higher baseline fat levels tend to gain more fat compared to the leaner ones (Goulding *et al.* 2003). My study however showed no correlation between baseline fat levels and subsequent change in FM over 6 months (refer to Figure 6-7). One possible reason might be that Goulding's sample were much younger than my sample (mean age = 4.5 years versus 15.5 years). Another reason may be that my sample all had very high baseline fat levels, and were all well above the

obesity cut-off level (mean BMI SDS = 3.5) whereas those from Gouding's study included a variety of children including many with lower fat levels.

6.3.11 Study limitations

This was a pilot study investigating how six months and one year of taking Metformin changes body composition. Since there were no controls, I cannot be absolutely confident that any differences in body composition measurements obtained were due to the intervention rather than other factors. Therefore, the next step is to do an RCT investigating the effectiveness of Metformin, and to try to control for other factors such as dietary intake.

Another limitation of the study is that not all subjects were assessed before starting the medication. Therefore baseline measurements included those that had already been on the medication for a year or so. Hence, even though there was no change in BMI SDS during the first 6 moths of taking Metformin, it may be that Metformin did significantly alter body composition during the first few months when it was prescribed, but then the different body components such as fat stabilized rather than continued to decrease.

Chapter 7: Bio-electrical impedance analysis for measuring body composition in obese children and adolescents

7.1 Introduction

There is no simple and accurate tool that can assess childhood body composition in clinics; hence proxy techniques such as BMI are currently being used. However BMI is a poor indicator of body adiposity and the disadvantages with using such a technique have been described in detail previously in chapter 3. Therefore validating a simple technique, such as BIA using the new TANITA machine (BC-418 MA), and producing a specific equation that can be used to predict body composition in obese children and adolescents would be very useful to use in routine clinics not only to assess body composition, but also to look at the effectiveness of the different weight loss strategies that are being implemented.

7.2 Hypothesis

A new BIA machine, TANITA BC-418 MA, can accurately measure body composition in obese children and adolescents compared to a reference method.

This hypothesis can be divided into two parts:

- To validate BIA using the TANITA machine (BC-418 MA) as a method for measuring body composition in obese children and adolescents against the 3C and 4C models

- To assess the success of evaluating absolute body composition and change of body composition over time using the TANITA machine (manufacturer equations versus my prediction equations) compared to the 3C model

7.3 Study design

This is a validation study investigating the accuracy and reliability of a BIA machine in estimating body composition in obese children and adolescents compared to a reference method. The reference method for estimating TBW is D_2O, and for estimating FM and FFM is the 3C or 4C model.

7.4 Recruitment

Obese children and adolescents were recruited from weight management clinics at GOSH and UCH in London, the LEAF clinic in Chichester, and from an ongoing body composition research project measuring healthy children and adolescents at ICH/GOSH.

7.5 Inclusion and exclusion criteria

Obese children and adolescents with BMI > 95th percentile; equivalent to BMI-SDS > 1.64 defined by the 1990 UK reference cut-offs (Cole *et al.* 1995) were eligible to take part in the study. It was previously described that different ethnic groups vary in their body composition (Deurenberg *et al.* 1998) therefore only those from White ethnic backgrounds were included, and children from other ethnic backgrounds were excluded from this part of the study. In addition, this study only included obese children and adolescents that were not on any pharmacological treatment; hence those on Metformin for example were not included.

For the first part of the hypothesis, only baseline measurements of body composition (or one of the measurements if the first measurement was not successful) were used for participants who were assessed more than once. Those with successful measurements from both the 3C and 4C models (FFM), D_20 (TBW) and the TANITA machine (R) were included in the analyses; whereas participants who had either one of the measurements missing were excluded from the study.

For the second part of the hypothesis, eligible participants were required to have two complete follow-up body composition measurements from the D_20, 3C model and TANITA machine. Participants did not have a DXA scan on their third visit, hence only the 3C model was used to estimate their FM and FFM. In addition, subjects used for part one analyses were not included in part two analyses to make sure that the two analyses (validation versus evaluation) were independent.

7.6 Sample size

It was difficult to decide on the appropriate sample size for the validation study. This is because there is not enough information on the relationship between impedance (HT^2/R) and TBW or FFM. We also do not know what the standard error of the estimate (SEE) for TBW or FFM in individuals: which is the level of predictive inaccuracy; and this varies according to the population. Therefore we could not predict the appropriate number of subjects required for the study. Most previous validation studies have used approximately 30 to 50 subjects, i.e. 15 to 25 subjects from each gender across a wide age range and with very few subjects within the obese population (Lazzer *et al.* 2003; Andreoli *et al.* 2002; Bell *et al.* 1998). However, such sample sizes are considered to be relatively small because, as mentioned before, body composition varies substantially between individuals even in obesity, and so we need to ensure that the sample size is large enough to include a wide range of age and body composition in each gender. Hence the aim was to recruit a total of 100 subjects; 50 males and 50 females, which should be sufficient to incorporate a wide range of body composition in obese children and adolescents within the age range measured.

7.7 Methods

TBW was measured using D_2O, and the 3C and 4C models were used to estimate FM and FFM by combining measurements from different methodologies (BODPOD and DXA). The TANITA machine (BC-418 MA model) was used to obtain R (details of these techniques and measurements can be found in chapter 4).

The main principle of the BIA method is that the opposition to electrical flow of a geometrical conductor (in this case the human body) is related to its length (or height) and inversely related to its cross-sectional area (Schoeller, 2000; Kushner, 1992). Therefore, it is assumed that the body is a conductor of uniform length and cross sectional area. The equations representing this are described in chapter 3.

7.8 Statistical analysis

All statistical analyses were performed using SPSS software.

Paired sample t-tests were used to compare measured (by D_2O, 3C and 4C models) versus predicted (from $TANITA_{manufacturer}$) differences in body composition.

Linear regression analyses were used to investigate the relationship between HT^2/R (from TANITA TBF-418 MA) and TBW (from D_2O) or FFM (from 3C and 4C models). The independent variable was assigned as HT^2/R and the dependent variable was assigned as TBW or FFM. Prediction equations for estimating TBW and FFM from HT^2/R were then produced for my obese sample.

Independent sample t-tests were used to investigate gender differences in age and other body composition parameters; gender was assigned as an independent variable.

Confounding variables such as pubertal status and gender were tested by including them in the regression analysis. The regressions were conducted in a step-wise manner, using the independent variables of sex (dummy code: male = 1 and female = 2), pubertal stage and pubertal hair development, and HT^2/R; the dependant variable was TBW or FFM.

Paired sample t-tests were used to compare predicted longitudinal change in TBW, FM or FFM obtained from the TANITA (manufacturer and prediction equations) versus actual change in TBW (from D_2O), or actual change in FM and FFM (from the 3C model).

Bland and Altman analyses were used to plot differences between the methods (TANITA-equation or manufacturer- versus D_2O, 3C or 4C) against their mean to investigate the relationship between the measurement error and true value (Bland and Altman, 1986). Agreement between methods can be described by calculating bias (difference between measurements) and standard deviation of the difference (SD). Limits of agreement between measurements would be ± 2 SD from the mean. The standard error (SE) was also used to report how precise estimates of body composition from TANITA versus multi-component model were. Correlations between magnitude of the bias and mean of the bias were used to report whether the bias changes if the child get smaller or bigger.

7.9 Results

7.9.1 Hypothesis 1

A total of 164 obese children and adolescents were measured. However, 86 had to be excluded because they did not fulfil the inclusion criteria described above. Table 7-1 shows the sample size excluded and the reason why they had to be excluded from this part of the study.

Table 7-1 Sample size and reason why subjects were excluded

Number excluded	Reason excluded
58	non-White
13	no impedance measurements
13	unknown ethnic background
2	H_{ffm} outside acceptable range; defined as 68 - 84%

The final sample size included in the analyses consisted of a total of 78 obese children and adolescents; 30 males and 48 females age ranging between 4.6 and 21.7 years. Table 7-2 provides a breakdown of the number of subjects that took part in the study and where they were recruited from.

Table 7-2 A breakdown of where the final sample was recruited from

Number included	Recruitment
42	Reference study
26	"Traffic Light Program" at GOSH
4	LEAF clinic in Chichester
3	UCH weight-management clinic
3	GOSH weight-management clinic

Table 7-3 The range, mean and standard deviation of some of the physical characteristics of the obese subjects measured

	Males (n = 30)				Females (n = 48)			
	min	***max***	***mean***	***SD***	***min***	***max***	***mean***	***SD***
Age (years)	5.0	20.0	12.0	3.4	4.6	21.7	11.3	3.5
Weight (kg)	28.2	110.5	65.1	20.6	21.9	90.8	60.1	16.3
HT (cm)	112.9	182.0	152.4	16.7	108.9	169.0	148.0	13.7
BMI (kg/m^2)	21.3	40.6	27.4	4.8	18.4	38.9	26.8	4.2
WT SDS	1.1	4.8	2.4	0.9	1.2	3.7	2.4	0.7
HT SDS	-2.2	3.1	0.6	1.2	-0.8	2.7	0.8	0.8
BMI SDS	1.7	4.7	2.7	0.8	1.6	3.9	2.5	0.7
TBW (D_2O)*	14.5	49.7	31.2	10.4	12.2	39.5	26.6	6.7
HT^2/R *	20.3	60.7	39.1	12.4	16.9	48.3	33.3	7.6
FM (4C)	9.4	58.6	24.8	10.7	5.76	49.5	25.2	9.0
FFM (4C)	18.8	68.6	40.3	13.7	16.1	52.3	35.0	8.9
% FAT (4C)	19.0	53.0	37.9	7.99	26.3	55.4	41.1	6.2
H_{ffm} (4C)	71.5	83.9	77.1	2.48	73.1	81.3	76.3	1.7
D_{ffm} (4C)*	1.05	1.11	1.08	0.01	1.07	1.11	1.09	0.01

Abbreviations: n= number per group; WT= weight; HT= height; SD= standard deviation; SDS= SD score; TBW= total body water; D_2O= deuterium oxide; R= resistance; FM= fat mass; FFM= fat-free mass; H_{ffm}= hydration of FFM; D_{ffm}= density of FFM

* Significant difference between males and females at $p < 0.05$

Table 7-3 shows a description of the characteristics of the obese sample included, separated by sex. The average age of the sample measured was 12.0 and 11.3 years for males and females respectively, with an average difference of 0.7 years. This difference however was not statistically significant ($p = 0.4$). The mean BMI SDS was 2.7 and 2.5 for boys and girls respectively. There were no significant gender differences in WT SDS, HT SDS, BMI SDS, FM (4C), FFM (4C), % fat (4C) and H_{ffm} (4C). However, on average boys had significantly greater TBW (measured by D_20) compared to girls (mean difference = 4.6, SE = 2.1 litres; $p = 0.04$), and boys had significantly lower D_{ffm} compared to girls (mean difference = 0.006, SE = 0.002 litres; $p = 0.01$).

Table 7-4 illustrates differences in body composition values between those obtained from TANITA (manufacturer) versus those that were measured (by D_20, 3C and 4C models). The results reveal that in obese children and adolescents, $TANITA_{manufacturer}$ overestimates TBW by 0.4 and 0.8 litres for males and females respectively; only the latter achieving statistical significance. $TANITA_{manufacturer}$ was also found to significantly underestimate FM by approximately 4 kg and to overestimate FFM by approximately 2.5 kg in both sexes.

Correlations between the difference (calculated as TANITA - 4C) and mean (calculated as average of TANITA + 4C) for FM and FFM were then performed to establish whether the error in estimating body composition in obese children and adolescents using $TANITA_{manufacturer}$ compared to the 4C model varied across the range of body composition (refer to Figure 7-1). The results reveal that there was a borderline significant positive correlation between the amount and magnitude of the error in estimating FFM from $TANITA_{manufacturer}$ compared to the 4C model ($r = 0.22$; $p = 0.06$). There was also a significant negative correlation between the amount and magnitude of the error in estimating FM ($r = -0.26$; $p = 0.03$).

Compared to the 4C model, the TANITA system therefore systematically overestimates FFM with slightly higher overestimation in children with higher FFM, and underestimates FM with greater underestimation in those with the lowest FM levels. Because in-built TANITA equations ($TANITA_{manufacturer}$) were found to be inaccurate at predicting body composition in obese children and adolescents, the next step was to predict body composition from impedance (the only direct outcome measured by

TANITA using data from the multi-component model to develop equations for predicting body composition in obese children and adolescents.

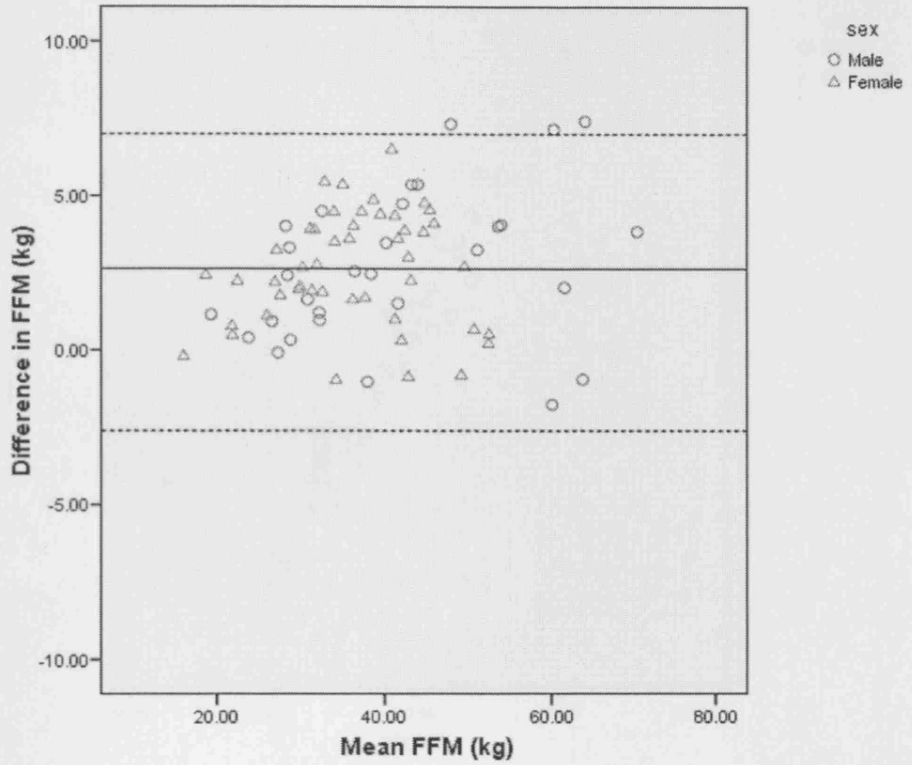
Table 7-4: Differences in body composition in obese children: measurements versus prediction from $TANITA_{manufacturer}$

Difference	**Males**				**Females**			
	n	D	SD	p-value	n	D	SD	p-value
TBW	30	0.4	2.2	0.4	48	0.8	1.2	<0.001
FM (3C)	30	-3.5	2.4	<0.001	47	-3.6	1.8	<0.001
FM (4C)	30	-4.0	2.4	<0.001	47	-4.1	1.9	<0.001
FFM (3C)	30	2.2	2.4	<0.001	47	2.1	1.8	<0.001
FFM (4C)	30	2.7	2.4	<0.001	47	2.6	1.8	<0.001

D = $TANITA_{manufacturer}$ - actual measured value

Abbreviations: n= number per group; D= difference; SD= standard deviation; TBW= total body water; FM= fat mass; FFM= fat-free mass; 3C= 3 component model; 4C= 4 component model

(a) FFM



(b) FM

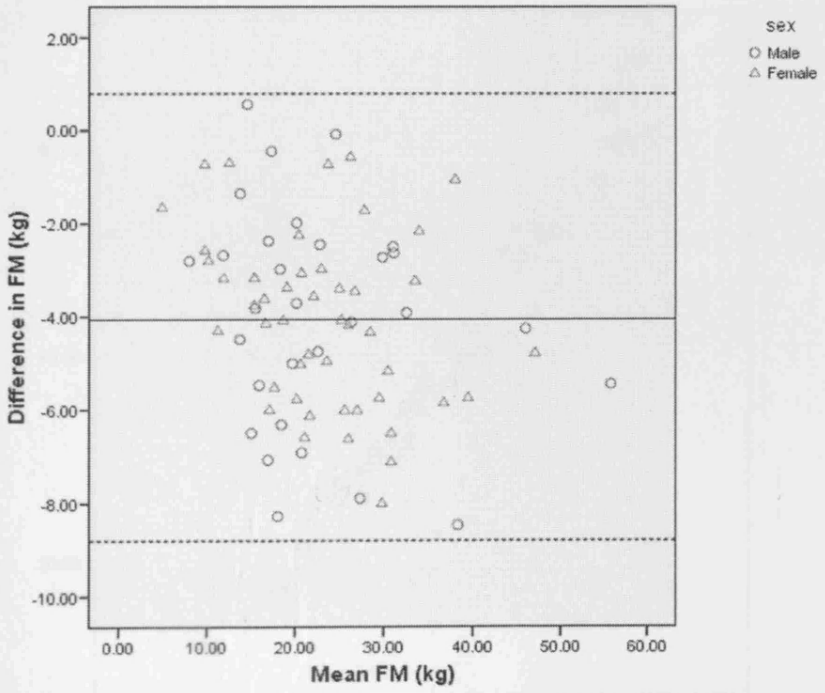


Figure 7-1: Bland-Altman plots showing the agreement between the differences ($TANITA_{manufacturer}$ values – 4C values) and mean ($TANITA_{manufacturer}$ + 4C) of (a) FFM ($r = 0.22$; $p = 0.06$), and (b) FM ($r = -0.26$; $p = 0.3$)

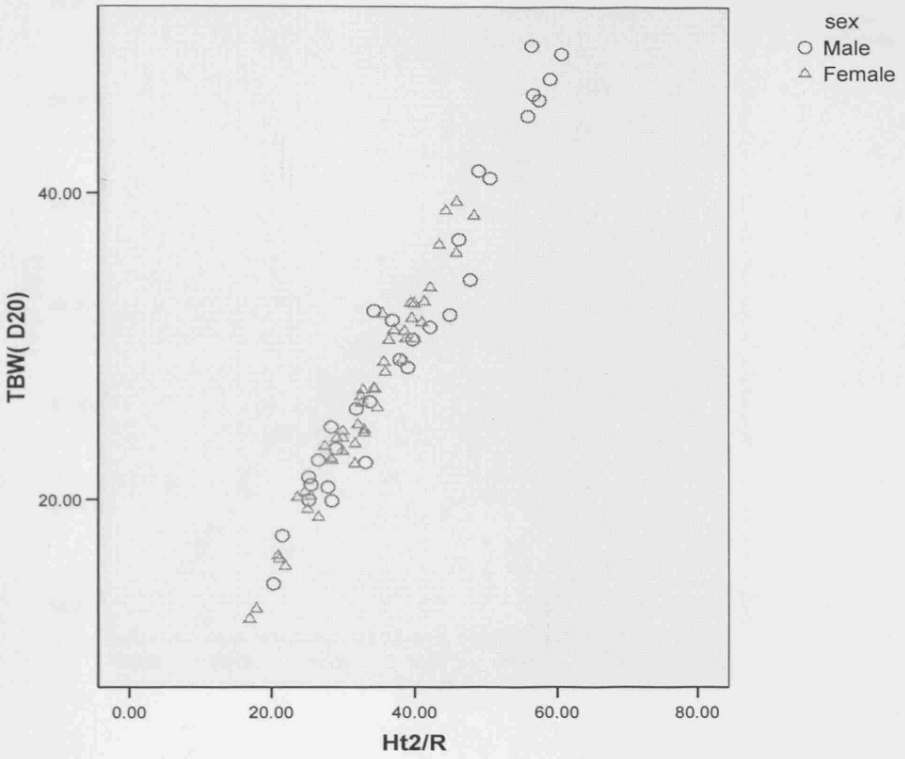


Figure 7-2 Relationship between HT^2/R and TBW by D_20 in obese males and females ($r = 0.98$; $p<0.001$)

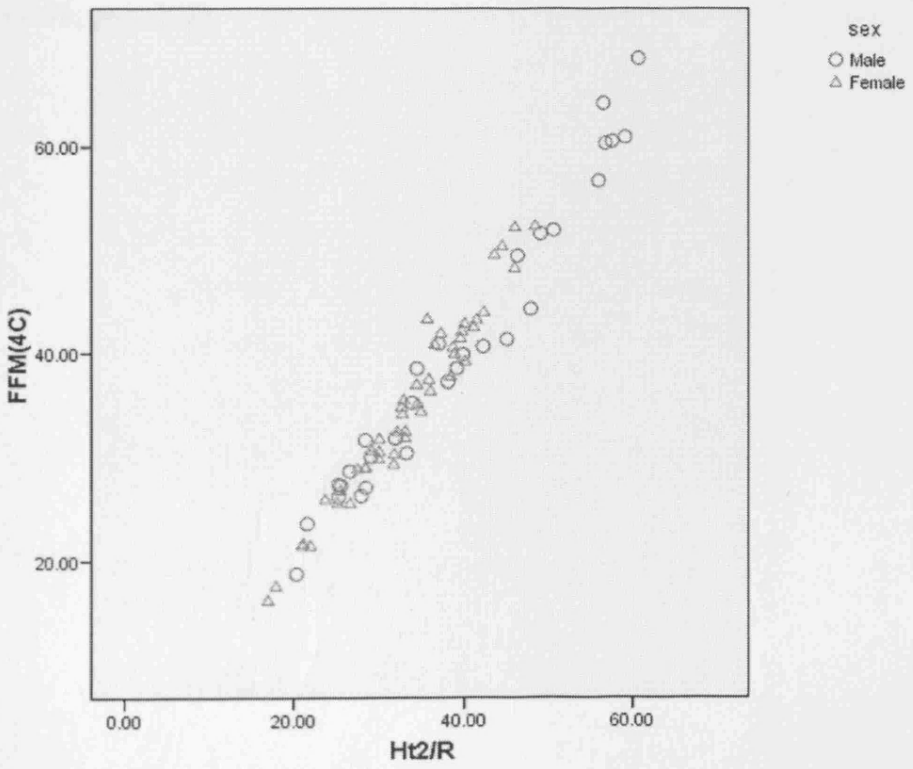


Figure 7-3 Relationship between HT^2/R and FFM by 4C model in obese males and females ($r = 0.98$; $p<0.001$)

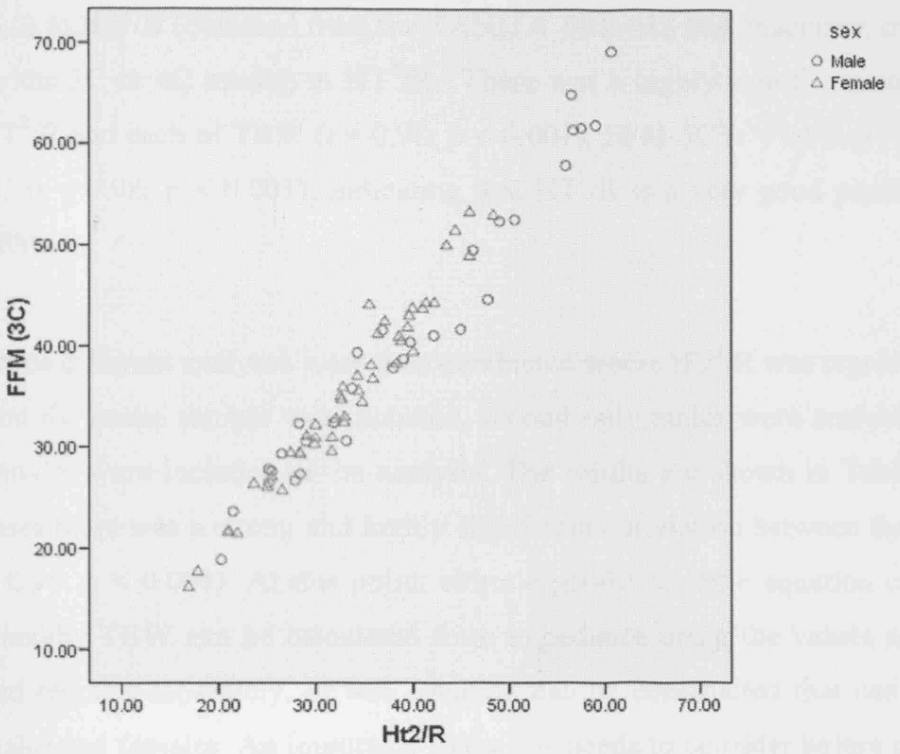


Figure 7-4 Relationship between HT^2/R and FFM by 3C in obese males and females ($r = 0.98$; $p<0.001$)

Figure 7-2, Figure 7-3 and Figure 7-4 show the scatter plots relating TBW (measured by D_20) to HT^2/R (obtained from the TANITA TBF-418 MA machine), or FFM (calculated by the 3C or 4C model) to HT^2/R. There was a highly significant correlation between HT^2/R and each of TBW ($r = 0.98$; $p < 0.001$), FFM-3C ($r = 0.98$; $p < 0.001$) and FFM-4C ($r = 0.98$; $p < 0.001$), indicating that HT^2/R is a very good predictor of TBW and FFM.

Three different analyses were then conducted where HT^2/R was regressed against TBW: first the entire sample was included, second only males were analysed, and third only females were included in the analysis. The results are shown in Table 7-5. In all three cases there was a strong and highly significant correlation between the two variables ($r^2 = 0.96$; $p < 0.001$). At this point, either a gender specific equation can be constructed whereby TBW can be calculated from impedance using the values obtained for males and females separately, or one equation can be constructed that can be used for both males and females. An important factor one needs to consider before deciding on which equation to use is the SEE i.e. the scatter of the points on the graph around the regression line. When the entire sample is included in the analysis the SEE is 1.72 litres whereas when males are only used the SEE is 2.22 litres; hence the equation with the entire sample included would be more reliable because the SEE is smaller in the former analysis. On the other hand the female SEE is 1.35 litres which is slightly lower than the SEE when the entire sample is included. This means that when calculating TBW in a female sample, using a female equation might be more reliable. This means that girls have less scatter on the graph whereas boys are grouped less tightly and are more scattered. The greater SEE found in males compared to females may be due to their smaller sample size ($n = 30$ for males versus $n = 48$ for females).

A further analysis was then performed where gender was incorporated into the analysis along with HT^2/R as the independent variable (refer to Table 7-6). A difference of 0.24 litres extra TBW was found for being a male. This difference was very small and did not achieve significance ($p = 0.6$).

Moreover, pubertal status, including stage of development and hair development, were also incorporated in the regression analysis to establish whether pubertal stage has an effect on the association between HT2/R and TBW (refer to Table 7-6).

Pubertal stage development made a significant contribution to the model (mean difference = 0.69 litres; $p = 0.002$). However, when both pubertal stage and hair development were incorporated in the model, the association was no longer significant ($p = 0.09$ and $p = 0.3$ respectively). The average difference of either including or not incorporating puberty into the analysis is approximately 0.7 litres of TBW, making a calculation error of approximately 0.95 kg of FFM.

A similar analysis was then performed where HT2/R was regressed against FFM (calculated by both the 3C and the 4C model) when the entire sample was included, when only males were included and when only females were included in the analysis (refer to Table 7-7 and Table 7-9). Similar to the results obtained when TBW was used, the SEE was lower when only females were included versus the whole sample. However an equation with the entire sample included was preferred because differences between SEE were not large.

Again, a further analysis was performed including sex, and pubertal stage in the equation to establish whether if they have any effects on the association between HT^2/R and FFM (calculated by the 3C and 4C models) (refer to Table 7-8 and Table 7-10). A difference of 0.78 kg or 0.85 kg of FFM calculated by the 4C and 3C respectively was found for being a male; this did not achieve statistical significance. Even though pubertal stage did have a significant effect on the association between HT^2/R and FFM when incorporated into the model ($p < 0.001$), it only improved SEE of FFM by 0.2 kg (3C) and 0.3 kg (4C).

As mentioned earlier, pubertal status was self-assessed by selecting pictures that closely resembled the subjects' appearance at the time of the measurement. Even though pubertal development showed a significant effect in the analyses, the method of collecting the data may be difficult and problematic, and the final error for calculating body composition if it were not included is small and not clinically significant. Therefore, pubertal status was not taken into account when constructing the final regression equations for calculating TBW and FFM from HT^2/R.

Table 7-5 A regression analysis of HT^2/R against TBW (by D_2O) in the entire sample versus males only versus females only

Sample	R^2	SEE	Y-intercept (SE)	HT^2/R coefficient (SE)	t-value (HT^2/R)	p-value
1. All included	0.96	1.72	-1.302 (0.722)	0.834 (0.026)	42.6	< 0.001
2. Males only	0.96	2.22	-0.976 (1.361)	0.822 (0.033)	24.7	< 0.001
3. Females only	0.96	1.35	-2.158 (0.889)	0.862 (0.026)	33.1	< 0.001

Table 7-6 Step-wise regression analysis of HT^2/R against TBW (by D_20) incorporating sex, stage and pubertal development in the analysis

Regression model	R^2	SEE	Y-intercept (SE)	Coefficient (SE)	t-value	p-value
HT^2/R	0.96	1.72	-1.302 (0.722)	0.834 (0.02)	42.6	<0.001
HT^2/R	0.96	1.73	-1.798 (1.142)	0.837 (0.02)	40.9	<0.001
Sex				0.236 (0.420)	0.6	0.6
HT^2/R	0.96	1.66	-0.996 (1.276)	0.777 (0.03)	26.1	<0.001
Sex				-0.044 (0.456)	0.1	0.9
stage development				0.690 (0.219)	3.2	0.002
HT^2/R	0.96	1.70	-0.508 (1.36)	0.759 (0.034)	22.2	<0.001
Sex				-0.063 (0.46)	-0.1	0.9
stage development				0.490 (0.284)	1.7	0.09
hair development				0.335 (0.301)	1.1	0.3

Table 7-7 A regression analysis of HT^2/R against FFM (by 4C) in the entire sample versus males only versus females only

Sample	R^2	SEE	Y-intercept (SE)	HT^2/R coefficient (SE)	t-value (HT^2/R)	p-value
1. All included	0.96	2.23	-2.032 (0.946)	1.096 (0.026)	42.6	<0.001
2. Males only	0.96	2.22	-0.976 (1.361)	0.822 (0.033)	24.7	<0.001
3. Females only	0.96	1.35	-2.158 (0.889)	0.862 (0.026)	33.1	<0.001

Table 7-8 Step-wise regression analysis of HT^2/R against FFM (by 4C) incorporating sex, stage and pubertal development in the analysis

Regression model	R^2	SEE	Y-intercept (SE)	coefficient (SE)	t-value	p-value
HT^2/R	0.96	2.23	-2.032 (0.946)	1.096 (0.026)	42.9	<0.001
HT^2/R	0.96	2.22	-3.649 (1.464)	1.106 (0.026)	42.0	<0.001
Sex				0.776 (0.539)	1.4	0.2
HT^2/R	0.97	1.99	-1.923 (1.544)	1.001 (0.036)	27.8	<0.001
Sex				0.047 (0.554)	0.08	0.9
stage development				1.197 (0.267)	4.5	<0.001
HT^2/R	0.97	1.96	-0.827 (1.605)	0.961 (0.04)	23.9	<0.001
Sex				0.006 (0.544)	0.01	1.0
stage development				0.739 (0.338)	2.2	0.03
hair development				0.76 (0.356)	2.1	0.04

Table 7-9 A regression analysis of HT^2/R against FFM (by 3C) in the entire sample versus males only versus females only

Case	R^2	SEE	Y-intercept (SE)	HT^2/R coefficient (SE)	t-value (HT^2/R)	p-value
1. All included	0.96	2.31	-2.211 (0.980)	1.115 (0.260)	26.7	<0.001
2. Males only	0.96	2.75	-1.929 (1.682)	1.095 (0.041)	26.7	<0.001
3. Females only	0.96	1.92	-4.050 (1.292)	1.179 (0.038)	31.3	<0.001

Table 7-10 Step-wise regression analysis of HT^2/R against FFM (by 3C) incorporating sex, stage and pubertal development in the analysis

Regression model	R^2	SEE	Y-intercept (SE)	coefficient (SE)	t-value	p-value
HT^2/R	0.96	2.31	-2.211 (0.980)	1.115 (0.260)	26.7	<0.001
HT^2/R	0.96	2.3	-3.980 (1.514)	1.126 (0.027)	41.3	<0.001
Sex				0.848 (0.557)	1.5	0.1
HT^2/R	0.97	2.02	-2.110 (1.562)	1.011 (0.036)	27.8	<0.001
Sex				0.069 (0.561)	0.1	0.9
stage development				1.311 (0.270)	4.9	<0.001
HT^2/R	0.97	1.98	-0.959 (1.620)	0.969 (0.041)	23.8	<0.001
Sex				0.028 (0.549)	0.05	1.0
stage development				0.833 (0.341)	2.4	0.02
hair development				0.794 (0.341)	2.2	0.03

Therefore, because there were no significant sex differences and the SEE differences between the genders was small, one equation can be constructed that can be used for White obese individuals within the age group measured. Using the slope and y-intercept obtained from the regression analyses shown in the above tables, the equations for calculating TBW and FFM (from 3C and 4C models) from whole body impedance measurement (R) are:

TBW = -1.302 + 0.834 (HT^2/R) **Equation 7-1**

FFM (4C) = -2.032 + 1.096 (HT^2/R) **Equation 7-2**

FFM (3C) = -2.211 + 1.115 (HT^2/R) **Equation 7-3**

FM can then be calculated as: WT – FFM **Equation 7-4**

In a sub-analysis where different ethnic groups, largely Asian (n = 21) and Black (n = 17), were included in the regression equation, ethnicity was found to significantly alter the prediction of TBW ($p < 0.001$). This confirms that people from different ethnic groups differ in the relationship between impedance and body composition, and should therefore be analysed separately. The sample size for other ethnic groups was not large enough to derive ethnic specific equations for estimating body composition. Also, because my sample was largely from a White background, I restricted my longitudinal analyses to White children and adolescents.

7.9.2 Hypothesis 2

The second part of the study is a longitudinal investigation of the accuracy of the TANITA machine in assessing change in body composition in obese children over six months. The reliability of the equation in estimating body composition in this group of obese children was also tested.

A total of 47 obese children and adolescents had longitudinal body composition measurements; however 29 had to be excluded from the analysis because they did not fulfil the inclusion criteria. Table 7-11 shows a list of subjects excluded from this part of the analysis and the reason for excluding them. Therefore, the final sample included a total of 18 subjects; 5 boys and 13 girls who had complete measurements of TANITA and TBW (by D_20) for both visits (2 and 3). One girl did not have a body volume measurement (by BODPOD) and therefore did not have any 3C data; her TBW data however was used in the analysis.

TBW and FFM (3C) were calculated from TANITA using the equations constructed from the above cross-sectional analysis:

$TBW = -1.302 + 0.834 (HT^2/R)$ **Equation 7-5**

$FFM\ (3C) = -2.211 + 1.115 (HT^2/R)$ **Equation 7-6**

FM was then calculated by subtracting FFM from total body weight.

As mentioned earlier, FFM from the 4C model was not calculated for this sample because subjects did not have a DXA scan during their third visit. Therefore, 4C data were not available and only the 3C equation was used to estimate FFM.

Table 7-12 shows the characteristic of the final sample included. Visit 2 obese children were between 8.9 and 13.4 years, and had an average BMI SDS of 2.8. Approximately six months after being either treated or on the waiting list of the traffic-light programme, the children's average BMI SDS increased by approximately 0.1 SDS.

As mentioned earlier, TBW was measured directly using D_2O or estimated using either TANITA's in-built manufacturer equations ($TANITA_{manufacturer}$) or using the new equations constructed from TANITA ($TANITA_{equn}$). Similarly, FM and FFM were

estimated by using either the 3C model or using $TANITA_{manufactirer}$ or using $TANITA_{equn}$. Differences in body composition over time using measured versus equations are shown in Table 7-13. Compared to D_20, both $TANITA_{manufacturer}$ and $TANITA_{equn}$ overestimated the difference in TBW by 0.3 litres and 0.05 litres respectively but not significantly. Also compared to the 3C model, the $TANITA_{equn}$ overestimated the difference in FFM and underestimated the difference in FM by 0.2 kg; this however did not achieve statistical significance ($p = 0.7$). Similarly, $TANITA_{manufactirer}$ overestimated FFM and underestimated FM by 0.1 kg; this difference however was not statistically significant ($p = 0.4$).

Scatter-plots illustrating the relationship between the differences in FM and FFM using $TANITA_{equn}$ versus actual measurements (by the 3C model) are shown in Figure 7-5. Differences in FM ($r = 0.76$; $p < 0.001$) and FFM ($r = 0.74$; $p = 0.001$) using my prediction equations were found to be significantly correlated with those obtained from the 3C model; indicating that the $TANITA_{equn}$ can predict approximately 64% and 50% of the variance in differences in FM and FFM respectively from the 3C model.

A Bland and Altman plot was performed to test whether the accuracy of predicting body composition change using prediction $TANITA_{equn}$ was dependant on the amount of FM or FFM the child gained or lost while they were on the treatment programme (refer to Figure 7-6). Results indicate that there were no significant differences in change of fat or lean, and magnitude of the error in estimating body composition from using these equations.

The same analyses were performed to test the accuracy of using $TANITA_{manufacturer}$ to predict change in body composition in obese children and adolescents. Similar to results obtained from using the constructed equations, compared to the 3C model $TANITA_{manufacturer}$ was able to predict 50% of the variance in differences in FM and FFM. No significant bias was found between the change in body composition and error from estimating change in body composition when using $TANITA_{manufacturer}$ versus the 3C model (refer to Figure 7-7 and Figure 7-8).

A further analysis was performed to investigate how well BMI can predict change in FM compared to the $TANITA_{equn}$. First, an equation was constructed from the cross-sectional study where BMI was regressed against % fat (calculated by the 3C); taking

into account age. Gender was not included because I have previously demonstrated in Chapter 5 that obese boys and girls did not differ in FM and FFM. The equation obtained was:

% fat (3C) = 17.48 + (1.51*BMI) – (0.817 *age) **Equation 7-7**

FM (3C) = (% fat/100)*WT **Equation 7-8**

FM was then calculated and changes in FM obtained by the 3C model were compared to those obtained from the above equation. Results show that change in FM calculated by the 3C model was significantly correlated with predicted change in FM from BMI (r^2 = 0.43; p = 0.003; SEE = 1.92). Predicting change in FM from my TANITA equation compared to the 3C model resulted in a 14% stronger correlation and lower SEE (r^2 = 0.57; p < 0.001; SEE = 1.71). This indicated that my prediction equation constructed from TANITA is better than BMI in predicting change in body composition in obese children and adolescents.

Table 7-11 A list of sample excluded from the longitudinal TANITA analysis

Number excluded	Reason
8	Treated with Metformin
7	Asian
6	Black
8	other non-White ethnic groups

Table 7-12: Characteristics of the obese sample for visits 2 and 3

		Visit 2				**Visit 3**			
	N	minimum	maximum	mean	SD	minimum	maximum	mean	SD
Age (years)	18	8.9	13.4	11.0	1.5	9.5	14.0	11.4	1.5
WT (kg)	18	45.1	101.7	67.2	17.9	50.6	110.1	71.0	17.4
HT (cm)	18	129.3	177.6	151.2	11.3	132.2	181.3	154.2	11.2
BMI (kg/m^2)	18	24.1	41.4	28.9	4.9	23.7	39.0	29.5	4.5
WT SDS	18	1.5	4.0	2.7	0.9	1.6	3.9	2.8	0.8
HT SDS	18	-2.0	3.1	1.1	1.3	-0.7	3.1	1.2	1.1
BMI SDS	18	1.8	4.0	2.8	0.6	1.5	3.7	2.9	0.6
TBW (D_2O)	18	18.4	42.4	28.6	6.7	21.3	46.9	30.6	7.0
TBW (from equation)	18	17.5	41.3	28.6	6.4	20.8	48.2	30.8	7.2
TBW (TANITA)	18	19.6	43.4	29.4	6.2	21.4	49.1	31.5	7.0
HT^2/R	18	22.5	51.0	35.8	7.6	26.5	59.3	38.5	8.6
FM (3C) (kg)	17	18.8	53.8	30.0	10.6	18.7	51.0	30.7	10.6
FM (3C) (from equation)	17	17.7	58.1	29.4	11.6	18.7	54.1	30.0	10.7
FM (TANITA)	18	14.0	55.5	25.7	11.3	15.6	50.5	26.7	10.0
FFM (3C) (kg)	17	23.6	55.1	37.9	8.6	27.3	61.8	40.8	9.2
FFM (3C)(from equation)	17	22.9	54.7	38.3	8.4	27.4	63.9	41.4	9.4
FFM (TANITA)	18	26.8	59.2	40.1	8.5	29.2	67.1	43.0	9.5

Abbreviations: N= sample size; WT= weight; HT= height; BMI= body mass index; SDS= standard deviation score; TBW= total body water; D_2O= deuterium dilution; R= resistance; FM= fat mass; FFM: fat-free mass

Table 7-13: Differences in body composition between visits 2 and 3 using measured (3C) versus $TANITA_{equn}$ and $TANITA_{manufacturer}$

	Difference (measured)		**Difference** ($TANITA_{equn}$)		**Difference** ($TANITA_{manufacturer}$)	
	mean	SD	mean	SD	mean	SD
TBW (l)	2.0	2.6	2.3	1.7	2.1	1.3
FFM (kg)	2.9	2.6	3.1	1.7	2.9	1.8
FM (kg)	0.7	2.5	0.5	2.6	1.1	3.0

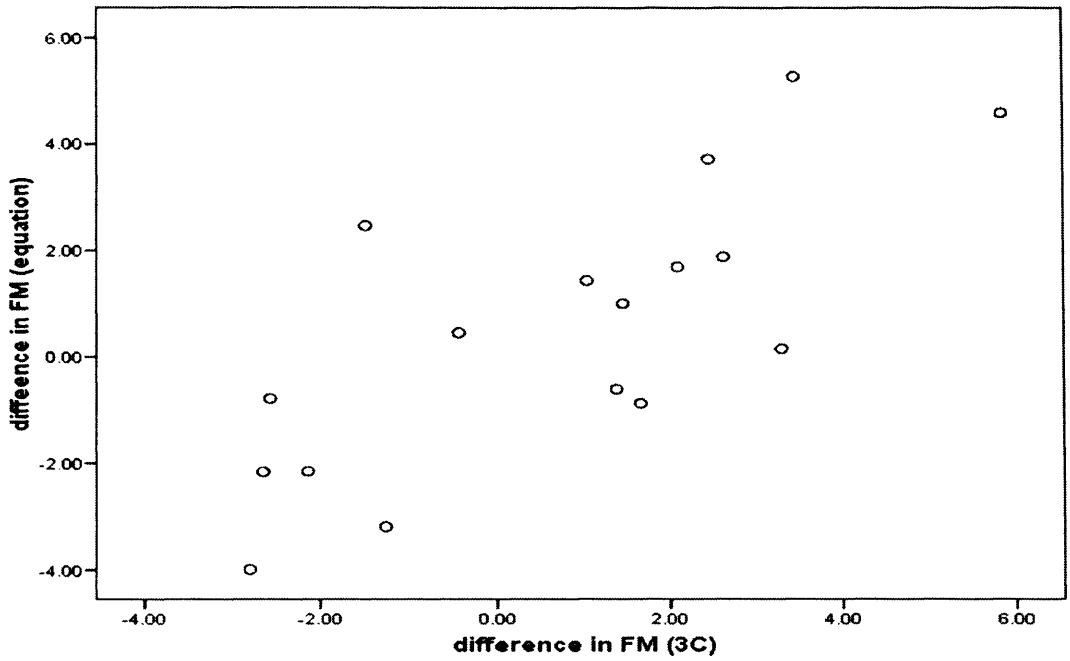
Abbreviations: SD= standard deviation; TBW= total body water; FFM= fat-free mass; FM= fat mass; SD= standard deviation
Difference = visit 3 – visit 2

Table 7-14: Bland-Altman analysis reporting difference in change in body composition: in-built TANITA equations and prediction equations versus the 3C model

	Difference ($TANITA_{equn}$ - measured)					**Difference** ($TANITA_{manufacturer}$ - measured)				
	mean	SD	p-value	r	p-value	mean	SD	p-value	r	p-value
TBW (l)	0.3	2.0	0.6	-0.49	0.04	0.1	2.1	0.9	-0.70	0.001
FFM (kg)	0.2	1.8	0.7	-0.16	0.5	0.1	1.8	0.8	-0.48	0.05
FM (kg)	-0.2	1.8	0.7	0.05	0.8	-0.1	1.9	0.4	0.06	0.8

Abbreviations: SD= standard deviation; TBW= total body water; FFM= fat-free mass; FM= fat mass; SD= standard deviation; r= correlation coefficient

(a) FM



(b) FFM

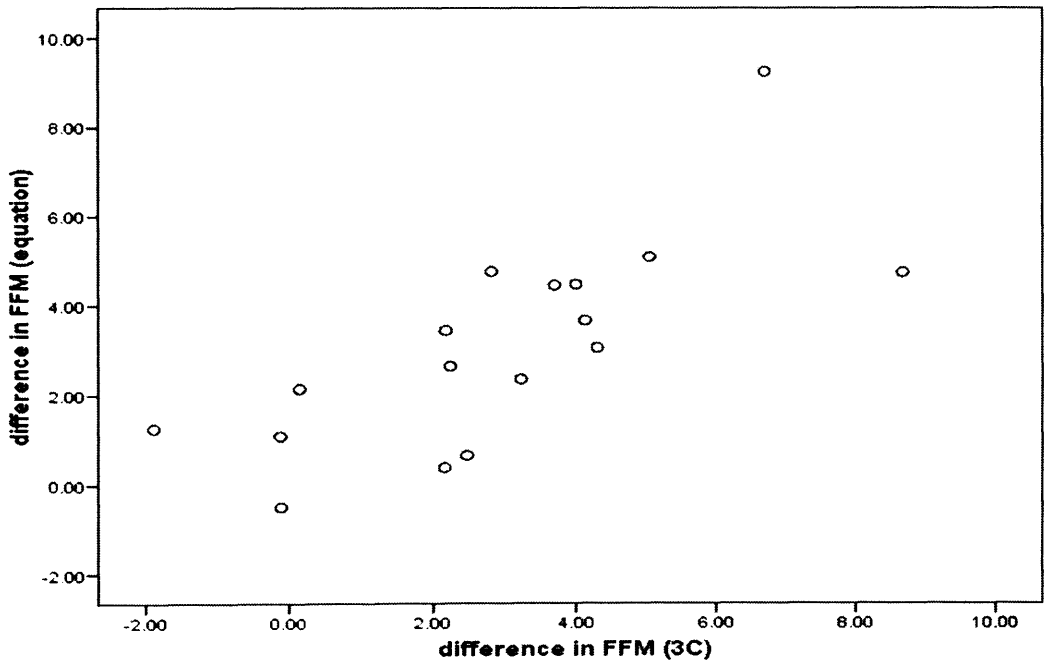
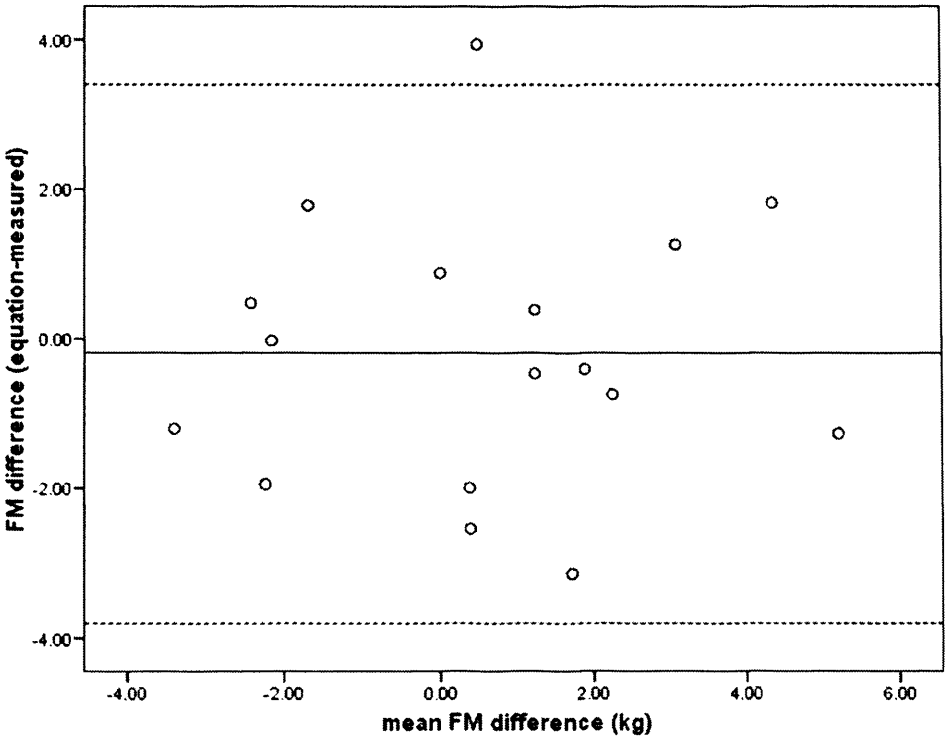


Figure 7-5: A scatter-plot of difference in change of (a) FM ($r = 0.76$; $p<0.001$), (b) FFM ($r = 0.74$; $p=0.001$) by using measured (3C) versus $TANITA_{equn}$

(a) FM



(b) FFM

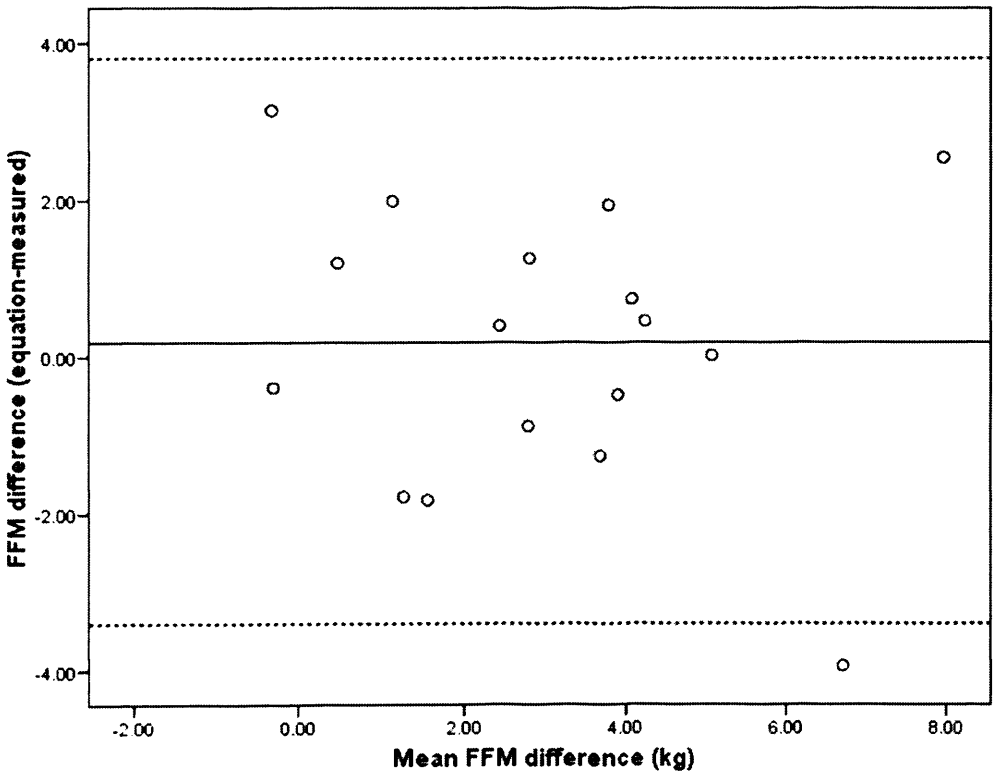
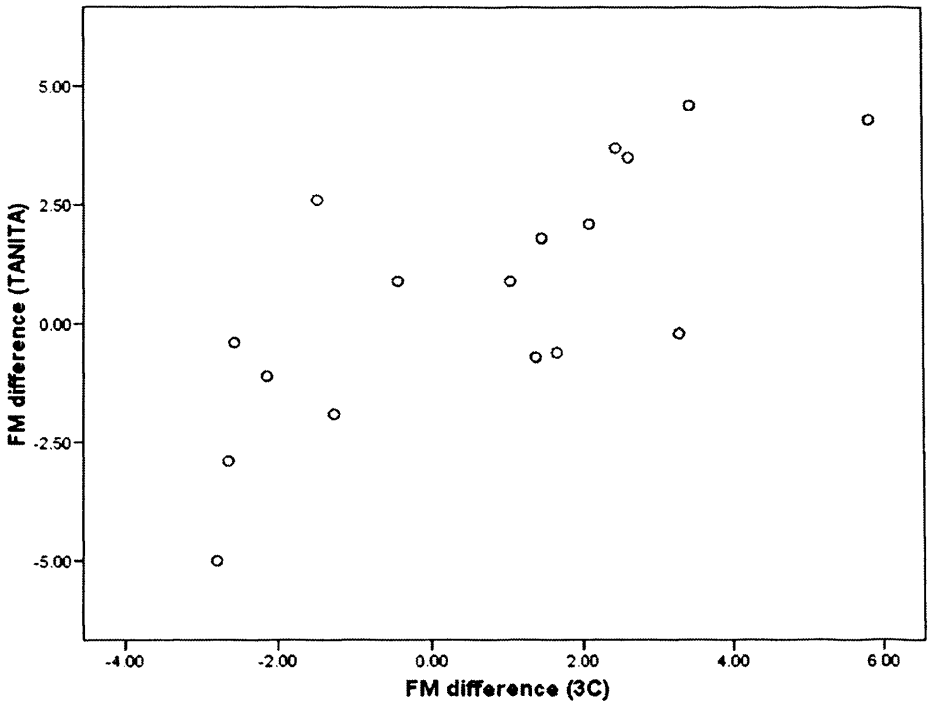


Figure 7-6: Bland and Altman plot showing the agreement between mean of the change in the difference of (a) FM (r = 0.05; p=0.8), (b) FFM (r=-0.16; p = 0.5) using measured (by 3C model) versus $TANITA_{equn}$

(a) FM



(b) FFM

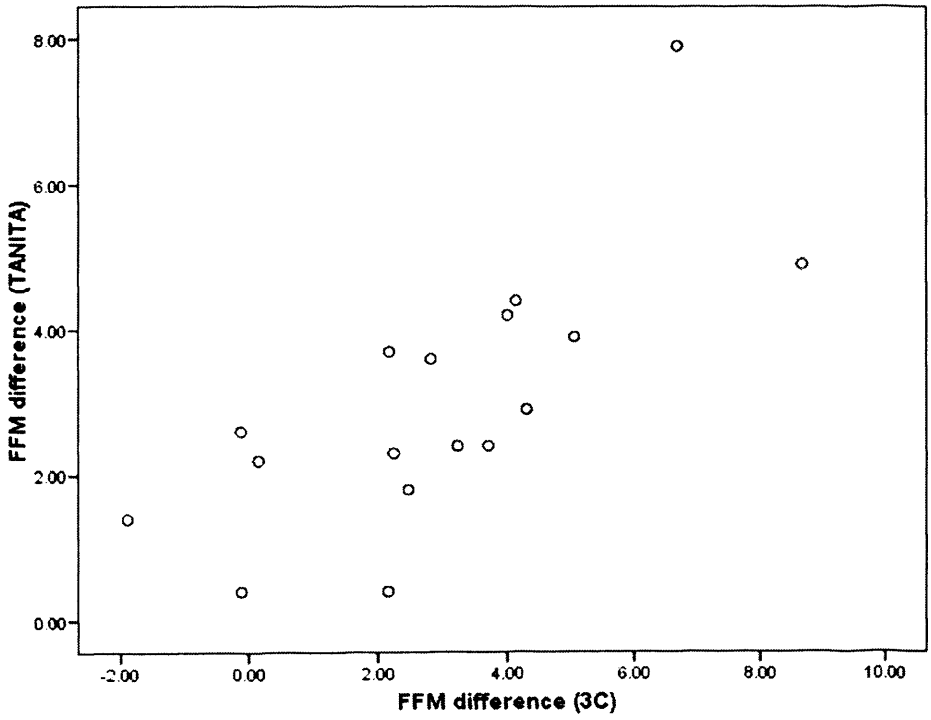


Figure 7-7 A scatter-plot of the difference in change of (a) FM (r = 0.74; p=0.001), (b) FFM (r = 0.73; p = 0.001) by using measured (3C) versus $TANITA_{manufacturer}$

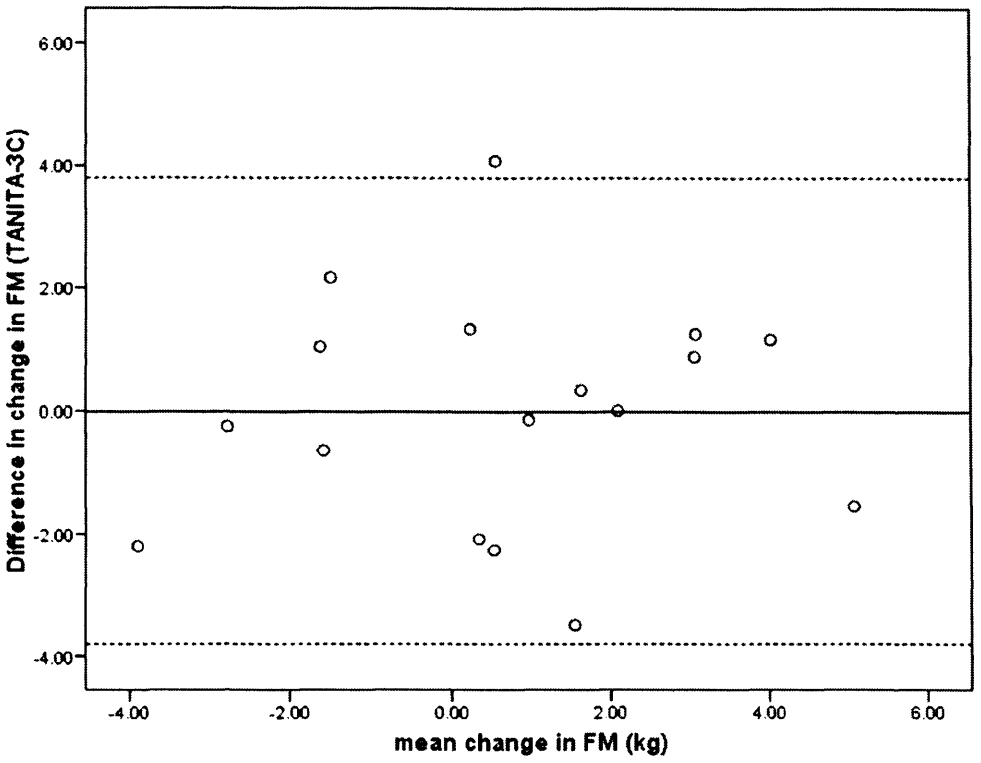


Figure 7-8 Bland-Altman plot showing the agreement between the difference in change in FM ($TANITA_{manufacturer}$ -3C) and mean of change in FM ($TANITA_{manufacturer}$ +3C) (r = 0.06; p = 0.8)

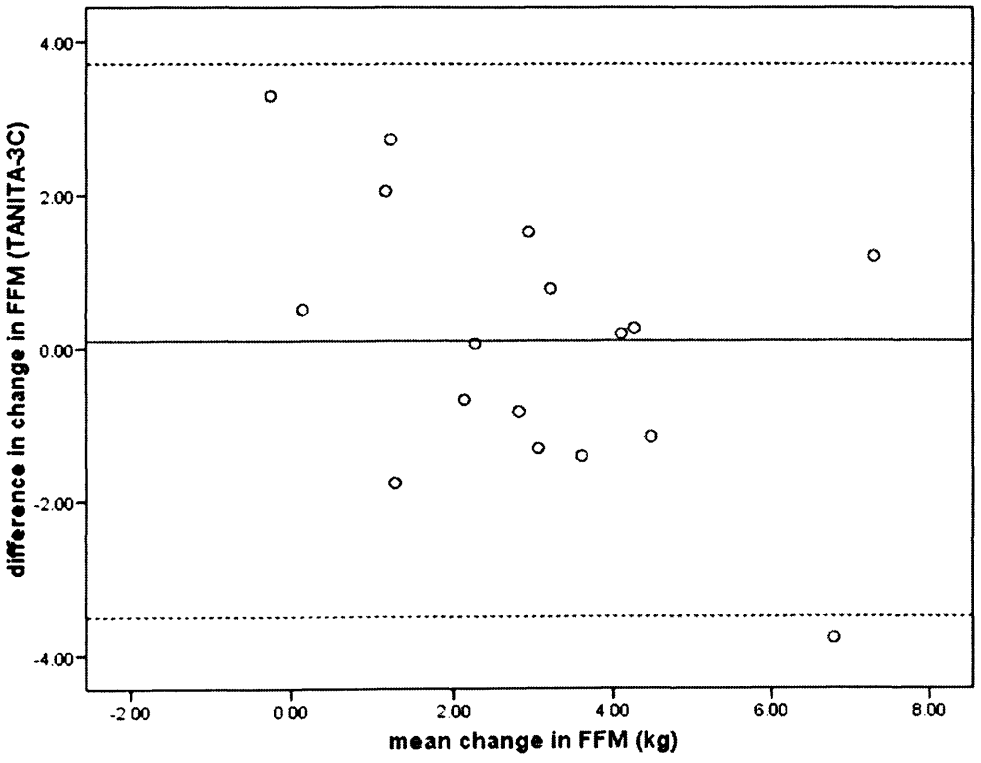


Figure 7-9 Bland-Altman plot showing the agreement between difference in change in FFM ($TANITA_{manufacturer}$ -3C) and mean of change in FFM ($TANITA_{manufacturer}$ +3C) (r = -0.48; p = 0.05)

7.10 Discussion

Measuring body composition accurately in obese children and adolescents is extremely important, particularly when looking at the effectiveness of various treatment strategies. BIA offers a rapid, simple, non-invasive and cheap way of predicting body composition. However, there has been very limited information on the validity of this technology in obese children and adolescents. This study compares the TANITA (BC-418 MA) machine against the most accurate techniques for calculating body composition: D_2O and multi-component models (3C and 4C models).

Results from this study show that raw predictions directly obtained from the TANITA machine ($TANITA_{manufacturer}$) should be interpreted with extreme caution when assessing this particular group. In obese children and adolescents, compared to the multi-component model, $TANITA_{manufacturer}$ significantly underestimated FM (by approximately 4 kg; $p < 0.001$) and overestimated FFM (by approximately 2.7 kg; $p < 0.001$). Previous studies evaluating the accuracy of BIA have been inconsistent.

There have been a limited number of studies evaluating impedance in assessing body composition in obese children, most relying on DXA as the reference method. DXA however has been shown to be unreliable for use in longitudinal studies especially when subjects undergo change in nutritional status, because the bias in estimating fat and lean mass was found to be inconsistent and dependant on subject's size and level of adiposity (Williams et al, 2006).

Similar results to mine were reported by Lazzer and colleagues (2003) when validating foot-foot impedance in 53, 13-16 year old overweight and obese adolescents against DXA (Lazzer *et al.* 2003). In addition, Frisard and colleagues (2005) reported that in overweight adults, foot-foot impedance overestimated FFM and underestimate FM compared to DXA (Frisard *et al.* 2005).

One possible reason for this finding is that impedance machines make assumptions concerning the H_{ffm}. I have previously demonstrated in chapter 5 that obese children and adolescents have significantly greater hydration levels compared to those non-obese; average H_{ffm} is approximately 76 - 77% in this group. Therefore FFM is over-estimated

and FM is underestimated in those with H_{ffm} > 73% (the hydration constant used in impedance machines).

On the other hand, Prins and colleagues (2007) validated a whole body impedance machine (TANITA BC-418 MA) in a group of 5 - 17 year old children from The Gambia against D_20, and found that TANITA underestimated FFM and overestimated % fat with a greater overestimation in thinner individuals (Prins *et al.* 2007). Differences in my results may be due to the ethnicity of subjects that took part in the study; Prins's subjects were African whereas my subjects came from a White background. Also, my study consisted of only obese children and adolescents whereas Prins's study population were not obese. Hence, differences subject characteristics between the studies may account for differences in outcomes obtained.

Another study by Jebb and colleagues (2000) evaluated a foot-foot impedance machine in 16-78 year olds against the 4C model (Jebb *et al.* 2000). They found that the impedance machine over-estimated FM by approximately 0.8 kg. A possible reason for this finding is that the body build of obese subjects is different from that of lean subjects; especially those with abdominal obesity. The trunk contains about 50% of body mass but contributes only about 10-20% of total body impedance (Deurenberg, 1996). Obese subjects with more abdominal mass will have more water (or FFM) located in the trunk, but the effect of that part of the body on total impedance will be low. This is because the trunk is relatively short and has a large diameter, and impedance is proportional to height but inversely proportional to area. Hence FFM and TBW in this body region may be underestimated.

This study also demonstrated that the error in estimating FM and FFM from $TANITA_{manufacturer}$ was inconsistent across the range of body composition. Compared to the 4C model, $TANITA_{manufacturer}$ under-estimated FM more in children with the highest FM and overestimated FFM more in those with the highest FFM. This phenomenon should not be overlooked when this technique is being used to assess body composition in obese children particularly when assessing changes in body composition during a weight loss programme. Ideally, specific equations should be constructed when assessing body composition in patients that may differ from the norm such as obese children and adolescents.

Equations constructed from TANITA ($TANITA_{equn}$) were found to estimate changes in body composition accurately in obese children enrolled in a 6-month weight-loss programme; underestimating a change in FM and overestimating a change in FFM by approximately 0.2 kg each when compared against the 3C model; this bias is negligible. In addition, the accuracy of the machine was not affected by the amount of fat and lean mass children lost or gained while they were on the treatment programme. This indicates that compared to the multi-component model, prediction equations constructed from TANITA ($TANITA_{equn}$) can provide reliable assessments of body composition changes in White obese children. This is extremely useful for weight-management clinics because TANITA is inexpensive, easy to use and provides more information than traditional weight and height measurements.

It has been reported that the magnitude of the weight loss may influence the accuracy of impedance machines in assessing change in body composition (Frisard *et al.* 2005). In obese populations, some studies reported that the H_{ffm} decreases following weight loss (Ritz *et al.* 2007), whilst others did not report such a change in H_{ffm} (Marken Lichtenbelt and Fogelholm, 1999; Leone *et al.* 2000). Therefore body composition measurements obtained using methods which rely on a fixed H_{ffm}, such as BIA, may not be accurate. In this population, the magnitude of change in FM and FFM did not significantly impact the accuracy of the TANITA machine. The current study population however comprised a small homogenous sample of White obese children. Consequently, the acceptability of this finding may be limited to populations specific to that examined.

In spite of the good assessment of change in body composition using TANITA's manufacturer's in-built equations ($TANITA_{manufacturer}$), it cannot be recommended for assessment of body composition in obese children and adolescents because of the large errors of individual estimates. Instead, equations predicted from impedance using the multi-component model as the reference ($TANITA_{equn}$) are recommended when assessing body composition in White obese children and adolescents because they provide a more accurate estimate of body composition.

Moreover, the accuracy of TANITA was examined against a common conventional measure of adiposity: BMI. Both methods were significantly correlated in predicting change in body composition over time; however prediction equations constructed from

TANITA ($TANITA_{equn}$) provided a 14% stronger correlation and 0.2 kg less error in predicting change in FM. Therefore, my TANITA equations can provide more accurate assessment of change in body composition than the approach traditionally used to assess body composition.

Further research looking at the different ethnic groups and constructing gender specific equations for obese children and adolescents would be extremely valuable. The equations above should only be used for White obese children or adolescents, because body composition differs significantly between different ethnic groups. For example Blacks have higher lean mass compared to Whites whereas Asians have higher FM (Deurenberg *et al.* 1998; Dudeja *et al.* 2001). Therefore, constants and equations derived from analysing data on White children may not be applicable in other ethnic groups.

7.11 Study limitations

Although R measurements can be reliably obtained from impedance machines such as the one used in this study, several factors may affect their accuracy. These include hydration status, food intake and exercise. The impedance measurement was the last measurement performed at the 1.5 hour appointment. Therefore, subjects had nothing to eat and no exercise at least one hour before the measurement was taken. In addition, the touching of limbs while the measurement is being taken may short-circuit the electric pathway and reduce impedance, thus over estimating TBW. Subjects were measured with trousers on, to avoid such inaccuracies and were also asked to void before the measurement

The TANITA (BC-418 MA) impedance machine used in this study uses a low frequency of 50 KHz, which flows mainly through ECW due to the high capacitance of the cell membrane (Kushner, 1992). At higher frequencies (> 200 KHz), the cell membrane is crossed by the electrical current and both the ECW and ICW compartments are measured. Multi-frequency BIA machines which provide resistance at multiple frequencies may be a better technique; however TBW, ICW, ECW and FFM are highly correlated among themselves (Schoeller, 2000). Thus, multi-frequency BIA may not provide a better prediction of ECW or TBW than single-frequency BIA. More research however is needed to confirm this hypothesis.

The reference method used for the longitudinal assessment of the accuracy of TANITA in estimating body composition in obese children and adolescents over time, was the 3C instead of the 4C model. For ethical reasons, obese children had a bone scan only for their first two visits but not their third; hence body composition was not estimated using the 'gold standard' 4C model and only the 3C model was used. However, I have demonstrated previously in Chapter 5 that body composition estimated from the 3C versus 4C models was not significantly different in obese children. Hence, the accuracy of the TANITA machine in predicting change in body composition using 3C prediction equations instead of 4C equations would have not been affected.

Chapter 8: Conclusion

This chapter will outline a summary of the findings derived from this thesis, and describe areas where further research may be beneficial.

8.1 Summary of findings

In chapter 5, I tested my first hypothesis by comparing the body composition of obese children with that of non-obese children and adolescents matched for age and sex. I found that obese children, especially girls, were taller than non-obese children. This confirms the need to adjust for body size when comparing body composition (including FM and FFM) in groups of children even after adjusting for age and sex differences. I also found the properties of FFM were not constant between children of the same age and sex; obese children and adolescents have increased H_{ffm} and reduced D_{ffm} compared to non-obese children. This has important implications when assessing body composition in obese children using techniques that assume constant properties of FFM. These techniques include DXA scanners and BIA, which have been widely used in many research studies and clinical work. To date, there is not enough information on the potential implications of this excess hydration. Regional body composition analyses using DXA further showed that obese children had increased FM especially in the abdominal region; which is correlated with increased risk of metabolic complications. Given that obesity is associated with so many body composition outcomes, investigations of the effect of treatment should ideally incorporate body composition measurements.

In chapter 6, I tested the effectiveness of two weight loss programmes on body composition in obese children and adolescents.

The first programme tested was an RCT evaluating the effectiveness of the TLP in a group of obese children and adolescents. Children were randomised to a treatment group and a control group, the former group received treatment immediately whereas the latter group had to wait for 6 months before receiving treatment. Results reveal that even though there was a slight reduction in BMI SDS in both the treatment and control groups; the groups did not significantly differ for any of the body composition

measurements, indicating that the TLP was not very successful. This was when the RCT was analysed; i.e. when treatment group were compared to controls (the period when they received no treatment). However, when a further analysis was performed whereby change in body composition between being treated then left versus being wait-listed then treated, the TLP was found to be successful. This analysis included all the children that received treatment, i.e. the controls when they were treated outside the RCT, and investigated change in body composition at different time-points. Those that were treated as opposed to being left showed a significant loss of FM and BMI SDS, and a significant increase in FFM, indicating the treatment programme was actually effective in improving body composition. Differences between the RCT analysis and the second analysis resulted because controls on the RCT performed better on the treatment programme compared to those who were part of the treatment group; thus when the controls who received treatment were included in the second analyses the TLP was found to be effective.

The second programme tested was a pilot study evaluating the effectiveness of Metformin on change in body composition in a group of obese children and adolescents. Results obtained from this study illustrated that 6 months and 1 years of taking Metformin resulted in a slight reduction in BMI SDS which was not significant. This programme was not an RCT, therefore the results obtained need to be confirmed using a larger sample size and using controls. Also, the programme included some that had already been taking Metformin, and so baseline body composition data before they started treatment was not available. Even though there was no change in BMI SDS between baseline (before Metformin was prescribed) and 6 months after taking Metformin (data obtained from clinic notes); it may be that there was a slight change in body composition.

Because childhood obesity has proven to be very difficult to treat, and weight loss programmes for obese children and adolescents are not very effective, it may be best to direct most effort to preventing the onset of obesity using public health programmes. Even though schools have been promoting healthy eating and physical activity the results are not especially successful, and it may be that this prevention should start at an even younger age.

Also treatment programmes in children may not be drastic enough; whereby some of the programmes for young children recommend weight maintenance instead of weight loss. This might work for overweight or slightly obese children who might 'grow into their weight'. However some of the children that were included in my treatment programmes were very obese (BMI SDS of approximately 3.5, which is well above the cut-off for childhood obesity), and therefore will need to decrease in weight rather than simply maintain it.

In chapter 7, a simple tool (TANITA BC-418 MA) for assessing body composition was validated against multi-component models to investigate the accuracy of using this machine to estimate body composition in White obese children and adolescents. Compared to the 3C and 4C models, $TANITA_{manufacturer}$ significantly underestimated FM and overestimated FFM; the bias was not consistent across the range of body composition. This indicates that in-built TANITA equations are not very accurate, and may be particularly inaccurate when assessing change in body composition during weight-loss programmes. Equations from impedance were then derived using multi-component models (3C and 4C models) as the reference methods that can be used to estimate body composition. The equation from the 3C model was then tested on a sample that had longitudinal body composition measurements. Results show that the equation was unbiased in predicting change in body composition. Hence, these equations are recommended when using impedance (TANITA BC-418 MA) to assess body composition in weight-management clinics. These equations (from impedance) are more accurate to use compared to traditional measurements that rely on weight and height, and are more practical and cost effective than imaging techniques such as DXA and MRI. However with a SEE of 2.2 kg, they are less accurate than MRI or DXA and are best considered a useful guide to body composition and its change over time rather than a definitive measure.

8.2 Future research

Based on my findings, I suggest several areas where further research may be beneficial.

Increased H_{ffm} was observed in obese children and adolescents, but the reason behind this is unclear. This phenomenon could be further examined by directly measuring ECW by sodium bromide dilution, and calculating ICW as the difference between TBW and ECW. It would then be possible to determine whether significant weight loss reduces this over-hydration.

The effectiveness of the TLP was only investigated 6 months after treatment ended. Therefore, a long-term follow-up into adulthood, investigating the effectiveness of TLP on body composition and health outcomes may be beneficial. This is planned by those running the programme.

The Metformin programme I evaluated was a pilot study, there were no controls and the sample included anyone who was taking Metformin. An RCT is therefore required for investigating the effect of Metformin on body composition in obese children and adolescents, assessing whole body composition by using the multi-component model to obtain accurate change in total body fat and lean mass, in addition to using MRI to examine changes in visceral fat. Even though there might not be significant changes in total fat, it may be that there are changes in visceral fat, which provides a more accurate marker for insulin sensitivity.

In chapter 7, I have shown in a sub-sample that TANITA equations developed for White obese children were not applicable to use in other ethnic groups. However, I did not have a large enough sample to develop ethnic-specific equations. Therefore a study evaluating BIA against the multi-components models in obese children and adolescents from other ethnic groups is recommended.

Age and sex-specific cut-offs for defining obesity and overweight in children and adolescents age 5 - 18 years have been proposed by McCarthy and Colleagues in 2006, using a BIA machine: TANITA model BC-418 MA (McCarthy *et al.* 2006). Given I have demonstrated in chapter 7 that TANITA (BC-418 MA) compared to the 4C model did not describe body composition accurately, it may be beneficial that these cut-offs

are revised or confirmed using a more accurate technique such as the multi-component model.

Behavioural programmes are generally used in young obese children, typically aged between 8 and 13 years, whereas pharmacological programmes tend to be used in older obese children and adolescents. Family based behavioural programmes have advantages in that the programme teaches the family to adopt a healthier lifestyle; hence targeting the family as a whole rather than concentrating on the individual obese child. Pharmacological programmes however tend to be used when all other options have failed; children on this programme are now older and more obese than those on behavioural programmes. Findings from my PhD illustrate that treating childhood obesity is challenging and generally not very successful in either age groups; and it may be that programmes working on preventing childhood obesity in the first place are more beneficial. There are very few public health programmes preventing childhood obesity, and very little research evaluating body composition and longitudinal effects of these programmes. Therefore, more research on the effectiveness of such programmes is needed.

Acknowledgements

I cannot fully express my gratitude to my primary supervisor, Dr. Jonathan Wells, for supervising and shaping every aspect of this work, and for the constant support and guidance, and endless patience. I am very thankful to my secondary supervisors, Dr. Mary Fewtrell and Dr. Margret Lawson for their help and superb guidance; their contributions have been of great value to me. Many thanks to all my colleagues from the Nutrition Unit; I could not have wished for better help, support and friendship.

I am deeply indebted to the Traffic Light Programme team and Metformin team at Great Ormond Street Hospital and University College hospital, including Helen Croker, Dr. Russell Viner and Dr. Terry Segal, for helping with the recruitment.

Thanks to my family and very special friends, Peter and Rima, for their faith, understanding and constant support.

I am grateful to the Child Growth Foundation for providing funding to carry out this project, and most importantly I would like to thank all the volunteers who have taken part in this research.

List of appendices

Appendix 1: ethical approval

Institute of Child Health
and Great Ormond Street Hospital for Children NHS Trust
UNIVERSITY COLLEGE LONDON

30 Guilford Street, London, WC1N 1EH. Telephone: 020 7242 9789 Fax: 020 7905 2201

The child first and always

21st July 2003

Dr M Fewtrell
Childhood Nutrition Research Centre
ICH

Dear Dr Fewtrell,

Title: **Body composition and bone mineralization in patients at GOSH**
Related to R&D number: **02NT01**
Ethics reference number: **1351**
Protocol number/version: **N/A**

Notification of ethical approval

The above research has been given ethical approval after review by the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee subject to the following conditions.

1. Your research must commence within twelve months of the date of this letter and ethical approval is given for a period of sixty months from the commencement of the project. If you wish to start the research more than twelve months from the date of this letter or extend the duration of your approval you should seek Chairman's approval.
2. You must seek Chairman's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature, eg. using the same procedure(s) or medicinal product(s). Each research project is reviewed separately and if there are significant changes to the research protocol, for example in response to a grant giving body's requirements you should seek confirmation of continued ethical approval.
3. Researchers are reminded that REC approval does not imply approval by the GOS Trust. Researchers should confirm with the R&D office that all necessary permissions have been obtained before proceeding.

The Queen's Anniversary Prizes 2000

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4. It is your responsibility to notify the Committee immediately of any information which would raise questions about the safety and continued conduct of the research.
5. On completion of the research, you must submit a report of your findings to the Research Ethics Committee. You may also be required to submit annual reports.
6. Specific conditions pertaining to the approval of this project are:
   - The use of the enclosed standard consent forms for the research. A copy of the signed consent form must be placed in the patient's clinical records and a copy must be kept by you with the research records.

This approval is generic, to cover the same measurements to be performed on various patient groups at GOSH. You will be required to submit a brief summary of the work to be carried out and relevant patient information sheets for each patient group to be included. You will then be issued with an approval letter confirming that the work is covered under this generic approval. Please quote the ethics reference 1351 in all correspondence relating to the inclusion of additional patient groups.

Yours sincerely

Laura Howe
Research Ethics Coordinator
l.howe@ich.ucl.ac.uk

Great Ormond Street Hospital for Children NHS Trust / The Institute of Child Health Research Ethics Committee

Institute of Child Health
30 Guilford Street
London
WC1N 1EH

Tel: 020 7905 2620
Fax: 020 7905 2201
Email: t.austin@ich.ucl.ac.uk

10 March 2006

Dr Jonathan Wells
MRC Childhood Nutrition Centre
Institute of Child Health
30 Guilford Street
London WC1N 1EH

Dear Dr Wells

Study title: **Body composition and bone mineralisation in patients at Great Ormond Street Hospital**
REC reference: **02NT01**
Protocol number: **21 July 2003**
EudraCT number: **N/A**

Amendment number: 1
Amendment date: 6 February 2006

Amendment: Extension of recruitment only (not consenting) to Dr Viner's obesity clinic at the Middlesex Hospital

The above amendment was reviewed at the meeting of the Sub-Committee of the Research Ethics Committee held on 1 March 2006.

Ethical opinion

The members of the Sub Committee gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Please see ensure that the proper R&D registration procedures are undertaken at the Middlesex.

Approved documents

The documents reviewed and approved at the meeting were:
Notice of Substantial Amendment, 6 February 2006

Membership of the Committee

The members of the Ethics Committee who comprised the Subcommittee were: Dr V Larcher (Consultant Paediatrician/ Chairman) and Dr Joe Brierley (Consultant Intensivist).

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

[REC reference number]:	02NT01	**Please quote this number on all correspondence**

Yours sincerely

Taki Austin
Research Ethics Coordinator

E-mail: t.austin@ich.ucl.ac.uk

Copy to: Institute of Child Health/ Great Ormond Street Hospital R&D Department

Great Ormond Street Hospital for Children NHS Trust / The Institute of Child Health Local Research Ethics Committee

Institute of Child Health
30 Guilford Street
London
WC1N 1EH

Tel: 020 7905 2620
Fax: 020 7905 2201
Email: l.howe@ich.ucl.ac.uk

3rd October 2003

Jonathan Wells
Nutrition
ICH

Dear Dr Wells,

Title:	**Body Composition and Bone Mineralisation in Patients At GOSH**
R&D registration number:	**02NT01**
Protocol number/version:	**N/A**

Thank you for your email dated 22nd September 2003. The Chairman of the Research Ethics Committee, Dr Victor Larcher, has on behalf of the Committee, approved the following amendments to the above project:

- Carrying out the measurements before and after clinical interventions. This amendment relates to all patient groups in this study. You must ensure that this is made clear to patients in the information provided to them.
- The recruitment of obese children from Chichester and The London Hospitals, providing appropriate agreement from the responsible clinicians and Research Ethics Committees is obtained.

The decision will be ratified at the full Committee meeting that will take place on Wednesday 5th November 2003 (Please note that you will not receive a letter confirming the above ratification).

Yours sincerely

Laura Howe
Research Ethics Coordinator

cc. Mary Fewtrell, Margaret Lawson

Appendix 2: information sheets for parents and children

(a) Parent information sheet

Parent information sheet
MRC Childhood Nutrition Research Centre
Institute of Child Health
30 Guilford Street
London WC1N 1EH
Tel 020 7905 2747

Title of project
Body composition changes during weight-loss

The aim of the study
To measure the changes in body composition that occurs during weight loss in children.

Why is the study being done?
Many children are now being treated for excess body weight. However, it is not yet known exactly how weight loss treatment influences the different components of weight, including muscle mass, bone mass and fat mass. Our study aims to make measurements to provide information on body composition during weight loss. This will help refine weight loss programmes for children in the future.

How is the study to be done?
We are recruiting children who are on programmes for weight loss. If you are willing to take part in the study, we will arrange an appointment at a time which is convenient for you to come up to the Hospital for Sick Children, Great Ormond Street, where our equipment is kept. We will reimburse any travelling expenses. The measurements will be made at the start of treatment, and again after 6 months on the weight loss programme.

At the appointment, we will
weigh your child and record his/her height.
perform three scans using our DXA (Dual X-ray Absorptiometer) scanner – one of the hip, one of the spine and one of the whole skeleton. The scans take a maximum of 5 minutes each, and are performed whilst wearing light indoor clothing (such as shorts and a t-shirt) and lying on a bed, keeping as still as possible. These scans give a measurement of the size and amount of mineral in the bones, as well as the proportions of fat and muscle. If there is any possibility that the person to be scanned is pregnant, the scan will not be performed.
perform a measurement of the strength of the bone in the wrist and lower leg, using an ultrasound machine. These measurements are painless, take a few minutes each and do not use X-rays.
measure the amount of water in the body. This measurement involves drinking some water containing heavy hydrogen molecules. These molecules are not radioactive, they simply weigh more than most hydrogen molecules and they occur naturally in all of us. Before and after the drink your child will be asked to provide a saliva sample using an absorbent cotton wool swab.

measure the volume of the body. This measurement involves your child sitting still inside a chamber called a BodPod for about 45 seconds while room air is gently blown around them. Two such measurements will be made. The test is performed with the child wearing a close fitting swimming costume (not swim shorts).
perform a measurement of bioelectrical impedance using a low level of electrical current (that is undetectable), passed between electrodes placed on the hand and foot. The test is harmless and painless and gives a measure of body water.
ask some questions about your child's general health, including any medicines being taken, illnesses such as asthma and broken bones, and use a short questionnaire to measure his or her calcium intake and activity level. For older children (above 9 years of age) we also need to know if any pubertal development has taken place as this affects the growth and mineral content of bones. To avoid any undressing, we will show your child some photos of the different stages of pubertal development and ask him or her to pick the one which is closest to them.
Measure your child's blood pressure with an electronic monitor. This measurement involves briefly inflating a cuff around the arm while the machine makes a measurement.

The whole appointment should last about 60 minutes.

Are there risks and discomforts?
All of the tests are painless and will not harm your child. DXA scans involve a tiny amount of radiation, which is less than half of a day's background radiation in the United Kingdom (to which we are all exposed), and less than one tenth of the radiation from a flight across the Atlantic. However, if there is any possibility that the person to be scanned is pregnant the scan will not be performed. During the blood pressure measurement, the cuff acts like a balloon being inflated while wrapped round the arm; it might feel a bit tight but it won't hurt.

What are the potential benefits?
The measurements provide more specific information than body weight about the level of body fat, which is what the weight loss programme is trying to reduce. The measurements of body composition will therefore provide accurate information about how much fat has been lost during the 6 months of treatment, while also showing any changes in lean mass. Most children also find the tests interesting and educational and each child will be given a printout of his/her skeleton to take home.

Who will have access to the research records?
Only the researchers and a representative of the Research Ethics Committee will have access to the data collected during this study. Each child will be given a study number, and names and addresses will not be computerised. The computerised information (weight, height, age and test results but no names or addresses) will be made into a reference database of children. This may then be used by other doctors wishing to compare results between children.

Do I have to take part in this study?
No. If you decide, now or at a later stage, that you do not wish to take part in the study, that is entirely your right.

Who do I speak to if problems arise?
If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via the Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or, if urgent, by telephone on 020 7905 2620, and the Committee administration will put you in contact with him.

What are the arrangements for compensation?
This project has been approved by an independent research ethics committee who believe that it is of minimal risk. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this project.

This research is covered by a no-fault compensation scheme which may apply in the event of any significant harm resulting to your child from involvement in the project. Under this scheme it would not be necessary for you to prove fault. You also have the right to claim damages in a court of law. This would require you to prove fault on the part of the Hospital/Institute and/or any manufacturer involved.

Details of how to contact the researchers:

MRC Childhood Nutrition Research Centre
Dalia Haroun
Tel: , email d.haroun@ich.ucl.ac.uk

Dr Jonathan Wells
Tel: email j.wells@ich.ucl.ac.uk

(b) Participant information sheet

Subject information sheet for children
MRC Childhood Nutrition Research Centre
Institute of Child Health
30 Guilford Street
London WC1N 1EH
Tel

Title of project
Body composition changes during weight loss

The aim of the study
To measure the changes in body composition that occur during weight loss in children.

Why is the study being done?
Many children are now being treated for excess body weight. However, it is not yet known exactly how weight loss treatment influences the different components of weight, including muscle mass, bone mass and fat mass. Our study will tell us which components of weight actually change during the programme, and will tell you how much fat you have lost.

How is the study to be done?
We are recruiting children aged who are on programmes for weight loss. If you are willing to take part in the study, we will arrange an appointment at a time which is convenient for you to come up to the Hospital for Sick Children, Great Ormond Street, where our equipment is kept. We will reimburse any travelling expenses. The measurements will be made at the start of treatment, and again after 6 months on the weight loss programme.

At the appointment, we will;
weigh you and record your height.
perform three scans using our DXA (Dual X-ray Absorptiometer) scanner – one of the hip, one of the spine and one of the whole skeleton. The scans take a maximum of 5 minutes each, and are performed with you wearing light indoor clothing (such as shorts and a t-shirt) and lying on a bed, keeping as still as possible. These scans give a measurement of the size and amount of mineral in the bones, as well as the amount of fat and muscle. **If there is any possibility that you may be pregnant the scans will not be performed.**
perform a measurement of the strength of the bone in the wrist and lower leg, using an ultrasound machine. These measurements are painless, take a few minutes each and do not use X-rays.
measure the amount of water in your body. This measurement involves drinking some water containing heavy hydrogen molecules. These molecules are not radioactive, they simply weigh more than most hydrogen molecules and they occur naturally in all of us. Before and after the drink you will be asked to provide a saliva sample using an absorbent cotton wool swab.

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perform a measurement of bioelectrical impedance using a low level of electrical current (that is undetectable), passed between electrodes placed on the hand and foot. The test is harmless and painless and gives a measure of body water.
ask some questions about your health, including any medicines being taken, illnesses such as asthma and broken bones, and use a short questionnaire to measure your calcium intake and activity level. We also need to know if any pubertal development has taken place as this affects the growth and mineral content of bones. To avoid any undressing, we will show you some photos of the different stages of pubertal development and ask you to pick the one which looks closest to you.
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The whole appointment should last about 60 minutes.

Are there risks and discomforts?
None of the tests will hurt you. DXA scans involve a tiny amount of radiation, which is less than half of a day's background radiation in the United Kingdom (to which we are all exposed), and less than one tenth of the radiation from a flight across the Atlantic. However, if there is any possibility that you may be pregnant the scans will not be performed. During the blood pressure measurement, the cuff will feel as if you were having a balloon inflated while wrapped round your arm; it might feel a bit tight but it won't hurt.

What are the potential benefits?
Taking part in the study will show you how much fat you have lost while taking part in the weight loss programme. Also, most people find the scan pictures interesting and educational and you will be given a printout of your skeleton to take home.

Who will have access to the research records?
Only the researchers and a representative of the Research Ethics Committee will have access to the data collected during this study. Each child will be given a study number, and names and addresses will not be computerised. The computerised information (weight, height, age and test results but no names or addresses) will be made into a reference database of normal children. This may then be used by other doctors wishing to compare results from sick children with those from normal children.

Do I have to take part in this study?
No. If you decide, now or at a later stage, that you do not wish to take part in the study, that is entirely your right.

Who do I speak to if problems arise?
If you have any complaints about the way in which this research project has been, or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via the Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or, if urgent, by telephone on , and the Committee administration will put you in contact with him.

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MRC Childhood Nutrition Research Centre

MRC Childhood Nutrition Research Centre
Dalia Haroun
Tel: , email d.haroun@ich.ucl.ac.uk

Dr Jonathan Wells
Tel: email j.wells@ich.ucl.ac.uk

Appendix 3: appointment letter

UCL INSTITUTE OF CHILD HEALTH

Parent/Guardian of XXX

Date:

Appointment for body composition study on ..... at .....
Thank you for taking part in this research project.
***If you enter the main entrance of the hospital in Great Ormond Street, make your way to the** X-RAY RECEPTION and ask to have a bone scan. **Either call me or tell the reception to call me on the** Extension: 2309 or 2747.*

If you have any problems attending this appointment, please call and leave me a message Tel: and I will organise another date.

In order to do an accurate measurement of body volume in the BODPOD, it is necessary to wear a close fitting swimming costume. Loose fitting shorts will affect the measurement and are not acceptable, but tight fitting shorts are acceptable. If you think you may have a problem let me know before the appointment.

The nearest underground is Russell Square
Please call me if you have any questions at all.

I look forward to meeting you all.

Yours sincerely,

Dalia Haroun
Tel:
Email:d.haroun@ich.ucl.ac.uk

Appendix 4: consent form for parents and participants, and assent form for children

(a) Consent form for parents

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARENTS OR GUARDIANS
of Children Participating in Research Studies

Title: Body Composition changes during weight loss

NOTES FOR PARENTS OR GUARDIANS

1. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.

2. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.

3. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice any present or future treatment.

4. You will be given an information sheet which describes the research project. This information sheet is for you to keep and refer to. ***Please read it carefully.***

5. If you have any complaints about the way in which this research project has been or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

CONSENT

I/We _____, being the parent(s)/guardian(s) of _____ agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

SIGNED (Parent (s)/Guardian (s))	**PRINTED**	**DATE**
_____	_____	_____
SIGNED (Researcher)	**PRINTED**	**DATE**
_____	_____	_____

(b) Assent form for children

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Assent Form for CHILDREN Participating in Research Studies

Title: Body Composition changes during weight loss

NOTES FOR CHILDREN

1. You have been asked to take part in some research. The person organising that study must explain the project to you before you agree to take part.

2. Please ask the researcher any questions you like about this project, before you decide whether to join in.

3. If you decide, now or at any other time, that you do not wish to be involved in the research project, just tell us and we will stop the research. If you are a patient your treatment will carry on as it would normally.

4. You will be given an information sheet which describes the research. This information is for you to keep and refer to at any time. *Please read it carefully.*

5. If you have any complaints about the research project, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the Chairman of the Research Ethics Committee, by post via The Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH or if urgent, by telephone on 020 7905 2620 and the committee administration will put you in contact with him.

ASSENT

I _____ agree that the Research Project named above has been explained to me to my satisfaction, and I agree to take part in this study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

SIGNED	**PRINTED**	**DATE**
---	---	---
SIGNED (Researcher)	**PRINTED**	**DATE**
---	---	---

(c) Consent form for participants

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee

Consent Form for PARTICIPANTS in Research Studies

Title: Body composition changes during weigh loss

NOTES FOR PARTICIPANTS

1. You have been asked to take part in some research. The person organising that study must explain the project to you before you agree to take part.

2. Please ask the researcher any questions you like about this project, before you decide whether to join in.

3. If you decide, now or at any other time, that you do not wish to be involved in the research project, just tell us and we will stop the research. If you are a patient your treatment will carry on as normal.

4. You will be given an information sheet which describes the research. This information is for you to keep and refer to at any time. *Please read it carefully.*

5. If you have any complaints about the research project, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the [named representative of the sponsor, with address details] or if urgent, by telephone on [phone number] and the committee administration will put you in contact with him.

CONSENT

I _____ agree that the Research Project named above has been explained to me to my satisfaction, and I agree to take part in this study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

SIGNED	**PRINTED**	**DATE**
_____	_____	_____
SIGNED (Researcher)	**PRINTED**	**DATE**
_____	_____	_____

Appendix 5: questionnaires

24396

WEIGHT LOSS STUDY

id OB / ___

Date of birth ___ / ___ / ____

Date of interview ___ / ___ / ____

Subject's surname

Subject's first name

Mother's surname Initials

Address

Post code .

Home telephone number (+code)

Work telephone number (+code)

GP's name

Address

Tel (+code)

Page 1.1

30276

BODY COMPOSITION: REFERENCE DATA

id O B / [ ][ ][ ]

Social Data

Today's date

[ ][ ] / [ ][ ] / 2 0 [ ][ ]

Number of people in home (incl subject) [ ][ ][ ]

Number of rooms in home (incl dining, living + bedrooms, excl kitchen + bathroom) [ ][ ][ ]

Is home own or rented? O Owned
O Rented

If home is rented, is it from: O Private landlord
O Council
O Housing association
O Not rented
O irrelevant

Mother's date of birth [ ][ ] / [ ][ ] / 1 9 [ ][ ]

1 No ed quals 2 <3 CSE's or GCSE's below C grade
3 >3 CSE's or any O levels or GCSE grade A-C
4 A levels, ONC/OND/BEC/TEC, SCE Highers, NVQ level 3,
5 Degree/HND/HNC professional training (incl SRN/RGN/RM/RHV), NVQ levels 4/5, BEC/TEC Higher

Mother's educational attainments (highest completed) [ ][ ][ ]

Mother's highest qualification

[ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Mother's occupation

[ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

How many months employed in the last year? [ ][ ][ ]

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BODY COMPOSITION: REFERENCE DATA

id O B / _ _ _

Social Data contd

Father's date of birth _ _ / _ _ / 1 9 _ _

1 No ed quals 2 <3 CSE's or GCSE's below C grade
3 >3 CSE's or any O levels or GCSE grade A-C
4 A levels, ONC/OND/BEC/TEC, SCE Highers, NVQ level 3,
5 Degree/HND/HNC professional training (incl SRN/RGN/RM/RHV), NVQ levels 4/5, BEC/TEC Higher

Father's educational attainments (highest completed) _ _ _

Father's highest qualification

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Father's occupation

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

How many months employed in the last year? _ _ _

Who is the primary earner for the family?
- O Father
- O Mother
- O Grandparent
- O Both parents
- O missing

Social class (use primary earner's occupation) _ _ _ Social code as below _ _ _

Code as: 1 = 1, 2 = 2, 3N = 3, 3M = 4, 4 = 5, 5 = 6 on primary earner's occupation
Single parent mother unsupported and not working = 7
Mother supported but partner and self never employed = 8
adopted / fostered child = 9

30276

BODY COMPOSITION: REFERENCE DATA

id O B /

Social Data contd

Ethnic origin

Please tick the box that you think best describes your ethnic origin

- White ○
- Black-Caribbean ○
- Black-African ○
- Black-other ○
- Indian ○
- Pakistani ○
- Bangladeshi ○
- Chinese ○
- Asian-other ○
- Other ○
- Refused ○

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BODY COMPOSITION STUDY: REFERENCE DATA O B .

Fractures

Has child ever had a fracture? ☐ yes=1, no=2 if no, turn to next section

First accident, bones fractured

01=humerus	05=tibia	09=skull	13=pelvis 17=other
02=radius	06=fibula	10=vertebrae	14=scapula
03=ulna	07=hand	11=ribs	15=patella
04=femur	08=foot	12=clavicle	16=sterum

fracture 1 ☐☐☐ which side ☐ other ☐☐☐☐☐☐☐☐☐☐☐☐

fracture 2 ☐☐☐ which side ☐ other ☐☐☐☐☐☐☐☐☐☐☐☐

fracture 3 ☐☐☐ which side ☐ other ☐☐☐☐☐☐☐☐☐☐☐☐

right= 1,left=2 n/a=3

Cause of first accident

01=fall playground apparatus	04=RTA in car	07=injury at home
02=fall from bike	05=RTA pedestrian	08=other
03= RTA bike	06=sports injury	

cause fracture 1 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

cause fracture 2 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

cause fracture 3 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Place where first accident happened

01=home	03=street/road
02=school	04=other

fracture 1 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

fracture 2 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

fracture 3 ☐☐☐ other ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Page 2.1

31869

BODY COMPOSITION STUDY: REFERENCE DATA

O B . | | |

Fractures continued

Second accident, bones fractured

01=humerus	05=tibia	09=skull	13=pelvis	99=other
02=radius	06=fibula	10=vertebrae	14=scapula	
03=ulna	07=hand	11=ribs	15=patella	

fracture 1 | | | which side | | other | | | | | | | | | | |

fracture 2 | | | which side | | other | | | | | | | | | | |

fracture 3 | | | which side | | other | | | | | | | | | | |

right= 1,left=2 n/a=3

Cause of second accident

01=fall playground apparatus	04=RTA in car	07=injury at home
02=fall from bike	05=RTA pedestrian	08=other
03= RTA bike	06=sports injury	

cause fracture 1 | | | other | | | | | | | | | | | | | |

cause fracture 2 | | | other | | | | | | | | | | | | | |

cause fracture 3 | | | other | | | | | | | | | | | | | |

Place where second accident happened

01=home	03=street/road
02=school	04=other

fracture 1 | | | other | | | | | | | | | | | | | |

fracture 2 | | | other | | | | | | | | | | | | | |

fracture 3 | | | other | | | | | | | | | | | | | |

31869

BODY COMPOSITION STUDY: REFERENCE DATA

O B . | | |

Fractures continued

Third accident, bones fractured

01=humerus	05=tibia	09=skull	13=pelvis	17=other
02=radius	06=fibula	10=vertebrae	14=scapula	
03=ulna	07=hand	11=ribs	15=patella	
04=femur	08=foot	12=clavicle	16=sterum	

fracture 1 | | | which side | | other | | | | | | | | | | | |

fracture 2 | | | which side | | other | | | | | | | | | | | |

fracture 3 | | | which side | | other | | | | | | | | | | | |

right= 1,left=2 n/a=3

Cause of third accident

01=fall playground apparatus	04=RTA in car	07=injury at home
02=fall from bike	05=RTA pedestrian	08=other
03= RTA bike	06=sports injury	

cause fracture 1 | | | | other | | | | | | | | | | | | |

cause fracture 2 | | | | other | | | | | | | | | | | | |

cause fracture 3 | | | | other | | | | | | | | | | | | |

Place where third accident happened

01=home	03=street/road
02=school	04=other

fracture 1 | | | other | | | | | | | | | | | | | | |

fracture 2 | | | other | | | | | | | | | | | | | | |

fracture 3 | | | other | | | | | | | | | | | | | | |

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BODY COMPOSITION STUDY: REFERENCE DATA

O B . [ ] [ ] [ ]

Medical Details

Has child had a significant illness during childhood [ ] yes=1, no=2
if no, continue to next section

Type of illness

01= asthma 04=renal disease
02= diabetes 99= other
03=epilepsy

illness 1 type [ ] [ ] [ ] duration (yrs) [ ] [ ] [ ] . [ ] [ ]

illness 2 type [ ] [ ] [ ] duration (yrs) [ ] [ ] [ ] . [ ] [ ]

illness 3 type [ ] [ ] [ ] duration (yrs) [ ] [ ] [ ] . [ ] [ ]

if other illness please state

illness 1

illness 2

illness 3

Has child been on long term medication/or currently taking medication [ ]
(yes=1, no=2 if no, turn to next section)

Type of medication

01= oral bronchodilator	06=xanthines	11=vigabatrin
02= inhaled bronchodilator	07=sodium valproate	12=antibiotic
03= oral steroid	08=carbamazepine	13=insulin
04= inhaled steroid	09=phenytoin	14=growth hormone
05= sodium cromoglycate	10=phenobarbitone	15=other

drug 1

type [ ] [ ] [ ] doseage [ ] [ ] [ ] [ ] [ ] units [ ] [ ] [ ] [ ]

name

date started [ ] [ ] / [ ] [ ] / [ ] [ ] [ ] [ ]

date stopped [ ] [ ] / [ ] [ ] / [ ] [ ] [ ] [ ]

time on medication [ ] [ ] [ ] mths

frequency [ ]

Frequency
1= once/day
2= twice/day
3= three/day
4= four/day
5= > four/day
6= alternate days
7= less than alternate days
8= missing, N/A

still taking medication ○ yes
○ no

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BODY COMPOSITION STUDY: REFERENCE DATA O B . [ ][ ][ ]

Type of medication

01= oral bronchodilator	06=xanthines	11=vigabatrin
02= inhaled bronchodilator	07=sodium valproate	12=antibiotic
03= oral steroid	08=carbamazepine	13=insulin
04= inhaled steroid	09=phenytoin	14=growth hormone
05= sodium cromoglycate	10=phenobarbitone	15=other

drug 2

type [ ][ ][ ] doseage [ ][ ][ ][ ][ ] units [ ][ ][ ][ ]

name [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

date commenced [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

date stopped [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

time on medication [ ][ ][ ] mths

frequency [ ]

still taking medication O yes
O no

Frequency
1= once/day
2= twice/day
3= three/day
4= four/day
5= > four/day
6= alternate days
7= less than alternate days
8=n/a, missing

01= oral bronchodilator	06=xanthines	11=vigabatrin
02= inhaled bronchodilator	07=sodium valproate	12=antibiotic
03= oral steroid	08=carbamazepine	13=insulin
04= inhaled steroid	09=phenytoin	14=growth hormone
05= sodium cromoglycate	10=phenobarbitone	15=other

drug 3

type [ ][ ][ ] doseage [ ][ ][ ][ ][ ] units [ ][ ][ ][ ]

name [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

date started [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

date stopped [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

time on medication [ ][ ][ ] mths

frequency [ ]

still taking medication O yes
O no

Frequency
1= once/day
2= twice/day
3= three/day
4= four/day
5= > four/day
6= alternate days
7= less than alternate days
8=n/a

31869

BODY COMPOSITION: REFERENCE DATA

O B

Vitamin and mineral supplements

In the past year has the child taken daily supplements O yes
O no if no, continue to next section

Calcium supplements O yes
O no

name of calcium supplement

date started / / date stopped / /

no capsules/day

still taking calcium supplements
O yes
O no

Calcium intake (mg)/day derived from Calquest analysis

Multivitamins O yes
O no

name of multivitamin

date started / / date stopped / /

no capsules/day

still taking multivitamins
O yes
O no

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BODY COMPOSITION: REFERENCE DATA

O B .

Family history of other disease:

With respect to subject (not parent), code 0 for no disease:

1 - mother	**2 - father**
3 - brother	**4 - sister**
5 - maternal grandmother	**6 - maternal grandfather**
7 - paternal grandmother	**8 - paternal grandfather**

High Cholesterol			
Heart disease			
Osteporosis			
Hypertension			
Diabetes - non-insulin dependant			
Diabetes - insulin dependant			

Has your child ever required surgery for any of the following:
(1 = yes, 2= no)

lung heart GI tract liver kidney

Please give details of any surgery in childhood

Has your child ever required medical treatment for any of the following:
(1 = yes, 2= no)

lung heart GI tract liver kidney

Please give details of any medical treatment in childhood

24421

BODY COMPOSITION STUDY: id OB.

Children's Exercise Questionnaire

How many PE lessons do you have per week

How long is each PE lesson, in minutes

How many hours per week do you spend watching TV and videos, plus playing on the computer and video games (school nights only)

How many hours per week do you spend watching TV and videos, plus playing on the computer and video games (weekend)

How many hours per week do you spend on each of these activities outside PE classes:

Riding bike		Tennis	
Swimming		Netball	
Running		Hockey	
Football		Basketball	
Aerobics/dancing		Rugby	
Gymnastics		Skating	
Walking		Other sport	

Other, please specify

24421

BODY COMPOSITION STUDY: REFERENCE DATA

id O B . [ ][ ][ ]

Parent's opinion of the child's physical activity levels

Total hours child spents in vigorous activity per week [ ][ ][ ]

Level of child's activity compared to peers [ ][ ][ ]

Pubertal Development (if 9 or above)

data to transfer from confidential data sheet

Breast/genital development stage (1-5) [ ][ ][ ]

Pubic hair development (1-5) [ ][ ][ ]

Age periods commenced (months) [ ][ ][ ]

Have periods started yes ○
no ○
not applicable ○

Oral contraceptive or implant? [ ][ ][ ] Yes = 1 No = 2

Date of first day of last menstrual period [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Number of days in whole menstrual cycle [ ][ ][ ]

For example; 5 days menstruation then 25 days to next menstruation = 30 day cycle.

Page 3.2

47423

BODY COMPOSITION STUDY: REFERENCE DATA

id OB.

Gender 1=male 2=female

Gestation .

Birth Weight (g)

Mother's reported weight .

Mother's reported height .

Father's reported weight .

Father's reported height .

Anthropometry

MUAC (cm) .

Head circum (cm) .

Waist circum (cm) .

Hips (cm) .

Thigh circum (cm) .

Calf circum (cm) .

47423

BODY COMPOSITION STUDY: REFERENCE DATA id O B .

BODPOD

Date / /

Time . Temp Pressure

Final Test System

SD Mean Volume .

Test Data

Raw Volume

Test One	Test Two	Test Three
.	.	.
.	.	.
.	.	.
Best Mean		
.	.	.
% Fat		
.	.	.
Raw Density (weight/volume)		
.	.	.

Weight . Height . Lung Volume .

Comments

47423

BODY COMPOSITION STUDY: REFERENCE DATA id OB . [ ][ ][ ]

DEUTERIUM DILUTION

Full bottle of diluted deuterium (g)
[ ][ ][ ] . [ ][ ]

Post dosing bottle weight (g)
[ ][ ][ ] . [ ][ ]

Post dose fluid intake (mls)
[ ][ ][ ][ ]

Time post dose saliva sample taken
[ ][ ] . [ ][ ]

BIOELECTRICAL IMPEDANCE

	Log no.	distance (cm)
Whole arm	[ ][ ][ ]	[ ][ ][ ] . [ ]
Upper arm	[ ][ ][ ]	[ ][ ][ ] . [ ]
Trunk	[ ][ ][ ]	[ ][ ][ ] . [ ]
Upper leg	[ ][ ][ ]	[ ][ ][ ] . [ ]
Whole leg	[ ][ ][ ]	[ ][ ][ ] . [ ]
Whole body	[ ][ ][ ]	[ ][ ][ ] . [ ]
Whole body	[ ][ ][ ]	[ ][ ][ ] . [ ]

Blood Pressure

Systolic	Diastolic
[ ][ ][ ]	[ ][ ]
[ ][ ][ ]	[ ][ ]
[ ][ ][ ]	[ ][ ]

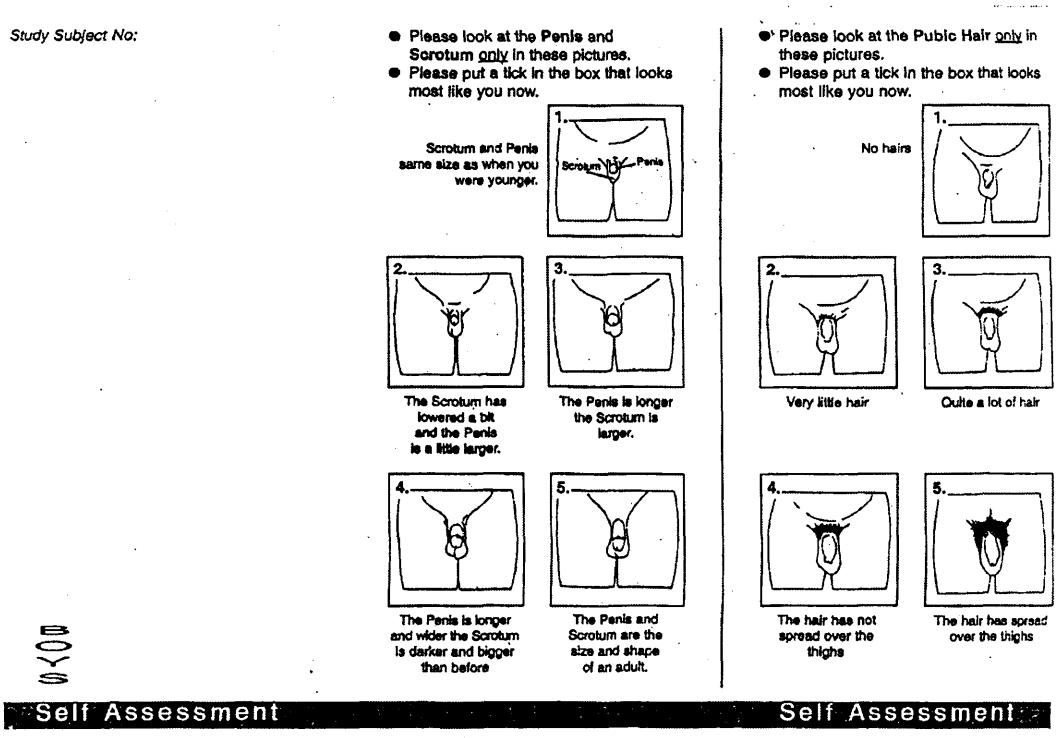
Cuff Size

[ ][ ][ ]

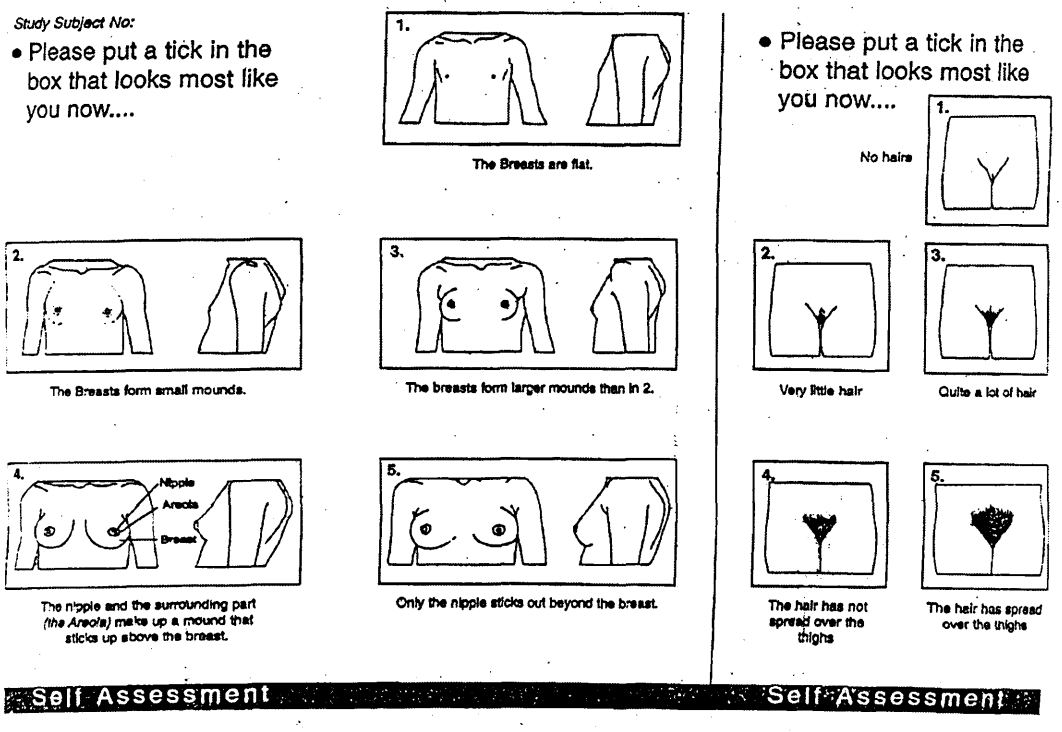
A; Adult
AL; Large Adult
XAL; Extra Large Adult

Appendix 6: pubertal status questionnaire

For boys:



For girls:



Appendix 7: instruction sheet for taking saliva sample

INSTRUCTIONS FOR TAKING SALIVA SAMPLE

Study No.
Date

We need you to take a sample of saliva after you get home and post it back to us in the envelope provided.

..... hours after your special drink at ..... we would like you to do another saliva sample in the same way you did the first. **Do not eat, drink or clean your teeth for 30 minutes before taking the sample.** Move the swab around your mouth until it is very wet without chewing on it.

It is **very important** that you take the sample at this time but if it is not possible it is better that you tell us the time it was taken.

Record time sample taken here .....

We also need to know how much you drank in the period between the special drink and the saliva sample you have done at home.

Record the amount of drink you have had: .....cups (125ml)
.....mugs (150ml)
.....small glasses (150)
.....large glasses (200)
.....cans (330ml)
.....bottles (500ml)

Place the cotton swab in the tube and replace the lid firmly. Put the tube in the plastic bag and seal carefully.

Please return this sheet and the sample in the envelope provided as soon as possible.

THANK YOU FOR TAKING PART IN THIS STUDY

Dalia Haroun
Research Assistant
MRC Childhood Nutrition Research Centre
Institute of Child Health
30 Guilford Street, London WC1N 1EH

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