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Weight status during and after childhood acute lymphoblastic leukaemia

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Table of Contents

List of Figures

List of Tables

Author's declaration

I hereby declare that I (Fahad Khalid Aldafiri) am the sole author of this thesis entitled: Weight status during and after childhood acute Lymphoblastic leukaemia and all the work herein supervised by Professor John Reilly unless otherwise stated. The information reported from any other author has been quoted with the name and source of publication. This is a true copy of the thesis, including required final revisions, accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Design, Method Development

I have developed and designed the methods used in the studies with input from my supervisor, Professor John Reilly.

Data Collection

In prospective studies, I have been responsible for recruiting subjects, conducting and measuring every aspect of the data collection. With the exception of some measurement data which collected using dual energy X-ray absorptiometry, blood pressure measurement, collection and biochemical analysis were done by King Faisal Specialist Hospital & Research Centre (KFSH&RC) staff and laboratories. Also, Mrs. Hanan AL-Mutairi (senior dietician at KFSH&RC) who measured the waist circumference of some of the female subjects to be sensitive to for the demands of Saudi customs and traditions. The retrospective data collected and obtained from The Clinical Trial Services Unit (CTSU) in Oxford.

Data Analysis, Interpretation, and Write-up

I have carried out all of the statistical analysis and interpretation of the data described in this thesis and all the writing is my own. I took advice from Professor John McColl and Dr. David Young (statisticians) on appropriate statistical tests. The writing is my own work under Professor John Reilly's supervision.

List of Publications

Published

- Aldhafiri, F., AL-Nasser, A., AL-Sugair, A., AL-MutairiI, H., Young, D. & Rielly, J. J. 2012. Obesity and metabolic syndrome in adolescent survivors of standard risk childhood acute lymphoblastic leukemia in Saudi Arabia. Pediatric Blood & Cancer, 59, 133-7. (See appendix A)

- Aldhafiri F, AL-Nasser A, Al-Sugair A, Khanna S, Ahmed F, Al-Mutairi H, Reilly J. Importance of Adjusting Dual Energy X-Ray Output For Body Size : An Example From Survivors Of Childhood Acute Lymphoblastic Leukemia. (In press in Journal of Pediatric Hematology and Oncology). (See appendix A)

- Aldhafiri F, McColl J, Reilly J. High prevalence of unhealthy weight status at diagnosis in patients with childhood Acute Lymphoblastic Leukemia: time for nutritional screening?. (Journal of Human Nutrition and Dietetics). (See appendix A)

In press

- Aldhafiri F, McColl J, Reilly J. Overweight and Obesity as Prognostic Factors in Children with Acute Lymphoblastic Leukemia. (Journal of Pediatric Hematology and Oncology) (See appendix A)

- Reilly JJ, Shepherd SK, Aldhafiri FK, Ahmed F. In Reply: Measurement of Bone Mineral Density in Children With Cancer. (ournal of Pediatric Hematology and Oncology).

Abbreviations

%TBF	Percentage total body fat
AAP	American Academy of Pediatrics
aBMD	Arial bone mineral density
AHA	American Heart Association
AML	Acute myeloid leukaemia
BA	Bone area
BFM	Berlin- Frankfurt- Munich
BIA	Bioelectrical impedance
$BMAD_{LS}$	Apparent bone mineral density of lumbar spine
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
CCG	Cancer Study Group
CDC	Centres for Disease Control and Prevention
CI	Confidence interval
CNS	Central nervous system
CRT	Cranial radiation therapy
CED	Chronic energy deficiency
CTSU	Clinical Trial Services Unit
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DXA	Dual-energy X-ray absorptiometry
EFS	Event free survival
FFM	Fat free mass
FM	Fat mass
HDL-C	High density lipoprotein cholesterol
IDF	International Diabetes Federation

IOTF	The International Task Force of Obesity
ISCD	International Society For Clinical Densitometry
KFSH&RC	King Faisal Specialist Hospital & Research Centre
LDL-C	Low density lipoprotein cholesterol
MRC	Medical Research Council
MS	Metabolic syndrome
MSC	Metabolic syndrome component(s)
NCEP III	The National Cholesterol Programme; The Adult Treatment Panel III
NICE	National Institute for Health and Clinical Excellence
OR	Odd ratio
RCT	Randomised controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TBF	Total body fat
TG	Triglyceride
UK	United Kingdome
UKALL	United Kingdom Acute Lymphoblastic leukaemia trial
USA	United State of America
WBC	White blood cell
WC	Waist circumference
WHO	World Health Organisation

Thesis overview

Background:

This thesis sits within the arena of weight status during and after childhood acute lymphoblastic leukaemia (ALL), with a particular focus on the prevalence of unhealthy weight status amongst (ALL), Saudi and UK populations. Each chapter in the thesis explores different aspects of unhealthy weight status in ALL which had been highlighted as gaps in the literature at a conference in Puebla, Mexico, at the end of 2006. A summary of each study is given below.

Study 1:

Background: This study estimated prevalence of unhealthy weight status and metabolic syndrome (MS) amongst Saudi survivors of standard risk ALL. **Methods**: We recruited 56 survivors, mean age 13.4 years (SD 4.1), a mean of 9.1 years (SD 4.1) post-diagnosis. The BMI for age was used to define weight status relative to national (Saudi) and international (Cole et al., International Obesity Task Force (IOTF), World Health Organisation (WHO), and Centre for Disease Control and Prevention (CDC)) reference data. We measured body composition by dual energy X-ray absorptiometry (DXA), waist circumference, blood pressure, lipid profile (HDL-C, Triglycerides), fasting glucose and insulin. **Results**: According to international definitions based on BMI for age, around half of the sample had unhealthy weight status. All of the approaches based on BMI for age underestimated over-fatness, present in 27/51 (53%) of the sample according to DXA. Prevalence of MS was 7.1% (3/42 of those over 9-years old) and 5.4% (3/56) by applying the International Diabetes Federation (IDF) definition and National Cholesterol Education Program Third Adult Treatment panel Guidelines (NCEP III), respectively. However, MS by the NCEP III definition was present in 19% of the overweight and obese survivors and 7.1% of the sample had at least two of the components of MS. **Conclusions**: Unhealthy body weight and over-fatness may be common amongst adolescent Saudi

survivors of standard risk ALL, though overweight and obesity may be no more common than in the general Saudi adolescent population. Defining weight status using BMI underestimates over-fatness in this population, as in other populations.

Study 2:

Background: Underweight, overweight, and obesity at diagnosis may all worsen prognosis in childhood ALL, but no studies have estimated prevalence of unhealthy weight status at diagnosis in large representative samples using contemporary definitions of weight status based on BMI for age. **Methods:** Retrospective study which aimed to estimate prevalence of underweight, overweight, and obesity at diagnosis for patients with childhood ALL on three successive UK treatment trials: UKALL X (1985-1990, n 1033), UKALL XI (1990- 1997, n 2031), UKALL 97/97-99 (1997-2002, n 898) .The BMI for age was used to define weight status with both UK 1990 BMI for age reference data and the IOTF definitions. **Results:** Prevalence of underweight was 6% in the most recent trial for which data were available. Prevalence of overweight and obesity was 35% in the most recent trial when expressed using IOTF definitions; 41% when expressed relative to UK 1990 reference data. **Conclusions:** Even with highly conservative estimates >40% of all UK patients with ALL were underweight, overweight, or obese at diagnosis in the most recent trial for which UK data are available (UKALL 97/99, 1997-2002).

Study 3:

Background: This study tested the hypothesis that overweight/obesity at diagnosis of childhood ALL was related to risk of relapse. **Methods and results:** In a national cohort of 1033 patients from the UK there was no evidence that weight status at diagnosis was related significantly to risk of relapse: log ranks test (p value= 0.90) with overweight and obesity as the exposure (n 917); individual (p value= 0.42) and stepwise (p value= 0.96) proportional hazards models, with BMI z score as the exposure (n 1033). **Conclusion:** The study does not support the hypothesis that overweight/obesity at diagnosis impairs prognosis in childhood ALL in the UK.

Study 4:

Background: In the sample of Saudi patients recruited to study 1 we compared DXA whole body and lumbar spine bone mineral density (BMD) using manufacturers software with a body size correction which derived bone mineral content (BMC) for bone area and Apparent bone mineral density of lumbar spine ($BMAD_{LS}$). **Methods and results:** The survivors of ALL were from Saudi Arabia (n 51, mean age 13.5 years). With no corrections, 29 patients (57%) had lumbar spine BMD z score < -1.0 and 21 (41%) had whole body BMD z score < -2. After correction, by using BMC for bone area method only 6 (12%) had lumbar spine BMC z score <-1.0 and 4 (8%) had whole body BMC z score <-2. By using $BMAD_{LS}$ method, 18 (35%) had BMC <-1.0 and 6 (11%) had BMC Z score <-2. **Conclusions**: Correction for body size seems essential to accurate interpretation of DXA bone health data in adolescent survivors of ALL. The three correction methods provided different conclusions, but bone health remains a concern after treatment for ALL.

Chapter 1

General introduction

1.1 Background

The issue of nutrition in children and adolescents is one of the main public health challenges of the 21st century. Malnutrition as used in this thesis refers to both overnutrition (being overweight/ obese) and undernutrition (being underweight/thin). Moreover, malnutrition remains one of the most significant issues in childhood health in both the developed and developing countries. It may have an effect on survival, development and growth and consequently can lead to reduced strength and capacity of those who are affected (Imdad et al., 2011).

1.2 Undernutrition

United Nations Children's fund (UNICEF) (UNICEF, 2009) has reported that 129 million children in the world are currently underweight, of whom 25% are less than 5 years old. Undernutrition can be assessed by using the individual's height-for-weight, height-for-age and body mass index (BMI); or assessing for deficiencies in their vitamins or minerals. Stunting which is defined as low height-for-age is considered a predictor for chronically undernourished children, it has been observed to be related to cognitive development in children; and low productivity and reduced stature in adulthood. According to United Nations Children's fund (UNICEF), there are 195 million stunted children in the world, 90% of whom are living in Asia and Africa (UNICEF, 2009). Wasting (defined as low weight-for-height) is an indicator for children who are acutely undernourished; which is also highly correlated with the mortality rate (Imdad et al., 2011). Definitions of undernutrition in children will be highlighted below.

From an underweight perspective, deficiencies have usually resulted as a consequence of the macronutrients associated with fat, carbohydrates and protein-energy malnutrition; or in the micronutrients, as in the case of vitamin or mineral deficiencies. The World Health Organisation (WHO) has defined protein-energy malnutrition as a pathological condition caused by diminishing protein-energy intake

which often appears in the first five years of life (Rodriguez et al., 2011). Black et al., (2008) have estimated that 0.6 million and 0.4 million deaths have resulted from vitamin A and zinc deficiencies; respectively. In the non-supplemented vitamin A population, relative risk (RR) of mortality related to vitamin A deficiency is 1.35 (95% CI: 0.96 - 1.89) for measles mortality and 1.47 (95% confidence interval (CI): 1.25 - 1.75) of diarrhoea mortality. Furthermore, zinc deficiency has also been associated with an increased risk of malaria, pneumonia and diarrhoea in the child population (Black et al., 2008) . The main causes of undernutrition are poverty (insufficient food), war and confliction, lack of health services, natural disasters, lack of education, natural disease and sometimes as a result of particular treatments e.g. cancer and its therapy (Rodriguez et al., 2011). Undernutrition may also be caused by poor gastrointestinal absorption, increased demands and high nutrient excretion. This has been represented in figure 1.2.1.

The short-term consequences of undernutrition are disabilities, morbidity and mortality (Imdad et al., 2011). It has been well-known for a long time that undernutrition is highly associated with increased morbidity and mortality rate. Undernutrition is the greatest cause of mortality in the first five-years of life for children in developing countries (Black et al., 2008).

In the early 1990s, Pelletier et al., (1995) reported that mild to moderate undenutrition was sufficient to increase mortality amongst children; and it potentiated the impact of infectious disease for increased risk of death in developing countries. This is because children are the most vulnerable group in accordance with their needs for growth and development. Thus malnourished children have greater susceptibility for infectious diseases such as respiratory and gastrointestinal infection as a consequence of the deterioration in the capacity of their immune systems in producing all of their cellular components (Rodriguez et al., 2011).

Figure 1.2.1: Causes of undernutrition and its consequences.
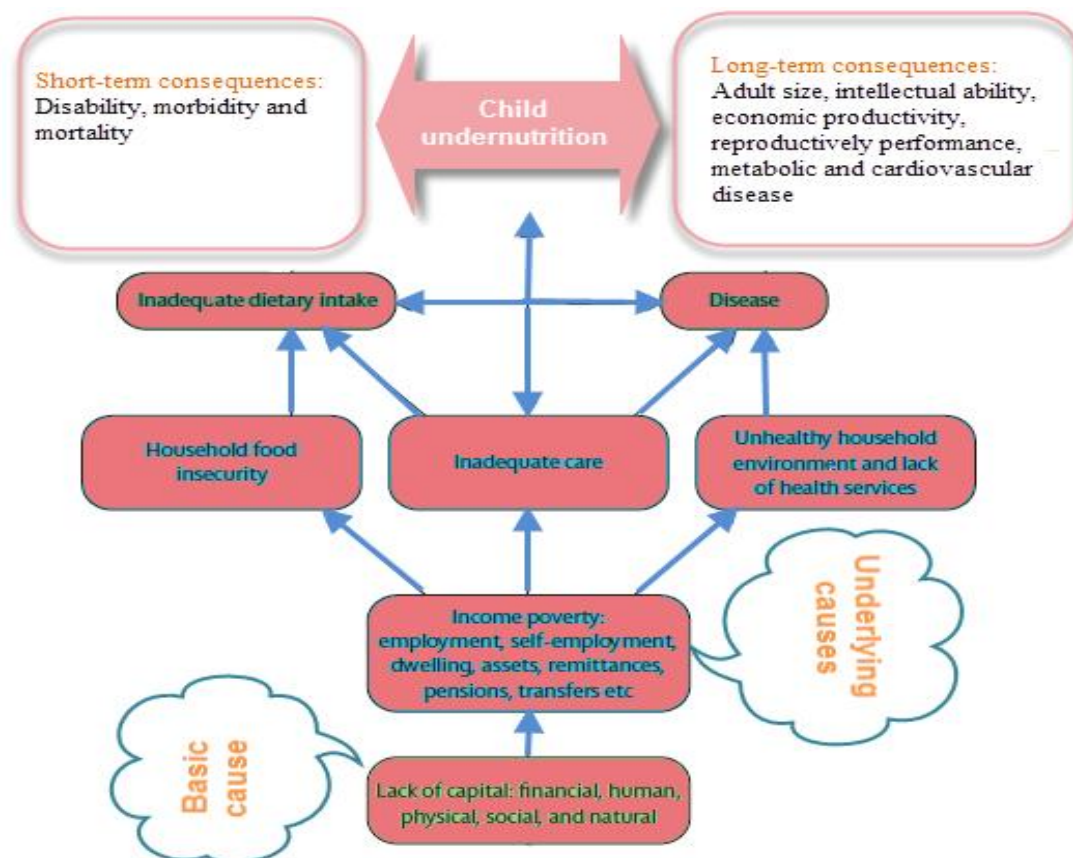
Source: Modified from Black et al., (2008)

A review article has estimated that around 2.2 million children deaths throughout the world have been caused by severe wasting, stunting and intrauterine growth restriction. Moreover, together these are responsible for 21% of disability-adjusted life years "which is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death" (Black et al., 2008).

In the long-term the consequences of undernutrition can cause reduced body size, poor intellectual ability, low life productivity and cardiovascular and metabolic disorders. Dewey and Begum (2011) reviewed a number of longitudinal studies and

reported strong evidence for the association between stunting in early life and short stature in adulthood. Moreover, they also reported that there was a relation between stunted men and lack of economic productivity. There is also a link between stunted women and low general health, survival of their babies and reproductive health. Undernutrition in children, for any reason even with/without repeated infection, may cause stunted and functional damage to the brain, which in turn, may lead to cognitive impairment (Kar et al., 2008).

It is worth noting that International Dietetics and Nutrition Terminology has defined malnutrition as " inadequate intake and/or energy over prolonged period of time resulting in loss fat stores and/or muscle wasting including starvation-related malnutrition, chronic disease-related malnutrition and disease or injury-related malnutrition" (American Dietetics Association, 2010). Also, worth defining chronic energy deficiency (CED) which is a condition of the body characterised by low body weight and low energy stores and possibly limited physical capacity due to deprivation of food over a long period of time, with body mass index (BMI) of less than 5th percentile for children and adolescents or less than 18.5 kg/m2 for adults. Moreover, based on WHO definition, CED is categorised according to BMI as having either grade III chronic energy deficiency (BMI: < 16.0), grade II chronic energy deficiency (BMI: 16.0–16.9) or grade I chronic energy deficiency (BMI: 17.0–18.49) (Gibney, 2005). Moreover, in the public health arena, starvation-related malnutrition is related usually to famine secondary to conflict or natural disasters. On the other hand, disease-related malnutrition usually refers to patients with chronic disease and an inflammatory component is commonly seen in various clinical settings. Figure 1.2.2 shows that anorexia is usually a result of some chronic or severe diseases such as cancer AIDS and chronic obstructive pulmonary disease (COPD) which results in disease-related malnutrition. Malnutrition combined with stress-associated catabolism related to inflammation elevates the risk of organ dysfunction, frequent infections and impaired healing (Norman et al., 2008). Also, acute illness such as infection and trauma can be a trigger for an inflammatory response to cause starvation or/and

stress-associated catabolism and which in turn exacerbates malnutrition (Norman et al., 2008).

Figure 1.2.2: Vicious of the development and progression of disease-related malnutrition
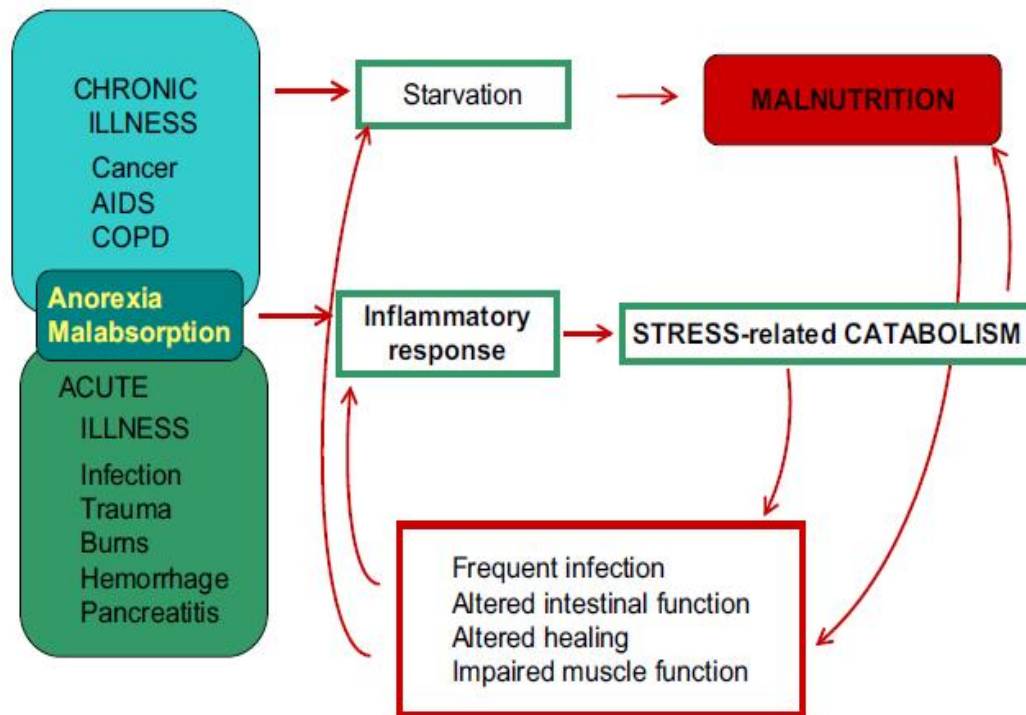
COPD: Chronic obstructive pulmonary disease

Source: Normal et al., (2008)

1.3 Childhood obesity

Childhood obesity is presently a major public health issue because it is widespread and has multiple implications for present and future child health. Childhood obesity has been made more complex as a consequence of many factors from multiple settings during the growth and development of children (Davison and Birch, 2001). WHO has defined obesity as the presence of a high body fat mass (FM) connected

with high co-morbidities (World Health Organisation, 2000). Definitions of childhood obesity will be discussed in the following section.

1.3.1 Global epidemic of childhood obesity

In recent years, obesity in children and adolescents has become a global epidemic. The occurrence of being overweight and obese has risen considerably in industrial countries since the early 1980s and in developing countries since the 1990s as shown in figure 1.3.1 (Bawa, 2005, Lobstein T, 2007). The prevalence of those who are overweight and obese has markedly increased 2.3 - 3.3 fold in the United State of America (USA) over 25 years; 2.0 - 2.8 fold in England over 10 years;, 1.8 - 2.3 fold in Scotland over 10 years and 3.9 fold in Egypt over 18 years (Ebbeling et al., 2002). In the 1970s, the prevalence of overweight and obese children and adolescents was defined as ≥85th percentile according to the Centres for Disease Control and Prevention (CDC) for those aged 2-19 years and around 15 % in the USA; whilst by 2003 - 2006 it had sharply risen to around 32 % (Ogden et al., 2008). In a recent study in Saudi Arabia the overall prevalence of overweight and obese children and adolescents had reached 35.4% (El Mouzan et al., 2010).

However, although the global epidemic of childhood obesity has been shown to be continuing to increase; a recent US study suggests that the prevalence of obesity defined as ≥95th percentile based on CDC has remained unchanged at around 17% over the period 2009 - 2010 when compared to the period 2007- 2008 (Ogden et al., 2012). A recent systematic review Rokholm et al., (2010) suggests that global childhood obesity has been levelling off in recent years. However, they emphasised that the current prevalence is much higher than before and could be in the future followed by new elevations; and therefore there are sufficient reasons to focus on cause, prevention and treatment (Rokholm et al., 2010).

29

Figure 1.3.1: Increasing childhood obesity in selected countries
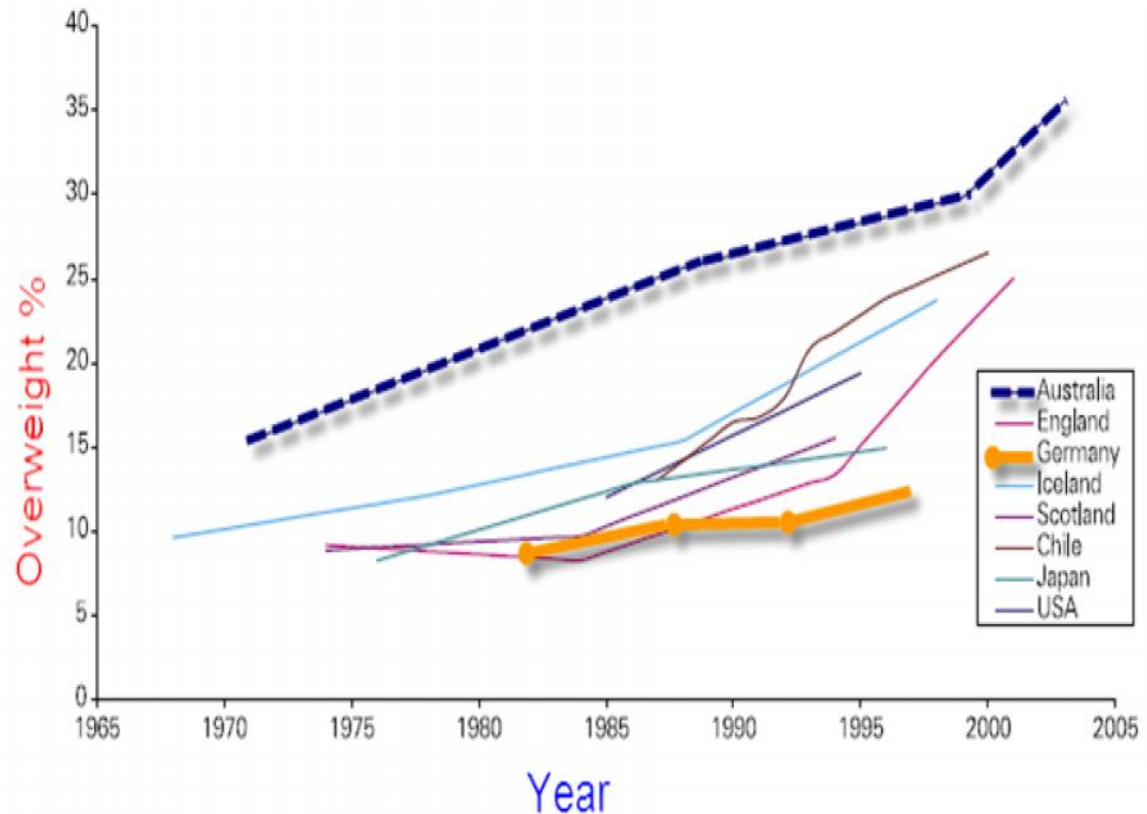
Source: Modified from Lobstein (2007)

1.3.2 Health consequences of childhood obesity

The co-morbidity of obesity and the impact on children's health is now well-established. There is numerous evidence which now points to the consequences of childhood obesity which can occur in both the short and long-term and has a potential effect on the lifespan (Reilly et al., 2003, Olshansky et al., 2005). A high BMI in children has a high linear correlation with risk of diabetes and impaired glucose metabolism, hypertension, fatty liver, gallstones, dyslipidaemia, cardiovascular risk factors and metabolic syndrome (MS) (Willett et al., 1999); and other medical complaints such as psychological co-morbidity, orthopaedic problems and sleep apnoea (Kiess et al., 2001) (summarised in figure 1.3.2). This thesis will briefly

discuss some of these consequences as some of them are beyond the scope of this research.

Figure 1.3.2: Consequences of childhood obesity
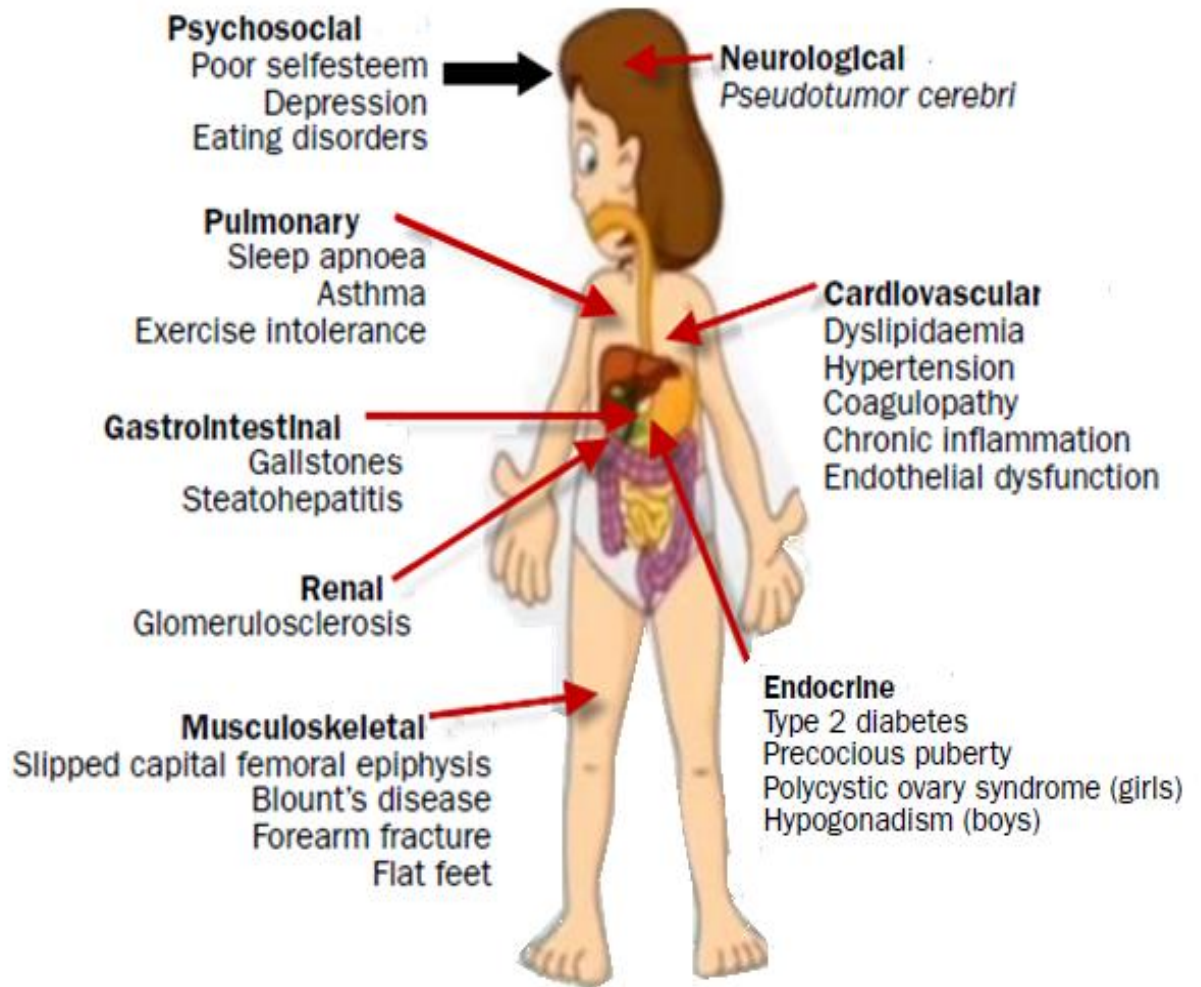
Source: Modified from Ebbeling et al., (2002)

1.3.3 Psychological co-morbidity

Psychological co-morbidity is highly related to the presence of obesity in children (Daniels et al., 2009, World Health Organisation, 2000). Griffiths et al., (2010) reported that obesity in children and adolescents had an impact on the lowering of their self-esteem and self-confidence and it could result in depression.

There are other psychological and social consequences which are related to childhood obesity such as social functioning, eating disorders, body dissatisfaction, discrimination, stigmatisation and prejudice (Griffiths et al., 2010, Daniels et al., 2009).

1.3.4 Obesity tracking into adulthood

Childhood is a critical phase because it is precursor of adulthood. It is one of the most concerning issues as a long-term childhood consequence. Three systematic review publications have examined the persistence of childhood obesity into adulthood. Firstly, 18 publications, all of them of longitudinal designs, were reviewed by Singh et al., (2008). They stated that all studies pointed to the fact that being overweight or obese in childhood increased the risk of being overweight or obese in adulthood. In addition these studies showed that the tracking of being overweight in adulthood was highly associated to the level of being overweight in childhood. High-quality studies indicated that overweight children who were at risk of being overweight in adulthood had at least a two-fold risk than normal weight children. Authors reported that the percentage of those being overweight in adulthood as a result of being overweight in adolescence ranged from 22 - 58% based on 3 high-quality publications. Moreover, the percentage of being overweight or obese in adulthood as a consequence of being obese in adolescence ranged from 24 - 90 %. Therefore, risk of being overweight or obese in adulthood is increasing consistent with the age of the groups of children. They concluded that the evidence associated with the persistence of childhood obesity into adulthood was 'moderate' (Singh et al., 2008). Similar findings were

stated in systematic reviews by Reilly et al., (2003) and Power et al., (1997). The review by Reilly et al., (2003) was the first systematic review regarding the impact of childhood obesity in the long-term based on critical appraisal. They appraised 47 studies and concluded that obesity during childhood was likely to track into adulthood. In addition a strong relationship was found between the percentage body fat in childhood and adulthood (Power et al., 1997). However, most of the systematic review evidence was based on either small numbers of subjects or old cohorts from before the second war era; this evidence is questionable, particularly because of the tracking of childhood obesity into adulthood in the modern 'obesogenic' environment.

There is strong evidence that childhood obesity leads to adulthood obesity according to the literature based on large sample sizes and conducted in the modern 'obesogenic' environment. For instance, in a recent longitudinal study, Reilly et al., (2011) examined a large sample (n = 2175) of 7-year olds over a 6 -year period (at age 13 years). They defined being overweight when BMI z scores ≥ 1.04 and obesity when BMI z score ≥ 1.64 according to UK reference data. The findings showed that there was an adjusted Odd Ratio (OR) of being obese at 13 years of age for being overweight at age 7-year old which was 18.1 (95% CI: 12.8 - 25.6). They also found that, at age 7, 34% children who had been considered to be overweight had been classified as being obese at aged 13. In addition, Freedman et al., (2005a) examined prospectively 2610 participants in the USA aged 2.5 - 17 years and followed them at age 18 - 37 years. They reported that the percentage of overweight (defined as BMI for age $\geq 95^{th}$ percentile) children being obese in adulthood (defined as BMI ≥ 30 kg/m^2) aged 2 - 5 years and 15 - 17 in males and females was 93% and 73%, 86% and 90%; respectively.

Many factors have arisen which may play a role in increasing the tracking of childhood obesity into adulthood in more recent years. These factors are low family socioeconomic class at birth, maternal obesity, early menarche, adolescent obesity and severity of obesity (Whitaker et al., 1997, Reilly et al., 2011, Laitinen et al., 2001).

1.3.5 Cardiometabolic risk factors

1.3.5.1 Impaired glucose metabolism

Rise of prevalence of diabetes in obese young people is now emerged. So, impaired glucose metabolism and diabetes in children is mainly the result of obesity as in the adult population. However, the pathological nature associated with the development of diabetes in adolescence remains unknown (Debelea et al., 1999). The prevalence of impaired glucose metabolism in US obese children was found to be 20%; 27% in Latino children living in the USA; whereas in France the prevalence was 15 - 20 % (Weiss, 2007). One dire prediction from CDC estimated that third of newborns born in 2000 will have diabetes if the rate of obesity remains on the same current pace.

In a review paper Kempf et al., (2008) showed that the prevalence of impaired glucose and diabetes was high in US children; whilst the rate was less noticeable in European countries. Therefore, ethnic background is an important risk factor of impaired glucose intolerance and diabetes.

There is good evidence of a relationship between adiposity in childhood and insulin resistance, impaired glucose tolerance and type 2 diabetes. Sabin et al., (2006) investigated the consequences of obesity in a clinical sample of 126 children with a mean age of 11.2 years. They reported that 10.3 % of the subjects had impaired glucose tolerance, which was the main precursor for diabetes. In addition, a large cohort Caucasian study in Germany conducted on 520 subjects (237 boys and 283 girls) aged between 8.9 - 20.4 years of age examined the prevalence of diabetes amongst obese children and adolescents by using a 2-hour oral glucose tolerance test. They found that 1.5 % of the children had diabetes, and 6.7 % had impaired glucose regulation. Weiss et al., (2003) have reported that obese children with impaired glucose tolerance, which is a strong predictor for diabetes type 2, are more likely to have insulin resistance, i.e. pre-diabetes, than those with normal insulin tolerance.

Consequently, the American Diabetes Association (ADA) suggests screening children and adolescents who have overweight (BMI≥ 85th) and having other risk factors of diabetes such as high blood pressure, high lipids profile or ethnic minority (American Diabetes Association., 2000). Furthermore, Daniels et al., (2009) have highly recommended the screening of overweight or obese children for impaired glucose metabolism in order for its prevention and management.

1.3.5.2 Cardiovascular diseases (CVD)

Many studies have shown a relationship between adiposity and CVD in adults (Ingelsson et al., 2007, Manson et al., 1990). Therefore, in the last few decades more attention has been focused on investigating this risk within paediatrics as obesity became globally epidemic. There are data linking between high level of serum lipids and lipoprotein during childhood and progression of the atherosclerosis in adulthood (Berenson et al., 1998). Fatty streaks which progress into plaque formation in the lining of the arteries, a condition known as atherosclerosis, can contribute to heart disease (Berenson et al., 1998).

Post-mortem studies (Berenson et al., 1998, McGill et al., 2001) have revealed that early atherosclerosis and advanced lesions are strongly associated with an increase in total cholesterol, LDL-C and low level of HDL-C as well as in the presence of other risk factors such as obesity, hypertension and smoking. Moreover, such studies have demonstrated that there is a relationship between being overweight during childhood and young adulthood and prevalence of atherosclerotic lesions in the aorta and coronary arteries. Pos mortem studies have shown that coronary calcium in later life could be predicted in those who are overweight during early life. Coronary calcium is known to be a marker of plaque formation in the arteries which can lead to myocardial infarction. Also, in the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) over 5 decades of study, Zieske et al., (2002) have concluded that there is an

abundance of evidence which supports the argument that atherosclerosis begins early in childhood.

Furthermore, findings from 3 pooled historical cohort studies, Lawlor et al., (2006) demonstrated that a high BMI in childhood tended to be connected with increased risk of adult CVD. Thus the adjusted hazard ratio per standard deviation of childhood BMI was 1.09 (95% CI: 1.01 - 1.19) and 0.94 (95% CI: 0.82 - 1.08) for ischemic heart disease and stroke; respectively. However, there was no observable correlation between stroke and being overweight or obese. Hence, they assumed possible explanations for these findings. Firstly, future CVD risk outcome has only been linked with a morbid obesity level during childhood. Secondly, being overweight in childhood has been unable to predict the CVD risk if other risk factors during the life cycle are not present or are controlled in a proper manner. Finally, the BMI is not a good indicator for child adiposity which has a link to both fat mass and fat free mass. Moreover, Korsten-Reck et al., (2008) examined the relationship between dyslipidaemia and obesity in children. Thus 546 obese patients aged 7-12 years old were observed. Obesity was defined as at or above the 97th percentile using the German reference. They found that 45.8% of overweight (at or above the 90th percentile) children had an abnormal lipid profile; 10% of children had high LDL-C; 15% of children had high LDL-C and high triglycerides (TG) and 18.9% had high TG and low high-density lipoprotein (HDL-C). Therefore, they demonstrated that obese children were more likely to have an abnormal lipid profile.

However, to our best knowledge, no longitudinal population-based studies have been conducted linking high lipid profile in childhood and actual CVD in adulthood. Furthermore, no randomised controlled trials have been conducted which show that improving adverse lipid profiles in childhood reduces actual CVD in adulthood. The mentioned studies indicate that adverse lipid profiles accelerate atherosclerosis processes from early life until late life, and consequently, point to the public health importance of primary prevention and management of obesity in early life.

Hypertension is one of main causes of cardiac problems such as stroke or heart attack in adults (Ong et al., 2007). Obesity may play a key role in elevated blood pressure in adults; and childhood obesity may also elevate the blood pressure. However, the pathogenesis of this mechanism is still not completely understood (Becton et al., 2012). Epidemiologic studies have established a link between hypertension and childhood or adult obesity. Rosner et al., (2000) showed that overweight children and adolescents were 2.5 - 3.7 times more likely to suffer from hypertension. In addition, researchers of the Muscatine study showed that the progression of being overweight during childhood was considered a good predictor for the level of hypertension during adulthood (Lauer and Clarke, 1989).

Moreover, hypertension is known to be persistence over time. Hypertensive adolescents are more likely to have hypertension in adulthood than non-hypertensive adolescents. The essential risk factors that remain high blood pressure tracking from childhood to adulthood are obesity, low physical activity, dietary pattern such as high sodium intake and smoking (Chen et al., 2008). Accordingly, these results are quite crucial from a clinical perspective that health primary providers can early and frequently investigate blood pressure in children and adolescents to identify pre-hypertension and even hypertension, therefore, early intervention and management can be offered.

Current recommendations have been made by the American Academy of Paediatrics (AAP) and the American Heart Association (AHA) with regards to the management of dyslipidaemia. The AAP has recommended the testing of children aged 2 years and above who have an unknown family history or present with one of the cardio metabolic risk factors such as diabetes, hypertension and obesity (Daniels and Greer, 2008). They have also found that increased screening of children has occurred with the increased prevalence of obese children (Daniels and Greer, 2008). The AHA has recommended the screening of children aged 2 - 18 years with consideration for high-risk individuals with a family history of diabetes, HIV infection, nephritic syndrome and

systemic lupus erythematosus. The AHA has also considered TG and HDL-C abnormal when the level is ≥ 150 mg/dl and is ≤ 35 mg/dl; respectively (McCrindle et al., 2007).

1.3.5.3 Metabolic Syndrome (MS)

MS is "a grouping of clinical characteristics including insulin and insulin resistance, abdominal obesity, impaired glucose tolerance, elevated blood pressure (BP), elevated TG and reduced HDL-C" (Saland, 2007). Moreover, the association between these components has been disputed since 1920 (Wannamethee et al., 2005). However, in 1988, Reaven illustrated the role of insulin resistance and its relationship in adults with other diseases such as obesity, type 2 diabetes, dyslipidaemia, hypertension and CVD (Bremer et al., 2012).

The prevalence of MS is found within around 25 % of the adult American population (Ford et al., 2002); and more attention has been paid to this condition since the sharp increase in obesity (Speiser et al., 2005). Obesity is known to be a strong indicator for CVD in adults (McGee, 2005). Consequently, the US national Heart, Lung and Blood Institute has recommended that the diagnosis and treatment of MS should take place in a clinical setting (Fernandez et al., 2009).

MS in childhood and adolescence has only recently been recognised; and some studies have found a relationship between CVD and obesity and insulin resistance in children (Falkner et al., 2002). To be more precise, CVD is a rare disease in early life and therefore it has received little attention from paediatricians. In fact, in children, it is the process which leads to diseases which begin early e.g. vascular damage which can occur in early life. Moreover, type 2 diabetes among obese children has recently increased and may lead to serious complications in the entire life cycle (Fagot-Campagna et al., 2000).

1.3.5.3.1 Defining Metabolic Syndrome in Paediatrics

There are a number of diverse definitions of MS and many of these have been developed for adults. For instance, definitions have been provided by the WHO (Alberti and Zimmet, 1998); the National Cholesterol Education Program the Adult Treatment Panel III (NCEP III) (Expert panel, 2001) the European Group for the study of Insulin Resistance (EGIR); the American College of Endocrinology Task Force on the Insulin Resistance Syndrome (Garber et al., 2004) and the International Diabetes Federation (IDF) (Zimmet et al., 2005). However, still there is no consensus as to which definition is recommended to use in defining MS in adults.

However, using MS adult definitions is unsuitable and would underestimate the prevalence of MS in children and adolescents. Therefore, paediatric MS is defined by a number of different approaches. Some of these definitions have been modified from an adult definition such as those provided by Cook et al., (2003) and Weiss et al., (2004) modified from the NCEP III definition; but produce different cut-offs. However in 2007, the IDF released a new international definition of MS in paediatrics. They aimed to produce a useful and unified definition (Zimmet et al., 2007). Subsequently, there has been no consensus in using the IDF definition by researchers and there has been confusion regarding which definition of MS is most appropriate.

Table 1.3.1 summarises definitions of MS in the paediatric literature. So, the prevalence of MS in the paediatric population has been broadly varied as a result of lack of an existing universal definition and lack of nationally representative samples. For example, a recent study was carried out on a small number of obese adolescents (n= 51) and those of normal-weight (n= 30) Danish adolescents aged 12 – 15 years (Gobel et al., 2012). They reported that the prevalence of MS amongst obese adolescents was 14% (7/51).

Table 1.3.1: Some studies on metabolic syndrome in paediatrics

References	Sample size Place Age (years)	Metabolic syndrome definition	Prevalence of metabolic syndrome
Globel et al., (2012)	• 51 (obese); M: 29, F: 22. 30 (normal weight);M: 13, F: 17 • Denmark • 12 - 15 years	IDF (having central obesity plus 2 or more criteria): • WC ≥ 90th • FG ≥ 100 mg/dl • TG≥ 150 mg/dl • HDL-C ≤ 40 mg/dl • DBP ≥ 130 or SBP ≥ 85 mmHg	• 14% of obese had MS • Non obese did not have MS
Al-Daghri et al., (2010)	• 1231; M: 760. F: 471 • Saudi Arabia • 10 – 18 years	NCEP III modified by de Farranti et al. (3 or more of the criteria): • WC≥ 75th • TG≥ 100 mg/dl • HDL-C < 50 (Girls) and < 45 mg/dl (boys) • FG ≥ 110 mg/dl • BP> 90th	• 9.4% diagnosed with MS • Prevalence of MS was 10.3% and 8.1% in boys and girls; respectively
Taha et al., (2009)	• 57 (obese); M: 33. F: 24 • Saudi Arabia • Mean (SD): 9.8 (3.5) years	NCEP III and WHO (3 or more criteria): • BMI > 95th • TG > 95th • HDL-C < 5th • SBP and DBP > 95th • FG > 110 mg/dl	• 29.7% of the sample met MS criteria
Eapen et al., (2010)	• 260 (obese); M: 153. F: 107 • United Arab Emirate • Mean (SD): 14.5 (2.6) years	NCEP III modified by Cook et al. (3 or more of the criteria): • WC> 90th • TG≥ 100 mg/dl • HDL-C ≤ 40 mg/dl • FG ≥ 110 mg/dl • BP >90th	• 44% of obese had MS
Al-Isa et al., (2010)	• 431 (girls) • Kuwait 10 -19 years	IDF and NCEP III modified by Cook et al. • Discussed above	• By using IDF, 14.8% met MS criteria • 9.1% had MS based on NCEP criteria

M: Male; F: Female; IDF: International Diabetes Federation; WC: Waist circumference; FG: Fasting glucose; TG: Triglycerides; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; NCEP: National Cholesterol Education Program; WHO: World Health Organisation.

In addition, there is no consensus in definition of MS in paediatrics even in the same country or the same region. For instance two Saudi studies used different MS definitions. Firstly, in a community-based cross-sectional study, Al-Daghri, (2010) examined (n=1231) for prevalence of MS. The overall prevalence of MS was found to be 9.4%. However, A hospital-based Saudi study was carried out on 57 children who were only obese with a mean age and standard deviation (SD) of 9.8 (3.5)(Taha et al., 2009). The prevalence of MS was found to be 29.7%. A review article by Tailor et al., (2010) found the prevalence of MS amongst children and adolescents around the world was around 10%, however, it varied from around 2% in those of normal weight up to around 32% in those defined as obese. Obese children and adolescents had an approximately 15-fold increased risk of having MS when compared to those defined as being normal weight (Tailor et al., 2010). Prevalence of obesity and MS was shown to be elevated in a parallel manner in the review by Tailor et al., (2010).

In addition, a United Arab Emirates study of 260 obese (defined as BMI > 95th percentile) adolescents with a mean age (SD) of 14.5 years (2.6) (Eapen et al., 2010) reported one of the highest prevalence amongst adolescents in the world at 44% with MS. In a Kuwaiti study amongst the female adolescent population aged 10 - 19 years old (Al-Isa et al., 2010) prevalence of MS was 14.8% and 9.1% according to IDF and NCEP III; respectively.

To sum up, the previous studies defined MS by using different approaches with hugely different sample sizes and types of samples; consequently, there are apparently enormous differences in MS prevalence even in same population. Reinehr et al., (2007) aimed to compare the prevalence of MS according to the criteria of Weiss, Viner, De Ferranti, Cook, WHO, European Group for the study of Insulin Resistance (EGIR), NCEP III and the IDF. This study was carried out on 1205 German, Caucasian overweight children between 4 and 16 years of age defined in line using IOTF criteria (Cole et al., 2000). They observed that the prevalence of MS varied significantly (p value < 0.001) (6 – 39 %) in these definitions and only 9% of participants conformed to all of the MS definitions. Also, some of MS definitions such

as IDF and NCEP definitions use age-adjusted indicator criteria which are important to classify MS according to a specific age because prevalence of MS is more likely to occur in adolescents than younger children.

Even though the majority of studies that defined MS in paediatrics included the following variables: anthropometrics, blood pressure, plasma glucose and lipid profile, there were substantial differences in defining abnormal values of individual MS components. For example, the cut-off level for TG and HDL-C are fixed with more than 150 mg/dl less than 40 mg/dl; respectively, by IDF definition. The NCEP III modified by de Ferranti et al., 2004 on the other hand used for TG more than 100mg/dl and less than 50 mg/dl for girls and 45 mg/dl for boys.

The recent existence of a standard MS definition helps answering to what extent MS affects children and adolescents, facilitates international comparisons of prevalence, assists in conducts and interpretation of clinical trials, helps in investigate the underlying pathological mechanisms and facilitates health professionals to identify and manage MS.

1.3.5.3.2 Metabolic syndrome from childhood to adulthood

Abundant studies have pointed out the association between MS in childhood and its persistence into adulthood. In a longitudinal study which followed children aged 9 years old at the beginning of the study for 6 years the tracking of MS from childhood to adulthood amongst 174 Swedish and 460 Estonian children (Martinez-Vizcaino et al., 2011). MS and its risk factors showed persistence from childhood to adulthood. Moreover, from the Bogalusa Heart Study, Freedman et al., (2001) examined 2617 subjects and followed them for up to 17 years; and 77% who had been overweight as children with a BMI ≥ 95th percentile stayed obese in adulthood. They also found that being overweight in childhood was related to the elevation of adverse risk factors such as high BMI, lipids, insulin, blood pressure (BP) and diabetes in adulthood; and

that this may be caused by the strong persistence of weight status between childhood and adulthood. Correspondingly, Morrison et al., (2008) stated that children and adolescents with MS and a family history of diabetes type 2 had significantly elevated risk of MS and diabetes type 2 in adulthood. Similarly, Srinivasan et al., (2002) stated that childhood obesity was connected to the likelihood of clustering of all four MS components (BMI, fasting glucose, BP, total cholesterol to HDL-C ratio to TG to HDL-C ratio) in adulthood. Children in the top quartile of BMI were 11.7 times more likely than those in the bottom quartile to develop clustering of MS in adulthood. Moreover, they concluded that obesity during childhood was considered to be a strong predictor of MS risk components in adulthood, this conclusion was supported by Chen et al., (2007) as well. The Quebec Family Study, Katzmarzyk et al., (2001) examined the stability of MS components from the paediatric phase to early adulthood. The sample included 76 males and 71 females. They found significant tracking of MS components from early childhood into adulthood. To some extent, MS in adulthood may be expected from an examination of children and adolescents; and therefore, when they have low HDL-C, high central obesity, BP, cholesterol, TG and fasting glucose, they are more likely to be at high risk in early adulthood.

However, an essential question is whether MS usefully predicts CVD and diabetes? Sattar et al., (2003) investigated the association between MS and CVD and diabetes. They recruited 6447 men to predict CVD and 5974 men (mean (SD) age 55.1 years (5.5)) to predict incident diabetes and followed over 4.9 years. By using modified MS definition, MS was associated with 70% higher risk of CVD in univariate model but, by using multivariate model the higher risk dropped to 30%. Besides, they measured fasting glucose at each 6 monthly visit. Men with MS were at 270% increased risk of incident diabetes. Therefore, MS modestly predicts CVD and more strikingly predicts incidence of diabetes. A meta-analysis (Gami et al., 2007) found that after adjusting for traditional risk factors around a 50% higher risk of CVD events and death in patients was found compared to those without MS. They included studies that had

cohorts without baseline disease, the pooled RR was 1.49 (95% CI: 1.37 – 1.61). Therefore, MS may be associated modestly with CVD in middle-aged people.

MS may be a weaker predictor of CVD than diabetes in part because high BMI or WC are around 10 times more strongly related to diabetes than CVD. Also, hyperglycemia in non-diabetics is not very predictive of CVD (Sattar et al., 2003). Likewise, high triglyceride concentration is more associated with diabetes than CVD (Sattar et al., 2003). Accordingly, by using an MS definition such as NCEP III and IDF, three out of five components are more closely associated with incidence of diabetes than CVD. Moreover, there are other critical risk factors which are not appreciated according to MS definitions and more closely aligned to risk of CVD such as age, LDL-C and smoking status (Sattar et al., 2008).

1.4 Nutritional assessment in children

From a historical perspective, nutritional assessment was originally used in detecting undernutrition and nutrient deficiencies especially with regards to energy and protein. Later on, there was awareness of an increasing prevalence of overnutrition (being overweight/obese) and recognition of undernutrition especially with regards to illness (Gibson, 2005). Therefore, the aims of nutritional assessment are: to diagnose whether the individual is over or under nourished, monitor the nutritional change over time in individuals, groups and the population and finally determine the prevalence of the under or overnutrition in groups and population (Gibson, 2005, Gibney, 2005).

Nutritional health is the cornerstone in maintaining children against illness. Consuming a balanced nutrient intake (adequate nutrition) is essential for proper development and growth. Any deficit in the energy intake is more likely to lead to malnutrition. Weight status is also implicated in predicting the persistence of chronic illness into adulthood (Yang et al., 2007, Herman et al., 2009).

Nutritional status assessment is a broad topic and there is no single exact tool for its use in clinical settings. Theoretically, it remains the ideal approach in assessing the nutritional status that can screen individuals and identify those who are at risk from morbidity and mortality (Mascarenhas et al., 1998). Consequently, there are several different approaches and concepts behind them to evaluate nutritional status. The main nutritional assessment approaches include: clinical, anthropometric, dietetic, biochemical and functional methods. Some of these approaches have been used in the present thesis; however the others are beyond the scope of the present thesis and are discussed very briefly.

1.4.1 Clinical approaches to nutritional assessment

This approach is historical in nature and is based on physical examination of features which would appear to be biologically meaningful. Furthermore, a medical history should be recorded. For example, any weight changes over the previous period of the patient and whether the changes were voluntary or not. In addition there are several questions in the patients' history which are necessary to provide a full picture such as their number and sizes of meals, appetite and satiety, chewing and swallowing, nausea and vomiting, bowel habits and use of herbal remedies or supplements (Gibson, 2005, Gibney, 2005). Thus, clinical nutrition assessment depends on the signs which are observed by the qualified examiner and symptoms which are stated by the patients (Gibson, 2005).

Subjective global assessment (SGA) is an example of a clinical approach for assessing malnourished patients. It is based on a medical history such as weight changes, changes to dietary intake and gastrointestinal symptoms; and physical status such as muscle wasting, oedema and loss of subcutaneous fat (Gibney, 2005). Nonetheless, this approach relies on signs and symptoms that are often not specific and may emerge at the end stage of nutritional deficiency. Subjective global assessment (SGA) has been validated in preoperative children according to Secker

and Jeejeebhoy (2007). They evaluated prospectively 175 31 day to 17.9 year old patients having major thoracic or abdominal surgery by using subjective global nutrition assessment (SGNA) which was adapted from Subjective global assessment (SGA). They tested the hypothesis that SGNA could predict nutrition-associated complications i.e. infection, use of antibiotics and length of stay. They reported that malnourished patients had significantly (p value= 0.04) higher rate of infectious complications than well-nourished patients. Also, postoperative length of stay was significantly (p value= 0.002) longer in malnourished patients (8.2 ± 10 day) than in the well-nourished (5.3 ± 5.4 day).

Moreover, the qualifications of the physical examiner play an intrinsic role in assessing the nutritional status of the patient; and inconsistency in observation is a possible disadvantage (Smith et al., 2008, Gibson, 2005, Gibney, 2005). As an example of the possible using clinical nutritional assessment of childhood obesity, Smith et al., (2008) asked 80 healthy professionals to observationally rate 33 children and adolescents aged between 10 - 17 using their full-length photographs. The health professionals assigned the children into one of six categories (from very underweight to obese) by using direct observation. There was significant under-recognition of obesity (compared BMI percentile) between health professionals. They concluded that health professionals should be aware of the limitations of the observational approach in assessing obesity rather than using formal measurements. A further discussion of clinical nutritional assessment is beyond the scope of this thesis.

1.4.2 Dietetic approach to nutritional assessment

Using this approach, inadequate nutritional intake as a result of low levels of the diet (primary deficiency) would possibly be detected. In addition it would help in the identification of secondary nutrient deficiency which had occurred according to nutritional needs in certain conditions such as drug-nutrient interactions or in some

diseases that influence nutrient absorption such as cystic fibrosis (Gibson, 2005). Therefore, the main advantage of this approach is identified in the individual who is at risk. So, Health professionals may be able to detect patients may be consuming less energy than they need to maintain healthy weight status. For instance, many studies reported that cancer treatments may cause low food intake, decrease gut absorption and elevated metabolic demand (Lai et al., 2005). Moreover, cancer patients are more likely treated with radiotherapy, chemotherapy and bone marrow transplantation, which can cause taste perception (sourness, bitterness and metallic taste), appetite and vomiting. These side effects might lower food intake and lead to malnutrition (Chiodi et al., 2000, Epstein et al., 2002).

This approach has different ways of measuring dietary intake in children the choices of which depend on the aim and characteristic of the sample of the study. The best way is probably the 3-day weighted record of food intake which subsequently analyses the data using a computerised analysis for nutrients and energy (Mascarenhas et al., 1998). In addition, 24-hour recall is used for estimating energy intake (Mascarenhas et al., 1998). In a systematic review of children it was suggested that 24 hours recall should be performed over at least a 3 day period, containing weekdays and weekends, for the most accurate approach when compared to the doubly-labelled water method as a reference (Burrows et al., 2010).

Nevertheless, this approach has been criticised because nutrient requirements are often unknown in accordance with the reference value weaknesses and biological variability in nutritional requirements. In addition, dietary assessment may be imprecise, inaccurate and impractical especially amongst children (Baxter, 2009, Black and Cole, 2001, Bingham, 1994). The dietetic approach to nutritional assessment was not used in this thesis and so is not described in any detail here.

1.4.3 Biochemical approach to nutritional assessment

The biochemical approach is used to assess the nutrients and its metabolites such as vitamins, minerals and protein in biological tissue, fluid and urinary excretion (Gibson, 2005). Therefore, it is essential for testing the vitamin and mineral status of the person, but it has a huge number of confounding variables. Moreover, some of biological ways to assess nutritional status include nitrogen balance and the creatinine high index.

Nitrogen balance is also used for measuring the changes of protein mass in the body. The assumption behind this is that net body nitrogen is incorporated into protein when protein has 16% nitrogen. A positive nitrogen balance means that nitrogen intake is higher than nitrogen excretion (Gibney, 2005). In diseased patients, for example, in cancer patients negative nitrogen balance may occur as a result of either inadequate protein intake or/and high body protein catabolism. Therefore, if the nitrogen negative balance is keeping on, this could lead to malnutrition which is a concern issue especially in patients undergoing anticancer therapy (Geibig et al., 1991). In diseased patients, many researchers found that improving nitrogen balance using high nitrogen parental nutrition than standard regimen and enteral nutrition (Geibig et al., 1991, Mulder et al., 1989). However, it has some disadvantages such as impracticality especially with regards to the difficulty in collecting urine for 24 hours and is often inaccurate in high protein consumers (Tarnopolsky et al., 1988).

The creatinine high-index is used as a proxy of muscle mass and it requires urine to be collected over a 24 hour period. When increase muscles breakdown in the body, creatinine excretion is increasing in the urine. It is a potentially helpful assessment to determine malnutrition, and the need to supply a nutritional supplement for repletion (Viteri and Alvarado 1970). Even though it is a simple predictor for nutritional status it is not always practical. In addition, it is inaccurate in some diseases such as cardiac and renal disease or for patients who receive diuretic treatment (Perrone et al., 1992,

Gibney, 2005). However, the biochemical approach to nutritional assessment was not used in this thesis and so is not described further.

1.4.4 Functional approach to nutritional assessment

This is comprised of biochemical and physiological functional approaches, but is beyond the scope of this thesis. Briefly, by using the biochemical approach, metabolic product abnormalities in plasma and urine which are related to malnourishment can be measured. For example, excretion of xanthuranic acid is associated with vitamin B-6 deficiency. Moreover, the growth and development process can be assessed for instance by using growth velocity in children which would indicate undernutrition (protein-energy deficiency). The functional approach is helpful in assessing changes in blood components or enzyme activity. Alteration in glutathione peroxidase activity in red blood cells is related to selenium status (Gibson, 2005, Gibney, 2005).

Vitamin C for example has a number of functions in the body. It works as a co-factor in hydroxylation reactions for instance to help in hydroxylation of proline and lysine in collagen. It acts also, as an electron donor in metabolism for example folic acid and histamine. In addition, it is used to produce certain compounds such as steroids. The immune system can be enhanced by vitamin C, but this is unclear. Therefore, an insufficient vitamin C status in the body can lead to impairment in its mentioned features (Gibson, 2005) and the functions of vitamin C can be measured to assess vitamin C status.

The physiological functional approach is used to test responses which may point to nutritional status. It includes the immune, muscle and respiratory function. Impaired immune function could be an indicator of nutrient deficiency. Delayed cutaneous hypersensitivity, which is used for the skin test, may show as decreased responses in the undernourished as well Rowland 1991). However, this test was developed for adults and need prior exposure to antigen; so, it is less used in paediatric clinical

settings in nutrition, though it is used widely in allergy clinics. In malnourished patients, the level of circulating of antibodies level can be affected and giving the malnourished patients a false negative reading for Delayed cutaneous hypersensitivity. Thus, an improvement in patient's nutritional status should increase reading of cutaneous hypersensitivity by stopping transitions from positive to negative (Rowland 1991). However, the limitations of immune function are technically difficult and the interpretation for detecting nutrient deficiency in the individual is also difficult (Gibson, 2005, Gibney, 2005).

The functional approach to nutritional assessment was not used in this thesis and so is not described further here.

1.4.5 Anthropometric approach to nutritional assessment

This is comprised of physical (growth) and body measurements. The physical measurement can include weight, length (height) and head circumference.

1.4.5.1 Anthropometric assessment of growth

1.4.5.1.1 Head circumference

This measurement is related to brain size which is rapidly enlarged during the first of 3 years of life (Mascarenhas et al., 1998). It is a useful clinic tool for detecting undernourished children. This approach could be used detect children who are severely undernourished (Gibney, 2005, Hadlock et al., 1982). It is not useful for certain illnesses which may cause macrocephaly or microcephaly (Mascarenhas et al., 1998).

1.4.5.1.2 Weight index

Weight for age alone as an index measurement is used to describe the body size and is a simple, invasive, cheap, easy and reproducible measurement (Power et al., 1997). It is used to describe malnutrition especially when measurement of height is impossible (Gibney, 2005). Although, weight alone as an index measurement is highly correlated to fat mass it is not recommended because it does not provide any information about the body composition components such as fat or protein mass and it will often over-estimate malnutrition (Uauy et al., 2001, Power et al., 1997). For instance, an athletic person would be considered to be heavy in weight and therefore their muscle mass would not be appreciated (Power et al., 1997, Kuczmarski and Flegal, 2000). In children, this measurement is influenced by the length/height and therefore tall children tend to be a heavier weight than those who are shorter within the same age group (Power et al., 1997). However, weight and height should be taken in hospitalised children and at outpatient visits (Power et al., 1997). In a small number of patients and in some specialities body weight is affected by abnormalities in body composition, fluid status, type of treatment and organ enlargement or tumour mass (Warner et al., 1997).

1.4.5.1.3 Weight-for-height/length index

Firstly height should be measured in the supine length/height position in children who are aged 2 years of age and under; and in the standing position in those over 2 years of age (Mascarenhas et al., 1998). The weight-for-height index measures the weight when adjusted to the current stature to provide the nutritional status without taking the specific age into account. The weight measure with an adjustment in the height for children is more meaningful than weight alone (Uauy et al., 2001).

This method is used to distinguish whether the child is actually wasting (defined as very low weight-for-height) when weight-for-height z score is below -2.0 or less than the 5th percentile by the National Centre for Health Statistics (NCHS)/WHO median

reference data (Mascarenhas et al., 1998, de Onis and Blossner, 2000). Its consideration of wasting is more useful than the underweight measurement alone. In addition, the weight-for-height index is used for detecting those who are overnutrition (defined as > 95th percentile through use of the NCHS/ WHO reference data) although it does not measure fat mass (Mascarenhas et al., 1998). In some parts of the world, dates of birth are not registered and therefore, this index is sensitive to the current nutritional status (Gibney, 2005). However, the main disadvantage of using this index is that it can lead to a biased outcome especially in infants and adolescents (Power et al., 1997). Weight or height index can classified children who have poor linear growth as a normal (Gibney, 2005).

1.4.5.1.4 Height-for-age index

Height-for-age measures the stature of children and how much they deviate from the normal reference population of children (Mascarenhas et al., 1998). Moreover, it is often used to indicate the nutritional status amongst the population instead of the individual (Gibney, 2005). This measurement represents the influence of nutritional status over a long-term period as stature is affected by long-term malnourishment (Mascarenhas et al., 1998).

The height-for-age index is a simple tool for the assessment of stunting. Stunting means low height/length for age which is a more useful measure than being underweight (Mascarenhas et al., 1998, Black et al., 2008). Stature is expressed as percentile which is defined in the following manner: 95th - 105th percentile is normal; and the 90th - 94th, 85th - 89th and < 85th percentile are indicated for mild, moderate and severe stunting; respectively based on NCHS/ WHO reference data (Mascarenhas et al., 1998). Stunting can occur as a result of micronutrient deficiency or as a complication of some diseases such as renal disease (Rosado et al., 1999) and anticancer therapy and steroids (Olshan et al., 1992).

1.4.5.1.5 The Body Mass Index (BMI)

The BMI is defined as weight (Kg) divided by height squared (m^2). This method has been in use for a long time to detect obesity in adults, and has proven to be helpful and low-cost (World Health Orgnisation,1995). The BMI in adults is usually classified into categories as shown in table 1.4.1.

Table 1.4.1: Classification of the Body mass index in adults (Gibney, 2005)

Definition*	Underweight	Healthy weight	Overweight	Obesity grade I	Obesity grade II	Obesity grade III
BMI (kg/m^2)	<18.5	18.5-24.9	25.0-29.9	30.0-34.9	35-39.9	>40

* Note that this is for European/ Caucasian adults; and different cut-offs are used in Asia for example

The BMI is now a widely-accepted means of diagnosing those who are overweight and obese in the child and adolescent population as well (Reilly, 2006a). However interpreting the BMI in children and adolescents is more complex than in adults, as differences in the BMI are found according to age, gender and maturation. Based on the LMS method (L: measures skewness, M: the median and S: the coefficient of variation) the BMI z score can be calculated (Cole and Green, 1992) by following the equation: $[(BMI/M)^L - 1]/(Lx S)$. Moreover, there is a straight connection which is interchangeable between the BMI z score and percentiles.

BMI for age can be used to define underweight, overweight and obesity with interpretation relative to national reference data and thresholds in the BMI distribution, or by applying international reference data and thresholds. As shown in table 1.4.2, several national and international definitions and cut-offs and how they were developed will be discussed in more detail in the general methods chapter. The advantage of using international definitions is to allow easy comparison with results from other populations. Also, these definitions help in direct comparisons of trends in

childhood unhealthy weight status worldwide (Chinn and Rona et al., 2002). On the other hand, the drawback of using international definitions is that they are based in heterogeneous mix surveys collecting from different countries with widely differing prevalence of unhealthy weight status (Cole et al., 2000). Additionally, Reilly et al., (2010b) found in a systematic review that BMI for age based on national reference data is superior with higher sensitivity (lower false negative rate) than based on the international reference data: international definitions have a higher false negative rate, in the other words, some obese (excessively fat) children may classified as non obese and therefore the international definitions underestimate the prevalence of excessive adiposity (Reilly et al., 2010b).

Table 1.4.2: Some of national and international thresholds

	National definitions		International definitions		
	Saudi (BMI)	UK (BMI SD)	CDC (BMI)	WHO (BMI SD)	IOTF/ Cole., 2000 (Pass through of adult BMI)
Underweight	$< 5^{th}$	---	$< 5^{th}$	< -2.0	≤ 18.5 kg/m^2
Overweight	$85^{th} – 94^{th}$	1.04 - 1.63	$85^{th} – 94^{th}$	$> +1.0 – 1.99$	25 - 30 kg/m^2
Obesity	$\geq 95^{th}$	> 1.64	$\geq 95^{th}$	$> +2.0$	≥ 30 kg/m^2

CDC: US Centers for Disease Control and Prevention; WHO: World Health Organisation. IOTF: The International Obesity Task Force

In theory, the BMI represents an index of the body mass independent of height, so that a greater percentage of body mass may be attributed to increased body fat at any age. A high BMI for age is now widely recommended e.g. in the WHO and Scottish Intercollegiate Guidelines Network (SIGN) as the method through which overweight and obese children and adults should be defined (Barlow, 2007, Scottish

Intercollegiate Guidelines Network, 2010). There are also practical reasons for recommending the use of the BMI because it is useful, cheap, non-invasive, simple and more reliable than other indices of children in clinical settings (Gibson, 2005, Dietz and Robinson, 1998). However, there is a debate whether it is useful to use the BMI with national or international cut-offs in defining childhood obesity. Reilly et al., (2010b) have emphasised using national BMI for age and percentiles rather than using the international BMI such as the IOTF.

The main drawback of the BMI is that it does not take into account the actual composition of body mass (Eto et al., 2004), For example, the taller child would sometimes be classified as being obese. Furthermore, adiposity is changed according to some variables such as age, gender, ethnicity and sexual maturity, sitting height and fat distribution (central adiposity) and these variables cannot be distinguished by the BMI. However, Warner et al., (1997) examined the validity of BMI compared to dual-energy X-ray absorptiometry (DXA) and skinfolds in diseased children with growth hormone deficiency, previously treated for cancer, and healthy children as a control group. They concluded that BMI in diseased children is imperfect in detecting excess adiposity. However, systematic reviews show that a high BMI for age and sex is highly predictive of excessive fatness and of co-morbid conditions. Reilly et al., (2010b) have concluded on the basis of systematic review and evidence appraisal (number of included studies was 27); that a high BMI for age in children and adolescents defines or diagnoses excessive fatness with high specificity (low false positive rate) and moderately high sensitivity (reasonably low false negative rate). In clinical settings, high specificity is considered as being of greater importance than high sensitivity to keep away from assessing some non-obese children as obese and then offering treatment which is not required and which risks stigmatisation of the child (Reilly et al., 2010b).

1.4.5.1.6 Waist circumference (WC)

In paediatrics, age and the gender-specific WC percentile is considered to be a reasonably good indicator for risk of cardiovascular diseases (Watts et al., 2008), hyperlipidaemia and metabolic syndrome (Bitsori et al., 2009) that will likely continue into adulthood (Goran et al., 1998). In children and adolescents, there is a relation between a high WC and cardiovascular risk such as hyperlipidaemia and hypertension (Taylor et al., 2000, Rudolf et al., 2007). It is used in paediatric research partly because it has become popular in adult research and is a straightforward and inexpensive tool.

The WC is also considered to be a good tool for assessing central adiposity. Fredriks et al., (2005) in a cross-sectional study assessed WC, hip circumference and waist-hip ratio on 14,500 Dutch participants aged between 0 - 21 years old and compared the results to the IOTF. They concluded that the WC was a useful tool for detecting increasing abdominal fatness. Similarly, Taylor et al., (2000) found that the WC identified a high trunk fat mass amongst 278 girls and 302 boys aged between 3-19 years old with DXA used as the reference standard, though DXA is not a reference or a standard for body fatness (Wells and Fewtrell, 2006).

Conversely, the WC has not been recommended by the SIGN (Scottish Intercollegiate Guidelines Network, 2010) because there is no evidence to support the fact that WC is a better predictor for either excessive body fat or cardiovascular risk factors in childhood than the BMI. A systematic review of studies which compared WC and the BMI for age found no advantage in using WC for diagnosis of excess fatness or cardio-metabolic comorbidities (Reilly et al., 2010a).

The WC changes with age and differs between the genders and should be interpreted in an age and sex- specific method. Therefore, there are many methods which measure WC in children. Rudolf et al., (2007) examined the consistency across

different waist measurement methods amongst 41 healthy children (75.6 % of whom were girls). The mean (SD) age was 12.4 years (3.3). The waist measurement methods involved the midpoint between the lowest rib and iliac crest, the creases upon lateral flexion and the 4 cm above the umbilicus method and subsequently compared them with the BMI z score from the UK 1990 reference data. As all methods were highly correlated to each other and to the BMI z score, they recommended using the 4 cm above the umbilicus method arguing that it would be the simplest option in clinical settings.

1.4.5.2 Anthropometric assessment of body composition

1.4.5.2.1 Skinfold thickness

This method is beyond the scope of the present thesis and so is described briefly here. It is used for estimating the subcutaneous adipose tissue and it allows an estimation of the total body fat (TBF) (Brozek and Keys, 1951). It is useful, cheap and invasive and it is appropriate for large sample surveys (Kuczmarski et al., 1994). Five different sites in which to use the skinfold thickness for estimating TBF are as follows: subscapular, triceps, biceps, mid-axillary and supra-iliac (Gibney, 2005). The principle behind this method is that there is association between skinfold thickness and body density.

In addition the independent predictor of body density amongst males and females is age (Gibney, 2005). The skinfold thickness relies on the age and sex equation in a certain population as it is affected by age, sex, race and level of physical activity (Heyward and Stolarczyk, 1996). The skinfold thickness method is not always practical because it is dependent on the skill of the examiner, subject characteristics, precision of skinfold thickness clippers and the used equation and its reference data. In addition, it is advisable to repeat the measurement to estimate the TBF (Gibney,

2005). Also, in diseased children, the reading of skinfold thickness method can be influenced by dehydration, fluid retention and steroid therapy (Manning et al., 1995).

1.4.5.2.2 Dual energy x-ray absorptiometry (DXA)

DXA was initially used for detecting bone mineral density (BMD) in the spine and hip by using single and dual photon absoptometry. DXA has become more attractive with regards to body composition as because it is relatively simple, fast and requires minimal participant effort. It is widely accepted for children beyond about 4 years old and it can also be used in infants (Wells and Fewtrell, 2006).

Moreover, a wide range of photo-energy is produced as a result of the beam that is created by the x-ray tube. In rectilinear scanning the supine body is divided into a series of pixels, therefore, this wide beam produces to only two distinct photoelectric peaks to distinguish between bones and soft tissue which is produced. As a response to low intensity neutron beam to the body, the DXA machine is based on an analysis of gamma rays emitted from the body (Ellis et al., 1994). The DXA assumes that the body has three main components: fat, bone and soft "lean" tissue. These components can be distinguished by their x-ray attenuation proprieties. Also, soft tissue (water plus organic compounds) decreases photon flux more than bone mineral which easily distinguished from those regions with no bone present. The composition of soft tissue is extrapolated to the soft tissue overlying bone to give percentage of whole body fat and soft tissue. This extrapolation is performed according to specific algorithms which vary between manufactories (Lindsay and Plank 2005). The whole body or a specific region such as the lumbar spine or hip can also be measured by this instrument (as illustrated in figure 1.4.1) (Fewtrell, 2003).

There are different types of DXA machines which are currently being manufactured. Firstly the Lunar DXA is based on narrow or pencil beam machines. It employs a

narrow x-ray that moves across the body or part of the body that needs to be scanned in a rectilinear scan path with detector(s) (Fewtrell , 2003, Bonnick, 2010).

Secondly, the Hologic DXA uses wide or fan-shape beams and array of detectors to employ alternating pulses power at 70 and 140 kV; respectively to the x-ray tube sources (Bonnick, 2010). Additionally, the latter is faster in its scanning times, but it produces higher radiation which is a most important issue amongst children. Conversely, even though the Lunar narrow fan beam is slower in time scanning, it has a lower radiation dose (Fewtrell, 2003).

However, some differences in outcome values were found between these different company machines. Lunar DXA showed lower absolute bone density values than the Hologic DXA even though high correlations between each other were reported for example (Laskey et al., 1992, Lai et al., 1992).

Figure 1.4.1: Real images from the present studies: (left) the total body bone image; (right) the total body composition image by Lunar DXA
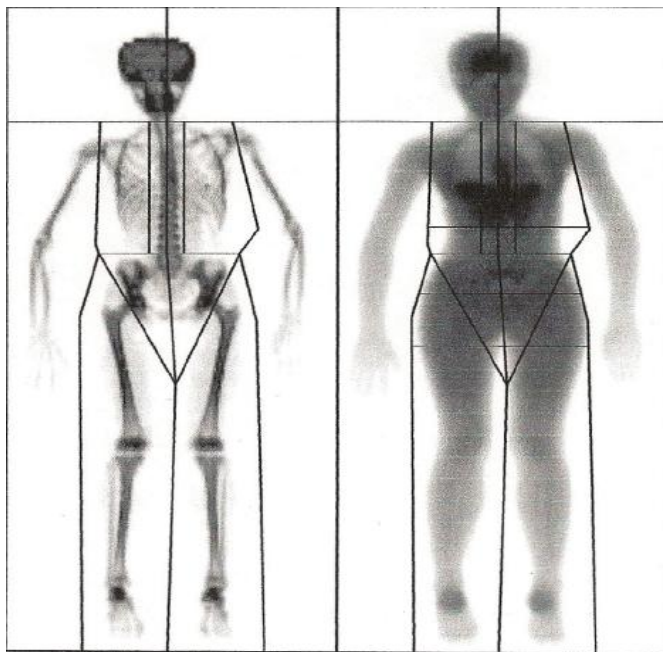
Moreover, DXA uses a very low radiation dose (the range: 0.5- 15 microseverts) but is not suitable during pregnancy. This measurement tool can detect two major components of the body composition: fat mass (FM) and BMD (represented in figure 1.4.2) (Wells and Fewtrell, 2006). It relies on different assumptions according to the manufacturer and is a two-component model; whilst the gold standard measurements are characterised as four-component models (Goodpaster, 2002). However, it has a relatively high precision when compared to other body composition methods (Jebb et al., 1993). The accuracy of DXA for measurement of body fat has had insufficient attention paid to it as it is broadly used in clinical paediatric settings. DXA measurement could be affected by age, fatness and underlying disease state in some cases. Therefore, more attention is required in interpreting the body composition data from children (Wells and Fewtrell, 2006).

DXA is used for research and clinical purposes. In research, the DXA machine is useful for measuring the impact of for example dietary and exercise intervention in different groups (Fewtrell, 2003).

DXA is becoming accepted for assessing body composition and bone health in clinical paediatric settings. Sala et al., (2007) examined 179 healthy Canadian 3 – 18 year olds by using Hologic DXA. They found that total body bone mineral content, fat mass and fat-free mass were highly correlated with directly measured body weight (r> 0.997) and BMI. They generated z scores for each facet of body composition and they recommended comparing ill children with healthy ones. However, the small representative normative data becomes a concern limitation even they compared their results with Argentina and Netherlands data.

Furthermore, DXA   is a commonly used technique in paediatric settings because it is precise, relatively low cost, safe and with widespread availability. Recently, DXA is recommended as the most appropriate technique in assessing bone health in children by the International Society for Clinical Densitometry (ISCD) (Gordon et al., 2007).

Also, patients in general are examined to identify risk of low BMD and for observing the impact of treatment. Moreover, there are some conditions which may increase of risk of low BMD in children such as systemic long-term corticosteroids, chronic inflammatory disease, apparent osteopenia on x-ray and hypogonadism (Fewtrell, 2003).

However, it is sometimes difficult interpreting DXA data, for instance, due to changing BMD in children and adolescents. Briefly, the difficulty of interpretation refers to significant gaps in this area, there are few large sets of representative normative data from healthy children and adolescents (for example small sample sizes in specific ethnic groups are common) and a lack of consensus in which the best method to adjust the results of DXA in children as it is discussed in details in general method chapter (Gordan et al., 2007).

In addition, some artifacts can falsely affect the results of DXA scans such as frames or plaster-casts, jean studs, surgical prostheses and navel rings. Therefore, unaffected areas have only to be included in the calculation and data interpretation (Gnanasegaran et al., 2007).

Figure 1.4.2: An example of total body composition data by DXA (extract from the thesis studies)

Region	Tissue (%Fat)	Centile	T.Mass (kg)	Fat (g)	Lean (g)	BMC (g)
Total	22.6	-	36.38	7,941	27,157	1,287.1

T. mass: Total mass; BMC: Bone mass content

1.4.5.2.3 Bioelectrical impedance (BIA)

The present thesis is dealing with BIA because it is useful clinically and so can be used in the thesis studies. BIA is a non-complex, convenient and relatively cheap instrument to assess body composition, which has become more popular in recent years in clinical settings and research (Sung et al., 2009). It does not require a high level of skill by the examiner and needs little subject cooperation (Schaefer et al., 1994).

BIA is based on two main principles. First of all, the technique measures the resistance (impedance) to a low level (at usually 50 kHz) electrical current travelling through biology tissues or opposition to the current electricity. There are high levels of water and electrolytes in a fat-free mass (FFM), and FFM is therefore an electrical current conductor. In the other words, at low frequencies (around 1 kHz), the current passes through only the extracellular fluids but at high frequency (at usually 50 kHz), it passes through interacellular and extracellular fluids when it passes cell membrane (Lukaski et al., 1987). Secondly, the impedance is a function of resistance and reactance, where $Z = \sqrt{R^2 + X_c^2}$. Whereas (R) is a measure of opposition to the current flow through the body and (X_c) is the opposition to current flow produced when it penetrates the cell membrane (Kushner et al., 1992).

In children, BIA seems to be correlated with body composition. Vizcaino et al., (2007) assessed in a cross-sectional study 1280 healthy children aged 8 - 11 years in Spain of whom 51.5% were female. Their percentage of body fat was measured using BIA (Tanita Corp.) with the use of DXA measurements as a reference standard method. They reported a strong correlation between BIA and the BMI and the triceps skinfold thickness, though as noted earlier in the thesis a high correlation need not mean agreement. However, other studies emphasised care in choice of regression equations which are essential in estimating total body water and fat-free mass

because they noted the significantly different outcomes in regression equations by using two different BIA devices (Warner et al., 2004).

Until now, BIA is less frequently used in previous cancer survivor studies than DXA and other anthropometric measurements (Link et al., 2004, Warner et al., 2004, Follin et al., 2006). Data on prognostic significance of BIA analyser estimates in assessing body composition are not presented. However, BIA analyser seems to be more reliable in children in case of presence other body composition techniques (Lewy et al., 1999).

Some devices have been developed based on homogenous subgroups to adjust the differences in prediction of fatness due to age, sex, race, physical activity level and adiposity. Generally speaking extrapolating equations developed from one population into a different population would produce a bias. There are limited body fat reference curves adjusted to specific age and sex for BIA estimates of body fat. Jebb et al., (2004) for example provided categories for body fat based on the age and sex of children. In addition, McCarthy et al., (2006) established BIA age and gender specific percentiles based on the estimation of FM in both boys and girls aged 5 - 18 years. However, McCarthy et al., (2006) and Jebb et al., (2004) emphasised that the estimate of body fat is specific to the model of the BIA device being used.

1.4.5.2.4 Magnetic Resonance Imaging (MRI)

MRI, is beyond the scope of this current thesis, but can be used to identify adiposities throughout the whole body, skeletal muscles, brains and visceral organs. It measures the hydrogen nuclei which is located in fat or water with a magnetic moment; and estimates the volume of the adipose tissue instead of the mass. It can also assess the regional differences in the body composition or changes in fat or muscle.

Nevertheless, it has several disadvantages in practice because MRI requires hundreds of images and that cost time, funds, and limited availability and require sophisticated software (Goodpaster, 2002, Wells and Fewtrell, 2006). In addition, it can estimate the FM that is only allocated in adipose tissue versus other body compositions such as hydrometry, densitometry and the multi-component model. However, it is a useful device for the assessment of regional body composition and is accurate in detecting intra-abdominal adipose tissue in children when compared with other approaches (Wells and Fewtrell, 2006).

1.5 Acute lymphoblastic leukaemia (ALL)

ALL is one of the forms of Leukaemia. It is characterised by producing high amounts of lymphoblast found in the bone marrow and is formed as immature cells normally differentiated to create mature lymphocytes, which is one type of white blood cells (WBC). Therefore, ALL is the cancer of WBC (Pui, 2006).

ALL accounts for about 25% of total childhood cancers (Link et al., 2004). In addition, ALL is one of the most common malignancies within Saudi paediatrics. The incidence of paediatric ALL in 2006 when compared to other malignancies was 72% and 75.1% in boys and girls; respectively (Saudi Ministry of Health, 2006) as shown in figure 1.5.1. In the UK, ALL is also the most common type of cancer. The numbers of newly diagnosed ALL cases in children each year in the UK are around 380 (Medical Research Council, 2006).

Figure 1.5.1: The most common paediatric malignancies in Saudi Arabia
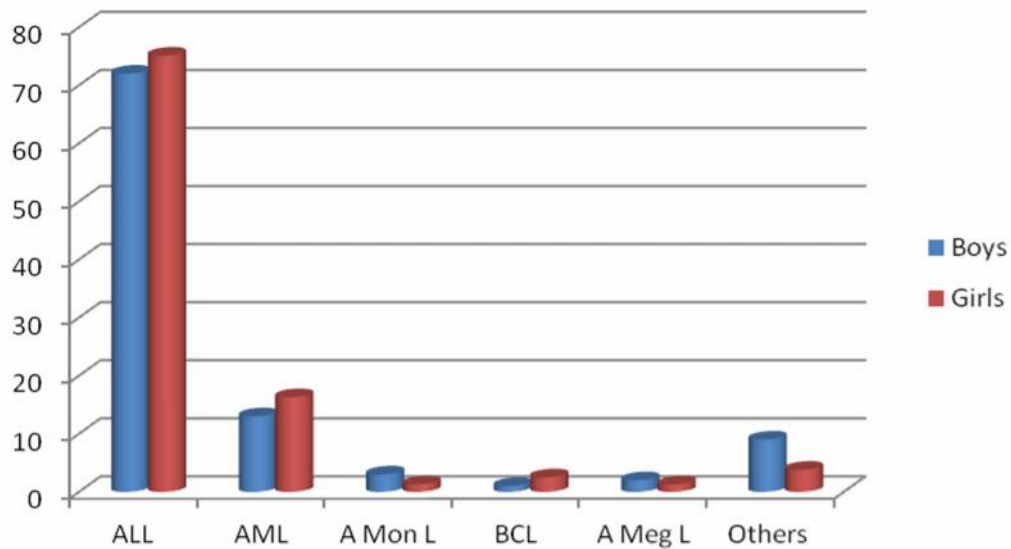
ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; A Mon L: Acute monocytic leukaemia; BCL: Burkitt cell leukaemia; A Meg L: Acute megakaryoblastic leukaemia

Source: Extracted from cancer incidence report in Saudi Arabia (Saudi Ministry of Health, 2006)

1.5.1 Survivors of ALL

The survival rate of ALL has increasingly improved in children. In the UK, the Medical Research Council (MRC), in 1955 established randomised controlled trials (RCTs) in many medical centres to improve treatment. Besides which, they also compared the potential new treatment based on the survival outcomes to reduce the possible side effects and improve treatment efficiency (Medical Research Council, 2006). Thus, tailoring of treatment to known prognostic factors has been established by the recent trials such as the MRC as summarised in the general method table 2.2.1 and US Cancer Study Group (CCG) as summarised in the general method table 2.1.1.

In the UK, for example, four out of five children with leukaemia now recover from the disease; whilst one out of five was cured 25 years ago (Medical Research Council, 2006). The survival rate of children with leukaemia has dramatically increased to 80% (Medical Research Council, 2006).

The percentage of event-free survivors of ALL has gone up to around 80% (Ries et al., 2006). In Saudi Arabia, for instance, overall 5-year survival has been significantly improved by using more advanced treatment protocols (Fryer, 2006). The 5-year survival rate for all patients in Jeddah (the second biggest city in Saudi Arabia) aged less than 15 years who have been treated by different protocols has shifted significantly over 15 years (Fryer, 2006). It was originally 55% by using the UKALL X protocol; 72% by using the United Kingdom Acute Lymphoblastic Leukaemia (UKALL XI) and the Berlin-Frankfurt-Munich (BFM) protocols and reached 87% when using the MRC 97 and CCG 199 (Fryer, 2006).

In general, survivors of childhood cancer are highly exposed to increased morbidity and premature mortality. Oeffinger et al., (2006) reported in a retrospective study that the occurrence of chronic health conditions affected up to 73.4% of surviving patients and life-threatening diseases or death resulted in 42.4% of cancer survivors. Obesity is one of the most common adverse health outcomes in survivors of childhood cancer (Robinson et al., 2008, Courneya et al., 2008); and obesity is particularly common in patients during and after a diagnosis of ALL (Razzouk et al., 2007, Baillargeon et al., 2006, Garmey et al., 2008, Reilly et al., 2000a, Nysom et al., 1999, Butturini et al., 2007, Chow et al., 2007, Oeffinger et al., 2003, Reilly et al., 1999b). Therefore, the following section will discuss the prevalence of those who are overweight, obese and underweight in this group and its effect on the prognosis for malignancies.

1.5.2 Medical therapy intervention for acute lymphoblastic leukaemia

Presently the treatment regimens for ALL categorises therapy as remission induction, consolidation and central nervous system (CNS) prophylaxis, and maintenance or continuous treatment phase. Induction chemotherapy typically consists of a 1-month treatment programmed of vincristine, prednisone, and L-asparaginase alone or with other agents; and has as its objective a reduction in blast cell percentage in the bone marrow to ≤5% (Oeffinger et al., 2000).

Subsequently, in the consolidation stage, the treatment is intensified, using antimetabolites and other agents together with intrathecal chemotherapy for CNS prophylaxis.   Following this there is maintenance therapy, which lasts for around two years in most moderate treatment protocols and depends to a great extent on the use of methotrexate and 6-mercaptopurine. Over the past twenty years, in the light of the discovery of variations in the phenotype of the leukaemic cells, the protocol has been modified to minimise the side effects of toxic drugs in the short and long-term and improve outcome. This has led to more effective treatments of the T-cell phenotype associated with childhood ALL using intensified regimens that incorporate cyclophosphamide, cytarabine, and anthracylines (Oeffinger et al., 2000). However, there is stratification of treatment the adjusting of treatment dependent on the risk profile at diagnosis.

Furthermore, there are several types of protocol for treating ALL; for example, CCG protocols, which have been used in many Saudi cancer centres such as the King Faisal Specialist Hospital and Research Centre (KFSH&RC) (Al-Nasser et al., 2008). In addition, Medical Research Council Protocols and MRC-UKALL protocols are used in the UK for treating children with ALL (Eden et al., 2000). The mentioned protocols will be discussed in the methodology chapter (summarised in the tables 2.1.1 and 2.2.1).

1.5.3 Weight status during and after treatment for childhood cancer

There is some controversy regarding the prevalence of obesity during and after treatment for childhood cancer (Meacham et al., 2005, Robinson et al., 2008, Miyoshi et al., 2008, Pietila et al., 2009, Courneya et al., 2008, Coups and Ostroff, 2005, Gurney et al., 2003). This is due to the complexity of evidence since most studies have been affected by a wide range of different factors; different cancers; different patient groups; different therapies; changes in therapy over time; population changes in obesity prevalence; different complications of therapy; different definitions of obesity used in different studies; the enormous range of diseases which can be termed 'cancer'; variety of therapies and outcomes; limited number of patients involved; use of non-recommended obesity definitions and the lack of comparison between patients with cancer with population reference data meaning that confidence about the prevalence of obesity in most childhood cancers is difficult (Reilly, 2009).

Moreover, the majority of the studies in this field have focused on the treatment of cancer which is mainly separated into two main categories. Older protocols which used cranial radiotherapy (CRT) widely and are mostly used in ALL and brain tumours; and treatment on modern protocols based on corticosteroid therapy which do not use CRT or restrict use of CRT and are mainly used in ALL patients (Brouwer et al., 2007).

1.5.4 Prevalence of unhealthy weight status in general malignancies

As mentioned above, other malignancies are not of one type and do not have unified treatments, therefore, it is hard to give an overall estimation of prevalence of unhealthy weight status in entire group of childhood cancer. Briefly, they are quite heterogeneous in terms of weight status. For instance, a Canadian study Collins et al., (2010) studied different cancer types in both child and adolescent patients (n=99) at diagnosis, median (range) age 7.1 years (2.1 -15.3), in order to explore nutritional status. It was found that the prevalence of underweight (BMI z <5th percentile) and

overweight/obesity (BMI z > 85th percentile) according to CDC reference data were 9.1% and 25.3%; respectively. However, the study had several of limitations such as small sample size, a heterogeneous sample which included patients with several types of cancer, and lack of comparison with a control group.

Moreover, weight status in other malignancies may depend on severity of the natural of the disease. A cross-sectional study of 20 Malawian patients (eight females, 12 males) aged between one and 8.5 years who had been diagnosed with a Wilms tumour reported that about half had underweight at diagnosis (BMI ≤ 5th percentile based on CDC definition), whereas in a community control group (n= 43) the figure was 11.0% (Israels et al., 2009). The high prevalence of underweight possibly according to limited number of patients and the study included metastatic disease patients (n=8) who are more likely to be undernourished because of the disease progression.

Schulte et al., (2010) examined weight status by using the BMI according to the CDC definition in 54 survivors aged 8 - 18 who had been treated for childhood brain tumours in Canada. The prevalence of those who were underweight at (15%) was high when compared to the normal population (4%). However, they included many types of brain tumours such as astrocytoma, medulloblastoma and others that treated by using different type of treatments. Also, they recruited a relatively small sample and without a comparison /control group. The lack of a representative sample, lack of a comparison group, inclusion of different cancer types with different treatments such as surgery, CRT and chemotherapy and progression of the disease are all likely to have had an on the prevalence of unhealthy weight status.

From previous studies, discussing in general malignancies in order to increase confidence of the prevalence of unhealthy weight status is complex and forked and it is beyond the present scope of this particular thesis.

1.5.4.1 Prevalence of obesity at diagnosis and during ALL treatment

Several studies dealt with the prevalence of obesity at diagnosis, during, and after ALL therapy as summarised in table 1.5.1. The literature (as summarised in table 1.5.1) reported a varying prevalence of obesity at diagnosis from 2% to around 17% and from 6% to around 30% during the therapy. This variation may be explained by many factors and these are discussed briefly below.

First of all, almost of all reviewed studies were conducted retrospectively, except the Withycombl et al., (2009) study which was prospectively performed with a relatively large sample size (n= 1638) and with ALL patients only treated with chemotherapy and all on the same protocol; however, prevalence and trends of unhealthy weight status over time was not studied. Moreover, the majority of these studies have had a relatively small sample size and were not nationally representative, usually conducted in one or two centres (Reilly et al., 2000, Asner et al., 2008). However, from the reviewed literature, only three studies recruited relatively large number of patients with ALL (Withycombl et al., 2009 , Reilly et al., 1999b , Butturini et al., 2007). Although, Reilly et al., (1999b) were evaluated the patients treated with the same protocol (UKALL X- discussed later), they used at that time of the study what would now be non consensus cut-offs for defining obesity in the UK. Butturini et al., (2007) included ALL patients who were treated with different treatment protocols (CCG 1881, CCG 1891, CCG 1882, CCG 1922) which may affect prevalence of obesity. Moreover, it is noted that most of literature dealt with the types of treatment of ALL such as chemotherapy and CRT as having similar outcomes in term of prevalence of unhealthy weight status when they are not (discussed later). However, Baillargeon et al., (2005) and Asner., (2008) studied patients who had been treated with only chemotherpy but both studies had a small sample size.

Nowadays, It is well known that the obesity has becomes epidemic but it is unknown if cancer patients have been affected by the obesity epidemic to the same extent as

the rest of the population. Therefore, it is hard to report that the prevalence of obesity at diagnosis is higher or lower than general population and whether the prevalence reflects what is happing in the general population rather than ALL specific problems.

Unfortunately, the majority of the studies to date have not compared the prevalence of obesity in their sample of patients with ALL with prevalence in the general population. Also, all of the reviewed studies relied on data not collected recently. For instance, the Withycombl et al., (2009) and Chow et al., (2007) studies included data up to 2003 whereas the others studied were based on even older data, for instance, the highly cited Van Dongen-Melman et al., (1995) study depended on data of ALL patients diagnosed between 1978 – 1990.

As shown in table 1.5.1, several different BMI reference data and BMI thresholds were used to define obesity in previous studies which would cause variation in the prevalence of obesity. Most studies used their national obesity definition but Asner et al., (2008) applied the international approach (IOTF) in Swiss patients.

Moreover, the evidence table 1.5.1 also shows an apparently clear picture of increasing obesity from the first year of treatment and at the end of treatment whereby a high prevalence of obesity reached up to half of the sample as reported by Odame et al., (1994). For example, Reilly et al., (2000b) pointed out that the prevalence of obesity (defined as BMI z score > 2.0) at diagnosis of ALL in the UK was < 2%. However, the prevalence dramatically increased during treatment to 4% during the 1st year; 9% during the 2nd year until it reached 16% by the 3rd year post-diagnosis in patients with ALL in first remission in the UK treated on protocol MRC UKALL XI.

Many factors could contribute to excess weight gain during treatment of ALL patients first of all the therapy itself (discussed below). Also, from another perspective the gaining of excess weight during the ALL therapy may be affected by the weight status

at diagnosis. Baillargeon et al., (2005) studied weight changes (based on the CDC definition) over the time of the treatment amongst 141 Hispanics aged 2 - 18 years. The weight status increased from the baseline until the age of 24 months and then was slightly reduced at 30 months in those patients of normal weight at diagnosis. Amongst those who were overweight (BMI ≥ 85th) at diagnosis there was no consistent increase or decrease in weight status over the process of therapy. Love et al., (2011) observed that 35.6% of ALL survivors (n=102) were classified as being at normal weight at diagnosis and they became by the end of the treatment classified as overweight (using the CDC definition); and half of them remained overweight at most of the subsequent follow ups.

In summary, the variation in the prevalence of obesity in different studies of patients with ALL is due to a combination of different therapy protocols; different definitions of obesity, different study design and sample sizes, and different times (as the obesity epidemic moved fairly quickly in the general population (Reilly and Dorosty (1999)). Also, the prevalence of obesity may have increased in ALL over time; but the available literature is complex and does not allow us to define time (secular) trends with any confidence.

Table 1.5.1: Prevalence of obesity at diagnosis, during and after ALL therapy

Reference	No. of subjects	Assessment period	Definition of obesity	At diagnosis (%)	During therapy (%)	After therapy (%)
Reilly et al., (1999b)	1019	Dx	BMI= 97th-98th	2	---	---
Withycombe et al., (2009)	1638	Dx + 3 yr	BMI ≥ 95th	14	23	---
Baillargeon et al., (2005)	141	Dx + 2.5 yr	BMI ≥ 95th	17	6	---
Asner et al., (2008)	54	Remission + 12 yr	BMI ≥ 97.5	13	14	18
Reilly et al., (2000b)	98	Dx + 3 yr	BMI > 2.0	2	9	16
Odame et al., (1994)	40	Dx + 4 yr	BMI > 97.7th	5	F: 43; M: 26	F: 57; M: 21
Van Dongen-Melman et al., (1995)	113	Dx + 4 yr	BMI> 90th	8	30	24
Chow et al., (2007)	165	Dx + 10.5 yr	BMI ≥ 95th	10.9	21	20
Butturini et al., (2007)	4260	Dx + 3 yr	BMI ≥ 95th	8	---	14
Razzouk et al., (2007)	248	Dx + 11.9 yr	BMI ≥ 95th	7	---	21
Breene et al., (2011)	77	Dx + 3 yr	BMI z score > 2.3	2	---	29
Didi et al., (1995)	114	Final height	BMI> 85th	---	---	46
Sklar et al., (2000)	126	Final height	BMI ≥ 85th	---	---	30
Nysom et al., (1999)	95	Dx + 11yr	BMI> 90th	---	---	25
Talvensaari et al., (1996)	50	Dx + 13 yr	BW> 120% ideal	---	---	32; Control: 10
van Beek et al., (2006)	90	12.7 yr	BMI ≥ 30 kg/m^2	---	---	8
Jarfelt et al., (2005)	35	20 yr	BMI 25- 29.9 Kg/m^2	---	---	34
Love et al., (2011)	102	1 yr	BMI ≥ 95th	---	---	21
Meacham et al., (2005)	1665	Adulthood	BMI ≥ 30 kg/m^2	---	---	M: 16; F: 18

M: male; F: female; yr: year; Dx: diagnosis; BW: Body weight

1.5.4.2 Prevalence of obesity in ALL survivors

As summarised in evidence table 1.5.1, overweight and obesity since diagnosis is more likely to progress during and after the treatment course. Therefore, the evidence is fairly clear that survivors of ALL might be expected to show an elevated likelihood of obesity in childhood, adolescence and adulthood. For example, a longitudinal study from the USA, Chow et al., (2007) illustrated that the prevalence of being overweight (defined as a BMI = 25 - 29 or the 85th - 94th percentile) and obese (defined as BMI ≥30 or 95th percentile) based on the CDC 2000 growth chart at the diagnosis of ALL were 12.7% and 10.9%, respectively. However, after completion of treatment, the rates were 17.0% and 21.2% (p value = 0.01); respectively.

However, it is not straightforward interpreting the prevalence of obesity amongst ALL survivors from the data of all reviewed papers (see table 1.5.1) because of several reasons. First of all, the majority of studies were cross-sectional and often retrospective. The studies performed prospectively generally recruited less homogeneous groups with smaller sample size, i.e. typically included patients who had been treated with both CRT and chemotherapy (van Beek et al., 2006 , Nysom et al., 1999 , Love et al., 2011), or they were conducted in long-term survivors (adult patients ; van Beek et al., 2006).

Moreover, almost all studies again used different treatment protocols and included patients who had different risk categories such as having high or standard risk. In addition, almost all studies analysed weight status in patients treated with CRT and combination chemotherapy. So, this could lead to increased heterogeneity in the survivors recruited and make it difficult to separate of influence of these major therapies. Also, the majority of reviewed studies were performed amongst relatively small and probably non-representative survivors. However, Butturini et al., (2007) recruited a relatively large sample size (n= 4260) but, patients were treated with several treatment protocols. Also, Meacham et al., (2005) assessed adult survivors (n=1665) rather than child or adolescent survivors.

In addition, excess weight gain was defined according to different cut-offs and using reference data in most studies. For instance, Talvensaari et al., (1996) defined obesity in survivors if their body weight was > 120% ideal. Few if any studies used even slightly more sophisticated measurements of body composition for defining excess body fat such as DXA or BIA. Finally, lacking any comparison with control or normative population data was noted from all the studies of survivors, except the Talvensaari et al., (1996) study. Also, the prevalence of obesity in the literature is probably time-dependent since the obesity epidemic progressed rapidly in most countries as described above. So, the majority of studies to date quite old data, for example, Didi et al., (1995) analysed patients who were treated between 1971 – 1987.

To sum up, the evidence has shown widely varied prevalence of obesity in survivors of ALL. Prevalence is likely to be affected by the therapy protocol, obesity definition the time of the study and the sample size. It is obvious from this literature review that there no study that focused on adolescent survivors from a quite homogenous ALL group patients (treated with the same treatment protocol), and using a modern and accepted obesity definition. Finally, almost all previous studies of weight status in survivors of ALL have been in western countries, and studies from non-western populations are lacking.

1.5.4.3 Prevalence of underweight at diagnosis and after ALL treatment

The Childhood Cancer Survivors Study (CCSS) Meacham et al., (2005) stated that male ALL survivors were at increased risk of being underweight (OR= 2.4; 95% CI: 1.6 – 3.6). Furthermore, Razzouk et al., (2007) reported a highest prevalence of underweight (23%; based on the CDC definition using BMI) whereas the prevalence was 29% amongst children between 0 - 6 years old.

Nonetheless, there is limited literature available as summarised in table 1.5.2, on the prevalence of underweight at ALL diagnosis. There are several limitations in the studies that could influence the prevalence of underweight at diagnosis in ALL patients. Limited sample size is common in the studies to date. For instance, a French study with 15 patients found that 20% (weight-for-height < 85%) of patients were underweight (Delbecque-Boussard et al., 1997). Only two studies to the best of my knowledge assessed patients at diagnosis with relatively large sample sizes. Firstly, Reilly et al., (1999b) analysed 1019 patients in the UK, a fairly homogeneous ALL group (standard risk ALL only), but they used an old definition of underweight. Secondly, Hijiya et al., (2006) recruited 621 ALL patients but, they were mixed between patient who had low, standard and high risk, consequently this was a heterogeneous group. Therefore, there is a great need for a relatively large and representative national sample in a fairly homogenous group of ALL patients, and which defines underweight based on a modern definition.

Table: 1.5.2: Prevalence of underweight at ALL diagnosis

Reference	No. of subjects	Definition of underweight	Prevalence at Diagnosis (%)
Hijiya et al., (2006)	621	BMI ≤ 10th	16.4
Razzouk et al., (2007)	248	BMI < 10th	23
Viana et al., (1994)	128	Height for age z score <-2.0	17.4
Delbecque-Boussard et al., (1997)	15	Weight for height < 85%	20
Reilly et al., (1999b)	1019	BMI z score <-2.0	7.4

1.5.5 Effect of nutritional status at diagnosis on prognosis of childhood cancer

The use of unhealthy weight status (defined here as being overweight, obese or underweight) as a prognostic factor and its effect on treatment outcomes has dramatically increased; but its usefulness is still limited and the studies which have focused on this field are limited in number and are also conflicting. This conflict in the findings may be related to the fact that the majority of the literature has used retrospective study design, different cancer treatment protocols, a small sample size or that cancer is not only of one type (heterogeneity of the disease). For instance, a large cohort retrospective study by Fernandez et al., (2009) looked at the effect of body weight on survival of children with a Wilms tumour: 1532 patients were enrolled with a median follow-up of 4.9 years. Authors found that 15% of children were underweight (< 10th BMI-for-age percentile) (p value < 0.00001) and 13% were overweight (> 90th BMI-for-age percentile) (p value < 0.001). This study demonstrated no relationship (p value= 0.28) between body weight and BMI-for-age at diagnosis and event-free survival (EFS) (defined as the time between diagnosis and death (Hargrave et al., 2001)).

Conversely, a retrospective study which reviewed 768 patients with AML at diagnosis aimed to determine the percentage of patients who were overweight (BMI ≥ 95th percentile) or underweight (BMI ≤ 10th percentile) at diagnosis according to the CDC definition. Lange et al., (2005) showed that the percentage of overweight patients at diagnosis was 14.8% (n = 114) and underweight at 10.9% (n = 84). They illustrated that overweight or underweight AML patients had a reduced chance of survival (hazard ratio= 1.88; p value = 0.002) and had high chance of treatment-related mortality (hazard ratio= 3.49; p value < 0.001) compared to healthy weight (BMI= 11-94 %) patients. Similarly, patients who were classified as being underweight had a reduced chance of survival (hazard ratio= 1.85, p value = 0.006) and had a greater chance of experiencing treatment-related mortality (hazard ratio= 2.66, p value = 0.003). In a South African study, Wessels et al., (1999) carried out on 59 patients with

a Wilms tumour, 35% of the patients were poorly nourished at diagnosis. However, there was no relationship between being poorly nourished at diagnosis and the prognosis and survival rate in children with Wilms tumours in this study. However the sample size may have been too small to be adequately powered in this case.

1.5.5.1 Role of nutritional status at diagnosis on prognosis in ALL patients

Clarifying the role of weight status (being overweight, obese and underweight) for ALL survival is one of the biggest questions in this field (as summarised in tables 1.5.3 and 1.5.4). To the best of our knowledge, only four studies have investigated the role of obesity at diagnosis on the outcome for ALL and they are in both developed and developing countries.

1.5.5.1.1 Effects of overnutrition

In developed countries- obesity and relapse risk in ALL patients

A study by Butturini et al., (2007) recruited 343 obese and 3971 non-obese ALL patients. The hazard ratio for events and relapse was 1.36 and 1.29 (p value = 0.40); respectively for obesity. They also found that obesity had a high impact on patients who were aged $\geq$ 10 years old at diagnosis; hazard ratio for events and relapse was 1.5 (p value= 0.01) and 1.5 (p value = 0.01); respectively. Although the obesity prevalence (based on the CDC definition defined as BMI $\geq$ 95th) was only 8.7%, they concluded that obesity played an intrinsic role in terms of predicting relapses and for paediatric ALL patients.

Table 1.5.3: Role of obesity at diagnosis on prognosis in ALL

Reference	Type of study No. of subjects Place	Age Ethnicity	Definition of obesity	Results	Findings
Gelelete et al., (2011)	− Retrospective − 181 − Brazil	− ≤ 10yr (n= 111), >10 yr (n= 5) − White (n= 62), non-white (n= 54)	− Obesity : BMI z score ≥ 2.0 , overweight: BMI z score ≥ 1.0 (based on WHO criteria)	− 35.9% were overweight or obese at Dx − In intermediate and high risk, 5 Event free survival was sig. decreased (p= 0.02).	− Overweight and obesity are prognostic factors
Butturini et al., (2007)	− Retrospective − 4260 (1733 were verified after 10 yr) − USA	− 1-10 yr − White, African American, Hispanic and other	− Obesity: BMI ≥ 95th percentile. At risk of obesity: 85th – 95th percentile (based on CDC definition)	− 8.7% of pt were obese at Dx Sig risk rate of relapse obese Pt than non-obese were 72% ± 2.4%, 77% ± 0.6%; respectively − Sig obese HRs for events were 1.36 (95% CI: 1.04 – 1.7; p= 0.021) and relapses were 1.29 (95% CI: 1.02- 1.56; p = 0.04). − 9.5 % of Pt ≥ 10 yr were obese −	− Obesity at Dx is predictive of a worse prognosis − Obesity among ALL children pt at Dx independently performs as prognostic and cure factors in > 10 yr
Hijiya et al., (2006)	− Retrospective − 621 − USA	− 1 – 16.9 yr − White, black and other	− Overweight defined as BMI ≥ 85th and < 95th percentile (based on CDC definition) − Underweight defined as BMI ≤ 10th percentile	− Overall survival was not Sig in weight status groups (p= 0.53) − Complete remission and incidence of relapse were not Sig (p value= 0.63) and (p value= 0.86); respectively	− BMI at Dx does not affect on the outcome
Baillargeon et al., (2006)	− Retrospective − 322 − USA	− 2-9 yr (n= 241), 10-18 Yr (n= 81) − Hispanic white, Non-Hispanic white	− Obesity: BMI ≥ 95th percentile. Overweight: BMI > 85th – 95th centile. (based on CDC definition)	− Obese prevalence was 15.2 % while overweight prevalence was 10.9 % − In all 2 age groups, obesity at Dx was not Sig correlated to reduce overall or event-free survival, HRs were 1.40 (95% CI: 0.69- 2.87) and 1.08 (95% CI: 0.65- 1.82), respectively	− Obesity at diagnosis does not play as prognostic factor at age 2-9 Yr − Obesity prognostic factor was absence at age 10 – 18 yr

Yr: year; CDC: US Centres for Disease Control and Prevention Program for Children; Pt: Patient; Sig: Significant; HRs: Hazard Ratio; CI: Confidence Interval; Dx: Diagnosis; Wt: Weight; ♂: Male; ♀: Female; Ht: Height; p: p value

Nevertheless, Baillargeon et al., (2006) found that obesity (defined as a BMI ≥ 95th based on CDC definition) had no role in ALL prognosis. They examined 322 predominantly Hispanic subjects (aged 2 - 18 years) who had been treated from 1990 - 2002. In their study, the percentage of those who were either overweight or obese (defined as BMI >85th and BMI > 95th percentiles; respectively) was 26.1%. Hazard ratio for overall survival of obesity was 1.4 but it was not significant (95% CI: 0.69 - 2.87). However, the sample size in this study was relatively small. This findings also supported by Hijiya et al., (2006). They examined 621 children who treated for ALL in USA to discover the influence of BMI on the outcome. The estimate of overall survival was not significant (p value= 0.53). They did not find any effect of high or low BMI on the outcome.

The cause of these inconsistent findings may be in part due to differences in sample size. The sample size was relatively small in Hijiya et al., (2006) and Baillargeon et al., (2006) . However, Butturini et al., (2007) had a relatively large sample size (n= 4260). Furthermore, there are other important confounders such as type of treatment protocol and severity of the disease (low risk, high risk or standard risk). The previous studies were not consistent in terms of ALL classifications (low risk, high risk or standard risk), and treatment protocols (Butturini et al., 2007). For example, Butturini et al., (2007) included ALL patients who had been treated by different protocols (CCG 1881, CCG 1891, CCG 1922) and so, CRT and chemotherapy were used, whereas Baillargeon et al., (2006) included only patients treated with chemotherapy.

In developing countries- obesity and relapse risk in ALL patients

Gelelete et al., (2011) recently studied the effect on survival of being overweight and obese (combined) in children with a diagnosis of ALL. They examined in a retrospective study 181 children which were treated according to BFM protocols in Brazilian hospitals. The median (range) follow up period was 4.8 years (3.2 - 6.3). They found that 35.8% of the sample were classified either as being overweight (BMI z score > 1.0) or obese (BMI z score > 2.0) using the WHO BMI reference data. In

addition, 5 years event-free survival was significantly (p value= 0.02) reduced in both intermediate and high risk group patients deemed overweight and/or obese compared to the non-overweight or obese (58.8%, 76.7%; respectively). However, in the standard risk group, the 5- year event-free survival was not shown significantly to be different between overweight or/and obese and non-overweight or obese (92.8%, 90.0%; respectively).

Nonetheless, in the study by Gelelete et al., (2011), the missing relationship between obesity at diagnosis and outcome may have been due to a lack of power as it was a relatively small sample. Generally speaking, in the studies pertaining to the developing countries regarding being underweight at diagnosis, it is likely that being underweight reflects other nutritional deficiencies and difficult socio-economic circumstances and a lack of access to chemotherapy which is less likely to be the case in developed countries.

1.5.5.1.2 Effects of undernutrition on survival in ALL

From the literature search, it would appear that a very limited number of studies have looked for a role regarding those who are underweight on prognosis of the disease as well in both developing and developed countries.

In Developing countries- undernutrition and relapse risk In ALL

A Mexican case-control study which involved 17 cases and 76 controls who had at least survived the induction and consolidation phases of ALL (Meji´a-Aranguré et al., 1999). They defined malnutrition when the subject had ≤ 80% of their weight expected for height. They found that amongst those who were undernourished at diagnosis, the risk of dying during the initial phase of therapy was 2.6 times greater than for those who had a normal nutritional status at diagnosis. They emphasised that being malnourished was a good predictor of mortality during the induction phase in

ALL patients. Similar findings were found by Viana et al., (1994) in Brazil who identified that the relapse risk was 8.2 times higher in 128 ALL patients than amongst the underweight (Undernourished detected as Ht-for-age z score < -2.0). They stated that undernutrition at diagnosis of ALL was a strong prognostic factor. Contrary to this, Pedrosa et al., (2000) studied 283 ALL patients with a median age at diagnosis of 4.9 years in Brazil and San Salvador. They defined malnutrition as weight-for-height, weight-for-age and height-for-age expressed as a z score < - 2.0. They reported that there was no association between nutritional status and the survival rate even when they added 160 solid tumour patients.

It is obvious that there is a conflict in the literature about the role of underweight at diagnosis on the prognosis of ALL. It may be because of the sample size in studies was relatively small. The definition of malnutrition that was used for example in Pedrosa et al., (2000) study was inconsistent with what had been used by other studies. Also, studies were based on different type of ALL patients and different therapy protocols which are considered as independent factors in the prognosis of the disease. Also, in the developing world, undernutrition and outcome may be confounded by factors related to socio-economic status such as ability to access treatment- those who are undernourished may be much poorer than those who are adequately nourished and so might not be able to afford treatment.

Developed countries- undernutrition and relapse risk In ALL

Few studies focused on the effect of underweight at diagnosis on prognosis of ALL. Hijiya et al., (2006) recruited 621 participants in the USA with ALL. They defined being underweight if the BMI ≤ 10th percentile and being overweight when the BMI ≥ 85th and < 95th percentile according to the CDC definition. They found that weight status did not have an impact on overall survival (p value = 0.533). They stated that the BMI at diagnosis did not affect the risk of relapse or complete remission.

However, they included patients with different types of ALL and who had been treated with different   therapy protocols.

In addition, an earlier Glasgow study carried out in one centre and in patients treated according to the same treatment protocol (UKALL X), Reilly et al., (1994) tested relatively small sample (n=78) of ALL patients at diagnosis and the impact of weight for height was expressed as a z score status. Being underweight was classified as having a weight for height z score < -0.5.   They reported a significant influence of low weight for height in the outcome. However, by using a much larger sample size from a multicentre UK trial, Weir et al., (1998) examined an entire treatment cohort retrospectively in the UK (n= 1025). They defined being underweight as a BMI z score <- 2.0 according to UK reference data. They reported that there was no significant relationship between weight status and relapse (p value= 0.553).

Table 1.5.4: Role of underweight at diagnosis on prognosis in ALL patients

Reference	Type of study No. of subjects	Age Ethnicity Place	Definition of obesity	Results	Findings
Weir et al., (1998)	– Retrospective – 1025	– 0.2 – 14.9 yr – European, Non-European – UK	– BMI z score >0.5 for overweight and < -0.5 for underweight	– No Sig relationship between BMI z score and relapse (p = 0.55). – After adjusted to WBC, age, sex and intensification, no Sig correlation between BMI z score and relapse risk (P = 0.72)	– In developed countries, nutritional status at Dx more likely do not affect expectation relapse risk
Meji´a-Aranguré et al., (1999)	– Case-control 17 cases (9 ♂, 8 ♀) 76 control (44 ♂, 32 ♀)	– Median age of cases and controls were 7.3 Yr and 5.1 yr; respectively. – Mexican	– Sever malnutrition, 1st degree malnutrition, normal and obese classified < 80%, 81% - 90 and > 91% of Wt for Ht; respectively	– Undernourished Pt had dying chance high, but not Sig (OR = 2.6, 95% CI: 0.55 – 11.89). – Sig association between sever under-nourished and risk of death (p= 0.04)	– Undernutrition plays a role in term of occurring of relapses or death – Malnutrition may be considered as early predictor for mortality during induction-to-remission phase of treatment
Viana et al., (1994)	– Prospective – 128 (68 ♂, 60 ♀)	– 0.9- 14 yr – Brazilian	– Undernourished detected as Ht-for-age z score < -2	– All undernourished Pt did not complete continuous remission (P>0.0001) – 7 of 10 Pt who classified undernourished, had relapsed – Relapses risk for z score < -2 was 8.2 times (95% CI: 30.1 - 21.9)	– After adjusting risk factor, percentage of prevalence of malnutrition in developing countries was high – Malnutrition affects on the outcome and the prognosis of ALL during treatment and remission in children
Pedrosa et al., (2000)	– Retrospective – 283	– Median age: 4.9 yr – El Salvador and North Brazil	– Undernutrition: W-for-HT, Wt-for- age and Ht-for-age z score < - 2.0	– No sig found between malnutrition and the survival outcome (p= 0.89)	– Underweight is not affected on prognosis of the outcome in developing countries
Reilly et al., (1994)	– Retrospective – 78 (47♂, 31 ♀)	– 1 – 13 yr – UK	– Underweight and overweight were classified as Weight-for-height z score < -0.5 and >0.5; respectively	– Weight status was sig affected the risk of early relapse (p= 0.01)	– Underweight as is prognostic factor

ALL: Acute lymphoblastic leukaemia; yr: year; CDC: US Centres for Disease Control and Prevention Program for Children; Pt: Patient; Sig: Significant; CI: Confidence Interval; OR: Odd ratio; Dx: Diagnosis; Wt: Weight; ♂: Male; ♀: Female; Ht: Height; IBW: Ideal body weight; TSFT: Triceps skin fold thickness; MUAC: Mid upper arm circumference

1.5.5.1.3 Conclusion

These studies which studied the role of nutritional status at diagnosis on prognosis in ALL patients have many limitations such as having inherent retrospective study disadvantages. The sample size has often been small, and in particular, obese and underweight percentages have been relatively low in the sample. Some of the studies have also relied on the BMI, which is not an ideal indicator for obesity or being underweight (Warner et al., 1997); and the follow-up BMI usually has not been taken just BMI around the time of diagnosis. Moreover, there are other confounding factors rather than simply the nutritional status which could lead to worse side effects. Examples are chemotherapy dose complications, type of medicine, WBC, severity of the disease, infections and nervous system status and socio-economic status.

Consequently, there is limited evidence on links between nutritional status and survival in ALL and much of it seems contradictory. This suggests the need for more survival analyses and more evidence in general to establish if there is any affect or association. For obesity and survival this may be especially important if the prevalence of obesity had increased in ALL patients over time, and if it continues to increase during and after therapy (Reilly, 2009).

1.5.6 Possible underlying mechanisms of development of obesity during and post treatment of ALL

The aetiology of obesity in ALL patients is complicated and could be produced by multiple-factors. The present thesis will briefly discuss the possible causes because a complete discussion is beyond the scope of this thesis.

1.5.6.1 Hypothalamic damage

CRT and to a lesser extent other forms of CNS prophylaxis such as chemotherapy has the potential side effect of hypothalamic damage. Therefore, obesity might be promoted according to many possible mechanisms: reduced resting energy

expenditure or energy spent in physical activity; insufficient growth hormone production, which in turn, changes fat deposition and substrate oxidation; hypothalamic damage may lead to impairment of food intake. Also, the low dose of irradiation could damage the more radiosensitive pathway of CNS, in which hypothalamus is included, involving the regulation of satiety or thermogenesis regulation (Wallace and Green, 2004).

Consistent evidence has shown a strong relationship between CRT and growth hormone deficiency(Gurney et al., 2006, Link et al., 2006, Brennan et al., 1999b). Old protocols that use CRT for treating patients with ALL are strongly related to obesity risk (Groot-Loonen et al., 1996, Odame et al., 1994). Other effects of hypothalamic damage also result for example in alteration to appetite regulation. Bulow et al., (2004) demonstrated that ALL patients with growth hormone deficiency had a high body fat mass, but when they were treated with growth hormone replacement for 12 months, body composition was normal. Moreover, Link et al., (2004) illustrated that 91% of ALL patients had growth hormone deficiency that was induced by CRT and that obesity prevalence was high in the sample when compared to the control. Even though growth hormone deficiency may occur in both chemotherapy and CRT (Haddy et al., 2006).

However, Brennan et al., (1999b) suggested that growth hormone deficiency was not the main cause of weight gain in ALL patients. Consequently, high body weight was observed whether chemotherapy was used alone or mixed with CRT (Birkebaek and Clausen, 1998, Reilly, 2009). Additionally, Davies et al., (2004) have pointed out that the role of leptin and Insulin-Like Growth Factor-I (IGF-I) which may be affected by CRT. Leptin is formed in adipose tissue and plays an intrinsic role in the regulation of appetite and energy expenditure. Some researchers believe there is a relationship between leptin and obesity risk (Blum et al., 1997). Davies et al., (2004) and Janiszewski et al., (2007) reported that leptin was significantly higher in irradiated ALL patients p value < 0.05 and p value = 0.03 and p value <0.05; respectively, compared

to the control. However, Insulin-Like Growth Factor-I (IGF-I), which is a proxy marker for growth hormone insufficiency, was low in ALL patients treated with CRT. Furthermore, they suggested that there was a relationship between reduced Insulin-Like Growth Factor-I (IGF-I) and adiposity

In summary, all treatment protocols using CRT as part of treatment probably lead to an increased risk of obesity; however this is not the only cause since obesity during and after treatment remains high even among patients with ALL who have not received CRT (Reilly et al., 2000b, Mayer et al., 2000, Birkebaek and Clausen, 1998, Reilly et al., 1996). Steroid agents could cause weight gain in ALL patients. The possible underlying mechanisms are increased energy intake (by increasing appetite), reduced energy expenditure (by lower physical activity) and substrate oxidation and fat deposition (Reilly et al., 2001a, Wallace and Green, 2004).

1.5.6.2 Physical activity

The loss of physical activity may firstly occur during hospitalisation of the patient. It may be due to a several factors such as diminished exercise capacity, impaired motor function, diminished interest in recreational physical activity and over-protectiveness of patient's parents (Jenney et al., 1995). Moreover, pathophysiological changes in the cardio- respiratory system and growth hormone deficiency may influence to minimise the physical activity in cancer patients (Reilly et al., 1998).

Physical activity in ALL patients has been measured during and after the end of treatment. A limited number of studies have focused on the evaluation of physical activity whilst the patients were being treated. A pilot study by Aznar et al., (2006) assessed physical activity during the treatment of 7 children with ALL aged 4 - 7 years. These children were compared with a control group of 7 children. Aznar et al., (2006) used an MTI actigraph accelerometer to measure the level of physical activity for a one week period and showed a significantly lower moderate-to-vigorous physical

activity amongst those with ALL during weekdays (p value = 0.048) when compared to the control group.

Tillmann et al., (2002) investigated physical activity in 28 surviving UK ALL patients (treated by UKALL XI protocol) by using an uniaxial accelerometer and questionnaire for 3 days at an average 5 years post-treatment survival, the physical activity measured was significantly less in the survivors than in the healthy controls. Similarly, Jansen et al., (2009) carried out a study in the Netherlands on 16 patients with ALL and 17 healthy siblings. Patients were evaluated during and between dexamethasone courses. Physical activity (measured by pedometer) and energy intake were measured by parental reporting records and a pedometer for counting steps. They found that patients gained weight between the time of diagnosis and the end of the study (mean change of the BMI z score was 1.4±1.1). Therefore, they stated that this weight excess gain may have occurred due to the consumption of high energy intake and inactivity during the dexamethasone treatment. Physical activity assessed by pedometer was lower in patients compared with the controls.

Reilly et al., (1998) attributed excess weight gain amongst 20 ALL patients to reduced total daily energy expenditure, (total daily energy expenditure = Basal Metabolic Rate + energy expended on physical activity + diet-induced thermogenesis), with mean paired differences of 282 kcal/day relatively to controls (n = 20) which was caused by lower physical activity thermogenesis.   Moreover, they found that energy expended on physical activity was lower and this was highly related to weight gain. Furthermore, Warner et al., (1998) assessed in the UK the total daily energy expenditure in 34 survivors with childhood ALL compared to 21 survivors of other malignancies and 32 healthy siblings by using heart rate technique. The median age (range) was 10.4 years (7.2 – 18.4). They found that the total daily energy expenditure amongst ALL survivors was significantly (p value< 0.01) reduced in ALL survivors than other malignancies survivors and the controls.

Therefore, the physical activity during and after ALL treatment changes happen not clear, it may be that children are overprotected by parents/guards for instance they encourage their patients to stay inside or even sometimes not become involved in play or games.

1.5.6.3 Energy intake

Few studies of energy intake of children with ALL have been published (Bond et al., 1992, Delbecque-Boussard et al., 1997, Reilly et al., 1998, Reilly et al., 2001a). As overeating probably leads to an energy imbalance, it might be important for weight gain. Also, it should take in account that these patients are usually exposed to treatments such as chemotherapy, radiation and some drugs that are likely to reduce appetite; the energy intake may be affected by being reduced or increased. However, it has been well-established that an increase of energy intake is related to ALL treatment. Reilly et al., (2001a) tested 68 ALL patients and excessive energy intake to marked positive energy balance was observed in patients who had been treated by prednisolone or dexamethasone. In addition, Jansen et al., (2009) demonstrated that increases in the energy intake of 16 patients with ALL and 17 healthy siblings were found with dexamethasone (p value < 0.05). Therefore, the evidence from patients indicates that the most of ALL patients regardless CRT undergo a considerable positive energy balance during the ALL treatment and the most of them continue the gain weight during and even post therapy (Gregory et al., 2004).

1.5.6.4 Adiposity rebound

Adiposity rebound is one of the possible causes of adult obesity in ALL. Adiposity rebound occurs when the BMI reaches to nadir at around 4 - 5 years old and starts to increase at around 5 - 7 years old. However, the mechanisms of Adiposity rebound that lead to obesity in adulthood are still unknown (Reilly et al., 2001b).

To the best of our knowledge, only one study has investigated the timing of Adiposity rebound in ALL. The study by Reilly et al., (2001b) included 68 Scottish paediatric patients (35 boys, 33 girls) with ALL; and Adiposity rebound was measured by visual inspection of BMI charts for the children. They found that Adiposity rebound occurred earlier in ALL children (p value < 0.001) than in a comparison group of children taking part in the Avon Longitudinal Pregnancy and Childhood birth cohort study. By the age of 3- 4 years old, adiposity rebound had occurred in 43% of the comparison group and in 81% of the patients. In addition, they argued that the positive energy balance typical of ALL treatment, as mentioned, can produce early Adiposity rebound.

Patients of ALL with early adiposity rebound or patients treated before assumed adiposity rebound showed increase in BMI post therapy compared to with those with late adiposity rebound (above age 5 – 6 years old) or with patients who diagnosed over 6 years old. Therefore, an early adiposity rebound (before age 4 years) may be one of aetiology of high prevalence of excess weight status in ALL patients (Oeffinger et al., 2003). However, the underlying cause of an early adiposity rebound is still unknown.

1.5.7 Late effects of childhood cancer

1.5.7.1 Metabolic syndrome

Taskinen et al., (2000) showed that impaired glucose tolerance, dyslipidemia and MS components appeared following childhood cancer treatments. Therefore, MS could present in short and long-term survivors of childhood cancer.

In a cross-sectional study, 52 survivors were assessed to define the prevalence of MS and its components amongst adolescent brain tumour survivors. The mean age (range) was 14.2 years (3.8 - 28.7). The median age at diagnosis (range) was 6.0 years (0.1 - 15.5). The mean time since being off therapy (range) was 6.2 years (1.2 -

14.8). MS was defined by applying the IDF definition (explained in method chapter). They reported that MS was present in 8% of this population.

1.5.7.2 Metabolic syndrome in ALL survivors

MS exists in survivors of childhood ALL and its prevalence might be higher than expected. For instance, a Swedish study was carried out on 44 ALL survivors with a median age of 17 years (Link et al., 2004). They were treated with CRT; according to Swedish child leukaemia group protocol, and were found to have a significantly high insulin concentration (p value = 0.01), serum glucose (p value = 0.01) and LDL-L, TG, fibrogen, apolipoprotein, and leptin (all p value ≤ 0.05) and low HDL-C (p value= 0.03). In addition, 91% of the subjects had growth hormone deficiency. Therefore, they argued that, ALL patients treated with CRT and chemotherapy had a significant risk for cardiovascular problems including MS. However, (Link et al., 2004) recruited a relatively small sample of heterogeneous ALL survivors (i.e. mixed low, standard and high risk groups) and the survivors were treated by different treatments (chemotherapy or/and CRT).

Furthermore, Oeffinger et al., (2001) studied young adult survivors of ALL (median age was 20.9) to examine MS risk factors. The survivors who were treated by CRT were 38% and other 62% were only treated by chemotherapy. MS risk factors were defined by Oeffinger et al (2001) as following: BMI ≥ 30; diastolic blood pressure (DPB) and systolic blood pressure (SBP) ≥ 85 and 130 mm Hg; respectively, total cholesterol ≥ 200 mg/dl; HDL-C < 35 mg/dl; LDL-C ≥ 130 mg/dl; TG ≥ 200 mg/dl; cholesterol to HDL ratio ≥ 5 mg/dl; insulin ≥ 14 µU/ml; and glucose ≥ 110 mg/dl. They reported that 61% of survivors had one MS risk factor whereas 30% had two or more risk factors. However, Oeffinger et al., (2001) were examined MS in long term survivors (in adulthood) and survivors had different ALL classifications at diagnosis and so, they were treated with very different therapy protocols.

To the best of our knowledge, in non-western countries, Reisi et al., (2009) has been the only study which has examined the prevalence of MS amongst survivors with ALL in childhood in the medium term. They assessed 55 survivors aged 6 - 19 years. MS was defined as NCEP III criteria modified by de Ferranti et al., (2004). They reported that 20% of the subjects met the criteria of MS; whereas 50.9% had one risk factor. However, this study was carried out on survivors who were treated by the ALL-BFM protocol (including CRT).

Conversely, Gurney et al., (2006) did not find a difference between the prevalence of MS in 75 ALL adult survivors (the mean age was 30.2 years at interview) (16.6%, p value = 0.87) and the 132 control (mean age was 30.9 years) (prevalence of MS was 17.5%) by using the NCEP III definition. Gurney et al., (2006) studied long term survivors but with a relatively small sample size and using an adult MS definition.

Thus evidence from surviving standard risk ALL patients in the short or medium term is therefore very limited at present and further studies are needed. Studies in non-western countries are also required to investigate the prevalence of MS in other populations of patients with ALL.

1.5.7.3 Bone mass concerns in children and adolescents with cancer

The anatomy of normal bone is comprised from two main elements: trabeculaor cancellous and cortical or compact bone. Normal BMD usually happens when balance occurs in between bone formation and resorption. Therefore, if there was a lowering in the bone formation level or elevation in bone resorption this would lead to occurrence of low BMD (Wallace and Green, 2004).

The T-score results from the DXA instrument refers to the observed BMD in adults when compared to healthy young adults. Therefore, in adults, definitions of osteoporosis or osteopenia (low bone mass) are well-established by the WHO in

order to predict the fracture risk. The thresholds of osteoporosis and osteopenia for adults are as follows: T-score ≤ -2.5 and T-score ≤ -1 (Fewtrell, 2003).

Generally, it is widely accepted that reaching a low peak bone mass in early life is more likely to be osteoporotic in later life (Hansen et al., 1991). Moreover, some osteoporosis research has reported that the peak of mass is generally reached in the early 20s; and possibly in girls earlier than boys (Matkovic et al., 1994, Gordon et al., 1991). However, the big challenge is for children when there is no guideline for testing BMD as adults(Gordon et al., 2008, Wallace and Green, 2004).

1.5.7.4 Bone mineral density in children with malignancies

Some studies (Al-Tonbary et al., 2011, Muszynska-Roslan et al., 2009) have shown low BMD and low bone turnover at diagnosis, during the treatment and off-therapy amongst children with cancer. Al-Tonbary et al., (2011) scanned the total body by DXA for 27 children (of whom 59% were boys) at the diagnosis of neuroblastoma. The mean (SD) age was 6.1 years (4.8). They reported that 11.1% of the sample had low bone mass in the lumbar spine and a total body BMD (z score < -2.0). In addition Muszynska-Roslan et al., (2009) ascertained whether the therapy of solid tumours related to low bone mass than leukaemia and Hodgkin's disease. They recruited 114 patients (34, 35 and 36 had been treated for ALL, Hodgkin's disease and solid tumours; respectively). The median (range) age was 8.4 years (7.3 - 27.2). They scanned the total body twice using DXA during and after therapy. The age and sex-adjusted bone z score was calculated (low BMD defined as z score < -2.0). They reported that in the first examination, 30.5% of patients with solid tumours had low BMD; whereas ALL and Hodgkin's disease patients had 10.5% and 6.9%; respectively. In the second examination, the patients who had low BMD were 16.6%, 8.7% and 6.9%; respectively. They concluded that there was a relationship between the radiation used in treatment and low BMD.

1.5.7.5 Bone mineral density in children with ALL

ALL patients are at risk of diminished BMD (Wallace and Green, 2004). Numerous studies have examined the low BMD and ALL patients from therapy and beyond (for more details see the bone chapter 6). At the diagnosis of ALL, many pathological alterations are manifested in bone mineral metabolism (Halton et al., 1996). In a Polish study, Swiatkiewicz et al., (2003) evaluated a small sample (n= 27) of ALL patients (of whom 48% were girls) with intermediate risk according to the Non-B- cell precursor ALL Berlin- Frankfurt- Munster (BFM)-90 protocol. From 1990 – 1995, 2300 patients were enrolled to participate in BFM-90 trial from 96 centres in Austria, and Switzerland. Non-B BMF-90 protocol Included both chemotherapy involved prednisone, vincristine, daunorubicin, asparaginase, cyclophosphamide, cytosine arabinoside, mercaptopurine, thioguanine, high dose methotrexate, doxorubicin, and dexamethasone and included CRT (12 Gy) as CNS prophylaxis.The patients in the study by Swiatkiewicz et al., (2003) were scanned by DXA (age and sex adjusted to the local reference data) twice at   diagnosis and during the treatment (between CRT and maintenance phase). The median (range) age was 10.5 years (5 - 18). They reported that 30% and 22.2 % of the sample had low (z score < 1.645) BMD and bone mineral content (BMC). CRT and growth hormone deficiency is an issue which the thesis deals with below. However, this study had a small and heterogeneous sample exposed to both CRT or/and chemotherapy and the authors did not adjust DXA output to bone area.

Moreover, there is some evidence that ALL patients are at risk of bone morbidity such as osteoporosis, osteopenia, osteonecrosis and fractures (Rayar et al., 2012, van der Sluis et al., 2002b). For instance, in a recent study, Rayar et al., (2012) studied 124 patients (aged 18 years old and less) with ALL who had been treated only by chemotherapy and they used DXA for diagnosis BMD status. They defined osteopenia as a lumbar spine BMD z score of – 1.01 – 1.99 and defined osteoporosis as a lumbar spine BMD z score ≤ -2.0. They reported that at diagnosis 30% patients

had osteopenia and 11% had osteoporosis. During the therapy, 39.5% had osteopenia and 8% had osteoporosis. Also, 18.5% of patients developed the risk of fractures during the continuation of the therapy. However, the DXA outputs were not adjusted to bone area which is recommended by ISCD 2007 (Baim et al., 2008) but, the authors reported only the DXA output.

In a longitudinal study, van der Sluis et al., (2002b) examined 61 patients with ALL (median age was 7.1 years) at diagnosis, during treatment and one year after off-therapy. They used Apparent bone mineral density of lumbar spine ($BMAD_{LS}$) (it will be described in chapter 2) for adjustment BMD. They found that risk of fractures increases markedly during the therapy and shortly after off-therapy as well. However, even though the survivors were not treated with CRT but they treated to different type of treatment according to classification of high or standard risk condition at diagnosis.

1.5.7.6 The possible underlying causes of low bone mineralisation in childhood cancer

The nature of cancer is not a single disease although the disease itself may play a role in alteration of the bone metabolism and bone mass. Halton et al., (1995) measured endocrine, vitamin D status and other biochemical indicators of minerals amongst 40 children (67% of whom were boys) with ALL. The median (range) age was 3.9 years (0.3 - 17). They scanned the patients using dual-photo absorptiometry. They suggested that the process of the disease was the causative factor for changing vitamin D and defects in the mineralisation. Conversely, Arikoski et al., (1999) showed that apparent volumetric BMD (measured by DXA) in ALL and other cancer patients at diagnosis was not affected when compared to controls. However, the conclusion from both studies was influenced by the method of measuring BMD. The latter study adjusted the BMD according to age and sex while the first had not. Adjusted BMD in children will be discussed in greater detail in the general methodology chapter (chapter 2).

1.5.7.6.1 Chemotherapy agents

Chemotherapy and steroids in particular may influence bone metabolism during and after therapy. Arikoski et al., (1999) found that chemotherapy significantly increased bone turnover and reduced the development of BMD. Furthermore, steroids during the therapy may play a role in the short and long-term amongst cancer patients (Halton et al., 1996). It could impair bone formation and relate to the lowering of osteocalcin levels (osteoblastic function marker) (Wallace and Green, 2004). Elmantaser et al., (2010) studied 186 ALL patients retrospectively who were measured using DXA with age and sex adjustment. They found patients who were treated by dexamethasone had a significantly (p value = 0.03) higher incidence of skeletal morbidity than those treated by prednisone. In contrast, van Beek et al., (2006) found that after using $BMAD_{LS}$ to adjust bone size, there was no difference in using dexamethasone or prednisone protocols amongst ALL survivors aged 8.6 - 38.5 years. However, they found that the total body BMD was reduced in patients who had been treated by CRT.

Chemotherapy has in almost all protocols for ALL involved methotrexate in the treatment of cancer. This is known to increase urinary calcium excretion (Wallace and Green, 2004). Meister et al., (1994) used different doses of methotrexate amongst infants with tumours without the use of steroids. They demonstrated that the patients who had osteopathy were those who had received high doses of methotrexate (20 – 135 g/m^2).

1.5.7.6.2 Growth hormone deficiency

The endocrine system is one of most sensitive systems in the body and may be disrupted by cancer treatments. Most of the ALL studies published until recently have used old protocols which have used CRT. In more modern treated protocols CRT has been replaced with chemotherapy for most patients .There are many long-term survivors who have been treated by "old protocols"; some with a lower height

compared to age and sex groups. Moreover, CRT is still being used widely in some types of cancers such as brain tumours and in patients with ALL considered to be at high risk.

Some studies have shown that bone mass is due to growth hormone deficiency in survivors of childhood ALL (Follin et al., 2011). For instance in a recent study, Follin et al., (2011) examined 44 (21 female) survivors treated for childhood ALL by using CRT and chemotherapy. The median age (range) was 25 years (22 - 32) and each patient was matched with a healthy control. $BMAD_{LS}$ was used by DXA for correction of the bone size. The survivors were followed over the period of 5 - 8 years. Some of them (n= 16) were given growth hormone therapy (0.5mg/day). They reported a significantly low z score at the fermoral neck which was noticed amongst patients with growth hormone deficiency. However, the study did not clarify the benefits of growth hormone therapy in BMD.

It is worth stating that growth hormone deficiency may not be such an issue for some of the studying in this thesis as CRT not used widely in patients in chapters 3 and 6 but may be more relevant to study in chapters 4 and 5.

1.6 Scope of this thesis

To summaries this literature, previous studies had several limitations and differences which led to large variations in prevalence of unhealthy weight at diagnosis. In the absence of studies that included a representative sample of ALL children who had been treated with same protocol, and using the most recent definitions of unhealthy weight status, prevalence of unhealthy weight status at diagnosis of ALL is unclear. Additionally, there is no study up to now which focused on the secular trends of unhealthy weight status over time at diagnosis amongst ALL children. Clinically in the UK there is no formal anthropometric or other nutritional screening for assessing unhealthy weight status in ALL. Therefore, It would be helpful to conduct a study based on a large nationally representative sample that included most of UK ALL

patients (80 – 95 %) (Mitchell et al., 2010) and which used evidence-based definitions of unhealthy weight status (Cole et al., 2007), and which assessed the secular trends of unhealthy weight status over time.

Furthermore, there are limited and conflicting studies that examined the role of unhealthy weight status at diagnosis on prognosis in children with ALL. The conflicting literature has been caused by a combination of small sample sizes, included heterogeneous ALL groups (mixed low, standard and high risk), different treatments (using CRT, chemotherapy or/and both) and applying different definitions for assessing unhealthy weight status. Therefore, the present thesis conducted a study that included a fairly homogenous sample of ALL children treated with same protocol (UKALL X), with a relatively large sample size and using evidence-based definitions and the most recent definitions (Cole et al., 2007) for defining unhealthy weight status to test the influence of weight status on risk of relapse of ALL patients.

In addition, the prevalence of obesity has becomes epidemic worldwide. In Saudi Arabia for example the prevalence of obesity in children and adolescents is now very high (34% overweight or obese) (El Mouzan et al., 2010). Studies that estimated prevalence of unhealthy weight status and MS amongst survivors ALL in first remission children in non-western countries are   scarce and no study applied modern definitions for defining weight status. Also, no study examined over-fatness in non-western countries in ALL survivors to observe whether over-fatness by using BIA and DXA is consistent with BMI for age for defining overweight or obesity. Therefore, the present thesis examined prospectively the weight status, over-fatness and MS amongst Saudi standard risk ALL survivors in medium term (to early intervention) of fairly homogenous group in first remission treated with modern and same protocol (no CRT used).

Finally, low bone mineralisation in childhood cancer survivors is a widespread concern (Elmantaser et al., 2011, Elmantaser et al., 2010, van der Sluis and van den

Heuvel-Eibrink, 2008, Warner et al., 1998b, White et al., 2005). However, many studies report conflicting conclusions, due largely to relatively small and not representative samples, different study designs, inclusion of heterogeneous groups, i.e. mixed survivors who had been treated with different type of treatment and protocols, and failure to use an adjustment to DXA output for body size (described in detail in general methods chapter). Therefore, the present thesis aimed to test for the effect of adjusting DXA output amongst a fairly homogeneous sample of Saudi ALL survivors in first remission.

Chapter 2

General methods

2.1 Chapters 3 and 6 methodology

2.1.1 Participants

Cross-sectional studies of Saudi survivors with childhood standard risk ALL (as defined below) in first remission (i.e. no relapse) were carried out from October 2009 until April 2010. The reason to include only standard risk ALL patients was to have a relatively homogenous group: to reduce variability due to disease (e.g. high risk vs. standard risk, more versus less aggressive disease and disease treatment),and patient age/development (high risk status is denoted by being very young at diagnosis and older at diagnosis); to control for treatment e.g. patients on older protocols with CRT, patients on mixed protocols where some received CRT, more homogeneity on modern protocols where CRT was not used for standard risk patients or not used at all.

All survivors who included in the Saudi studies in the present theses had been treated according to the modified CCG 1891 protocol (summarised in table 2.1.1 and for more details see appendix C) at KFSH&RC between 1994 and 2009. In Saudi Arabia, there are few centres that deal with childhood cancer. KFSH&RC is placed in the capital the Kingdom of Saudi Arabia (Riyadh) and it served all regions in the country. Also, it is the most famous and one of the most modern hospitals in the Middle East region (see figure 2.1.1).

2.1.1.1 Saudi Arabia in context

The country was established by King Abdul-Aziz Bin Saud in 1932. The capital is Riyadh. It has the second largest oil reserves and in the second largest exporter in the world. Saudi Arabia is growing rapidly and per capita income was £15,200 in 2010 compared to £9,400 in 2006. The total population according to the last census (2010) was 27,448,000 (United Nations, 2012).

Also, stability in politics and economic is helping in improving reducing level of morbidity and mortality rates. The government provides free education and health for citizens. The mortality rate (per 1,000) under-five was sharply decreased over 40 years ago from 179 in 1970 and reached to 17.5 in 2010 (Child mortality estimates, 2011) as show in figure 2.1.2.

Figure 2.1.1: King Faisal Specialist Hospital & Research Centre (KFSH&RC) view

Also, female and male adult mortality rate (per 1,000 adults) reached in 1960 up to 325 and 418; respectively. However, the curve sharply decreased to 97 and 129 in female and male adults; respectively (United Nations, 2012).

However, as a result of fast economic transition in very short period, the Saudi life style has had a profound shift in both dietary habits and physical activity patterns a 'westernisation' of life style. Al-Hazzaa et al., (2011) reported that about half of male Saudi adolescent and about 75% of female Saudi adolescent were insufficiently active based on the physical activity daily guidelines. Also, they found high prevalence of unhealthy dietary habits such as the majority of adolescents did not consume the daily requirements of milk and fruit; however, there is no specific Saudi milk recommendation.

Figure 2.1.2: Mortality rate, under-5 (per 1,000)
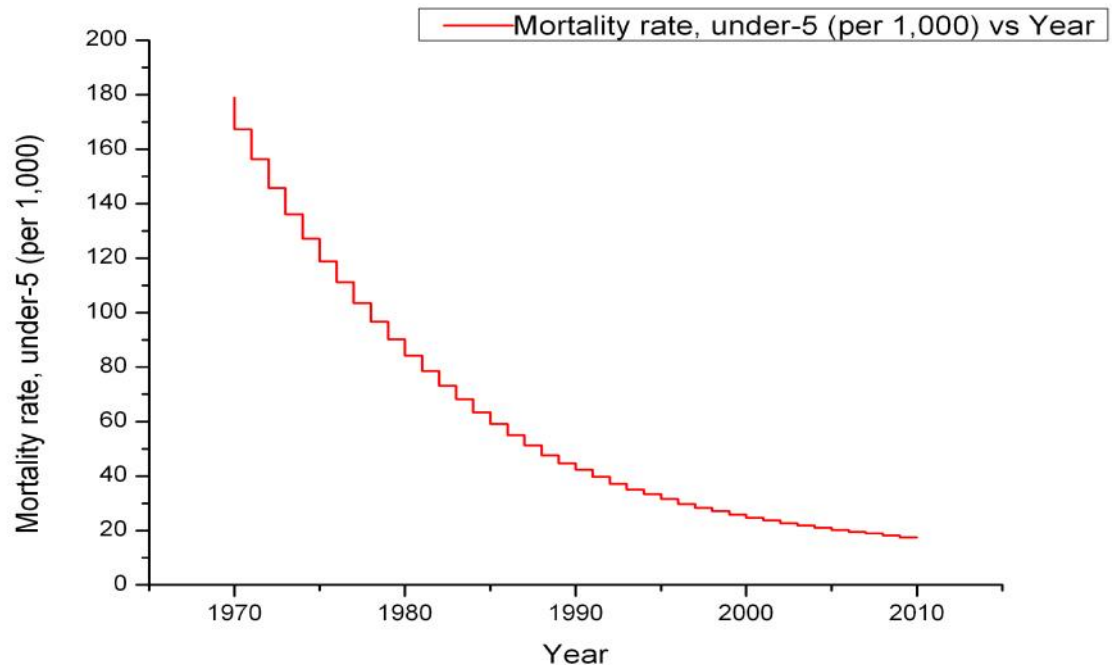
Source: extracted the data from the United Nations Inter-agency Group for Child Mortality Estimation (Child mortality estimates, 2011)

Table 2.1.1: The modified CCG 1891 protocol therapy at KFSH&RC

Phase I. Induction (4 weeks) Dose	Phase II. Consolidation (4 weeks) Dose	Phase III. Interim Maintenance I (8 weeks)	Phase IV. Delayed Intensification I		Phase V. Interim Maintenance II (Begun at Day 49)	Phase VI. Delayed Intensification II		Phase VII. Maintenance (12 weeks)
			Re-induction: (0 – 27 days)	Re-consolidation (28 - 49)		Re-induction (0 – 27 days)	Re-consolidation (28 – 49 days)	
Dexamethasone 6 mg/m^2/day	Dexamethasone 3 mg/m^2/day	Methotrexate 20 mg/m^2/ Week	Dexamethasone 10 mg/m^2	Dexamethasone Complete taper	6-Mercaptopurine 75 mg/m^2	Dexamethasone 10 mg/m^2	Dexamethasone Complete taper	Methotrexate 8, 10 and 12 mg based on age
Vincristine 1.5 mg/m^2 IV	6-Mercaptopurine 75 mg/m^2	Vincristine 1.5 mg/m^2 IV	Vincristine 1.5 mg/m^2 IV	Cyclophamide 1000 mg/m^2	Methotrexate 20 mg/m^2	Vincristine 1.5 mg/m^2 IV	Cyclophamide 1000 mg/m^2	Vincristine 1.5 mg/m^2 IV
L'Asparaginase 6000 U/ m^2	Methotrexate 8, 10 and 12 mg based on age	Dexamethasone 6 mg/m^2	Adriamycin 25 mg/m^2 IV	6-thioguanine 60 mg/m^2	Vincristine 1.5 mg/m^2 IV	Adriamycin 25 mg/m^2 IV	6-thioguanine 60 mg/m^2	Dexamethasone 6 mg/m^2
Methotrexate 8, 10 and 12 mg based on age	Vincristine 1.5 mg/m^2 IV	6-Mercaptopurine 75 mg/m^2	L'Asparaginase 6000 U/ m^2	Cytosine Arabinoside 75 mg/m^2 /day IV	Dexamethasone 6 mg/m^2	L'Asparaginase 6000 U/ m^2	Cytosine Arabinoside 75 mg/m^2 /day IV	6-Mercaptopurine 75 mg/m^2
			Methotrexate 8, 10 and 12 mg based on age	Methotrexate 8, 10 and 12 mg based on age.			Methotrexate 8, 10 and 12 mg based on age	Methotrexate 20 mg/m^2

2.1.1.2 Inclusion criteria for studies in chapters 3 and 6

Saudi citizens aged between 5 and 20 years in first remission for ALL at the end of ALL therapy with standard risk were selected in order to ensure a fairly homogenous sample as explained above.

The standard risk criteria were applied using KFSH&RC's Department of Paediatric Haematology oncology criteria in which patients with precursor B-cells are considered standard risk only if all of the following criteria apply:

- Age > 1 year and < 10 years at diagnosis.
- Initial WBC < 50 x 10^9/L.
- DNA index (The ratio of ALL test divided by standard DNA fluorescence) ≥ 1.16 or ≤ 1.6. DNA Index in ALL patients has been used as prognostic tool. Also, some protocols have relied on DNA index to classify the risk categories (Rachieru-Sourisseau et al., 2010).
- Lack of adverse cytogenetic/molecular genetic studies (t(9;22)/ BCR-ABL; t (1;19)/ E2A-PBX1; t (4; 11)/AF4–MLL).
- Negative for central nervous system or testicular involvement.
- Note: all other criteria are considered as high risk.

It should be emphasised that "10 years old" refers to the age at the time of diagnosis. However, the age range in this study (5 -20 years) refers to the age at the time of conducting the present study. The age range (5 – 20 years) was based on the ages allowed in the ALL survivors' clinic at the KFSH&RC.

2.1.1.3 Exclusion criteria for studies in chapters 3 and 6

Patients were excluded if they:

- Had relapsed at any stage. Patient who relapsed will undergo in another therapy protocol and may receive intensive more treatment than the group.

- Currently or previously had a secondary malignancy that would increase the variability in the sample for instance patient with secondary malignancy will be exposed to different type of treatments than the group in the first remission.
- Were younger than five or older than 20 at the time of the present study. This criterion is based on practical reasons because the KHFSH&RC survivors' clinic included patients 5 – 20 years old.
- Had high risk ALL (High risk ALL patients have different and more intensive treatment than standard risk patients).
- Were being or had been treated for MS or related diseases such as diabetes before the diagnosis of ALL. The present study was aimed to investigate the 'late effects' of ALL amongst survivors and not to examine the late effects in patients who already had these diseases.
- Had longbone fractures because it was impractical to take measurements for most nutritional assessments.

The potential participants who were treated in the same protocol and had their annual follow in the survivors' clinic during the period of the carried out of the present study were 77 survivors aged between five and 20 years.

Survivors were ineligible if:
⇒   They had relapsed (n= 3).
⇒   Were pregnant (n=2).
⇒   Had pre-existing type I diabetes before diagnosis of ALL (n=1).

 Or
⇒   Had a longbone fracture in plaster (n=2).

Note: This left 69 potential eligible survivors for the present study who were invited to take part.

Comments on Recruitment:

♦ They or their parent (s) were contacted by telephone before attending their annual follow-up appointments at the Department of Paediatric Haematology/Oncology in KFSH&RC.

♦ Seven survivors living in Riyadh who did not have appointments at the hospital were telephoned after obtaining permission from their physicians. Of the potentially eligible survivors, 56 (81%) agreed to participate (see figure 2.1.3).

♦ No control group such as a healthy control group or a "positive control" group with chronic disease was collected because of limited resources (budget). Also, the study was restricted by limited time by the author's sponsor (i.e. no more than 3 months at a time outside the UK) and restrictions placed by the University of Glasgow (no more than 12 months outside of Glasgow in total in the three year period).

2.1.1.4 Confidentiality

All participants' data were collected confidentially. All information relating to personal identities, such as names, file numbers or contact numbers, was coded. Each participant was assigned a coded number to link them to their data.

2.1.2 Ethical approval

The study proposal was submitted to the Research Advisory Council (RAC) at the KFSH&RC. The RAC was reviewed and the proposal was approved on 26 October 2009 (see appendix B). The consent form was written according to the RAC procedure. It was singed by the participant's parent. All consent forms were kept in the participant's medical files according to KFSH&RC instructions.

Figure 2.1.3: Chapter 3 and 6 studies recruitment follow diagram
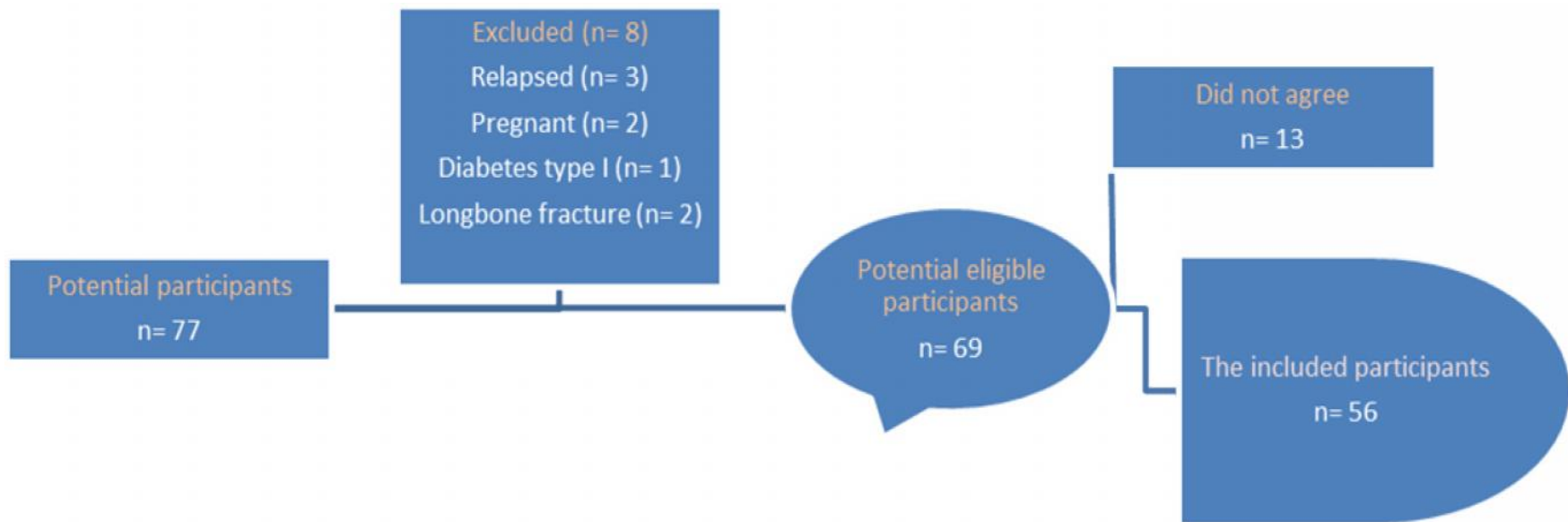
2.1.3 Anthropometric measurements

2.1.3.1 Height, weight and BMI

Height and weight were measured to 0.1cm and 0.1kg; respectively. All Saudi survivors' heights and weights in the present studies were measured using a Scale-Tronix 5002 stand-on scale (shown in figure 2.1.4). They were wearing light clothes and removed shoes and outdoor clothes. Height was measured as participants stood in front of a wall looking straight ahead (Gibney, 2005). One reading was recorded.

BMI was calculated using the following equation: Weight (kg)/Height (cm) [2]. However, BMI was expressed with age and sex-specific z scores or percentile if the BMI z score was not available such as in Saudi reference data (El-Mouzan et al., 2007). Various BMI sex and age-specific reference data was used for the classification of weight status in present studies as summarised in table 1.4.2; Saudi (El-Mouzan et al., 2007), CDC (Kuczmarski et al., 2000), WHO (de Onis et al., 2007), IOTF (Cole et al., 2000) and Cole et al., (2007) reference data. All the present studies survivors were Saudis and so, the national (Saudi) reference data were also used. Also, the present studies used the international reference data such as CDC (Kuczmarski et al., 2000), WHO (de Onis et al., 2007), IOTF (Cole et al., 2000) and Cole et al., (2007) population reference data as they widely used in the literature and recommended in clinical for obesity management and epidemiological surveillance (Scottish Intercollegiate Guidelines Network, 2010, Reilly et al., 2010b).

Figure 2.1.4: Scale-Tronix 5002 stand-on scale

2.1.3.1.1 Saudi reference data for BMI

In 2007, El-Mouzan et al., (2007) produced the Saudi growth (BMI for age) charts for both genders . Data from a stratified multistage probability sample were based on representative samples of healthy children and adolescents collected from 13 regions in Saudi Arabia between 2004 and 2005. This national survey examined 11,874 apparently healthy children and adolescents who were subjected to anthropometrics measurements (Al Herbish et al., 2009). They also, used for chart percentiles Epi info 2002 software program produced by CDC and LMS method proposed by Cole et al., (1992) for curve construction.

Data were available in the form of centile charts for boys and girls and BMI z scores were unavailable (El-Mouzan et al., 2007). Study participants were defined, therefore, manually (by plotting of data on BMI charts) by the author as: obese (BMI ≥95th percentile), overweight (BMI 85th to <95th percentile) and underweight (BMI <5th percentile) (Al Herbish et al., 2009, El-Mouzan et al., 2007). However, as far as the author is aware, no research on the validity to detect fatness or thinness, ability to predict co-morbidity or premature mortality of using BMI for age with the Saudi BMI for age reference data exists.

2.1.3.1.2 US CDC reference data for BMI

BMI z scores were calculated for study participants based on the US CDC 2000 reference data (Kuczmarski et al., 2000) by using software available at: http://stokes.chop.edu/web/zscore/result.php. The CDC reference data (Kuczmarski et al., 2000) of children and adolescents are based on four nationally representative surveys in the USA conducted between 1963-1965 and 1976-1980. A survey of children aged two to five was carried out from 1988-1994. Participants aged between two and 20 years were included. The national survey designs are based on stratified, multistage probability samples of the civilian, noninstitutionalised population. The anthropometric measurements (weight and length), age and gender were recoded. They used the modified LMS method proposed by Cole et al., (1992) to produce smoothed percentile curves.

Use of CDC reference data is customary to classify weight status according to BMI for age and sex as follows: obese: (BMI ≥95th percentile), overweight (BMI 85th to <95th percentile) and underweight (BMI <5th percentile) (Kuczmarski et al., 2000), so these definitions were used in the present study.

Freedman et al., (2005b) studied the validity of BMI (based on US CDC reference data) to define high body fatness amongst 1,196 healthy children and adolescents

aged between five and 18 using the DXA instrument. Accuracy of BMI was found to vary depending on the degree of fatness. The FM index (FM in kg divided by height^2 in cm) highly correlated with BMI≥ 85th centile (r= 0.85- 0.95). However, a weaker correlation between BMI for age < 50th and FM (r= 0.22- 0.65) than for the FFM index (r= 0.56 – 0.83) was observed. Therefore, they concluded that a high BMI for age based on US CDC reference data is a good predictor in term of detecting high adiposity and it is moderately sensitive and specific for high fatness. Moreover, Reilly and Kelly (2011) reviewed studies where the US CDC reference was used to define excessive fatness and showed that those with overweight and obesity as defined by a high BMI are risk of morbidity and premature of mortality in adulthood. Mei et al., (2002) investigated (sample was 11,096 aged 2 – 19 years) the validity of BMI for age and weight for stature in term detecting underweight (defined as below the 15th percentile) and overweight (defined as above the 85th percentile) compare with DXA and skinfold thickness. They concluded that BMI for age is to some extent a better proxy for underweight and overweight than weight for stature in children and adolescents.

2.1.3.1.3 WHO reference data for BMI

The WHO updated the BMI for age and sex reference data for children and adolescents in 2007 but it is based largely on data from National Centre for Health and Statistics (NCHS)/ WHO which were conducted from 1977 growth reference for who age 1– 24 years old. They used three data sets for developing WHO reference data. The first data set was from the National Health Examination Survey (NHES) Cycle II (6–11 years), the second data set was from Cycle III (12–17 years) and the third data set was from Nutrition Examination Survey Cycle I (1 to 24 years) (de Onis et al., 2007). The sample size was 22 917 (11 410 boys, 11 507 girls). The Box-Cox power exponential (BCPE) method was used to generate BMI percentile curves.

BMI z scores were calculated using the WHO Anthro version 3.2.2, January 2011 software available at: **http://www.who.int/childgrowth/software/en/**. The WHO reference data for children and adolescents aged between two and 19 years was used (de Onis et al., 2007). The BMI z score was converted to weight status categories as follows: overweight as >+ 1SD (conceptually equivalent to BMI 25 kg/m^2 at age 19 years), obesity as >+ 2 SD (conceptually equivalent to BMI 30 kg/m^2 at age 19 years) and underweight/thinness as < -2 SD (de Onis et al., 2007).

2.1.3.1.4 International Obesity Task Force (IOTF)

In 1997, the IOTF working group recommended the use of BMI as an indicator of excessive fatness in children and adolescents (Bellizzi and Dietz, 1999). Consequently, Cole et al., (2000) established standard cut-offs to define overweight and obesity for children and adolescents aged between two and 18 years and they were published in 2000. Data were collected from Brazil (1989), UK (1978 - 1993), Hong Kong (1993), the Netherlands (1980), Singapore (1993), and the United States (1963 - 1980). They had a data set for children and adolescents from birth to 25 years old and it consisted of 97,876 and 94,851 males and females; respectively. Subsequently, they extrapolated the classification for BMI in adult (overweight ≥ 25 and obesity ≥ 30) in the six countries datasets at age 18 years afterward created a curve which passed through these cut- offs the ages from adulthood at 18 years old until childhood at 2 years old. In other words, the cut-off points are conceptually equivalent to adult BMI-based definitions of overweight and obesity of 25 and 30kg/m^2 respectively and were applied in the present study using software (available at www.healthforallchildren.com). They established and recommended the use of this definition for international epidemiological studies.

However, there is no consensus on the adoption of this definition nationally or internationally (Reilly et al., 2010b). The argument was mainly focused on the sensitivity of the definition and usefulness in clinical settings. Reilly et al., (2000a)

showed that IOTF (Cole et al., 2000) has high specificity but it is associated with low sensitivity i.e. a high false negative rate for excess fatness. Also, a review article for example, found that 40 – 50% of children with excessively high body fatness were not classified as obese by using the IOTF definition (Reilly, 2006a). Furthermore, a systematic review paper showed that using national BMI is superior to using IOTF (Cole et al., 2000) and the national BMI reference generally has higher sensitivity and similar specificity to use of IOTF definition (Reilly et al., 2010b).

2.1.3.1.5 Cole et al. (2007) definition of underweight

More recently, Cole et al., (2007) proposed an international definition of children and adolescent underweight "thinness" based on BMI for age and gender using same data used in Cole et al., (2000) from the same six countries. Underweight was classified for children and adolescents aged between two and 18 years as three grades corresponding were extrapolated to an adult BMI of 16, 17 and 18.5 kg/m^2 which is proposed by WHO. They merged data and produced a curve which passed through these cut- offs the ages from adulthood at 18 years old until childhood at 2 years old. These are conceptually equivalent to (at age 18 years old) a BMI ≤18.5, namely "chronic energy deficiency as defined by the WHO" (James et al., 1988, World Health Organization, 1995). However, this thesis will define all different underweight grades as one grade instead of Cole et al. (2007) classification as: grade 1, 2 and 3 underweight. (For values to define thinness at each age and in both sexes)

Underweight was assessed by Tuan and Nicklas (2009) using CDC and Cole et al. (2007) definitions in 53,826 Vietnamese, 11,756 Indonesian and 1600 Chinese children aged 2 – 18 years. They found that according to the Cole et al. (2007) definition, the prevalence of underweight in Chinese, Indonesian and Vietnamese was 6%, 10% and 13%; respectively and 10%, 13% and 19%; respectively based on the CDC reference data. They reported that there are age, sex and ethnic differences in prevalence of underweight by different definitions. So, they advised the evaluation of

any international definition before using in any specific-population. As a result the Cole et al., (2007) of thinness is used continuously in this thesis.

2.1.3.2 Waist circumference (WC) measurement

Interest in WC measurements has increased in recent years as it may be used as an indicator for cardiometabolic risk factors in both children and adults (McCarthy et al., 2003, Speiser et al., 2005). The waist size of all Saudi participants in the present studies (chapters 3 and 6) was thus measured using measuring tape. The measurement was taken by two trained observers (a female dietician (Mrs. Hanan Almutairi) measured some of girls (n= 19) and the author measured boys and some of girls). The measurement was taken to the nearest 0.1 cm while the participant stood without any compressions on the skin and the waist was measured at a site 4 cm above the umbilicus (Rudolf et al., 2007).

The WC changes with age and differs between the sexes. So, it must be interpreted in an age- specific and sex- specific methods measured WC in children. Rudolf et al., (2007) examined the consistency across different waist measurement methods amongst 41 healthy children (75.6 % was girls). The mean (SD) age was 12.4 years (3.3).The waist measurement methods were the midpoint between lowest rib and iliac crest, crease on lateral flexion and 4 cm above umbilicus and compared them with BMI z score from UK 1990 definition (Cole et al., 1995). As all methods were highly correlated to each other and to BMI z score, they recommended using 4 cm above umbilicus method arguing that it would be the simplest option in clinical settings as described in section 1.4.5.1.6.

2.1.4 Blood pressure (BP) measurement

BP was measured in all Saudi participants using an automated electronic vital signs monitor that included BP monitoring (CASMED® 740 monitor) (see figure 2.1.5). The

measurement was performed by staff nurses at KFSH&RC. Before the measurement, subjects were seated for at least five minutes in a waiting room. Participants were seated comfortably on a chair for the BP measures. The cuff was covered at least one-third of the right upper arm between the olecranon and acromion. The BP reading was repeated twice and the average of both readings recorded (Bird and Michie, 2008). The definition of hypertension depends on MS definitions as discussed below.

Figure 2.1.5: CASMED® 740 monitor for blood pressure (BP)

2.1.5 Body composition measurement

BMI for age and sex is a simple and cheap indicator of high and/or low body adiposity, as noted above (Reilly et al., 2010b). Nevertheless, body composition may

be considered as more informative than the BMI method in healthy children and adolescents (Wells and Fewtrell, 2008) as well as amongst survivors of childhood cancer (Warner et al., 1997). It has also been highlighted by the IDF consensus group as a useful parameter to collect when considering metabolic syndrome and its potential use in future research studies was emphasised by IDF, even though the IDF panel did not recommend body fatness to be included as one of the MS criteria (Alberti et al., 2006). Warner et al., (2004) also recommended that in clinical settings such as ALL more than one body composition method should be used. Body composition was hence measured using two instruments in the present studies: DXA and BIA. These two methods are convenient and practical for clinical use and were available in the KFSH&RC (as explained in general introduction chapter).

Levels of total body fat % which are excessive (because of associations with adverse cardiometabolic risk profiles) have been established by previous studies (Lohman, 1992). Over-fatness was defined in this thesis as percentage total body fat (%TBF) was more than 25% in males and 32% in females amongst survivors aged 18 years and more. However, For those aged 5- <18 years, over-fatness was defined as % BF more than 25% for boys and more than 30% for girls (Lohman, 1992).

2.1.5.1 Bioelectrical impedance (BIA)

After receiving training on the use of the BIA instrument from the charge staff under KFSH&RC supervision, 53 Saudi survivors of childhood ALL were measured by BIA. The instrument could not analyse the remaining participants (n=3) because they were so young and it was difficult to stand on the device.

All BIA procedures were performed by the author. Total body bioimpedance was measured by using a Biospace Inbody 3.0 Composition Analyser (Biospace © 2001) (see the figure 2.1.6). General prediction equations for estimation of body water (and

body water can be used in turn to estimate body composition) were proposed by Cha et al., (1995) as following:

1. " The resistance (R) of the body is a function of the resistivity (p), the length (L), and the cross-sectional area of the conductor (A):

    $R = p \times (L/A)$

2. Multiplying the numerator and denominator by L yields:

    $R = p \times (L \times L)/(A \times L)$

3. A x L is the volume of the conductor (V):

    $V = p \times (L^2/R)$

4. When R at low frequency (R_{low}) is included in the above equation, V approximates extracellular water (ECW); when R at high frequency (R_{high}) is included, V approximates total body water (TBW). Because the specific resistivity is different between ECW and TBW (p1 and p2, respectively), as expressed:

    $ECW = p1 \times (L^2/R_{low})$

    $TBW = p2 \times (L^2/R_{high})$

5. The ratio ECW/TBW can be expressed as the ratio of two equations above:

    $ECW/TBW = p1 \times (L^2/R_{low})/p2 \times (L^2/R_{high})$

    $\qquad\qquad = p1 \times (L^2/R_{high})/p2 \times (L^2/R_{low})$

6. Assuming that p1 and p2 are constant:

    $ECW/TBW \ \alpha \ R_{high}/R_{low}$ "

BIA Inbody 3.0 uses a direct segmental multi-frequency bioelectrical analysis to measure the trunk, arms and legs. This instrument was maintained by the biomedical engineering department. Personal information (ID, age, gender, weight, and height) was entered and this information will be used in an algorithm for prediction of body composition which is commercially sensitive. The instrument has eight point tactile electrodes (two front sole electrodes, two rear sole electrodes, two thumb electrodes and two palm electrodes). Total body impedance was measured at a 50 kHz frequency.

All participants measured did not eat or drink and were asked to go to the bathroom before the test as instructed by the instrument's manufacturers. The test was performed at room temperature. Participants were instructed to touch the palm electrode using four fingers, to place their thumb on the thumb electrode and to press gently. They stood on the foot electrodes but were instructed to place the heel on the rear sole electrode before their forefoot touched the front sole electrode. They were advised to stand comfortably; the angle between the arm and side was about 15 degrees. The BIA total body fat percentage (%TBF) results were then used. One reading was recorded.

Figure 2.1.6: Biospace Inbody 3.0 Composition Analyser (Biospace © 2001)

Validity of the Biospace BIA monitor

The Segmental multi-frequency BIA (InBody 3.0 Biospace Co. Ltd. Soul, South-Korea) used in the present study has been evaluated for validity and reliability

purposes, but in studies which used DXA a gold standard measurement for body compositions (which it is not). For instance, Kriemler et al., (2009) aimed to examine the cross-validation of tetrapolar BIA (4-BIA model 101A, RJL system, MI, USA) and octopolar (8-BIA; Inbody 3.0, Biospace, Seoul, Korea) analysers for assessment of body composition with DXA as a reference method. They recruited 333 Swiss children and adolescents aged 6 -13 years old. Total body fat-free mass and appendicular lean tissue mass were assessed by Lunar DXA. They reported that 8-BIA analyser (used in the present thesis) was more accurate in total body fat-free mass assessing than 4-BIA (root mean square error= 0.90 kg and 1.12 kg; respectively, equivalent to 3.2 % and 3.7 %). Also, that 8-BIA analyser was more accurate for estimation of appendicular lean tissue mass (root mean square error ≤ 0.10 kg for arms and ≤ 0.24 for legs) assessing than 4-BIA. Therefore, they concluded that the 8-BIA analyser is a superior and more accurate predictor of segmental body composition than the 4-BIA analyser.

Furthermore, Lim et al., (2009) studied the validity of multifrequency BIA with eight tactile electrodes or BIA-8 (Inbody 720, biospace, Seoul, Korea) in assessing FM, FFM and %BF compared to Lunar DXA. The sample size was 166 (86 boys and 80 girls) healthy children and adolescents (mean (SD) age was 11.4 years (3.1)). The correlations between BIA and DXA were r= 0.995 (p value< 0.01) for FFM, r= 0.981 (p value< 0.01) for FM and r= 0.926 (p value < 0.01) for %BF. By using linear regression analysis between DXA and BIA, r^2= 0.99 (standard error was 1.16 kg) for FFM, r^2= 0.93 (standard error was 1.34 kg) for FM and r^2= 0.86 (standard error was 3.03%) for %BF. A Bland-Altman plot was used to analyse the limits of agreement and the differences for FMM, FM and %BF-the limits of agreement were 0.7 ± 2.3 kg for FFM, 0.9 ± 2.9 kg for FM and 2.2 ± 6.1% for %BF. They concluded that even though the BIA analyser was not interchangeable with DXA in assessing body composition, it remains useful in healthy and diseased children because of its high precision and reasonable accuracy.

Jensky-Squires et al., (2008) carried out a study in 254 adults aged 21 – 80 years old and 117 children and adolescents aged 10 – 17 years old. They evaluated %BF by using BIA (InBody 3.0 Biospace Co. Ltd. Soul, South-Korea) analyser, Omron body analyser (Omron healthcare, Inc., Veron Hills, IL, USA), Bod-eComm near- infrared interacatance (uses wavelengths of harmless low intensity near- infrared light absorbed by body fat and reflected by lean body mass). In adult subjects, they compared their %BF with DXA and compared the outcome of BIA (Inbody 3.0) with underwater weighing in children. However, the underwater weighing method is not a gold standard, and it can be influenced by hydration, the subject's comfort and ability to expire air (Thomson et al., 1991). They found that all used body composition methods were correlated with DXA (r= 0.54, p value ≤ 0.01), except Bod-eComm in elderly women (r= 0.54, p value= 0.12). BIA (Inbody 3.0) was significantly correlated with underwater weighing in both boys (r= 0.69, p value ≤ 0.01) and girls (r= 0.79, p value ≤ 0.01). By using Bland- Altman analysis, all body composition methods underestimated %BF except BIA (Inbody 3.0) which overestimated %BF in boys and girls. There were large individual errors for all methods.

2.1.5.2 Dual energy X-ray absorptiometry (DXA)

DXA was performed by two trained technicians working in the nuclear medicine division at the (KFSH&RC). The % TBF was measured by DXA using a whole body scanner (DXA Lunar Prodigy, software version 9.15) (see the figure 2.1.7). Coefficient variation for total body BMD was 0.73% and lumbar spine was 1.0% as they have been reported by Crabtree et al., (2005). According to the KFSH& RC laboratory's intra-assay variation coefficient for fat mass was 0.76± 0.41%.

Figure 2.1.7: DXA Lunar Prodigy, software version 9.15

A total of 56 Saudi ALL survivors were recruited and booked in for a scan appointment. However, five of them did not attend the appointments in the main hospital (which is situated about 45 minutes by car from the oncology centre) as their flight time was at the same time of DXA procedure. Therefore, the number of survivors scanned for the present studies was 51.

Before the scan, survivors were instructed to remove shoes and metal objects such as keys, watches and rings. They were scanned whilst lying comfortably in a supine position. The whole body was scanned from the head to feet. The scanning procedure took approximately seven to 15 minutes depending on the height of the survivors and their cooperation during the procedure. The dose of radiation participants were exposed to using DXA is very small and at a safe level (<0.05 mSv) (Laskey, 1996).

The outcome from DXA instrument measurements consisted of body FM (g), % TBF, lean fat mass (g), body mass content (BMC) (g), bone area (BA) (cm^2) and areal (aBMD)/ BMD (g/ cm^2), illustrated in figure 2.1.8 . It should be evident that DXA is composed of two separate sets of equations, each used to describe a 2-C model. However, there is big debate as which is the best method to adjust BMD so, the author explains the different approaches below.

2.1.6 Measuring bone mass in children

First of all, children are not little adults. Childhood is affected by different factors that might lead to misinterpretation of the results of bone mass assessment. For example, it is a consistent bone growth phase and bone age is not closely related to the chronological age (Bonnick, 2010). The DXA instrument calculates BMD as an areal (aBMD) or a 2-dimensional measurement by measuring BMC and projected bone area (BA). The equation is the following: (BMC (g) ÷ BA (cm^2)). Therefore, aBMD (combined cortical and trabecular bone) is affected by BMC and bone size rather than the true density (Fewtrell, 2003).

Volumetric density, such as Quantitative Computed Tomography, uses 3-dimensional measurements to produce height, width and depth to obtain volumetric density (Kroger et al., 1995). Even though the computed tomography machine is based on a 3-dimensions measurement (volumetric measurement), which is an advantage, it requires a high dose of radiation to be exposed which is unacceptable for children and adolescents (Warner et al., 1998b) and so it was not used in the present studies.

Therefore, aBMD as produced by DXA is a not true volumetric density because the anterior and posterior diameter of the bone are not measured (Kroger et al., 1995). Consequently, aBMD seems to be overestimated in large children and underestimated in small ones (Fewtrell, 2003). The aBMD should therefore ideally be

adjusted to the bone size to avoid mislabelling of children as osteoporotic, possibly receiving unneeded treatment. Also, it is important when labelling children with "low bone mass" to prevent future risk fractures (Ahmed et al., 2004). Consequently, there is controversy as to how to diagnose a low BMD in children with DXA and what approach is the best to correct the bone size on areal measurements (2-dimension measurements) to something closes to true density.

Figure 2.1.8: An example of ancillary lumbar spine data by Lunar DXA. (This real image is extracted from the present study).

Region	BMD (g/cm²)	Young-Adult (%)	Young-Adult T-Score	Age-Matched (%)	Age-Matched Z-Score	BMC (g)	Area (cm²)	Width (cm)	Height (cm)
L1	0.817	-	-	101	0.1	6.65	8.13	3.0	2.73
L2	0.873	-	-	100	0.0	7.71	8.82	3.2	2.76
L3	0.881	-	-	101	0.1	8.73	9.91	3.6	2.77
L4	0.761	-	-	87	-1.0	9.55	12.54	4.2	2.99
L1-L2	0.846	-	-	103	0.2	14.35	16.96	3.1	5.49
L1-L3	0.859	-	-	102	0.1	23.08	26.86	3.3	8.26
L1-L4	0.828	-	-	97	-0.2	32.63	39.40	3.5	11.25
L2-L3	0.877	-	-	100	0.0	16.43	18.73	3.4	5.53
L2-L4	0.831	-	-	95	-0.4	25.98	31.27	3.7	8.52
L3-L4	0.814	-	-	93	-0.6	18.28	22.44	3.9	5.76

L: lumber spine; BMD: Bone mineral density; BMC: Bone mineral content

In figure 2.1.9, The small box dimensions are 2 x 2 x 2 = $8cm^3$, which is the volume of the small box, and the large box dimensions are 3 x 3 x 3 giving a volume = 27 cm^3. True density of a material is defined by weight divided by volume in centimetres cubed (cm^3). Therefore, if you imagine the small box to be made up of 8 x small 1cm cubes each weighing 2g, (16g divided by 8 = $2g/cm^3$) and the large box is made up of 27 x small 1cm cubes each weighing 2g (54g divided by 27 = $2g/cm^3$). This is the

true volumetric density and will remain so, no matter how many cubes 2g/cm^3 you piled on top of either box in the diagram. With areal density (or aBMD), which is what the DXA scan gives as a result, the projected area is given (computed by a pixel by pixel account of bone edge detection) in cm squared (not cm cubed).

In the second small box in the diagram under the small box that is 2 x 2 cm^2 to represent the areal density of this cube = 4cm^2, and a box that is 3 x 3 cm^2 or 9cm^2. When the mineral weight of each box is divided by the areal density or projected area as with DXA, the diagram below shows 16/4 = 4g/cm^2 for the small box and 54/9 = 6g/cm^2 Hence, a larger value for a larger box. This means that the technique of DXA scanning to measure bone density is size-dependent and will systematically overestimate bone density in larger patients and underestimate it in smaller patients unless some adjustment made.

In reality- a patient example

If we imagine that two healthy boys are identical in age and in true volumetric density, but one of them is large in size for his age and the other is very small for his age. A different aBMD result and an age specific z score will be generated by the software will be obtained for each boy (for example: z= + 2.5 for the large and z= -2.5 for the smaller boy), neither of the results will reflect the true volumetric density, but the size of the child. Consequently, aBMD should be adjusted to the bone size or it could lead to misinterpretation (see figure 2.1.10). This will involve comparing the paediatric patient to other healthy children of the same size rather than the same age.

Figure 2.1.9: Concept of volumetric density
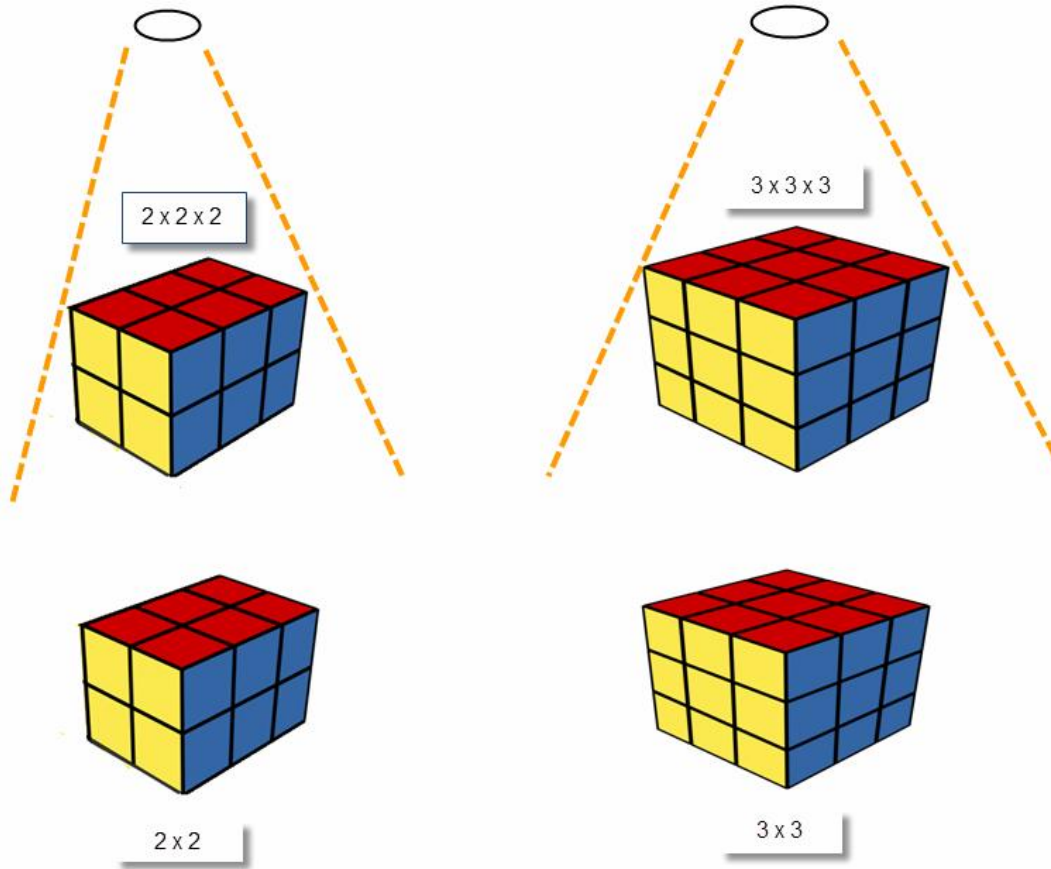
Mineral weight = 16 g

Volume= 8 cm^3

Projected area= 4 cm^3

Volumetric density = 2 g/ cm^3

Mineral weight = 54 g

Volume= 27 cm^3

Projected area= 9 cm^3

Volumetric density = 2 g/ cm^3

Source: Adapted from Bonnick (2010)

Figure 2.1.10: Three healthy children (aged 3.5, 4.5 and 6.7 years old respectively) with different height for age

Note: Niece (left), daughter (middle) and niece (right) of the author

2.1.6.1 Approaches to identify osteoporosis in children and adolescents:

The International Society For Clinical Densitometry (ISCD) in the office position statement (2007) recommended that diagnosis of osteoporosis in children and adolescents aged 5 – 19 years old should not made only on the basis of manufacture's DXA results alone (Baim et al., 2008). It was emphasised that children with chronic disease may have shorter bones than healthy children (Ahmed et al., 2004) and so particular care has to be taken when interpreting DXA bone data in children and adolescents with chronic disease, or survivors of chronic disease.

In addition, according to the ISCD (Baim et al., 2008) the diagnosis of osteoporosis required the presence of the following:

First, child has to have clinical significant fracture history for the diagnosis. It includes one or more the following:

- Of the lower extremities, one or more long fracture.
- Of the upper extremities, two or more long bone fractures.
- Vertebral compression fracture.

Second, the child has to be diagnosed with low BMC or low aBMD. Low BMC or aBMD are defined as z score ≤ -2.0 which is adjusted for specific- age, sex and body size as appropriate. This adjustment is for avoiding the large body size variation, though the position statement does not suggest what adjustment should be made (Baim et al., 2008).

There are two adjustment methods for body size. Firstly, DXA software does apparent adjustment for age and sex to produce z score. Secondly, there is a need for an additional adjustment for body size as described above and the in next section.

2.1.6.1.1 Tackling of bone size issues using DXA

There are different approaches that use in adjustment of DXA body size, however, still no consensus exists (Fewtrell, 2003, Bonnick, 2010).

2.1.6.1.1.1 Apparent bone mineral density of lumber spine (BMAD$_{LS}$)

It can be assumed that the lumbar body has a cylindrical-shape rather than the bone area. Therefore, BMAD$_{LS}$ can be calculated according to Kroger et al., (1995) equation as following: BMAD$_{LS}$= aBMD$_{LS}$ X [4/ (Ω X width)] where the width is the mean of the second, third and fourth of lumbar spine (L2-L4) (illustrated in figure 2.1.11) as it is accepted as the average BMD and Ω is constant value (Ω= 3.14). Then, we can adjust BMAD$_{LS}$ according to mean (SD) age and gender reference data as suggested by van der Sluis et al., (2002) in a study based on 444 healthy Dutch

children, adolescents and young adults aged 4 – 20 years. For how to calculate BMAD$_{LS}$ see appendix E.

Figure 2.1.11: Lumbar spine bone density image (this real image is extracted from the present study).
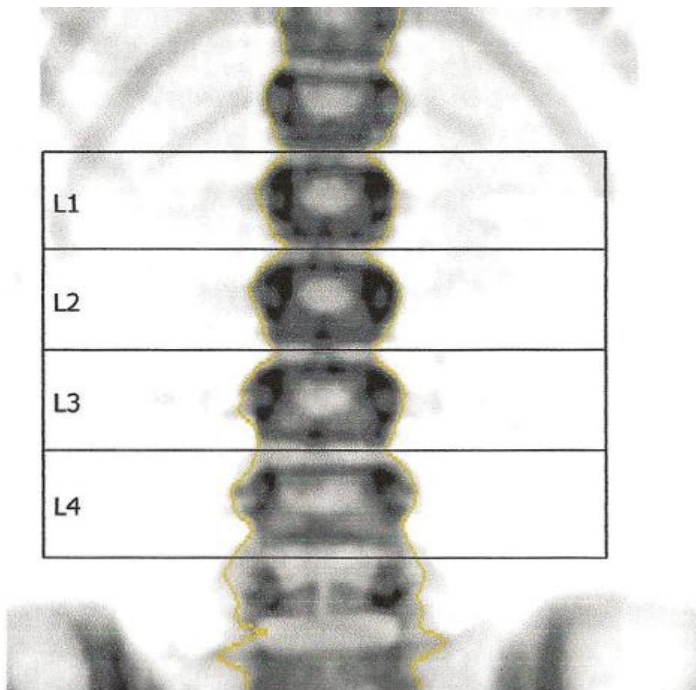
Kroger et al., (1995) examined the validation of this model compared with in vivo to magnetic resonance imagining (MRI) provides volumetric density measurements as described above. They recruited 24 men and 8 women aged 25-69 years. They reported that BMAD$_{LS}$ from DXA was correlated moderated with MRI (r= 0.665 – 0.822). However, they emphasised that the calculated volume here is only estimated lumbar spine volume not the true volume.

2.1.6.1.2 Warner et al., (1998b) approach

Similarly, Warner et al., (1998b) described an approach to minimising the relation between aBMD and BA. They suggested that adjusting BMC for BA (a size-adjusted measure of DXA-derived BMD) based on assuming that BMC is related to BA. The Warner et al., (1998b) approach also, adjusted other independent variables that could influence the measurement of BMD using DXA. These variables are age, gender, pubertal status and body size (height and weight) as means of correcting for short stature.

By using the van der Sluis et al., (2002) (based on healthy Dutch children) reference data and by applying linear interpolation to calculate percentage predicted BA for age according to the reference data, a chid with low percentage predicted BA for age would have a either short bones (short stature) or narrow bones, or a combination of both when compared to his/her age matched peers.   In addition, by comparison of the child actual BMC to the size matched rather than age matched reference data, percentage predicted BMC for BA can be calculated and expressed as BMC for BA z score. Hence, a child with low BMC for BA Z-score would have a low degree of mineralisation for his/her size regardless of whether his/her bones were short/tall or wide/narrow (Ahmed et al., 2004, Ahmed et al., 2005).

2.1.7 Blood collection and biochemical analysis

All survivors or one of their parents were telephoned before the study to instruct them to fast for at least 12 hours prior to blood collection the following morning. Blood was withdrawn by lab technicians using the venipuncture technique; therefore, the antecubital vein was used. All participants were advised to sit in a comfortable position. The forearm was supported by a cushion to ensure it was in a downward position. The antecubital vein was allocated using a tourniquet above the elbow. Blood was withdrawn using a needle and syringe.

Blood samples were analysed at the KFSH&RC laboratories. Collected samples were therefore split into two different tubes:

- o 4ml of blood was drawn in a plasma separating tube with lithium Heparin. This was centrifuged immediately for seven minutes at 3000 revolutions per minute. The plasma was used for total cholesterol, TG, HDL-C, and glucose fasting tests.

- o 4ml of blood was taken in a red top tube with serum clot activator. It was then left for 30 minutes at room temperature to clot and centrifuged for seven minutes at 3000 revolutions per minute. The serum was transferred into an aliquot tube for the fasting insulin test.

Total cholesterol, TG, HDL-C and LDL-C was quantified by using the enzymatic colorimetric test in-vitro assay (Roche/Hitachi 912 analyser). In enzymatic in-vitro assay, glucose was measured using an ultraviolet test (Roche/Hitachi 912 analyser). The in-vitro quantitative determination of plasma insulin was measured via immunoassay. The period of the test was about 18 minutes (Cobas e immunoassay analyser). The coefficient of variation for intra-assay and interassay for total cholesterol were 2.1% and 2.7%; respectively, for TG were 2.3% and 2.5%; respectively, or HDL-C were 3.3% and 3.8%; respectively, for glucose were 0.8% and 1.3%; respectively, for insulin were 3.4% and 3.9%; respectively, for LDL-C were 0.9% and 1.9%; respectively. All these mentioned assays were performed in accordance with the manufacturer's instructions.

2.1.8 Metabolic syndrome (MS) definitions

Two widely accepted MS definitions were selected for this study: the IDF approach (Zimmet et al., 2007) and NCEP III approach modified by Cook et al., (2008). Both of the definitions are summarised in appendix D.

2.1.8.1 IDF approach in defining MS in children and adolescents

The IDF approach defines MS as having central obesity plus two criteria based on age. According to the definition, children aged between five and < 10 years old cannot be diagnosed with MS. However, the MS definition for those aged between 10 and 15 years was:

➢ Central obesity assessed by WC ≥ 90th centile based on Fernandez et al., (2004).

➢ plus two or more:

       1. TG ≥ 1.7 mmol/L.

       2. HDL-C < 1.03 mmol/L.

       3. SBP ≥ 130 or DBP ≥ 85 mm Hg.

       4. Fasting glucose ≥ 5.6 mmol/L.

 Additionally, the MS definition amongst those aged ≥ 16 years was:

➢ Central obesity assessed by WC ≥94 cm for men and WC ≥ 80 cm for women.

➢ Plus two ≥ 2 MS criteria:

    1. TG ≥ 1.7 mmol/L.

    2. HDL-C < 1.03 mmol/L in males and < 1.29 for females.

    3. SBP ≥ 130 or DBP ≥ 85 mm Hg.

    4. Fasting glucose ≥ 5.6 mmol/L.

2.1.8.2 NCEP III approach to defining MS in children and adolescents

The NCEP III approach defines MS as:

➢ Having ≥ 3 MS criteria according to two age groups. For patients aged 5- 19 years, the MS criteria recommended by NCEPIII were:

    1. Central obesity, WC ≥ 90th centile based on cut-offs established by Li et al., (2006) as recommended by Cook et al., (2008) who modified the NECP III for children and adolescents.

    2. TG ≥ 1.24 mmol/L.

    3. HDL-C ≤ 1.03 mmol/L.

4. SBP and DBP ≥ 90th centile based on the National Heart Lung and Blood Institute table (available at: http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.pdf) as recommended by Cook et al., (2008).

5. Fasting glucose ≥ 6.1 mmol/L.

➢ For those ≥ 19 years, the NCEPIII MS criteria were:

1. Central obesity assessed by WC ≥102 cm for men and WC ≥ 88cm for women.

2. TG ≥ 1.69 mmol/L.

3. HDL-C ≤ 1.03 mmol/L for men and HDL-C ≤ 1.29 mmol/L for women.

4. BP ≥ 130/85 mm Hg.

5. Fasting glucose ≥ 6.1 mmol/L.

2.1.9 Homeostatic model-assessment of insulin resistance (HOMA-IR)

HOMA- IR from plasma glucose and insulin concentration was first published in 1985 (Matthews et al., 1985) and has since become widely accepted and of interest to researchers. HOMA-IR is used as a proxy for insulin resistance because HOMA-IR is most viable method for assesses insulin resistance (Alvarez et al., 2006). The IDF consensus group has consequently suggested also using HOMA-IR in research studies as it appears to be related to MS (Alberti et al., 2006), though it is not one of the MS criteria as defined by the IDF, as noted above.

HOMA-IR was calculated in the present study using a HOMA calculator (software version 2.2.2) ©University of Oxford 2004. This software was developed by Levy et al., (1998) and is also based on Matthews et al., (1985). The following equation is used: serum fasting glucose (mmol/L) × insulin (µIU/ml)/22.5. Any participant with HOMA- IR ≥ 2.5 is then classified as having insulin resistance (Sharma et al., 2011). However, there is a debate around the best cut-offs for HOMA-IR in children and adolescents as one of MS criteria instead of fasting glucose. Some studies supported

that but they used different cut-offs: HOMA-IR ≥ 1.77 (Arshi et al., 2010) , ≥ 2.5 (Sharma et al., 2011) and HOMA-IR > 3.16 (Bitsori et al., 2009) as one of MS criteria instead of fasting glucose in children and adolescents. Therefore, there is currently no consensus as to the optimal cut-offs for HOMA-IR amongst children and adolescents, and it is likely that different cut-offs will produce different prevalence estimates for abnormal values. This thesis will use the following cut-off HOMA-IR ≥ 1.77 (Arshi et al., 2010) as it seems to have been used most widely in the relevant literature. Further original research as to the optimal cut-off was beyond the scope of the present study, and the present study was not able to make more direct measures of insulin resistance.

2.2 Chapter 4 and 5 methodology

2.2.1 Participants

UK children and adolescents with ALL at diagnosis were studied retrospectively, using national data was collected at the time of diagnosis by clinical staff who were responsible for entering the patients onto the trial in the UK (Reilly et al., 1999b). Around 80 – 95% of UK patients with ALL were entered into the one of national trials covering the period of the studies (summarised in table 2.2.1) described in this thesis (Mitchell et al., 2010).

2.2.2 Ethical approval:

The Clinical Trial Services Unit (CTSU) in Oxford argued that as all UKALL trials data are anynomised and no specific informal consent was needed for studies in this thesis. The original trial consent forms included a statement that data could be used by other researchers in future.

2.2.3 Exclusions

- The present study excluded patients whose height, weight, age or sex was not recorded in national trial records, as these variables are required for the calculation and interpretation of BMI.

- In addition, it was not possible to define the weight status of all patients due to their age not being covered in the Cole et al., (2007) and IOTF (Cole et al., 2000) definitions of weight status. Patients below the age of two at diagnosis had to be excluded from these definitions of weight status as the Cole et al., (2007) and the IOTF (Cole et al., 2000) definitions do not include this age range.

- Girls aged 2 – 9 years who were deemed low risk of relapse (presenting WBC < 20 x 10^9/L) from the UKALL X dataset (as it is explained below).

2.2.4 UKALL trials studied in the present thesis

2.2.4.1 UKALL X protocol

The UKALL X trial involved 1,635 patients aged between one and 14 years. However, 23 patients were subsequently excluded from UKALLX trial as they were misdiagnosed (Chessells et al., 1995). A total of 1,612 eligible patients therefore entered into the trial between January 1985 and September 1990 (Chessells et al., 1995, Mitchell et al., 2010).

This thesis will exclude patients of UKALL X data deemed to be high risk (Down's syndrome, diagnosed with CNS or presenting WBC > 100 x 10^9/L) and girls deemed to be low risk (aged 2- 9 years old and presenting WBC > 20 x 10^9/L). Standard risk was defined at the time of the trial as patients who had no CNS disease, initial WBC < 100 x 10^9/L (Weir et al., 1998). In the present study, 12 patients were excluded as they were diagnosed with CNS disease at presentation because it is considered as a confounder as it affects risk of obesity and affects risk of relapse. The exclusion included 213 diagnosed as high risk to relapse that included patients with Down's

Syndrome because it is considered as a confounder since Down's Syndrome both increases the risk of obesity and increases risk of relapse in ALL; 347 girls were diagnosed as low risk (Weir et al., 1998). Therefore, the present study comprised data on 1,040 ALL patients, all of whom were defined as standard risk as described above.

The aim of this trial was to examine of the advantage of post-remission intensification (Mitchell et al., 2010). Under the basic protocol treatment design, patients received a four-drug induction therapy containing daunorubicin and L-asparaginase. In addition, all patients received CNS directed therapy based on the child's age, comprising intrathecal methotrexate (three doses during induction, three doses during CRT and one dose with each intensification block) and CRT (18 or 24 Gy) (Chessells et al., 1997a, Wheeler et al., 1996). The five-year-survival rate for those with complete remission was 98%, EFS (defined as the time between diagnosis and death) was 62% and the overall survival (defined as the time since diagnosis until relapse or death for any reason) was 77% in the total trial patients (Hargrave et al., 2001).

2.2.4.2 UKALL XI

The UKALL XI treatment protocol was for patients aged between one and 14 years and covered all UK patients with ALL who consented to enter the trial from 1991 to 1997. A total of 14 patients were excluded from the trial due to misdiagnosis. The number of patients entered into the trial was 2,090 (Mitchell et al., 2010). However, patients who died before 28 days may not have been not included as a result of no early randomisation and no binding requirement to register them in the trial (Hargrave et al., 2001). UKALL XI was then modified during the trial up to the UKALL 92 protocol version; 1,688 of 2,090 patients were treated by UKALL 92 protocol (Hann et al., 2001).

Standard risk ALL patients were defined as presenting with WBC < 50 x 10^9/L and aged 1 – 9 years old. However, the high risk patients were defined as initial WBC > 50 x 10^9/L and age less than one or more than 10 years old (Chessells et al., 2002). So, patients with initial WBC < 50 x10^9/L were randomised to receive intrathecal methotrexate with or without high dose intravenous methotrexate. However, patients presenting with WBC > 50 x10^9/L were randomised to receive high dose systemic methotrexate and CRT up to dose of 24 Gy (Mitchell et al., 2010).

There were some differences in the treatment protocols between UKALL XI and UKALL 92 but these are broadly and generally considered to be the same trial (Hann et al., 2001). For instance, induction anthracycline was used in UKALL XI, but was cancelled in UKALL 92. Moreover, in UKALL XI, all patients were randomised (regimen D) during early intensification (Week 5) whilst all UKALL 92 patients underwent this stage. On the other hand, the UKALL XI protocol had a third intensification stage which the UKALL 92 protocol lacked (Hargrave et al., 2001, Richards et al., 1998). In both protocols, patients with positive CNS were treated with 24 Gy of CRT. The complete remission percentage was 99%. EFS and overall survival at five years were 63% and 85%; respectively, for patients who had been treated using the UKALL XI protocol (Hargrave et al., 2001)

2.2.4.3 UKALL 97/97-99

The UKALL 97/97-99 (1997-2002) data comprised 1,935 patients who were entered into the trial, whilst 13 patients were excluded due to misdiagnosis (seven AML, two mature B-cell ALL, three non-Hodgkin's lymphoma, one isolated CNS disease) (Mitchell et al., 2005). Standard risk ALL patients were those aged less than 10 years old and initial WBC < 50 x 10^9/L whereas the high risk patients were those aged more than 10 years old and with initial WBC > 50 x 10^9/L (Mitchell et al., 2005).

The UKALL 97 trial enrolled patients aged between one and 18 years and began in April 1997. UKALL 97 was broadly similar to previous protocols, namely UKALL XI

(1992-1997). Induction anthracycline was not used in UKALL 97. Short intensification blocks were given at weeks 5 and 20 and patients were selected at random to receive a third intensification (Hann et al., 2001).

In 1999, MRC-UKALL amended UKALL 97 to resemble the US Children's CCG trial 1992 protocol and labelled it UKALL 99.

In the case of the UKALL 97 protocols, CNS-directed therapy in all patients used 16 doses of intrathecal methotrexate based on the age of the child. Nonetheless, UKALL 99 used protocols based on Regimen A (23 doses of intrathecal methotrexate for boys and 19 for girls) and Regimens B and C (26 doses of intrathecal methotrexate for boys and 22 for girls). Patients with CNS disease at diagnosis were treated during induction with additional intrathecal therapy and received CRT (24 Gy) during the consolidation stage (Mitchell et al., 2005). EFS and overall survival at five years were 77% and 86%; respectively (Mitchell et al., 2010).

2.2.5 Confidentiality

Data were totally anonymised by CTSU in order to not identify any patients in any way and each had a unique study ID. No personal ID, file numbers or anything related to patients was shown in the data which the CTSU provided to the authors.

2.2.6 Anthropometric measurements

2.2.6.1 Height, weight and BMI

Height and weight were measured to 0.1cm and 0.1kg respectively in clinic at or around the time of entry into the trials. Weight and height were therefore measured for clinical rather than for research-based purposes, which could potentially lower the quality of some of the measurements used. However, Power et al., (1997) note that obtaining a high degree of precision in typical weight measurements is unlikely to

require trained observers and continuous quality control. There is also an issue of whether any individual errors are likely to be biased as the individual error is very likely but the study was dealing with group assessments of nutritional status here and these will only be affected if measures are biased rather than just erroneous. Furthermore, it is worth noting that drug dosage depended on the methods (weight and height) which might raise measurement standards.

Calculation of BMI was described earlier in this chapter, Software applying the LMS method (available at :
http://www.healthforallchildren.com/index.php/shop/product/Software/Gr5yCsMCONpF39hF/0.) was used to calculate BMI z score in this study according to the UK reference population from 1990 (Cole et al., 1995).

Table 2.2.1: Comparison of UKALL trials

	UKALL X (1985 - 1990)	UKALL XI (1991 - 1997)		UKALL 97-99 (1997 - 2002)	
Entered	n= 1635	n= 2090		n=1935	
		Pre-1992	**Post-1992**	**Pre-1999**	**Post-1999**
Induction Anthracycline	Yes	Yes	No	No	No
Early intensification (week 5)	Randomised (Arm B + D)	Randomised (Arm D)	Yes	Yes	Yes
Second intensification (week 20)	Randomised (Arm C + D)	Randomised (Arm C + D)	Yes	Yes	Yes
Third intensification (week 35)	No	No	Randomised	Randomised	Yes
High dose MTX	No	Randomised WBC < 50: IT MTX WBC > 50: CRT		Randomised WBC < 50: IT MTX WBC > 50: CRT • Pre-1999: the dosage based on age. • Post-1999: the dosage based on gender.	
CRT	Yes (18 or 24 Gy)	CNS-diseased (24 Gy)		CNS-diseased (24 Gy)	
Period of therapy	2 years	2 years		2 years	
The protocol results (5 yr)	CR: 95% EFS: 62% OS: 77%	CR: 99% EFS: 63% OS: 85%		CR: 99% EFS: 77% OS: 86%	

IT: Interathecal, MTX: Methotrexate, CRT: Cranial radiation therapy, WBC: White blood account (x 10^9/l), CR: complete remission, EFS: Event-free survival, OS: overall survival, Gy: Gray

2.2.6.1.1 UK 1990 reference data for BMI

Prevalence estimates in this study for overweight and obesity used UK BMI population reference data from 1990 (Cole et al., 1995). The use of BMI for UK children for age and sex expressed relative to national references has a significantly higher sensitivity with no loss of specificity (few non-obese children will be classed as obese) compared to the IOTF definition based on BMI (Reilly et al., 2010b, Reilly et al., 2000b).

BMI z scores were calculated based on the UK 1990 reference (a survey of 15,636 males and 14,899 females was carried out between 1978 – 1990, which relied on a combination of 11 distinct surveys). The UK 1990 reference data was proposed to represent weight, height and BMI in UK children (Cole et al., 1995). Centile curves for UK children from 33 weeks gestation to 23 years were presented by (Cole, 1994) on Cole's LMS method to allow all individuals to be measured according to the z score score. BMI distribution was adjusted for skewness (Cole et al., 1995) and z scores and centiles can be calculated using software downloaded from www.healthforallchildren.com. Weight status was classified as follows: healthy weight (BMI SDS <1.04 (less than the 85th centile)), overweight (BMI z score 1.04≤ 1.64 (above the 85th centile, but < 95th centile)) and obese (BMI z score >1.64 (above the 95th centile)) (King et al., 2010, Cole et al., 1995, Barlow and Dietz, 1998, Reilly et al., 2010b).

Validity of UK 1990 reference data as a means of describing weight status and growth of British children in 1990

A number of studies have stated that the UK 1990 reference data (Cole et al., 1995) are applicable in terms of growth and weight status assessments. For instance, Savage et al., (1999) examined the validity of the UK 1990 reference data for assessing growth and nutritional status in 127 infants whose BMI was calculated at the ages of six, nine, 12, 18 and 24 months. It was concluded that the UK 1990

reference data contained only small biases and was clinically useful. Moreover, a longitudinal study examined the validity of the UK 1990 reference data amongst 694 primary school children in Leeds (Rudolf et al., 2001). They were first measured between the ages of seven and nine and three years later when aged between nine and 11. The use of the UK 1990 reference data in monitoring growth was recommended. Reilly et al., (1999a) studied a community sample of 240 Scottish prepubescent children (124 boys, 116 girls) whose mean age was 8.5 years (0.4) and recommended applying the UK 1990 reference data to the assessment of obesity. A growth reference group also reviewed the UK 1990 reference data and found it suitable for monitoring weight relative to height (Wright et al., 2002). However, as the prevalence of overweight and obesity has increased substantially over time (Reilly et al., 1999a, Kinra et al., 2000, Rudolf et al., 2001, Lobstein et al., 2003), it is recommended that growth references should not be updated when comparing rates of childhood obesity, as this will be affected by changes in obesity rates over time. Updating them would thus define obesity as normal after the obesity epidemic (Wright et al., 2002).

2.2.6.1.2 International Obesity Task Force and Cole et al. (2007) definitions

IOTF (Cole et al., 2000) and Cole et al. (2007) definitions were discussed in detail in sections 2.1.3.1.4 and 2.1.3.1.5 in this chapter.

Chapter 3

Weight status and metabolic syndrome in adolescent survivors of standard risk childhood acute lymphoblastic leukaemia in Saudi Arabia

3.1 Introduction

As noted in chapter 1, briefly, Overweight and /or obesity in childhood and adolescence leads to increase of risk of many well-recognised complications, notably cardiovascular risk factors for instance hyperlipidaemia, hyperglycaemia and hypertension (Freedman et al., 1987, Freedman et al., 1999, Han et al., 2010). Moreover, underweight is also, related to short and long- term complications such as disabilities, morbidity, mortality, adult size, intellectual ability, and metabolic and cardiovascular disease (summarised in figure 1.2.1 and 1.2.2).

Using the recently developed Saudi growth chart for BMI for age (El-Mouzan et al., 2007), a recent Saudi study (El Mouzan et al., 2010) (the national sample size was 19,317) concluded that amongst 19317 children and adolescents aged 5- 18 y, the prevalence of overweight ($\geq 85^{th}$ percentile) was 23.1%, while prevalence of obesity was 9.3% ($\geq 95^{th}$ percentile) and 2% of the sample was defined as severely obese ($\geq 97^{th}$ percentile). Since the Saudi BMI for age chart is a very conservative way of defining obesity, as it has very high BMI values at standard percentiles such as the 95th centile, this suggests that obesity prevalence among adolescents in Saudi Arabia is now extremely high.

According to some studies, obesity risk in ALL patients increases at or after treatment (Chow et al., 2007 , Meacham et al., 2005). A longitudinal study from the USA illustrated that the prevalence of being overweight (defined as BMI= 25- 29 or 85th - 94th percentile) and obese (defined as BMI ≥ 30 or 95th percentile) based on CDC 2000 growth chart at the diagnosis of ALL were 12.7% and 10.9%, respectively. However, after completion of treatment, the rates were 17.0% and 21.2% (p value= 0.01); respectively (Chow et al., 2007). Furthermore, it has been reported in the Childhood Cancer Survivors Study (CCSS) in the US that the OR for being underweight in ALL survivors was 2.4 (Meacham et al., 2005). However, the estimated prevalence of unhealthy weight status according to all reviewed literature

(as listed in table 1.5.1) was influenced by many factors. First of all, the survivors were studied retrospectively with sometimes small sample sizes. Also, most of the previous studies included heterogeneous groups of survivors diagnosed with different ALL types and treated with different protocols which included CRT and chemotherapy in most studies (van Beek et al., 2006 , Nysom et al., 1999 , Love et al., 2011), and all of these differences are likely to have an influence on weight status. Furthermore, good estimates of prevalence of unhealthy weight status in the long-term for more modern protocols are needed so that proper intervention by health practitioners can be considered.

MS may be more common than might be expected in children or adolescents who are survivors of ALL. Gurney et al., (2006) examined the prevalence of MS as defined by NCEP III criteria and growth hormone deficiency in adult survivors (the mean age was 30 years) of childhood ALL. The sample size was 75 (25 did not receive CRT, 25 received < 24 Gy CRT, 25 received ≥ 24 Gy CRT) survivors randomly selected. They reported that 11 (14.7%) of the survivors met MS criteria. Moreover, 9/11 who had met MS criteria had received CRT. Nevertheless, several major problems exist in the literature on MS in childhood ALL: to our knowledge most of the studies to have taken place in survivors were very limited. No studies were carried out children and adolescents from outside western countries world except the Iranian study that was mentioned above (Reisi et al., 2009).   However, no evidence to date has shown the prevalence of MS outside the western world amongst children and adolescent survivors with Standard Risk ALL (Reisi et al., 2009).

3.2 Aims

The present study was not hypothesis testing, but aimed to provide estimates of the prevalence of unhealthy weight status and MS in medium term survivors of standard risk ALL in Saudi Arabia, providing evidence that should be useful in the future planning of clinical nutritional services for ALL survivors. A secondary aim was

methodological, i.e. to test the extent to which the different definitions of unhealthy weight status and different definitions of MS produced differences in prevalence.

3.3 Methods

The present thesis methods are described in detail in section 2.1; however, it is worth mentioning some of methods briefly here.

3.3.1 Participants and study design

The present study is a cross sectional study in which, the survivors recruited numbered 77. The number of survivors excluded was 8. The potentially eligible participants numbered 69, and 56 of these survivors agreed to take part in the study, 13 did not. This sample numbering 56 had characteristics that were similar to the sample of 69 though the small number of those who did not consent precluded statistical analysis of differences between those who consented and those who did not (see table 3.3.1) - the characteristics available from the KFSH&RC system were gender, age, age at diagnosis and period of the therapy, therefore. The limited sample size and limited number of potential variables meant that for some aspects of the present study only an exploratory statistical analysis could be made.

3.3.2 Anthropometric data

Height and weight were measured to the nearest 0.1 cm. WC was measured using the 4 cm above umbilicus method as recommended by Rudolf et al., (2007) and as described above in section 1.4.5.1.6.

3.3.3 Classification of weight status

The international BMI reference data related to age is available and provided by the WHO(de Onis et al., 2007), the CDC (Kuczmarski et al., 2000), IOTF (Cole et al., 2000) and Cole et al., (2007). These definitions were also applied within the study.

Table 3.3.1: Characteristics of the potentially eligible survivors who did not agree (n=13) and who agreed (n= 56) to participate

	Patients not consented	Patients consented
	Total group, mean (± SD)	
Gender	69.2% (n= 9) boys,30.8% (n= 4) girls	60.7% (n= 34) boys, 39.7% (n= 22) girls
Age (yr)	13.2 (5.5)	13.4 (4.1)
Age at Diagnosis (yr)	4.2 (1.5)	4.3 (1.9)
Period of chemotherapy (yr)	2.9 (0.5)	3.0 (0.5)

3.3.4 Body composition

Body composition was measured by using, firstly, DXA Lunar Prodigy hardware, and software version 9.15. The number of survivors who were examined was 51 as described above in section 2.1.5.2 and adult and paediatric manufacturer's reference data were used. Secondly, a BIA instrument (Body Composition Analyser; Inbody 3.0; Biospace © 2001) was used to estimate body composition 53 out of 56 survivors as described above in section 2.1.5.1. The algorithm used by the BIA analyser was unknown and is a commercial secret.

3.3.5 Blood collection

The Blood sample was withdrawn by the lab technicians. The sample was analysed to test HDL-C, TG, fasting glucose and fasting insulin at KFSH&RC laboratories (see section 2.1.7).

3.3.6 Metabolic syndrome: definition and measurement

The present study was able to determine the presence or absence of MS by using: the IDF approach (Zimmet et al., 2007) and NCEP III as modified by Cook et al., (2008) as described above in section 2.1.8. Blood pressure measurement was performed by staff nurses at KFSH&RC using CASMED® 740 monitor for measuring BP as described above in section 2.1.4. Also, HOMA calculator (version 2.2.2) was used for HOMA-IR as described earlier in section 2.1.9.

3.3.7 Statistical analysis, power and sample size

A fixed number of standard risk ALL Saudi survivors of ALL were available, treated at KFSH&RC on protocol 1891. No formal power calculation was therefore carried out for the present study, since the number of survivors available was fixed. However, the number of survivors who were recruited was similar or larger from many previous studies of weight status and MS in ALL (Reisi et al., 2009a, Pakakasama et al., 2010, Warner et al., 2004b). For some aspects of the studies formal post-hoc power calculations were available and could show that the sample available was sufficient for those particular studies (Warner et al., 2004).

Means (SD) are presented in the results unless otherwise stated. Normality of data was tested by using Normality tests in Minitab 15.1.30.0 software package and the data were considered to be normally distributed when $p > 0.05$. Minitab 15.1.30.0 software was used for all statistical analyses except for the weighted kappa (k) analysis described below. A p value of < 0.05 was considered as significant.

A two-sample t-test for normal distribution was used to test the significance of the difference in the mean between the numerical variables in different groups. Also, two proportions tests were applied to compare between two proportions. Multivariate linear-regression analyses were performed to test for associations between BMI z score and a number of different explanatory variables in exploratory analyses. Exploratory analyses were statistical analyses which were used to examine possible associations in the data which had been proposed by other studies. These were exploratory because they might not have been adequately powered. Also, the age variable was split into the age at the time of study and age at diagnosis to test the influence both of them on weight status, body fatness and MS.

The k test was used to identify the degree of agreement between the different approaches to defining underweight, healthy weight, overweight, obesity, and over-fatness with calculation of 95% CI. We also used the k analysis as a preliminary test of agreement between the two definitions of paediatric MS. The k statistics were interpreted as recommended by (Landis and Koch, 1977): ''slight agreement'' 0.0–0.20; ''fair agreement'' 0.21–0.40; ''moderate agreement'' 0.41–0.60; ''substantial agreement'' 0.61–0.80; ''almost perfect agreement'' 0.81–1.00). The k statistic analyses were performed using Medcalc software version 11.5.0.0.

3.4 Results

Characteristics of study participants

The number of consented survivors was 56 (34 male, 22 female). The mean (SD) weight of the sample was 46.7 kg (17.5). The mean (SD) age at the time of the study was 13.4 years (4.1). The mean (SD) age at diagnosis was 4.3 years (1.9). Mean time (SD) from diagnosis was 9.1 years (4.1), and time from end of therapy was 6.2 years (3.9) Characteristics of study participants are shown in table 3.4.1.

Table 3.4.1: Overall sample characteristics, mean (SD)

	Males n= 34 (60.7%)	Females n= 22 (39.7%)	Total group Mean (SD)
Age (yr)	13.0 (4.6)	14.0 (3.1)	13.4 (4.1)
Height (cm)	1.49 (0.20)	1.51 (0.11)	1.50 (0.17)
Weight (kg)	42.0 (16.9)	49.3 (18.4)	46.7 (17.5)
Age at diagnosis	3.9 (1.9)	4.9 (1.9)	4.3 (1.9)
Time from diagnosis (yr)	9.1 (4.5)	9.1 (3.2)	9.1 (4.1)
Time since completion of therapy (yr)	5.9 (4.5)	6.7 (3.1)	6.2 (3.9)
CDC BMI-z score *	-0.17 (1.6)	0.16 (1.3)	-0.03 (1.48)
WHO BMI-z score^	0.14 (2.0)	0.31 (1.5)	0.21 (1.77)
% Body Fat by BIA (for 31 M, 22 F) [§]	20.7 (8.6)	29.1 (9.4)	24.2 (9.8)
% Body Fat by DXA (for 33 M, 18 F) [§]	24.7 (10.6)	37.6 (8.8)	29.2 (11.7)

CDC: US Centres for Disease Control and Prevention; WHO: World Health Organisation; BIA: Bioelectrical impedance; DXA: Dual-energy X-ray absorptiometry; yr: years
[§] % total body fat >25% and >32% in males and females amongst > 18 years. For who aged 5- 18 yrs defined as % total body fat > 25% for males >30% for females
* No significant difference between genders (p vale= 0.4; 2 sample t-test)
^ No significant difference between genders (p vale= 0.7; 2 sample t-test)

3.4.1 Prevalence of overweight and obesity

The prevalence of combined overweight and obesity was lower when using the local

Saudi BMI reference data (El-Mouzan et al., 2007) (prevalence 21.4%; 12/56

survivors) than when applying the alternative approaches (prevalence of combined overweight and obesity varied between 28.6% (n= 16/56) and 32.1% (n= 18/56) for CDC (Kuczmarski et al., 2000), IOTF (Cole et al., 2000) and WHO (de Onis et al., 2007) approaches. Prevalence data are shown in figure 3.4.1 and table 3.4.2 for more details.

3.4.2 Prevalence of underweight

Underweight prevalence slightly differed between the four approaches, as illustrated in table 3.4.2 and figure 3.4.1. The highest prevalence of underweight survivors was 21.4% (n= 12), using the Cole et al., (2007) definition, however, the lowest prevalence was 8.1% (n= 5) estimated using the national definition (El-Mouzan et al., 2007). Use of the WHO (de Onis et al., 2007), and CDC (Kuczmarski et al., 2000) definitions the prevalence of underweight ranged from 12.5% (n= 7) -17.9% (n= 10).

Table 3.4.2: Prevalence of obesity, overweight and underweight by four different approaches

Reference approaches	Obesity (n), %	Overweight (n) %	Underweight (n),%
Saudi*	(4) 7.1	(8) 14.3	(5) 8.9
IOTF and Cole et al. (2007) [§]	(5) 8.9	(13) 23.2	(12) 21.4
CDC*	(6) 10.7	(10) 17.9	(10) 17.9
WHO†	(6) 10.7	(12) 21.4	(7)12.5

* Obesity defined as ≥95th percentile; overweight defined as 85th to <95th percentile and underweight defined as <5th percentile; † BMI z score defined Overweight as >+ 1 z score; obesity as >+ 2 z score and underweight/ thinness as < -2 z score; [§] Definitions for underweight, overweight and obesity tabulated values of BMI for age and sex for who aged between 2- 18 years

Figure 3.4.1: Prevalence of Overweight and Underweight by different approaches
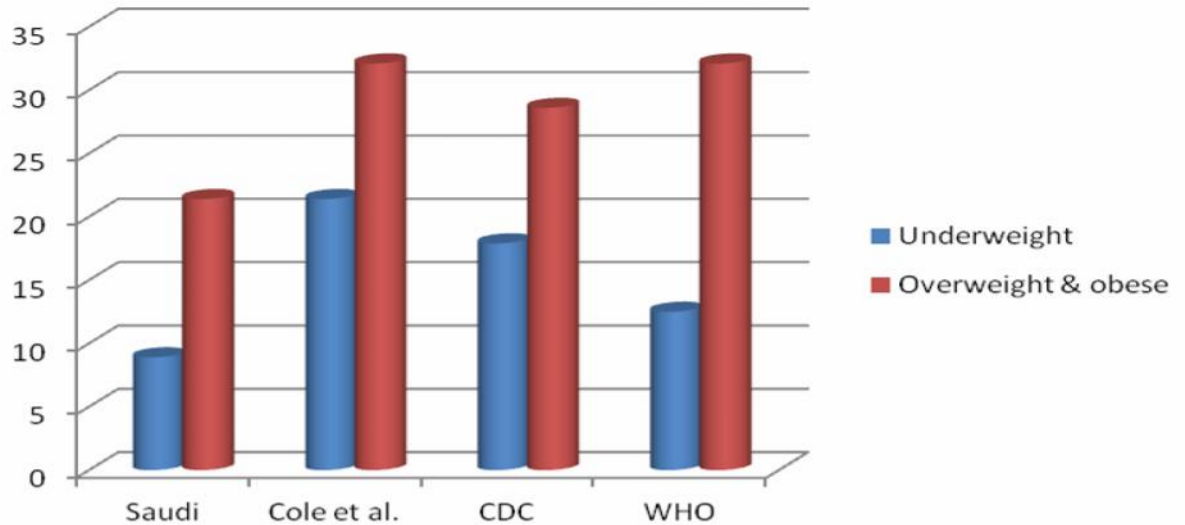
CDC: US Centres for Disease Control and Prevention; WHO: World Health Organisation. Cole et al: the international obesity task force (IOTF) and Cole et al. (2007)

3.4.3 Body composition of the sample by BIA and DXA

The mean (SD) of % total body fat (%TBF) by using DXA was 24.7% (10.6) for males and 37.6 % (8.8) for females. The difference in %TBF between males and females was significant (2 sample t-test; 95% CI for difference: (7.1, 18.8); p value < 0.001). The mean (SD) %TBF by using BIA was 20.7 (8.6) for males and 29.1% (9.4) for females-this was a significant difference between males and females (2 sample t-test; 95% CI for difference: (- 13.3, -13.4); p value < 0.001).

According to the DXA estimates of body fatness, more than half (52.9%, 27 out of 51) survivors had over-fatness. By using BIA, more than third of the sample had over-fatness (35.9%, 19 out of 53).

3.4.4 Exploratory analysis of factors associated with weight status and body fatness of the sample

BMI z scores were not significantly different between male and female survivors when using both CDC (Kuczmarski et al., 2000) (2 sample t-test; 95% CI for difference: (-1.136, 0.807); p value=0.4) and WHO reference data (de Onis et al., 2007) to calculate the z scores (2 sample t-test; 95% CI for difference: (-0.450, 1.122); p value=0.7)).

In this section, the survivors were separated into those diagnosed ≥6 or < 6 years old, and this is a 'natural' breakdown of age for ALL patients, into those diagnosed at a typical time and those diagnosed later (mean age of diagnosis usually around age 4 years) which has been used in a number of other studies. So, BMI z score was not significantly different between males and females diagnosed ≥ or < 6 years old (2 sample t-test; p value=0.07). However, none of the patients diagnosed at age ≥ 6 years old were underweight using Saudi (El-Mouzan et al., 2007), CDC (Kuczmarski et al., 2000), IOTF and WHO (de Onis et al., 2007) definitions.

The over-fatness by using DXA was 11.8% (6 out of 13), 21.6% (11 out of 21) and 19.6% (10/17) for survivors aged 5 - 10 years, 10 -15 years and >16 years; respectively. By Using BIA, over-fatness for survivors aged 6 -10 years was 5.7% (3 out of 11), for who aged 10 -15 years was 16.9% (9 out of 24) and for who >16 years was 13.2% (7 out of 18).

Moreover, prevalence of over-fatness by using DXA was higher in those diagnosed at < 6 years (43.9% (18 out of 41)) than those diagnosed ≥ 6 years (90.0% (9 out of10)) (p value <0.0001, 95% CI: -0.70 , -0.22; two proportions method). Similarly, over-fatness by using BIA was higher in those diagnosed < 6 years (6 out of 10) than those aged ≥ 6 years (13 out of 43) but it was not significant (p value= 0.08, 95% CI: -0.03, 0.63; two proportions method).

153

Since the above mentioned exploratory analyses were univariable, multivariate regression was also carried out in the exploratory analyses., In the multivariate, analysis BMI z score was not significantly influenced by gender (p value = 0.63), age (p value= 0.06), and period off therapy (p value= 0.61).

3.4.5 Agreement between different approaches in defining weight status

Agreement between the different approaches based on BMI for age, using weighted Kappa statistics (k) (Landis and Koch, 1977), was "moderate-substantial" (Landis and Koch, 1977) between use of the Saudi (El-Mouzan et al., 2007) approaches versus those from the CDC (Kuczmarski et al., 2000) (k = 0.70; 95% CI: 0.55- 0.85) and WHO (de Onis et al., 2007) (k = 0.67; 95% CI: 0.51- 0.83). There was poorer agreement between the Saudi approach (El-Mouzan et al., 2007) and the Cole et al., (2007) and IOTF (Cole et al., 2000) approaches to defining weight status (k = 0.47; 95% CI: 0.27 – 0.67).

"Almost perfect" (Landis and Koch, 1977) agreement was shown between CDC (Kuczmarski et al., 2000) and WHO (de Onis et al., 2007) approaches (k = 0.86; 95% CI: 0.75- 0.96). CDC (Kuczmarski et al., 2000) and IOTF (Cole et al., 2000) had substantial agreement (k = 0.63; 95% CI: 0.45- 0.81), whereas "moderate" agreement was found with IOTF (Cole et al., 2000) and WHO (de Onis et al., 2007) approaches k= 0.52; 95% CI: 0.33- 0.71) as shown in table 3.4.3.

Table 3.4.3: Extent of agreement (weighted kappa statistic) between different Approaches

Weight status approaches	Weighted kappa	95% Confidence interval	Level of agreement (Landis and Koch, 1977)
Saudi vs. CDC	0.70	0.55 - 0.85	Substantial
Saudi vs. IOTF	0.47	0.27 - 0.67	Moderate
Saudi vs. WHO	0.67	0.51 - 0.83	Substantial
CDC vs. IOTF	0.63	0.45 - 0.81	Substantial
IOTF vs. WHO	0.52	0.33 - 0.71	Moderate
CDC vs. WHO	0.86	0.75 - 0.96	Almost perfect

CDC: US Centres for Disease Control and Prevention; WHO: World Health Organisation. IOTF: The International Obesity Task Force

3.4.6 Agreement between different approaches in assessing over-fatness:

The agreement between the various approaches that defined overweight and obesity using the BMI for age with measures of over-fatness using DXA when assessed by weight kappa analysis was "fair" when based on Saudi reference data (El-Mouzan et al., 2007) ($k= 0.24$; 95% CI: 0.08 – 0.39), the CDC (Kuczmarski et al., 2000) ($k= 0.34$; 95% CI: 0.16 – 0.51), the WHO (de Onis et al., 2007) ($k= 0.39$; 95% CI: 0.21 – 0.57) and IOTF (Cole et al., 2000) approaches ($k= 0.22$; 95% CI: 0.03 – 0.41). Also, "Fair

agreement" was also found between DXA and BIA (k= 0.34; 95% CI: 0.13- 0.55) (as shown in table 3.4.4).

Table 3.4.4: Extent of agreement (weighted kappa statistic) between different approaches for defining over-fatness

Over-fatness references	Weighted kappa	95% Confidence interval	Level of agreement (Landis and Koch, 1977)
DXA vs. BIA	0.34	0.13 - 0.55	Fair
DXA vs. Saudi	0.24	0.08 - 0.39	Fair
DXA vs. CDC	0.34	0.16 - 0.51	Fair
DXA vs. IOTF	0.22	0.03 - 0.41	Fair
DXA vs. WHO	0.39	0.21 - 0.57	Fair
BIA vs. Saudi	0.24	0.02 - 0.46	Fair
BIA vs. CDC	0.47	0.25 - 0.69	Moderate
BIA vs. WHO	0.48	0.26 - 0.70	Moderate
BIA vs. IOTF	0.27	0.04 - 0.51	Fair

CDC: US Centres for Disease Control and Prevention; WHO: World Health Organisation; IOTF: The International Obesity Task Force; BIA: Bioelectrical impedance; DXA: Dual-energy x-ray absorptiometry

Defining overweight and obesity based on BMI for age by using different approaches versus measurement of over-fatness by BIA was "fair-moderate agreement" by using Kappa statistics. The Saudi (El-Mouzan et al., 2007) and IOTF (Cole et al., 2000) approaches had the lowest agreement with BIA (k= 0.24; 95% CI: 0.02- 0.46) and (k= 0.27; 95% CI: 0.04- 0.51); respectively. However, "moderate agreement" was observed between BIA and CDC (Kuczmarski et al., 2000) approaches (k= 0.47; 95% CI: 0.25- 0.69) and the WHO approach (k= 0.48; 95% CI: 0.26- 0.70); as shown in table 3.4.4.

3.4.7 Descriptions and prevalence of MS and 'metabolic syndrome components' (MSC)

Characteristic of the MS and metabolic syndrome component(s) (MSC) for the sample is shown in the table 3.4.5.

In the overall sample, 5.4% of survivors (3/56) were defined with MS using the NECP III definition, as well as 7.1% (3/42) with MS by the IDF definition. Prevalence of survivors who had 1 MSC were 37.5% (21/56), 35.7% (15/42) by applying NECP III and IDF criteria; respectively. Also, by using both criteria, 7.1% (4/56) and 11.9% of survivors had 2 MSC; respectively.

Table 3.4.5: Characteristic of metabolic syndrome components (MSC)

Cardiometabolic risk factors	Mean (SD)	IDF	NCEP III
		% (n) of patients above criteria	
Waist circumference (cm)	67.2 (12.0)	10.7 (6)	7.1 (4)
Systolic blood Pressure (mmHg)	112.8 (11.6)	16.7 (7)	25 (14)
Diastolic blood Pressure (mmHg)	68.1 (9.3)		
Fasting glucose (mmol/l)	5.20 (0.53)	16.7(7)	14.3 (8)
Triglycerides (mmol/l)	0.83 (0.40)	4.8 (2)	3.6 (2)
HDL-C (mmol/l)	1.36 (0.31)	0 (0)	0 (0)

IDF: the International Diabetes Federation; NCEP III: The National Cholesterol Education Program Third Adult Treatment Panel guidelines modified by Cook et al. (2008), HDL-C: High density lipoprotein cholesterol

Metabolic syndrome components above IDF and NCEP III criteria

Prevalence of each single individual MSC (table 3.4.5) amongst the survivors was as follows: WC was above the normal range in 10.7% (6 out of 42) aged 10 and above according to IDF criteria. However, 7.1% (4 out of 56) were diagnosed with central obesity by using NCEP III criteria. One quarter of the patients (14 out of 56) had abnormal BP by applying NCEP while IDF defined 16.7 % (7 out of 42) of the patients with abnormal BP. Hyperglycaemia was present amongst 16.7% (7 out of 42) and 14.3% (8 out of 56) of the patients by using IDF and NCEP III as modified by Cook et al., (2008) criteria; respectively.

In both definitions, 2 patients were diagnosed with high triglycerides and all of them were either overweight or obese male (defined by CDC BMI (Kuczmarski et al.,

2000)). By applying NECP III and IDF criteria, the percentage of male patients diagnosed with high BP was 14.3% and 9.5%, respectively, and for female patients was 10.7% and 7.1%, respectively. Insulin resistance was identified in 29.1% of the survivors by using HOMA-IR defined as ≥ 1.77 (Arshi et al., 2010).

3.4.8 Metabolic syndrome components (MSC) in different age groups

All patients were divided into 3 age group periods, those age groups suggested by the IDF, to spotlight the number and percentage of risk factors by using both IDF and NCEP III definitions as shown in table 3.4.6 and figure 3.4.2. The IDF does not provide a definition of MS for any child 5 – 10 years old.

One quarter of the patients had one MSC by applying IDF criteria and about one third of them had one risk factor when NCEP III was applied. In both definitions, half of patients aged ≥16 years old had one MSC, whereas 11.1% (2 out of 18) and 5.6% (one out of 18) of them were identified with two MSC by IDF and NCEP III definitions; respectively.

Table 3.4.6: Prevalence MSC according to different age group

Age Period	IDF		NCEP	
	1 MSC n, (%)	**2 MSC** n, (%)	**1 MSC** n, (%)	**2 MSC** n, (%)
5-10 yr (25%)	- - -*	- - -*	5/14 (35.7)	1/14 (7.1)
10-16 yr (42.9%)	6/24 (25)	3/24 (12.5)	7/24 (29.2)	2/24 (8.3)
≥16 yr (32.1%)	9/18 (50)	2/18 (11.1)	9/18 (50)	1/18 (5.6)

IDF: the International Diabetes Federation; NCEP III: The National Cholesterol Education Program Third Adult Treatment Panel guidelines modified by Cook et al. (2008). MSC: Metabolic syndrome component. * IDF definition does not define metabolic syndrome for any child aged 6 – 10 years

3.4.9 Metabolic syndrome components and weight status classification

Amongst the overweight and/or obese (defined by CDC (Kuczmarski et al., 2000)) survivors, who had 12.5% (2/16), had one MSC while a quarter of them (4/16) had 2 MSC. However, non- overweight survivors who had 1 MSC were 37.5% (15/40) although only 5% (2/40) had 2 MSC. Approximately a fifth of overweight and obese survivors were defined with MS (defined by NECP III), but non-overweight survivors were not defined with MS defined by NCEP III, as shown in figure 3.4.3.

Figure 3.4.2: Prevalence metabolic syndrome components/risk factors according to different age groups

A: Based on NCEP III definition
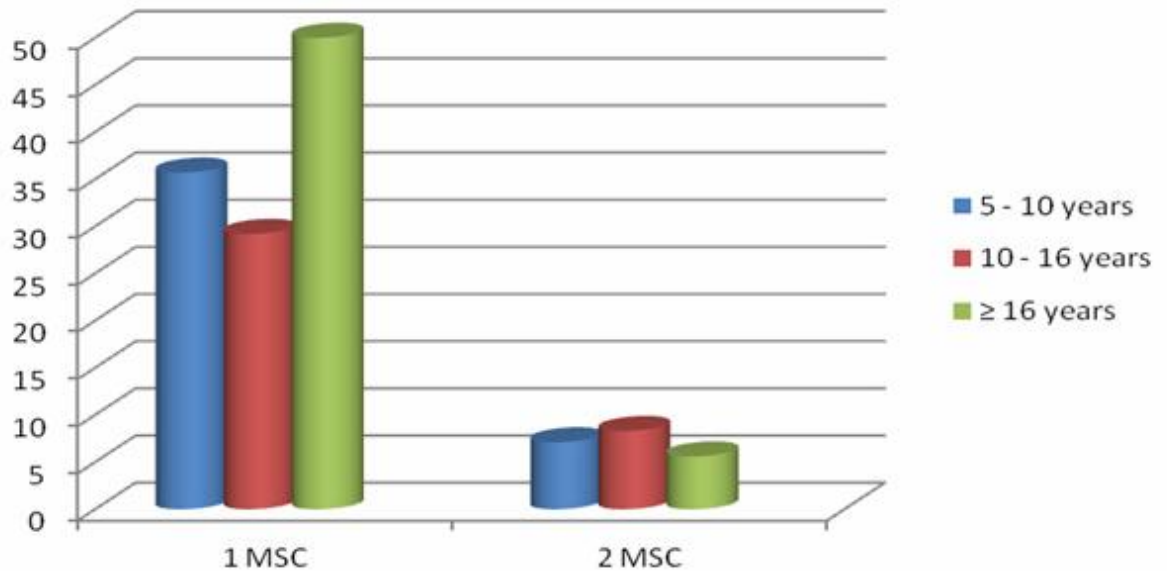
B: Based on IDF definition
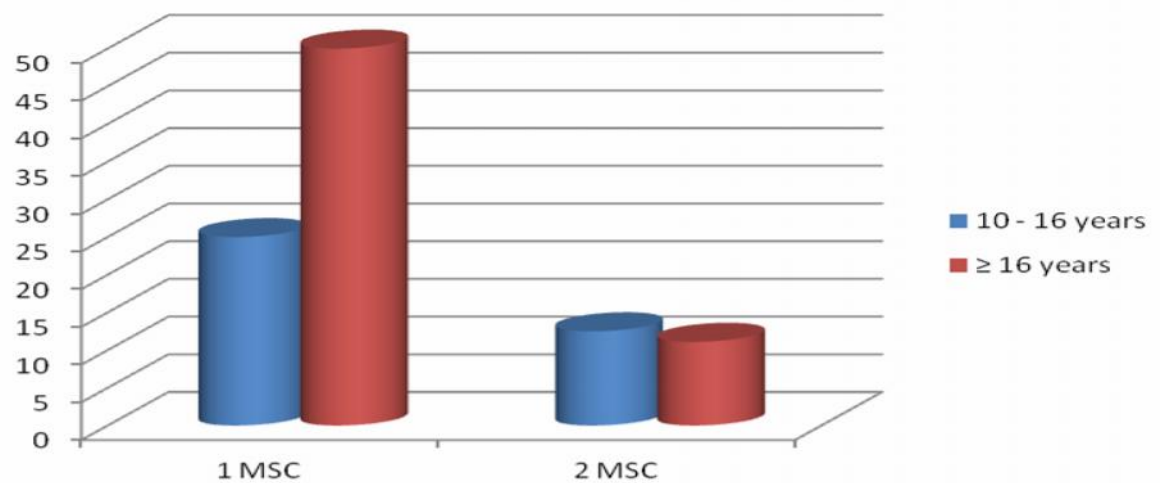
IDF: The International Diabetes Federation; NCEP III: The National Cholesterol Education Program Third Adult Treatment Panel guidelines modified by Cook et al. (2008); MSC: Metabolic syndrome component(s)

Figure 3.4.3: Weight classification defined by CDC definition and MSC defined by NECP III definition
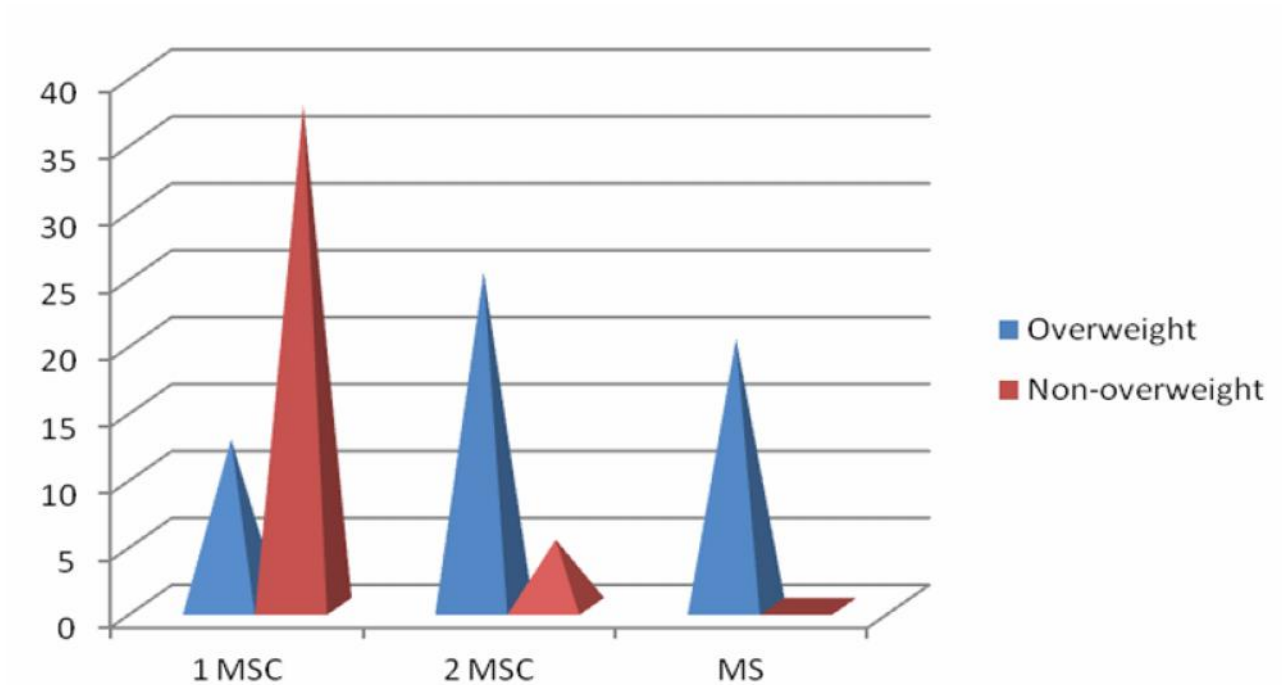
NCEP III: The National Cholesterol Education Program Third Adult Treatment Panel guidelines modified by Cook et al. (2008); CDC: US Centres for Disease Control and Prevention; MS: Metabolic syndrome; MSC: Metabolic syndrome component(s)

3.4.10 Metabolic syndrome and metabolic syndrome components and age at diagnosis

All survivors defined with MS using NCEPIII criteria (n= 3) were diagnosed with ALL when they were less than 6 years old. The number of survivors diagnosed after 6 years old with one MSC was 5 (8.9%), while 28.6 % (n= 16) had one MSC for those diagnosed before 6 years old.

Survivors diagnosed before 6 years old with 2 MSC were 7.1% (n= 4), while only one survivor (1.8%) had 2 MSC for those who diagnosed after 6 years old. None of survivors who diagnosed after 6 years old had MS, as shown in figure 3.4.4.

Figure 3.4.4: Metabolic syndrome components (defined by NCEP III) amongst patients diagnosed with ALL before and after 6 years old
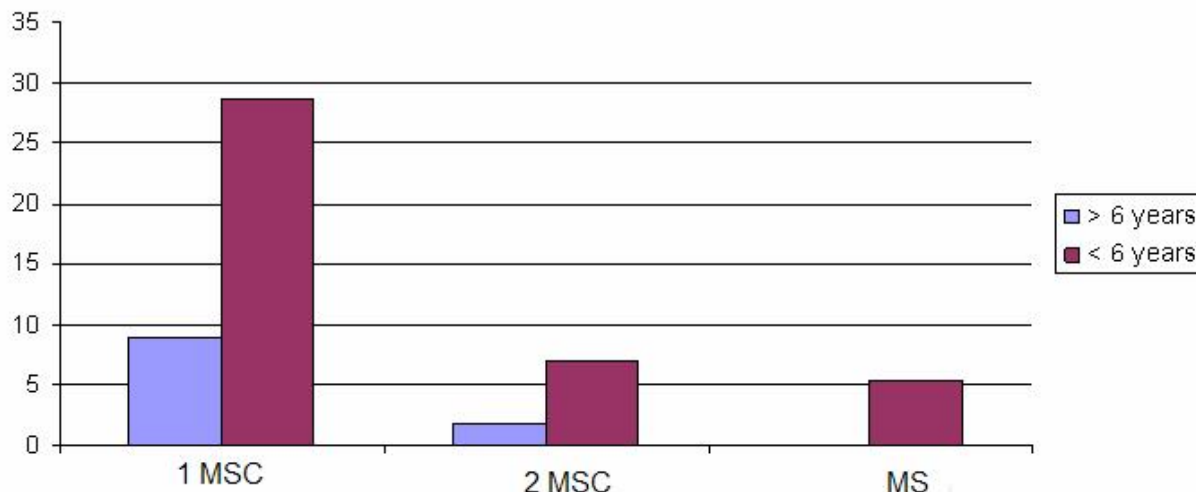
3.4.11 An exploratory analysis of factors associated with MSC

The WC absolute value measurement was not significant different between male and females (Mann-Whitney; p value= 0.72). WC was correlated with TG, LDL-C, HDL-C and HOMA-IR (r=0.38, 0.35, -0.29 and 0.27 and p value= 0.004, 0.01, 0.03 and 0.046; respectively). Moreover, there was a significant correlation between high WC measurement and high BP reading which are based on IDF cut-offs (r=0.43; p value= 0.001). According to NECP III criteria, 75% (3 out of 4) of central obese (defined as high WC) survivors were hyperglycaemic, while 40% (2 out of 5) who met IDF criteria for non-central obese (defined as high WC) survivors were hyperglycaemic.

A higher CDC BMI z score was significantly correlated with high TG or LDL-C similarly (r=0.35; p value=0.01). Also, There was an association between the periods of chemotherapy and serum TG (Pearson correlation=0.37; p value=0.005).There was no correlation between fasting glucose and CDC BMI z score and LDL-C. There was a significant correlation between high insulin resistance and high %TBF by DXA (r=0.31; p value= 0.03) and trunk %TBF by DXA (r= 0.33; p value= 0.02).

Furthermore, a significant correlation was found between fasting insulin and WC and %TBF by DXA and BF% by DXA (r= 0.26, 0.31 and 0.33; p value=0.05, 0.03 and 0.02, respectively). There was a significant correlation between LDL-C and fasting insulin (r=0.72; p value=0.049).

3.5 Discussion

3.5.1 Main findings and implications

The present study shows that nearly half of the survivors of childhood ALL at one centre in Saudi Arabia had unhealthy weight status (underweight, overweight or obesity) by applying international approaches to defining weight status based on BMI for age and 30.3 % had unhealthy weight by applying Saudi approaches based on BMI for age (El-Mouzan et al., 2007) after an average of 6.2 years completion of chemotherapy. While this was a small single centre study if these results were replicated across other non-western countries they would give cause for concern about unhealthy weight status in survivors of ALL. The causes of unhealthy body weight in ALL Saudi survivors are beyond the scope of the present study, therefore, future studies for the investigation is recommended, but factors which have been shown to be related to the development of obesity in ALL were described in chapter 1 (section 1.5.6). The important clinical implication for the present study is that promoting regular physical activity and behavioural and dietary interventions designed to prevent unhealthy body weight amongst ALL survivors would seem to be important given the fact that over-fatness was quite common. Moreover, preventing unhealthy body weight is likely to be more effective than weight reduction programmes for those patients/survivors already overweight or obese. The intervention programmes for weight reduction in cancer survivors that involved the patients and their family in behavioral, dietary and physical activity modification are more likely to be effective than dietary modification alone (Slawta et al., 2006). Further research is needed to evaluate the effectiveness of prevention and intervention programmes for unhealthy

body weight in survivors of ALL in Saudi Arabia and this point is discussed in the final chapter of this thesis.

Secondary aims of the present study were to examine over-fatness from DXA and BIA in the first remission amongst Saudi standard risk ALL survivors. Over-fatness was present in over half of the sample by using DXA and over one third of the sample by using BIA. It is possible that DXA might identify more cases of overnutrition or undernutrition than simpler measures based on BMI for age and sex. BMI for age has limited ability to identify body fatness rather than lean mass information (Wells and Fewtrell, 2008). It is likely that BMI based approaches to defining overweight and obesity will underestimate the scale of the problem in survivors of ALL as discussed in the introduction chapter (section 1.4.5.1.5). Underestimation of overweight and obesity might be even greater using the local (Saudi) reference data, and this is probably because the Saudi BMI reference data had been collected in the period 2004 – 2005 probably after the childhood obesity epidemic had affected Saudi Arabia (El Mouzan et al., 2010). To be more precise, Al-Hazzaa, (2007b) studied a nationally representative sample from 1988 to 1996. They showed that for adolescents age 10 – 20 years BMI at 50th percentile and 90th percentile was rising during the 8 years prior the data collected by El Mouzan et al., (2010) (clarified in figure 3.5.1).

Estimates of obesity prevalence using the IOTF approach (Cole et al., 2000) are known to be highly conservative in their assessment of overweight and obesity (Reilly et al., 2010b) (as discussed in section1.4.5.1.5) i.e. they have a high false negative rate (a high proportion of those defined as obese by BMI using IOTF (Cole et al., 2000) method will have over-fatness) and yet the estimate from use of Saudi population reference data (El-Mouzan et al., 2007) was even more conservative. For example, in the present study, the IOTF (Cole et al., 2000) definition identified 32% of the survivors as either overweight or obese while the Saudi definition (El-Mouzan et al., 2007) only found 21%.

Figure 3.5.1: BMI at 50th percentile and 90th percentile trends over 8 years in Saudi adolescents
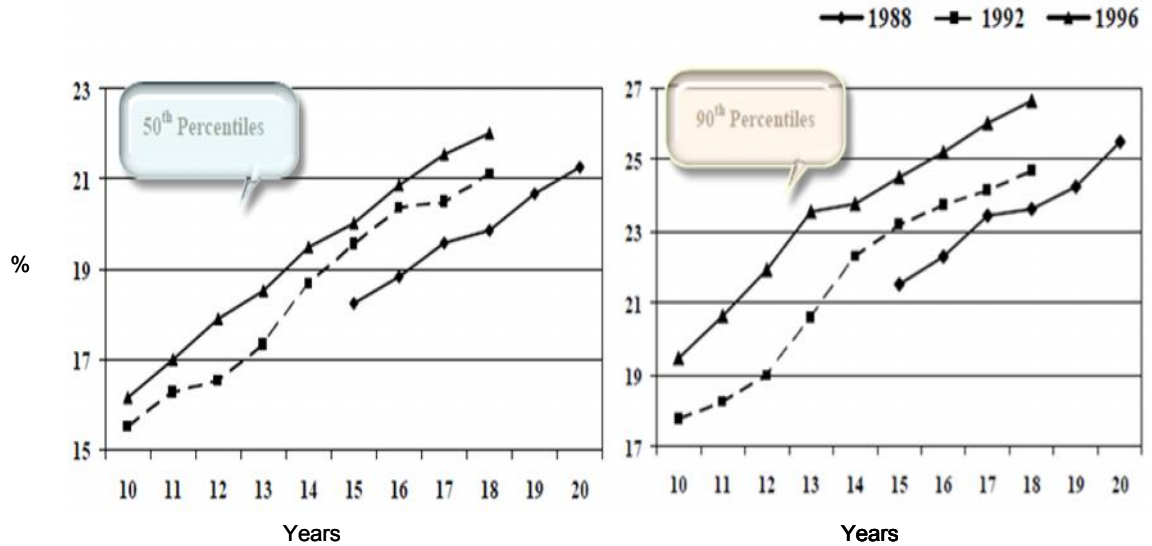
Source: modified from Al-Hazzaa, (2007b)

The present study therefore suggests that caution should be used when applying BMI for age to define paediatric overweight and obesity in ALL survivors, and even more caution should be used when considering whether or not to use local (national) reference data for BMI when these reference data have been 'contaminated' by the obesity epidemic. Some believe that ideally such reference data should have been collected in the period that pre obesity epidemic; such data might then be considered as a "standard". Data that have been collected in recent years shows a relatively higher prevalence of increase in unhealthy weight status described norms, El-Ghaziri et al., (2011) examined the impact of the using national vs. international IOTF (Cole et al., 2000), Cole et al., (2007), WHO (de Onis et al., 2007), CDC (Kuczmarski et al., 2000) amongst 499 (age: 10 – 14 years) Kuwaiti adolescents. They found that prevalence of combined of overweight and obesity was 36.7% and prevalence of obesity was 14.6% by using Kuwaiti reference data and these prevalence were significantly (p value < 0.01) lower when compared to the international approaches

they tested. They concluded that more recent national reference data for BMI should be considered with caution in terms of defining unhealthy weight status. The present study may support the argument that using the international definitions for defining weight status is superior to the Saudi definition in ALL survivors.

MS in children and adolescent has no universally accepted definition, and MS prevalence depends on the definition of MS being used. By using both of the currently common definitions, prevalence of MS amongst the survivors was uncommon; however, it was more common in the overweight and obese survivors rather than non-overweight. Similarly, Goodman et al., (2005) found same findings that obesity in children is stronger predictor of cardiovascular risk factors (Martinez-Vizcaino et al., 2011).

 However, the present study has shown that the prevalence of   metabolic syndrome component(s) was common and they were probably increasing with survivor age. Previous studies such as The Quebec Family Study, (Katzmarzyk et al., 2001) found significant persisting of MS components from childhood into adulthood as described in section 1.3.5.3.2. Moreover, Berenson et al., (1998) have shown that pathological processes associated with the progress of atherosclerosis or CVD, fatty streaks and fibrous plaques in the coronary and aorta arteries began during childhood. With these MSC manifesting in ALL survivors in medium term, early existence of cardiovascular risk factors will emerge as major and challenging in clinical settings. Therefore, health professionals should pay more attention to overweight and obesity among survivors. Also, early screening for unhealthy weight status, various MSC, and early intervention MS or MSC amongst ALL survivors should be considered. Further research focused on effectiveness of promotion of modification of lifestyle in survivors of ALL is needed as discussed in the final chapter of this thesis.

3.5.2 Unhealthy weight status prevalence in the general population in Saudi Arabia

There has been a marked increase in overweight and obesity in Saudi children and adolescents in the last two decades (Al-Hazzaa, 2007a) as described elsewhere in this thesis. In Jeddah, for example, (the second largest city in Saudi Arabia) school children were surveyed in 1994 (n= 2708) and 2000 (n= 2542). The researchers found BMI percentiles at the equivalent percentiles were elevated between 1994 and 2000 (Abalkhail, 2002). It is shown clearly in figure 3.5.1 modified from Al-Hazzaa, (2007b).

The present study findings regarding the apparently high prevalence of overweight and obesity by applying the international approaches, prevalence of overweight and obesity combined was (by CDC (Kuczmarski et al., 2000) and WHO (de Onis et al., 2007) approaches) broadly resembled the more recent national Saudi survey (El Mouzan et al., 2010) that applied a multi-stage probability random sampling design: and which investigated 19,317 (50.8% boys) healthy children and adolescents aged 5- 18 yr old. El Mouzan et al., (2010) estimated the prevalence of overweight and obesity (defined by BMI Z score +1 and +2 according to 2007 WHO cut-offs) and (CDC defined BMI >85th for overweight percentile and >95th percentile for obesity) relative to 2005 Saudi reference data for BMI from Al Herbish et al., (2009) . This large cross-sectional study found that prevalence of overweight and obesity combined in the overall sample according to WHO and CDC approaches was 33.2 and 26.1%; respectively. However, the prevalence of overweight and obesity combined defined according to Saudi reference data by El Mouzan et al., (2010) in Saudi children was 34.4% whereas the present study found the prevalence was much lower (21.4%) by using same reference data. This suggested that although the prevalence of overweight and obesity for the ALL survivors in the present study (shown in table 3.4.2) seemed high with all four definitions used, the prevalence may actually be lower in the sample than the prevalence in the general population in Saudi Arabia,

due possibly to differences in sample size between the current study and El Mouzan et al., (2010) study the nature of the disease, its treatment, and their impact on obesity risk.

El-Hazmi and Warsy (2002) reported that 18.8% of children and adolescents in Saudi Arabia aged 6 –18 yrs, recruited from different Saudi regions between 1994 - 1998 (n= 11,080), were overweight or obese combined (according to the IOTF (Cole et al., 2000) definition). However, the present study found much higher prevalence (32.1%) by using same definition if the data collection period is not taken in the account. The difference in prevalence between the prevalence of overweight and obesity in the present study and El-Hazmi and Warsy (2002) in probably due to the time period of about 8 years between the two studies.

To best our knowledge, there is no literature that uses the new Saudi reference data to investigate the prevalence of underweight in children and adolescents in Saudi general population. Moreover, there is no study Saudi study of underweight prevalence which was nationally representative. However, in a study that aimed to investigate the prevalence of anaemia and nutritional status at high altitude, 14.2% of 513 children and adolescents aged 6–13 years were underweight defined by WHO (BMI for age < 5th percentile) in 2005 (Abou-Zeid et al., 2006). That is quite similar to the prevalence of underweight obtained from the present study sample of ALL survivors (12.5%) using the same one definition and same age group.

The present study findings found the lowest prevalence of underweight (8.9%) was produced by Saudi reference data (El-Mouzan et al., 2007) versus the other international approaches. The prevalence was highest by the CDC approach (17.9%). These findings were inconsistent with Al Herbish et al., (2009) when they found that there is more underweight in Saudi children compared to the USA, it implies that a high prevalence of underweight may be 'normal' for Saudi Arabia by using international definitions such as CDC approach.

3.5.3 Comparisons with studies of medium term survivors

A few studies have reported on weight status in medium-term (defined as the period after end of treatment up to 5 years) survivors of childhood ALL (see table 1.5.1). For instance, Chow et al., (2007) in the USA found that out of 165 ALL childhood survivors (103/165 standard risk), the prevalence of overweight (defined as BMI= 25-29 or BMI= 85th – 94th percentile) and obesity (defined as BMI≥ 30 or BMI≥ 95th percentile) after completion of therapy was 32%. Quite a similar finding using same reference data CDC was reported by the present study (29%) that the similarity may be because both studies used modern treatment protocols (with chemotherapy but no CRT) and most /all survivors in both studies were diagnosed as having standard risk ALL.

Breene et al., (2011) assessed 77 ALL survivors (7.8% treated by high risk protocol in one English centre). They reported that prevalence of overweight and obesity combined (defined as BMI z score > 1.2 – 2.3 and BMI z score > 2.3 relative to UK reference data) was 47.2%. In contrast, by applying the international and national definitions, the prevalence of overweight and obesity seemed to be lower in Saudi survivors than the UK survivors. Breene et al., (2011) recruited, from a single centre, a mixed type of ALL survivors who had been treated with chemotherapy and CRT and so was a less homogenous group than in the present study. Love et al., (2011) recruited 102 childhood survivors of ALL and reported the prevalence of overweight and obesity (defined as BMI > 85th based on CDC reference data) was 45%, higher than the present study findings by all four definitions used: some of them had been treated with CRT (included both who received 18 Gy and >20 Gy radiation doses) which may increase overweight or obesity risk. Moreover, Oeffinger et al., (2003) reported that survivors treated with >20 Gy CRT have an increased risk of overweight compared to their siblings, although lower radiation doses have also been associated with increases BMI over time (Garmey et al., 2008).

Therefore, it seemed that the prevalence of overweight and obesity in medium term post end of the therapy is highly influenced by many factors such as type of ALL at diagnosis, treatment protocols, including CRT either low or high doses, obesity definition and sample size.

3.5.4 Comparisons with studies of long term (from after end of treatment up to 20 years) survivors of ALL

It is worth noting that the present study was carried out in medium term, adolescent, survivors, and so, one of big challenges is tracking of unhealthy adolescent weight into adulthood. In adulthood, the prevalence of overweight and obesity in 1,765 US adults who had survived childhood ALL (median age was 23.0 years) were 29.8% and 13.8%; respectively, and the prevalence was lower than the prevalence of overweight and obesity combined in US general population (64.5%) during the same period (1999- 2000) (Oeffinger et al., 2003, Ogden et al., 2006). However, the prevalence of overweight and obesity in the present study (28%) was much lower than Oeffinger et al., (2003) study of US adults.

As mentioned in the Method chapter, the present study was based on modern ALL treatment protocol in which CRT was not used, Similarly a retrospective Swiss study showed that the rates of obesity and of being overweight amongst 54 standard risk ALL survivors who were all not treated with CRT and diagnosed between 1990 – 2000 were 18% and 30%, respectively (Asner et al., 2008).

In a study with a large sample size in adults, a report of the childhood cancer survivors study (CCSS) in USA (data collected between 1995- 1996) found that the prevalence of overweight and obesity amongst 1,665 ALL adult survivors (aged 20- 47 years) were 22.5% and 18.5%, respectively (Meacham et al., 2005). Therefore, the prevalence of overweight and obesity was highly increased according to the

present study, but in adults, by using the same reference data (Meacham et al., 2005).

A longitudinal study in the USA that examined 248 ALL and lymphoma patients diagnosed between 1979 – 1984 who were treated according to standard risk (CRT used for (n=89/190) and high risk (n=50) protocols found that the prevalence of overweight (85th – 94th percentile for BMI) and obesity (≥ 95th percentile) was 35.0% for those aged <18 years and 39.3% for those aged ≥ 18 years at the last evaluation (Razzouk et al., 2007). Relatively similar findings were found by the present study when same reference data (CDC definition) was used in medium term even though Razzouk et al., (2007) study recruited survivors who were treated before obesity became epidemic in the USA. CRT may play intrinsic role in increasing body weight than using modern protocols.

In contrast, a few studies have reported a relatively low prevalence of obesity in long term survivors of childhood cancer. For instance, in a Swedish study of childhood ALL survivors aged 20 – 32 years, 47 ALL survivors (19 had CRT) 34.3% of adult survivors were reported as being overweight but no one was obese (BMI ≥30 kg/m^2) (Jarfelt et al., 2005). However, even though they recruited survivors who had been treated with CRT they found no obesity amongst them possibly due to the relatively small sample size.

It should be emphasised that there is no study, to our best knowledge, which in standard risk ALL survivors examined the tracking of unhealthy weight status from childhood into adulthood, therefore, future studies of this kind are recommended. The above comparisons of ALL studies in long term survivors with the medium term survivors (present study) could be influenced by differences in obesity definitions, ALL classifications at diagnosis, using different treatment protocols, notably using CRT in treatment. Also, comparison with general population is highly recommended to clarify the question "Is the prevalence of unhealthy of weight status in ALL survivors more

common than norms population?" as it is not clear from most previous studies of survivors.

3.5.5 Comparison with studies from non-western countries

Prevalence of unhealthy weight status might be different in the general population in non-western countries than in western countries, and rates of change in obesity prevalence are likely to be different since the 'nutrition transition' has occurred at different times across the world (Popkin and Penny, 2004). Few comparisons with other non-western literature can be made though, because there are so few studies in non-western countries, which used modern protocols for ALL with no CRT, and which used the most modern/accepted definitions of weight status which were used in the present study. Moreover, to our best knowledge, studies of weight status in ALL patients and ALL survivors outside western countries are very scarce. A quarter of children and adolescents (mean age 10.4 years) who were Iranian ALL survivors (14/55) who were treated with chemotherapy only or chemotherapy and CRT between 2003 – 2007 (35 months since completion the therapy) were obese (BMI> 95th percentile relative to Iranian reference) (Reisi et al., 2009). Moreover, the prevalence of overweight (BMI> 75th and < 95th percentile) amongst those Iranian survivors was 20%. However, this prevalence of both overweight and obesity was much higher than the present study (21%) although they Iranian study recruited a similar sample size in medium term survivors and used national BMI reference data rather than the international approaches. The Iranian study included survivors who had been treated with CRT whereas the present study did not, which might contribute to differences between the two studies..

In a study in Thailand carried out between 2003 - 2005, ALL survivors (n =258; 46.9% standard risk) with median (range) age 12.2 years (3.6 - 23.2) obesity/ overweight (not defined in this paper) prevalence amongst those who had not been treated by CRT (n= 91) was 10% which was lower than all definitions used in the

present study, however, the prevalence was higher (32%) amongst those who had been treated by CRT (Pakakasama et al., 2010). However, the survivors were treated according to different treatment protocols which may be considered as heterogeneous group of survivors and the definition of obesity may be influenced in reporting weight status.

3.5.6 Factors associated with overweight/obesity in ALL

3.5.6.1 Impact of age of diagnosis on weight status in ALL

Razzouk et al., (2007) suggested that weight status at diagnosis of ALL is crucial in predicting weight status in adulthood. In UK and USA studies there is a tendency for patients diagnosed with ALL at younger ages to be at greater risk of later obesity and excessive weight gain (Oeffinger et al., 2003, Reilly et al., 2000b). To be more precise, Razzouk et al., (2007) found that being overweight and obese significantly increased amongst those diagnosed with ALL or lymphoma between the ages of 0-6 from 6% at diagnosis up to 41% at adulthood. This finding was consistent with the present study findings.

The present study found that use of definitions of weight status from the Cole et al., (2007) , IOTF (Cole et al., 2000), CDC (Kuczmarski et al., 2000) and WHO (de Onis et al., 2007) identified that the proportion of both overweight and obese survivors aged 6 years or less at the time of diagnosis was higher than those who were older than 6 years old at diagnosis. Also, exploratory analyses in the present study suggested that underweight (defined by WHO (de Onis et al., 2007) and CDC (Kuczmarski et al., 2000)) was possibly more common for those were diagnosed at age 6 years or younger. However, in the exploratory analyses in the present study BMI z score was not related significantly to age at diagnosis. Further research with larger samples will be needed to examine how age at diagnosis plays role in excessive weight gain in countries such as Saudi Arabia.

3.5.6.2 Impact of gender on weight status

High BMI for age in this present study was not apparently affected by gender. In contrast, in large multi-centre retrospective cohort study (n= 1,765) found amongst ALL adult survivors that female patients who had been treated by CRT ≥20 Gy were at risk of obesity (BMI ≥ 30 kg/m^2) than males (Oeffinger et al., 2003). A large sample size for a future study to investigate the impact of gender on weight status in homogeneous group would be useful.

3.5.7 Over-fatness

The DXA used in the present study provided a direct estimate of body composition with high precision and possibly reasonable accuracy compared with most 'field ' methods of body composition (Fewtrell, 2003). Animal studies have shown a linear correlation, and fairly good agreement too, between lean fat mass and FM assessed by DXA and by chemical carcass analysis (Brunton et al., 1997; Fusch et al., 1999). DXA also, is a simple, fast and safe measurement in clinical settings compare to other approaches such as underwater weighing approach which is inappropriate in some hospitalised cases. Warner et al., (2004) recommended using DXA in ALL survivors suggesting that it was a more accurate measurement than other non-invasive methods such as BIA, isotopic water dilution. However, DXA measurements in at least some studies (Wong et al., 2002) have been shown to be less accurate relative to 4 components models might and so DXA might produce an overestimate or underestimate the true value of %TBF (Wong et al., 2002). Nevertheless, 4 component model approaches are too complicated in measuring body composition in clinical practice.

In addition, BIA is also, a fast, simple and safe device and it shows less inter-observer variation than some alternative methods (Schaefer et al., 1994). Pietrobelli et al., (2003) recommended BIA devices for measuring body composition in children.

However, Warner et al., (2004) found that the accuracy of BIA depends on the regression equations which are used for predicting total body water and/or FFM.

The question of whether ALL survivors might be over- fat even if they did not have a high BMI for age, was asked in part because of general concerns over the ability of BMI to identify excessively fat individuals, and in part because of the possibility that ALL survivors might have a condition resembling sarcopenic obesity with very low lean body mass (Prado et al., 2008). A previous showed that over-fat children with ALL might not have a high BMI (Warner, 2008). In the present study over-fatness from DXA was present in over half of the sample, but prevalence of overweight and obesity from BMI based definitions was lower. Consequently, the present study found that DXA for definition of over-fatness had "fair agreement" with the Saudi approach (El-Mouzan et al., 2007) for obesity and the other international approaches.

However, by using BIA, over-fatness prevalence (35.9%) was closer to the prevalence estimates which were produced by the international approaches for overweight and obesity other than the national approach. Therefore, BIA was scored from fair to moderate agreement with all approaches. Similarly, Sampei et al., (2001) examined the agreement between BMI and %TBF by using BIA device in 10- and 11 year old Japanese adolescents (n= 436), and reported the kappa analysis value of 0.49, which was higher than the present study results by using all BMI based definitions.

This finding suggests that the weight and height based measures and definitions of overweight and obesity from Cole et al., (2007), IOTF(Cole et al., 2000), CDC (Kuczmarski et al., 2000), WHO (de Onis et al., 2007) and Saudi reference data (El-Mouzan et al., 2007) all using BMI for age tend to be quite conservative and may underestimate the prevalence of over-fatness in childhood, adolescent and young adult survivors of ALL. This is consistent with expectations based on BMI because it does not take the actual body composition into account. The use of BMI based

definitions of obesity tend to be conservative in the general population, but there is less evidence from children and adolescents with chronic disease. Warner et al., (1997) investigated the validity of BMI for assessment of excess adiposity by using DXA and skinfold thickness measurements to estimate fatness amongst 143 (43 were long-term cancer survivors) UK patients with chronic disease. They concluded that BMI underestimates the excess of adiposity in children with chronic disease. Also, more generally it is known that BMI based definitions using as screening tool for obesity have a high false negative rate in children and adults (Reilly et al., 2010b). More excessively fat individuals exist in clinical and population samples than are identified by a high BMI for age.

Jarfelt et al., (2005) found that in Swedish ALL young adult survivors (n= 47) aged 20-32 years (19 was treated by CRT) had high %TBF assessed by DXA for both males (29.2 %, range (24.0- 37.5)) and females (37.5% (25.4- 44.5)). %TBF in female survivors was high (35.9%, range (23.4- 42.3)) for those were treated without CRT. Furthermore, a high % TBF for those treated with CRT only existed in girls (33.5%). In contrast, Marinovic et al., (2005) found that the elevation of %TBF assessed by DXA for one year (35 out of 37 were standard risk) after completion of ALL therapy in survivors (median age was 7.9 years) was slightly lower than the control healthy group (n= 74). However, the short time after completion of the therapy in Marinovic et al., (2005) study might influence to the ability to find a difference in %TBF between ALL survivors and control group.

Most of the DXA-based studies to date have concluded that over-fatness is common in ALL survivors (Murphy et al., 2006, Warner, 2008a, Janiszewski et al., 2007, Jarfelt et al., 2005, Nysom et al., 1999). However, all of these studies are from patients from the western world and many of these studies were of patients who had CRT, and not all were studies of patients in 1st remission after completion of therapy. The present study suggests that over-fatness is not confined to ALL patients during treatment, nor

confined to the western world, nor confined to patients treated for ALL on older
protocols using CRT.

The present study found different estimates of over-fatness provided from using DXA
and BIA methods. Both of devices are based on different assumptions and prediction
equations. It was reported that it is difficult and might be unreliable to make
comparisons between studies used different brands of BIA as they are based on
different prediction equations (Warner et al., 2004). Moreover, BIA and DXA devices
that used in the present study are depended on different reference data and
population based reference values. Therefore, Warner et al., (2004) stated that when
the general applicability of impedance equations can not be assumed in malignancy
survivors so, recommended the use of more than one body composition analyser, as
in the present study. Furthermore, very lean and very obese subjects are more likely
to lead to greater errors in prediction of body composition because some of the body
composition methods are produced from subjects close to the average body
composition values (Fogelholm et al., 1996). Also, the present study supports
producing a large representative population based reference data values and trends
over different populations. Future studies needs to validate these devices used in the
present study in diseased patients such as those with malignancies and MS.

3.5.8 Metabolic syndrome

3.5.8.1 Metabolic syndrome in Saudi Arabia general population

There is scarce MS literature in Saudi childhood or adolescents. Al-Daghri (2010) in a
cross-sectional study examined a large sample of 1,231 healthy children aged 10 –
18 year olds for prevalence of MS (defined according to NCEP III definition). The
overall prevalence of MS by Al-Daghri (2010) was 9.4% which was quite similar to the
present study when compared using the same age group and same definition (8.1%).
Therefore, the existence of MS in children and adolescent amongst Saudi ALL

survivors may be reflect what is happening in the general population. Gurney et al.,
(2006) studied the prevalence of MS (defined as NECP III definition) amongst 75 (50
survivors had CRT) adult survivors of childhood ALL compared to population norms
(n= 730) from 1999 - 2002 National Health and Nutrition Examination Study (NHNES)
data in the USA. The mean age and time since diagnosis was 30 years and 25 years;
respectively. They showed that prevalence of MS amongst survivors was (16.6%)
while population norms was 17.5%, which was not significantly different (p value=
0.87). However, 60% of the survivors treated by CRT had two or more MS
components compared to the 20% that did not receive CRT. Moreover, one important
issue in presence of MS during childhood is tracking into adulthood. By using similar
modified MS definitions for children in the present study (5.4%), the prevalence of MS
was increased comparing Gurney et al., (2006) study.

A hospital-based Saudi study was carried out on 37 obese children (57.9% male)
from the Endocrinology clinic at KFSH&RC and the mean age (SD) was 9.8 years
(3.5) (Taha et al., 2009). They defined MS according to modified NCEP III and WHO
definitions and obesity as BMI > 95th percentile based on CDC definition. The
prevalence of MS was 29.7% in Taha et al., (2009) study higher than the prevalence
of MS (18.8%) amongst overweight or obese survivors in the present study.
However, the sample size of Taha et al., (2009) study was too small to be
representative of the general population and they recruited only obese children.

3.5.8.2 Metabolic syndrome components and metabolic syndrome in survivors with ALL

Relatively few studies have considered metabolic syndrome among medium term
survivors of ALL. For instance, Trimis et al., (2007) carried out a study in 80 (50 was
males) survivors of ALL and median interval since completion of therapy was 6.3
years. Out of 80, 62 survivors were treated only by chemotherapy (Group A) whereas
the others (n = 18) had been treated with CRT (18 Gy) (Group B). They defined MS

according to NCEP III definition modified by Weiss et al., (2004). Trimis et al., (2007) found MS prevalence in the overall sample was 11%. However, the MS prevalence amongst group A was 8% which was not far away from the present study finding (5.4%) based on the same definition but slightly different criteria. In group B, MS was present in 22% (Trimis et al., 2007). Therefore, the present study and Trimis et al., (2007) revealed that MS was present in survivors post end of therapy. Even though survivors who had received CRT in treatment in Trimis et al., (2007) study had doubled prevalence of MS, the present study and Trimis et al., (2007) are highlighted a possible role of chemotherapy in these disturbances. Similarly, in a longer term study, Oeffinger et al., (2001) studied cardiovascular risk factors amongst 26 young adult (median age: 20.9 years) survivors of childhood ALL. The median time off-therapy was 13.3 years. Ten of the sample had been treated by CRT, whereas the remaining patients were treated with chemotherapy only. Cardiovascular risk factors were defined as follows: BMI ≥ 30; SBP ≥ 130 mm Hg; DBP ≥ 85 mm Hg, total cholesterol ≥ 200 mg/dL; LDL-C ≥ 130 mg/dL; cholesterol-to-high-density lipoprotein ratio ≥ 5.0; TG ≥ 200 mg/dL; glucose ≥ 110 mg/dL; insulin ≥ 14 μU/ml. Survivors with 2 or more cardiovascular risk factors comprised 27% of the total sample. They also reported that 19% (3 out of 16) of those treated only by chemotherapy had ≥ 2 cardiovascular risk factors, compared to 40% (4 out of 10) of those treated with CRT. Therefore, the prevalence of MS in paediatrics by both used definitions in the present study.

No study was found in the literature search that addressed MS in survivors with childhood standard risk ALL treated on modern protocols outside western countries. However, an Iranian study was found that did not use a modern protocol in treating ALL (ALL-BFM chemotherapy protocols which includes CRT routinely) (Reisi et al., 2009). They examined prevalence of MS (defined as NCEP III modified by de Ferranti et al. (2004)) amongst 55 children aged 6- 19 years (mean age was 10.4 years). They found that 20% of the sample had the MS: MS was present in 71% of obese survivors (defined as BMI> 95th percentile). Moreover, they demonstrated that the prevalence of

MS was high in survivors treated with CRT (26%) versus chemotherapy (12%); however, this finding was not statistically significant (p value= 0.15), possibly due to the small sample size. So, they reported high prevalence of MS in ALL survivors than the present study even with similar sample size may be due to the Iranian study used different MS definition and some of survivors were treated with CRT.

Obesity has a central role in the MS components as it is associated with a higher body fatness. Indeed, in Saudi survivors central obesity (defined by WC measurement) was positively associated with HOMA-IR, triglycerides, and BP and inversely associated with HDL-C. Also, almost half of the survivors by using both used of central obesity cut-offs had hyperglycaemia. Survivors of childhood ALL are at increased risk for late obesity, 10 to 20 years after therapy (Oeffinger et al., 2003).

A high HOMA-IR (defined as 1.77 (Arshi et al., 2010) was found in almost a third (29.1%) of the sample. Sharma et al., (2011) used HOMA-IR instead of fasting glucose to define MS (defined according NECP III modified by de Ferranti et al., (2004)) amongst African American children. The sample was 105 (57% girls) aged 9 to 13 years. They found that the specificity and sensitivity of HOMA-IR as one of the MS components to define MS were 83% and 88%; respectively. Therefore, the prevalence of MS was found to be doubled (38%) in the sample studied by Sharma et al., (2011) when using HOMA-IR but only 17% when using blood glucose as one of the MSC. Sharma et al., (2011) preferred using HOMA-IR instead of fasting glucose as it was claimed to be related to insulin resistance to predict MS. Furthermore, as indicated from the correlations between HOMA-IR index and serum parameters, insulin resistance is correlated with an abnormal lipid profile. Different cut-offs for HOMA-IR have been reported in the paediatric literature and these will alter the prevalence of abnormal HOMA-IR, but a further discussion of this point is beyond the scope of the present study.

Interestingly, time-dependent variables did not influence the present study results except in serum TG, even though some survivors had completed therapy just 1 month to 1 year before the present study. Our findings showed that metabolic alterations, suggestive of MS and MS components were detectable relatively early after the completion of therapy.

The present study supports the view that chemotherapy without radiotherapy leads to MS and associated cardiovascular risk factor development in ALL survivors. Prevalence of the MS components was quite high in Saudi survivors. Therefore, early prevention and intervention strategies should be investigated and developed by further future studies. Efforts should be directed by health professionals and their families at the identification of survivors at high risk. Early modification of life style after the end of therapy such as healthy diet, increasing physical activity and stress reduction may vital to prevent cardiovascular risk factors in ALL survivors in future (Trimis et al., 2007).

3.5.9 Weaknesses and Strengths of the present study

Sample size

Some limitations in the present study affect the interpretation of the results. First, small sample size of standard risk ALL survivors and the cross-sectional study design are limitations. In the present study, 77 survivors were available at the study time and 72% of them were eligible. Sample sizes in other studies that were carried out prospectively amongst short term ALL survivors are also usually small. For instance, Pakakasama et al., (2010) recruited 258 ALL survivors (median age was 12.2 years), however, only 121 of them were standard risk ALL and no body composition measurements were made. In addition, Reisi et al., (2009) studied 55 and of the survivors 30 had been treated by chemotherapy with CRT. Moreover, the Warner et al., (2004) study carried out amongst 35 children ALL survivors who had CRT to

identify body composition and obesity. On the other hand, the present study sample was fairly homogenous i.e. all survivors were standard risk ALL, all treated on same protocol and all treated on same centre and none got CRT.

Study design and methods

No gold standard for body weight status was used in the present study, so differences between the different approaches can be described, but it is difficult to assess the accuracy of the methods. Specifically, it is not clear which definition of underweight is correct (as described in 1.4). Since no gold standard for definition of underweight exists. For underweight evidence of a link to health outcomes would help validate any underweight definition.

For obesity, gold standards of measuring body fatness would be needed to define excess body fatness highly accurately (multi-component models) (Wells et al., 1999) and none were available. So, the present study used several approaches to predicting body fatness such as BMI, DXA and BIA devices. A recent systematic review concluded that a high BMI for age is a good simple proxy for excessive fatness (Reilly et al., 2010b). Also, BIA showed a good correlation with BMI and triceps skinfold thickness (Vizcaino et al., 2007), with relatively a higher precision of the DXA than other body compositions methodology (Jebb et al., 1993).

The Third caveat is that some details were out of the scope of the present study for instance, physical activity and nutritional habits of the study participants could not be measured given constraints on time and financial resources. Future studies of lifestyle of ALL patients and ALL survivors outside the western world would be useful, and these have been very useful in understanding the causes of obesity in ALL patients and survivors in the western world (Reilly, 2009)

Fourth, using a control group or a comparison group was not practical in the present study. A healthy control group or a 'positive control' group with chronic disease would

have been useful to compare prevalence of unhealthy weight status in ALL patients with that of the control or comparison group- this would have allowed us to test if what seemed like a high or low prevalence was specific to ALL or was just the result of the 'background' prevalence in the general Saudi population. As an alternative to having a comparison group the present study used the most recently available data from the general Saudi population on prevalence of obesity and MS.

Another limitation was the short time was between end of the therapy and the present study (mean= 6.2 years)-longer term follow up studies would be more useful, but studies of long term survivors in ALL are very scarce and almost non existent outside the western world. The present study showed the prevalence of MS and weight status in medium-term which is an essential for early control and prevention of the diseases. In addition, long-term follow up of ALL survivors who had been treated on modern protocols will not be possible for some time and will need future studies.

Finally, the weighted Kappa statistic (k) may be not valuable in the case of rare observations. The small sample size and low prevalence of some of the categories of weight status meant that some of the prevalence estimates were based on very small numbers and this limits the kappa statistic and resulted in quite large confidence intervals for the k statistics test in the present study (Viera and Garrett, 2005). The sample sizes were small for some of the analyses in this chapter and so these were described as exploratory, and some analyses were not undertaken as these would probably have been too exploratory to have been useful (e.g. reasons for misclassifications between different methods, or patterns of misclassifications, where numbers classified differently were often just 1-4 patients).

3.5.10 Conclusions

The prevalence of underweight, overweight and obesity, as well as over-fatness, was quite high amongst standard risk ALL Saudi survivors in the present study, though it

cannot be confirmed if the prevalence of unhealthy weight status was higher or lower than in the general population. MS is present in overweight or obese survivors, but apparently not in those of healthy weight.

In future, weight status should be evaluated by a health professional such as qualified dietician in ALL late effect and follow up clinics, by frequent assessments for weight status. Managing any abnormal weight status and prevention as a first line management would be useful. There are also many documents on paediatric weight management, e.g. Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Guidelines Network, 2010) (see appendix F), National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence, 2010) and The American Academy of Pediatrics (AAP) recommendations (Spear et al., 2007) which recommend monitoring overweight children, adolescents and adults because no Saudi weight management guidelines are available yet.

Chapter 4

Prevalence and secular trends in weight status at diagnosis in patients with Childhood acute lymphoblastic leukaemia in the UK

4.1 Introduction

An unhealthy weight at the point of diagnosis of childhood malignancies has been found to have adverse effects in at least some studies. Lange et al., (2005) retrospectively reviewed 768 children and young adults from the USA aged between one and 20 who had been diagnosed with AML. The prevalence of obesity (BMI ≥95th percentile) and underweight (BMI ≤10th percentile) according to the CDC definition at diagnosis was 14.8% and 10.9% respectively. Survival hazard ratio was 1.85 (95% CI = 1.19- 2.87) (p value= 0.006) and 1.88 (95% CI = 1.25- 2.83) (p value= 0.002) in underweight and obesity patients; respectively. It was concluded that being either underweight or obesity at diagnosis could reduce the survival rate of AML patients.

Moreover, underweight and overweight/obesity may have specific adverse effects on the success of treatment of childhood ALL as noted in chapter 1. A retrospective study examined 4,260 patients aged between two and 19 to evaluate the effect of obesity (defined as BMI ≥ 95th based on the CDC reference) on the prognosis of ALL treatment (Butturini et al., 2007). The five-year EFS rate and risk relapse was significantly reduced (p value =0.02) in non-obese (72%) versus obese patients (77%). It was therefore concluded that obesity at diagnosis is an independent predictor of the relapse risk in children with ALL. Another retrospective study from Brazil examined the prognostic impact of overweight in 181 children (median (range) age: 4.8 years (range: 3.2-6.3)) with newly diagnosed ALL on five-year EFS (Gelelete et al., 2011). It was found that 35.9% of them were either 'overweight' (BMI score > +1.0) or 'clinically obese' (BMI z score > +2.0) relative to WHO reference data. Obesity and overweight were shown to be predict the relapse risk- the five-year EFS was significantly lower (p value= 0.02) in the overweight/obese (58.8%) compared to the non-overweight (76.7%) patients.

Weight status is vital and plays an important role as described above. However, the lack of investigation into the role of weight status in childhood cancer research is

increasingly being acknowledged (Rogers and Ladas, 2011). Moreover, increasing attention is now being paid to the importance of an unhealthy weight status as a prognostic factor of treatment-related complications. Despite a paucity of evidence of the impact of weight status on childhood cancer, nutritional/weight status is becoming a cause for concern to some clinicians responsible for the care of patients with ALL and other childhood malignancies (Rogers and Ladas, 2011). The effect of an unhealthy weight status has also received increasing attention as child and adolescent obesity becomes more common. In a number of the more common childhood malignancies, overweight or obesity is a common consequence of the disease, its treatment, or lifestyle responses to treatment among families (Reilly, 2009).

One under-researched issue concerns the prevalence of an unhealthy weight status among children at the diagnosis of malignancy. Likewise, little is known about the related issue of secular changes in weight status in patient populations over time. The accuracy of data on prevalence may be hindered by the definition of weight status used and limitations imposed by the sample size; many different definitions and reference datasets have been used, and many previous studies have used very small samples. Prevalence estimates have been limited by the absence of agreed definitions of the terms underweight, overweight, and obesity. The emergence of recent definitions of underweight, overweight, and obesity based on BMI for age provides an opportunity to estimate the prevalence of unhealthy weight status (Cole et al., 2007, Cole et al., 2000) as discussed in section 2.1.3.

Accurate prevalence estimates have also been hindered by the use of small and possibly unrepresentative samples of children with cancer. For instance, Breene et al., (2011) examined the changes in weight status in 134 UK children with ALL who were treated by UKALL 97/97-99 protocols at a single UK centre. Therefore, prevalence estimates for being underweight or overweight and obesity are not

currently available for large nationally representative samples of patients. In addition, older studies generally did not base their prevalence estimates on what are now well-established definitions of weight status (Reilly, 2010) using BMI for age (Cole et al., 2000, Cole et al., 1995, Reilly et a; 2010) some of which became available only recently such as the definition of underweight from Cole et al., (2007).

4.2 Aims

The prevalence of unhealthy weight status at diagnosis of ALL is still unknown and this may be why there is no formal requirement to screen ALL patients for weight status at diagnosis at the moment. Therefore, the present study aimed to investigate the prevalence of unhealthy weight status at diagnosis of ALL in different trials, and also to examine secular trends in weight status in ALL amongst UK children. In order to avoid the problem of small sample sizes at single treatment centres, the researcher can benefit from the availability of anonymous existing UK national trial data for childhood ALL. These trials are particularly valuable because most patients in the UK are included (80 – 95% of UK patients with ALL) (Mitchell et al., 2010). The present study will therefore aim to utilise the UK national trial data to describe prevalence and secular trends in unhealthy weight status in childhood ALL. The measures used to define unhealthy weight status will be consistent with the most recent evidence-based definitions of what constitutes an unhealthy weight, and the most recent definitions which are accepted internationally e.g. Cole et al., (2007).

4.3 Methods

4.3.1 Participants

This is a retrospective study of anonymised national trial data obtained at or around the time of diagnosis of ALL by clinical staff responsible for entering patients with ALL onto trials in the UK. All patients enrolled were ALL patients diagnosed in the UK who were entered into the trial protocols from successive UKALL national treatment trials

covering the period 1985 to 2002, as the present thesis explained in details in section 2.2. Also, inclusion and exclusion criteria were given in the general method chapter in section 2.2.

4.3.2 UKALL trials

Sample of UKALL X trial, UKALL XI trial and UKALL 97/ 97-99 was 1635 patients (1-14 years), 2090 patients (1 – 14 years) and 1935 patients (1 – 18 years); respectively, as described in the general method chapter, section 2.2.

4.3.3 Measures and definitions of unhealthy weight status

4.3.3.1 Weight, height and BMI

Weight and height were measured to 0.1 kg and 0.1 cm respectively. The present study was based on anonymised clinical measures of weight and height which were made around the time of diagnosis, to estimate body surface area in order to calculate drug dosages. So, they were measured for clinical purpose by different nurses, as described in section 2.2.6.1.

BMI was calculated using the following equation: weight (Kg)/ height (m)^2. Further details are outlined in the Methods chapter. Weight status was classified based on three definitions.

4.3.3.2 IOTF and Cole et al. (2007) definitions

The BMI-based definitions of children and adolescents overweight and obesity described in the IOTF (Cole et al., 2000) have assumed increasing popularity over recent years (Reilly et al., 2010b). These facilitate international comparisons of obesity prevalence and use age and gender-specific cut-offs for absolute BMI.

Overweight and obesity are defined in this study according to the IOTF approach
(Cole et al., 2000).

Furthermore, Cole et al., (2007) more recently proposed underweight/ thinness for
children and adolescents. Underweight cut offs are corresponding to 16, 17 and 18
kg/m^2 adult BMI grades. However, the present study classified the different grades of
underweight by Cole et al. (2007) as underweight instead of using the terms used by
Cole et al. (2007): grade 1, 2 and 3 underweight, these terms were all collapsed with
one underweight category which is conceptually equivalent to BMI of < 18 at age 18.

4.3.3.3 UK 1990 definition

Weight status using BMI for age relative to UK 1990 population reference data was
defined in the present study as the following: healthy weight (BMI z score <1.04 (less
than the 85th centile)), overweight (BMI z score 1.04≤ 1.64 (above the 85th centile,
but below 95th centile)) and obese (BMI z score >1.64 (above the 95th centile)) (King
et al., 2010, Cole et al., 1995, Barlow and Dietz, 1998, Reilly et al., 2010b). BMI z
score was calculated by using software available in: www.healthforallchildren.com.

4.3.4 Statistical analysis

Results are expressed as median (Interquartile range: Q1, Q3) unless otherwise
stated. Data normality was tested using normality testing (parametric when p value
>0.05). Differences in the prevalence of an unhealthy weight status between boys and
girls were tested for significance using a Pearson's Chi Square and Fisher's exact
tests. Secular trends in unhealthy weight status at diagnosis (BMI z score) between
the three UKALL trials were tested for significance using the Kruskal-Wallis and
Mann-Whitney tests by using Minitab software version 16.1.1. Trends in the
prevalence of unhealthy weight status were tested for significance using a Chi Square
Test for Trends by using Medcalc software version 11.5.0.0.

The weighted kappa (k) test (Landis and Koch, 1977) as described in figure 3.3.1 was used to test agreement between the different definitions of weight status, i.e. Cole et al., (2007)/IOTF (Cole et al., 2000) and UK 1990 (Cole et al., 1995) definitions with a calculation of a 95% confidence interval (CI); k statistic scores were interpreted based on (Landis and Koch, 1977).

4.4 Results

4.4.1 UKALL X trial

4.4.1.1 Characteristics of the sample

 As illustrated in figure 4.4.1, 1,040 patients were potentially eligible for inclusion in the present study, based on the dataset provided by the CTSU at Oxford of whom 75.0% (n= 780) were boys and 25.0% (n= 260) girls (most of the girls were classified as low risk as discussed in section 2.2.4.1).

All patients had the data (weight, height, age and gender) that are essential to calculate BMI z score based on UK 1990 definition (Cole et al., 1995) except 7 patients who had missing data (number of missed height: 7 patients; weight: 3 patients and weight and height: 4 patients). Consequently, 1,033 patients potentially eligible for the present study (74.9% males, 25.1% Females) with UK 1990 reference data.

Furthermore, some patients who were ineligible because their weight status could not be calculated according to the Cole et al., (2007) and IOTF (Cole et al., 2000) definitions because some patients were beyond the Cole et al., (2007) and IOTF (Cole et al., 2000) definitions ranges of age. Therefore, patients who were ineligible for the Cole et al., (2007) and IOTF (Cole et al., 2000) definitions only (age was < 2.0 years) were 116 and so 917 patients were included with definitions based on Cole et al ., (2007) and IOTF (Cole et al., 2000) as illustrated in figure 4.4.1. The median age

(range) at diagnosis of ineligible patients by the IOTF (Cole et al., 2000) definition was 1.6 years (1.3, 1.8) with no significant difference between genders (Mann-Whitney test; p value= 0.85). Also, the median (range) BMI z score for those patients was - 0.46 (-1.32, 0.49), and there was no significant difference between boys and girls (Mann-Whitney test; p value= 0.08) as shown in table 4.4.1.

Table 4.4.1: UKALL X trial summary anthropometric measures of ineligible patients at diagnosis of ALL, median (Q1, Q3)

	Boys (n= 64, 55.2%)	Girls (n= 52, 44.8%)	Total sample (n= 116)
Age (yr)	1.6 (1.3, 1.8)	1.6 (1.1, 1.9)	1.6 (1.3, 1.8)
Height z score [©]	0.29 (-0.23, 1.12)	-0.41 (-0.91, 0.13)	- 0.01 (-0.60, 0.81)
Weight z score [©*]	- 0.12 (1.12)*	- 0.60 (1.16)*	- 0.23 (1.20)*
BMI z score [©]	- 0.39 (-1.01, 0.60)	- 0.9 (-1.80, 0.29)	- 0.46 (-1.32, 0.49)

[©] z score calculated by comparing patients against UK reference population (Cole et al., 1995);
* Normal distribution; mean (SD) was used

Figure 4.4.1: UKALL X trial flow diagram
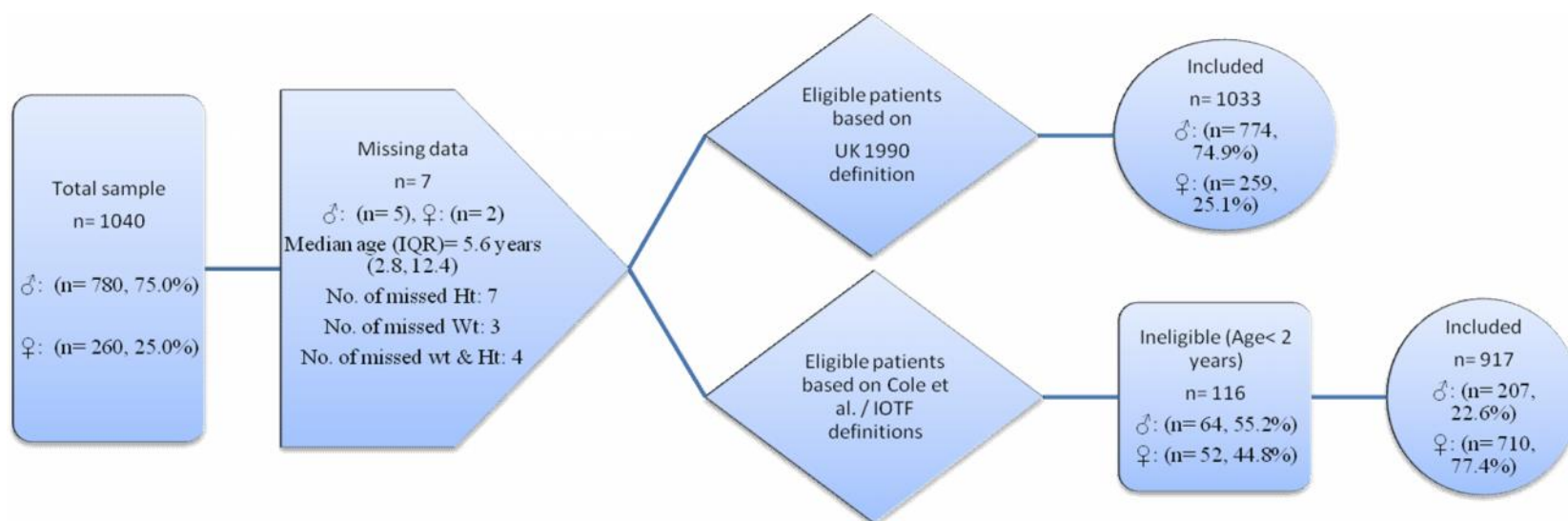
♂: Male; ♀: Female; Ht: height; Wt: weight; UK 1990 definition (Reilly et al., 2010b), Cole et al., (2007) , IOTF: International Obesity Task Force(Cole et al., 2000)

The median (range) age of the eligible sample (shown in table 4.4.2) based on UK 1990 (Cole et al., 1995) definition was 4.5 years (2.9, 8.1) with no significant difference between genders (Mann-Whitney test; p value= 0.68). The median BMI z score of the whole sample was -0.28 (-1.06, 0.47) with no significant difference between boys or girls (Mann-Whitney test; p value = 0.65).

Table 4.4.2: UKALL X trial summary anthropometric measures at diagnosis of ALL, median (Q1, Q3)

	Boys (n= 774, 74.9%)	Girls (n= 259, 25.1%)	Total sample (n= 1033)	P value
Age (yr)	4.5 (2.9, 7.2)	4.4 (2.5, 10.6)	4.5 (2.9, 8.1)	0.68
Height z score [©]	0.13 (-0.59, 0.84)	-0.11 (-0.80, 0.60)	0.10 (-0.67, 0.78)	0.01
Weight z score [©*]	- 0.11 (1.03)*	- 0.26 (1.16)*	- 0.14 (1.06)*	0.06
BMI z score [©]	- 0.27 (-1.05, 0.47)	- 0.38 (-1.09, 0.48)	- 0.28 (-1.06, 0.47)	0.65

[©] z score calculated by comparing patients against UK reference population (Cole et al., 1995);
* Normal distribution; mean (SD) was used

4.4.1.2 Weight status of UKALL X sample

4.4.1.2.1 Weight status defined by different definitions

As shown in table 4.4.3, applying the Cole et al. (2007)/IOTF (Cole et al., 2000) definitions showed that the prevalence of patients with healthy weight status (not underweight, not overweight, not obese) was 70.3% (n= 645). The prevalence of

underweight amongst the sample was 19.4% (n= 178). Overweight and obesity were present in 8.7% (n= 80) and 1.5 % (n= 14) patients at diagnosis; respectively using the Cole et al. (2007) and IOTF (Cole et al., 2000) approaches.

Table 4.4.3: Prevalence of weight status at diagnosis in UKALL X trial

Weight status	Cole et al.[1]/IOTF[2]		UK 1990[3]	
	N	%	N	%
Thinness	178	19.4%	----- *	----- *
Healthy	645	70.3%	895	86.6
Overweight	80	8.7%	85	8.2
Obesity	14	1.5%	53	5.1
Overweight/ obesity	94	10.2	138	13.3

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. cut offs Cole et al., (2007); [2] Healthy, overweight and obesity calculated by comparing patients BMI against age and gender according to IOTF cut offs (Cole et al., 2000); [3] UK 1990 defined weight status as healthy weight (BMI z score <1.04), overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64) (King et al., 2010); * There is no definition for underweight by using UK 1990 reference data.

The prevalence of different categories of weight status was also assessed by applying the definitions based on UK 1990 reference data (Cole et al., 1995). Patients who were a healthy weight accounted for 86.6% (n= 895) of the total sample. However, the prevalence of patients defined as being overweight or obese was 8.2% (n= 85) and 5.1% (n= 53) respectively.

Patients ineligible had median age (range) at diagnosis for thin and overweight/obese patients was 4.3 years (3.3 , 9.3) and 3.9 years (2.9 , 5.9); respectively, with no significant difference between them (Mann-Whitney test; p value= 0.05). Also, the median (range) BMI z score for thin was -1.8 (-2.3, -1.5) and for overweight/obese was 1.6 (1.4, 2.1).

4.4.1.2.2 Weight status according to gender

Using the Cole et al. (2007)/ IOTF (Cole et al., 2000) definitions according to gender, the prevalence of healthy weight status was similar in both boys and girls: 70.4% (n= 500) and 70.1 % (n= 145) respectively. Underweight/thinness was present in 144 boys (20.3%) and 34 (16.4%) girls. Boys who were overweight or obese accounted for 9.3 % (n= 66) of the sample and girls 13.5% (n= 28). The prevalence of weight status did not differ significantly between genders (Pearson chi-square test; p value=0.53).

By applying the UK 1990 definitions (Cole et al., 1995), 87.5% (n=678) of boys and 83.8% (n=217) of girls were of a healthy weight at the diagnosis of ALL. Patients who were identified as overweight or obese accounted for 12.5% (n=96) of boys and 16.3% (n=42) of girls, as shown in table 4.4.4.

Table 4.4.4: Prevalence of weight status categories at diagnosis defined by Cole et al. / IOTF and UK1990 definition according to gender in UKALL X trial

		Thinness		Healthy		Overweight		Obesity	
		n	%	N	%	n	%	n	%
Cole et al. / IOTF	Boys	144	20.3	500	70.4	56	7.9	10	1.4
	Girls	34	16.4	45	70.1	24	11.6	4	1.9
UK 1990	Boys	----$^\Delta$	----$^\Delta$	678	87.5	60	7.8	36	4.7
	Girls	----$^\Delta$	----$^\Delta$	217	83.8	25	9.7	17	6.6

$^\Delta$ There is no definition for underweight by using UK 1990 reference data

4.4.2 UKALL XI trial

4.4.2.1 Characteristics of the sample

The present study potential sample size was 2,090 patients. However, a number of patients at diagnosis who could be classified for their weight status had missing data (height or weight) needed to calculate BMI z score (n=59). Hence, the present study included 2,031 patients (56.8% boys, 43.2% girls) according to UK 1990 definition (Cole et al., 1995).

However, some patients ineligible for the Cole et al., (2007)/IOTF (Cole et al., 2000) definitions (age < 2.0 years) :154 in total (53.2% boys, 46.8% girls) while 1877 (57.1 % were males) patients were eligible as illustrated in figure 4.4.2.

Figure 4.4.2: UKALL XI trial flow diagram
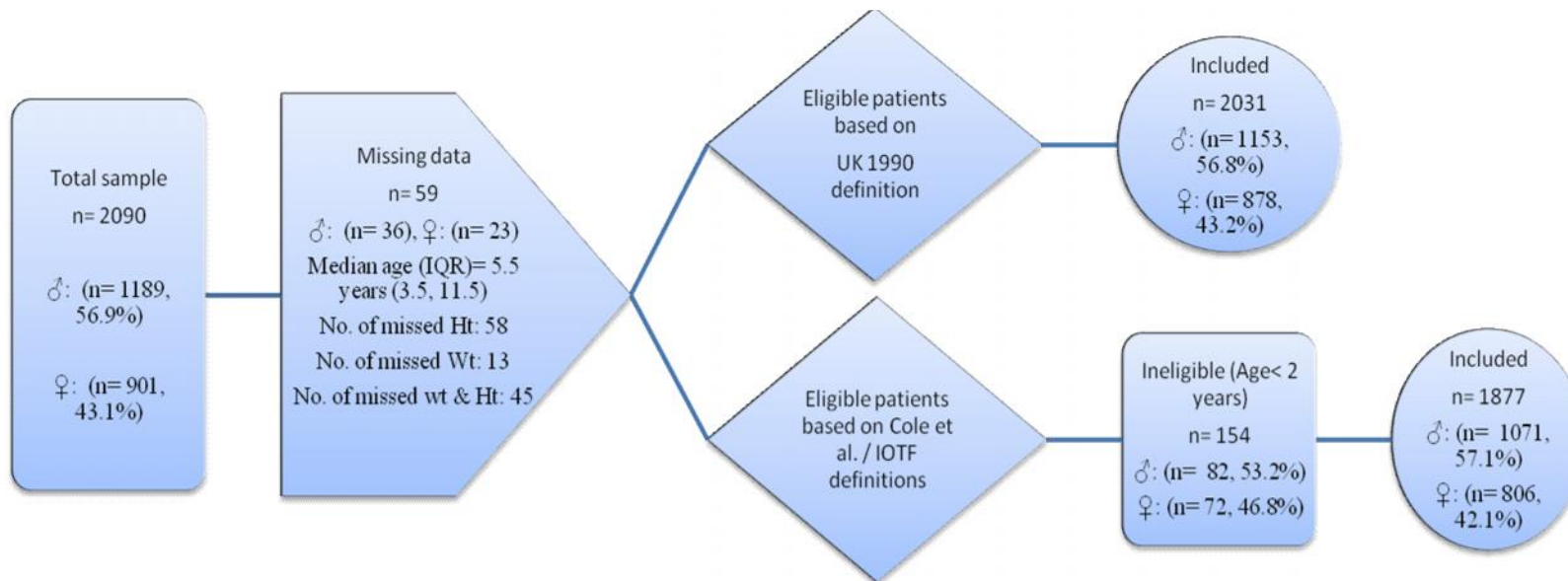
$\male$: Male; $\female$: Female; Ht: height; Wt: weight; IQR: Q1, Q3; UK 1990 definition (Reilly et al., 2010b), Cole et al. Cole et al., (2007) , IOTF: International Obesity Task Force(Cole et al., 2000)

The median age (range) at diagnosis of ineligible patients by IOTF (Cole et al., 2000) definition was 1.5 years (1.5, 1.5) with no significant difference between boys and girls. Also, the median (range) BMI z score for those patients was 0.01(-0.77, 0.92) with no significant difference between boys and girls (Mann-Whitney test; p value= 0.50) as shown in table 4.4.5.

Table 4.4.5: UKALL XI trial anthropometric measures of ineligible ALL patients at diagnosis

	Boys (n= 82, 53.2%)	Girls (n= 72, 46.8%)	Total sample (n= 154)
Age (yr)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)
Height z score [©]	0.79 (0.12, 1.89)	0.24 (-0.53, 1.92)	0.91 (-1.92, 1.89)
Weight z score [©]	0.49 (-0.43, 1.23)	- 0.91 (-0.13, 1.20)	0.50 (-0.42, 1.24)
BMI z score [©]	- 0.12 (-0.92, 0.73)	- 0.10 (-0.87, 1.12)	0.01(-0.77, 0.92)

[©] **z score calculated by comparing patients against UK reference population (Cole et al., 1995)**

The median (range) age of the eligible sample (table 4.4.6) for which the UK 1990 reference data were used (Cole et al., 1995) was 4.5 years (2.5, 7.5); age differences were not significant between genders (Mann-Whitney test, p value = 0.79). The median (range) BMI z score of the sample was -0.10 (-0.82, 0.77), with no significant difference in BMI z score between boys and girls (Mann-Whitney test; p value=0.31).

Table 4.4.6: UKALL XI trial anthropometric measures at diagnosis

	Boys (n= 1153, 56.8%)	Girls (n= 878, 43.2%)	Total sample (n= 2031)	P value
Age (yr)	4.5 (3.5, 7.5)	4.5 (2.5, 7.5)	4.5 (2.5, 7.5)	0.79
Height z score [©]	0.16 (-0.69, 1.00)	0.20 (-0.55, 1.04)	0.17 (-0.66, 1.01)	0.38
Weight z score [©]	0.20 (-0.75, 0.86)	- 0.10 (-0.69, 0.91)	0.12 (-0.72, 0.88)	0.96
BMI z score [©]	- 0.02 (-0.81, 0.79)	- 0.10 (-0.85, 0.72)	- 0.10 (-0.82, 0.77)	0.31

[©] **z score calculated by comparing patients against UK reference population (Cole et al., 1995)**

4.4.2.2 Weight status of UKALL XI sample

4.4.2.2.1 Weight status defined by different definitions

Applying the Cole et al. (2007) and IOTF(Cole et al., 2000, Cole et al., 2007) definitions healthy weight accounted for 70.9% (n=1,330) of the sample. The prevalence of underweight in the eligible patients based on Cole et al., (2007) was 16.0% (n=301). Moreover, overweight/obesity using IOTF (Cole et al., 2000) was found in 13.1% (n=246) of the patients.

Using the UK 1990 definition (Cole et al., 1995), a healthy body weight was found in 81.6% (n=1,657) of patients, whilst patients who were either overweight or obese accounted for 18.2% (n=374) of the sample (see table 4.4.7).

Patients ineligible had median age (range) at diagnosis for thin and overweight/obese patients was 4.5 years (3.5 , 8.3) and 4.5 years (3.5 , 6.8); respectively, with no significant difference between them (Mann-Whitney test; p value= 0.40). Also, the

median (range) BMI z score for thin was -1.7 (-2.3, -1.5) and for overweight/obese was 1.7 (1.5, 2.1).

Table 4.4.7: Prevalence of weight status in UKALL XI trial

Weight status	Cole et al.[1] /IOTF[2]		UK 1990	
	n	%	n	%
Thinness	301	16.0	---[*]	---[*]
Healthy	1330	70.9	1657	81.6
Overweight	202	10.8	228	11.2
Obesity	44	2.3	146	7.2
Overweight/ obesity	246	13.1	374	18.2

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. cut offs Cole et al., (2007); [2] Healthy, overweight and obesity calculated by comparing patients BMI against age and gender according to IOTF cut offs (Cole et al., 2000)]; [3] UK 1990 defined weight status as healthy weight (BMI z score <1.04), overweight (BMI z score $1.04 \leq 1.64$) and obese (BMI z score >1.64) (King et al., 2010); * There is no definition for underweight by using UK 1990 reference data.

4.4.2.2.2 Weight status according to gender

When the sample was divided according to gender, the prevalence of underweight amongst boys was 16.3% (n=175), whereas overweight/obese patients at diagnosis accounted for 12.5% (n=134) based on the Cole et al., (2007)/IOTF (Cole et al., 2000)

definitions. In girls, underweight was found in 15.6% (n=126) of patients whilst 13.8% (n=112) were overweight/obese. No significant difference between the genders in terms of weight status was found (Pearson chi-square test; p value= 0.61).

When the UK 1990 definition (Cole et al., 1995) was used, the prevalence of overweight/obesity was 19.1% (n= 221) amongst boys and 17.5% (n=153) amongst girls, whilst the remaining patients were classified as being of a healthy weight (80.8% boys, 82.6% girls). (See table 4.4.8)

Table 4.4.8: Prevalence of weight status at diagnosis defined by Cole et al. (2007)/ IOTF and UK1990 definition according to gender in UKALL XI trial

		Thinness[1]		Healthy[2]		Overweight[2]		Obesity[2]	
		n	%	n	%	n	%	n	%
Cole et al.[1]/ IOTF[2]	Boys	175	16.3	762	71.5	114	10.6	20	1.9
	Girls	126	15.6	568	70.5	88	10.9	24	2.9
UK 1990[2]	Boys	---[Δ]	---[Δ]	932	80.8	138	11.9	83	7.2
	Girls	---[Δ]	---[Δ]	725	82.6	90	10.3	63	7.2

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. (2007) definition; [2] Healthy, overweight and obesity calculated by comparing BMI against age and gender by applying IOTF and UK 1990 definitions; [Δ] There is no definition for underweight by using UK 1990 reference data

4.4.3 UKALL 97/ 97- 99 trial

4.4.3.1.1 Characteristics of the sample

The sample comprised 1,935 patients (56.0% boys, 44.0% girls). A large number of patients had missing data (number of missed height: 1037 patients; weight: 385 patients and weight and height: 652 patients). For 1037 (57.4% boys, 42.6% girls) patients BMI could not be determined. Therefore, the number of patients eligible based on UK 1990 definition (Cole et al., 1995) was 898 (54.3% boys, 45.7% girls). The median (range) age was 4.5 years (3.5, 7.5) with no significant difference between boys and girls (Mann-Whitney test; p value=0.36).

However, 50 patients were also too young to be classified according to the Cole et al., (2007)/IOTF (Cole et al., 2000) definitions of weight status (age < 2.0), and so, 848 (54.4%were males) patients were included in the analyses with Cole et al., (2007) and IOTF (Cole et al., 2000) definitions as illustrated in figure 4.4.3.

 Median age (range) at diagnosis of ineligible patients by IOTF (Cole et al., 2000) definition was 1.5 years (1.5, 1.5) with no significant difference between boys and girls. Also, the median (range) BMI z score for those patients was 0.41(-0.51, 1.42) with no significant difference between boys and girls (Mann-Whitney test; p value= 0.70) as shown in table 4.4.9.

Figure 4.4.3: UKALL 97/97-99 trial flow diagram
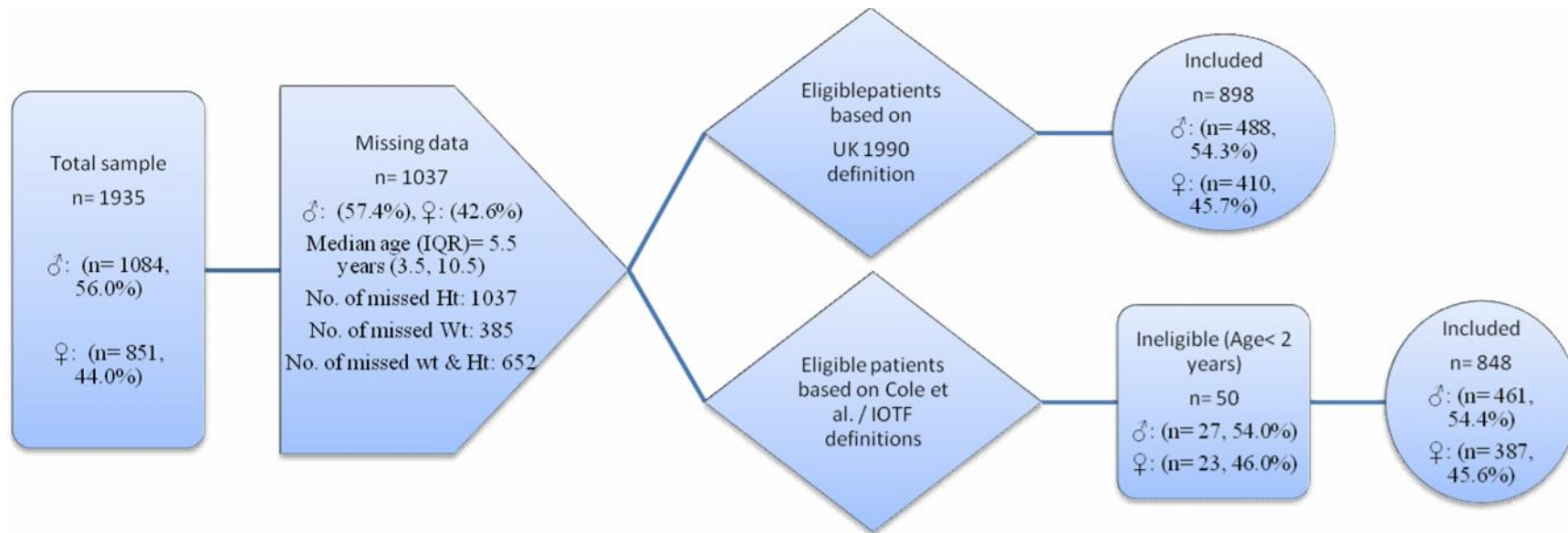
♂: Male; ♀: Female; Ht: height; Wt: weight; IQR: Q1, Q3; UK 1990 definition (Reilly et al., 2010b), Cole et al. (2007), IOTF: International Obesity Task Force(Cole et al., 2000)

Table 4.4.9: UKALL 97/ 97-99 trial anthropometric measures of ineligible ALL patients at diagnosis

	Boys (n= 27, 54.0%)	Girls (n= 23, 46.0%)	Total sample (n= 50)
Age (yr)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)
Height z score [©]	0.87 (0.42, 2.21)	1.21 (0.53, 1.94)	1.22 (-0.30, 2.23)
Weight z score [©]	0.49 (-0.50, 1.92)	- 0.93 (1.60, 2.42)	0.54 (0.21, 1.92)
BMI z score [©]	- 0.32 (-0.42, 0.79)	- 0.50 (-0.81, 1.90)	0.41(-0.51, 1.42)

[©] z score calculated by comparing patients against UK reference population (Cole et al., 1995)

The median BMI z score of the sample based on UK 1990 definition (Cole et al., 1995) was 0.78 (-0.18, 1.52) with no significant difference between the sexes (Mann-Whitney test; p value = 0.48). More details are shown in table 4.4.10.

Table 4.4.10: UKALL 97/ 97-99 trial anthropometric measures at diagnosis

	Boys (n= 488, 54.3%)	Girls (n= 410, 45.7%)	Total sample (n= 898)	P value
Age (yr)	4.5 (3.5, 7.5)	4.5 (3.8, 8.5)	4.5 (3.5, 7.5)	0.36
Height z score[©]	0.25 (-0.54, 1.09)	0.23 (-0.86, 1.02)	0.24 (-0.66, 1.02)	0.11
Weight z score[©]	0.71 (-0.24, 1.46)	0.57 (-0.14, 1.45)	0.66 (-0.18, 1.46)	0.13
BMI z score[©]	0.78 (-0.13, 1.59)	0.72 (-0.29, 1.49)	0.78 (-0.18, 1.52)	0.48

[©] z score calculated by comparing patients against UK reference population (Cole et al., 1995)

4.4.3.2 Weight status of UKALL 97/ 97-99 sample

4.4.3.2.1 Weight status in overall sample of UKALL 97/ 97-99 sample

Using the Cole et al., (2007) /IOTF (Cole et al., 2000) classifications for unhealthy weight status show, 5.8% (n=49) of the patients were underweight and that more than one-third (34.5%) of the patients (n=293) were overweight or obese. By applying the UK 1990 definition (Cole et al., 1995), the prevalence of overweight/obese patients was 40.9% (n=367), with 531 (59.3%) patients classified as being of a healthy weight, as illustrated in table 4.4.11.

Table 4.4.11: Prevalence of weight status in UKALL 97/97-99 trial

Weight status	Cole et al.[1] /IOTF[2]		UK 1990[3]	
	n	%	n	%
Thinness	49	5.8	--- [Δ]	--- [Δ]
Healthy	506	59.7	531	59.3
Overweight	218	25.7	169	18.8
Obesity	75	8.8	198	22.1
Overweight/ obesity	293	34.5	367	40.9

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. (2007) cut offs; [2] Healthy, overweight and obesity calculated by comparing patients BMI against age and gender according to IOTF cut offs; [3] UK 1990 defined weight status as healthy weight (BMI z score <1.04), overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64); [Δ] There is no definition for underweight by using UK 1990 reference data

Patients ineligible had median age (range) at diagnosis for thin and overweight/obese patients was 4.5 years (3.5 , 10.0) and 4.5 years (3.5 , 7.5); respectively, with no significant difference between them (Mann-Whitney test; p value= 0.69). Also, the median (range) BMI z score for thin was -1.9 (-2.6, -1.5) and for overweight/obese was 1.8 (1.5, 2.3).

4.4.3.2.2 Weight status according to gender

Using the Cole et al., (2007) /IOTF (Cole et al., 2000) definitions weight status did not significantly differ between boys and girls (Pearson chi-square test; p value=0.07). Underweight at diagnosis of ALL was observed in 6.1% (n=28) of boys and 5.4% (n=21) of girls. Moreover, about one-third (31.0%) of boys (n=143) and 38.7% (n=150) of girls were overweight or obese.

Overweight prevalence defined by UK 1990 definition (Cole et al., 1995) in boys and girls was significantly different (Fisher's exact test, p value= 0.008) and overweight prevalence accounted for 15.6% (n=76) and 22.7% (n=93) of the sample respectively. Moreover, obesity was present in 23.8% (n=116) and 20.0% (n=82) of boys and girls respectively (not significant, Fisher's exact test, p value= 0.20). Further details are shown in table 4.4.12.

Table 4.4.12: Prevalence of weight status at diagnosis defined by Cole et al. / IOTF and UK1990 definition according to gender

		Thinness[1]		Healthy[2]		Overweight[2]		Obesity[2]	
		N	%	n	%	n	%	n	%
Cole et al/ IOTF	Boys	28	6.1	290	62.9	102	22.1	41	8.9
	Girls	21	5.4	216	55.8	116	29.9	34	8.8
UK 1990	Boys	---[Δ]	---[Δ]	296	60.7	76	15.6	116	23.8
	Girls	---[Δ]	---[Δ]	235	57.3	93	22.7	82	20.0

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. definition;
[2] Healthy, overweight and obesity calculated by comparing BMI against age and gender by applying IOTF and UK 1990 definitions; [Δ] There is no definition for underweight by using UK 1990 reference data

4.4.3.3 Trends in prevalence of unhealthy weight status over time a cross all three trials

Prevalence of unhealthy weight status at diagnosis in UK ALL in the three trials as summarised in table 4.4.13.

Table 4.4.13: Prevalence of unhealthy weight status at diagnosis in the three trials

Weight status	UKALL X trial		UKALL XI trial		UKALL 97/97-99 trial	
	Cole et al.[1] /IOTF[2] %	UK 1990[3] %	Cole et al.[1] /IOTF[2] %	UK 1990[3] %	Cole et al.[1] /IOTF[2] %	UK 1990[3] %
Thinness	19.4	----- *	16.0	----- *	5.8	----- *
Overweight	8.7	8.2	10.8	11.2	25.7	18.8
Obesity	1.5	5.1	2.3	7.2	8.8	22.1
Overweight/ obesity	10.2	13.3	13.1	18.2	34.5	40.9

[1] Thinness calculated by comparing patients BMI against age and gender based on Cole et al. cut offs Cole et al., (2007); [2] Healthy, overweight and obesity calculated by comparing patients BMI against age and gender according to IOTF cut offs (Cole et al., 2000)]; [3] UK 1990 defined weight status as healthy weight (BMI z score <1.04), overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64) (King et al., 2010); * There is no definition for underweight by using UK 1990 reference data

4.4.3.3.1 Trends using Cole et al. (2007) / IOTF definitions of weight status

The prevalence of overweight and obesity (combined) using the IOTF (Cole et al., 2000) definition increased from 10.2% in UKALL X to 13.1% in UKALL XI and 34.5% in UKALL 97/97-99 (see figure 4.4.4). The trend in the prevalence of overweight and obesity between the three trials was statistically significant (Chi-square test for trend; p value<0.0001). In contrast, the rate of underweight Cole et al., (2007) stood at 19.4% in UKALL X and decreased substantially to reach to 5.8% in UKALL 97/97-99 (Chi-square test for trend; p value <0.0001) . Consequently, the prevalence of a

healthy body weight was almost 70% at the beginning (UKALL X) of the trials but fell to 59.7% in the most recent trial for which data are available (UKALL 97/97-99).

Figure 4.4.4: Prevalence of weight status defined by IOTF/ Cole et al., (2007) definitions trends over UKALL trials
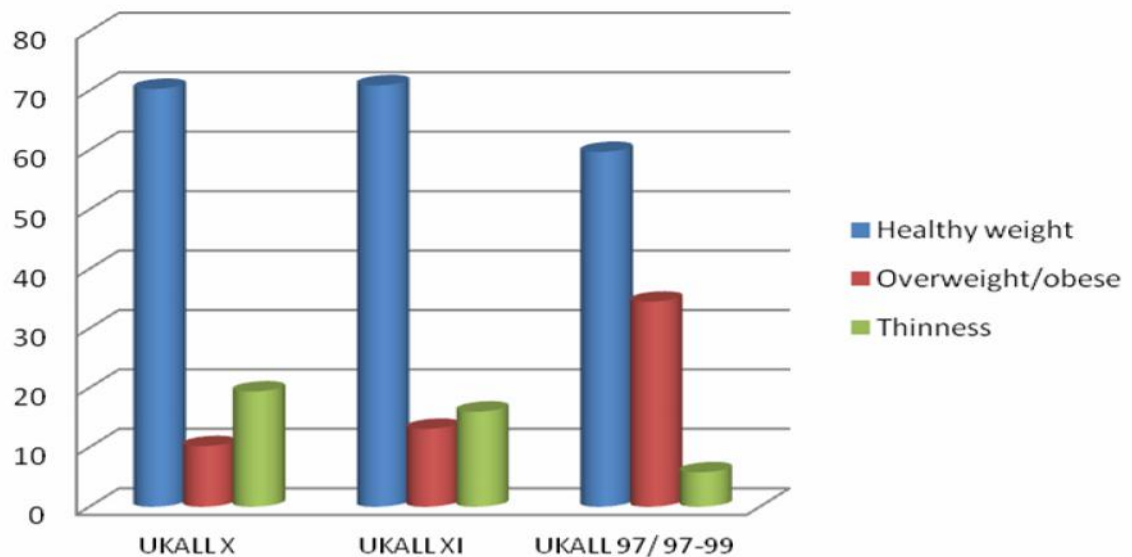
Healthy weight, overweight and obesity calculated by comparing BMI against age and gender by applying IOTF, Thinness child classified as cut-offs defined to pass through absolute BMI ≤18.5 at age 18

4.4.3.3.2 Weight status trends using the UK 1990 reference data (Cole et al., 1995) a cross the three trials

The prevalence of overweight and obesity (combined) across the three trials using the UK 1990 definitions (Cole et al., 1995) of weight status increased from 13.3% in UKALL X to 18.2% in UKALL XI and to 40.9% in UKALL 97/97-99. The trend in prevalence of overweight and obesity between the three trials was statistically significant (Chi-square test for trend; p value< 0.0001). The prevalence of a healthy body weight consequently fell from 86.6% to 59.3% in the most recent trial for which data are available (Figure 4.4.5).

211

Figure 4.4.5: Prevalence of weight status defined by UK 1990 trends over UKALL trials
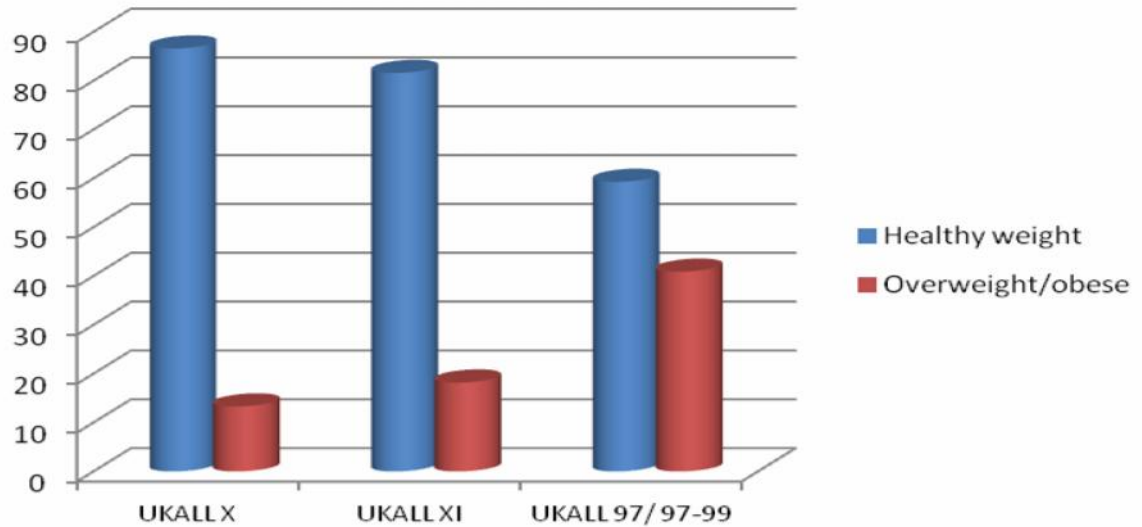
UK 1990 defined weight status as healthy weight (BMI z score <1.04), overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64)

4.4.3.4 BMI z score trends over periods a cross all three trials

As shown in figure 4.4.6, the median BMI z score trend significantly increased between the three different trials (Kruskal Wallis test; p value < 0.0001). There was also a significant shift in BMI z score trend between the UKALL X and UKALL XI trials (Mann-Whitney test; p value < 0.0001).

Figure 4.4.6: BMI z score trend over UKALL X, UKALL XI, and UKALL 97/97-99
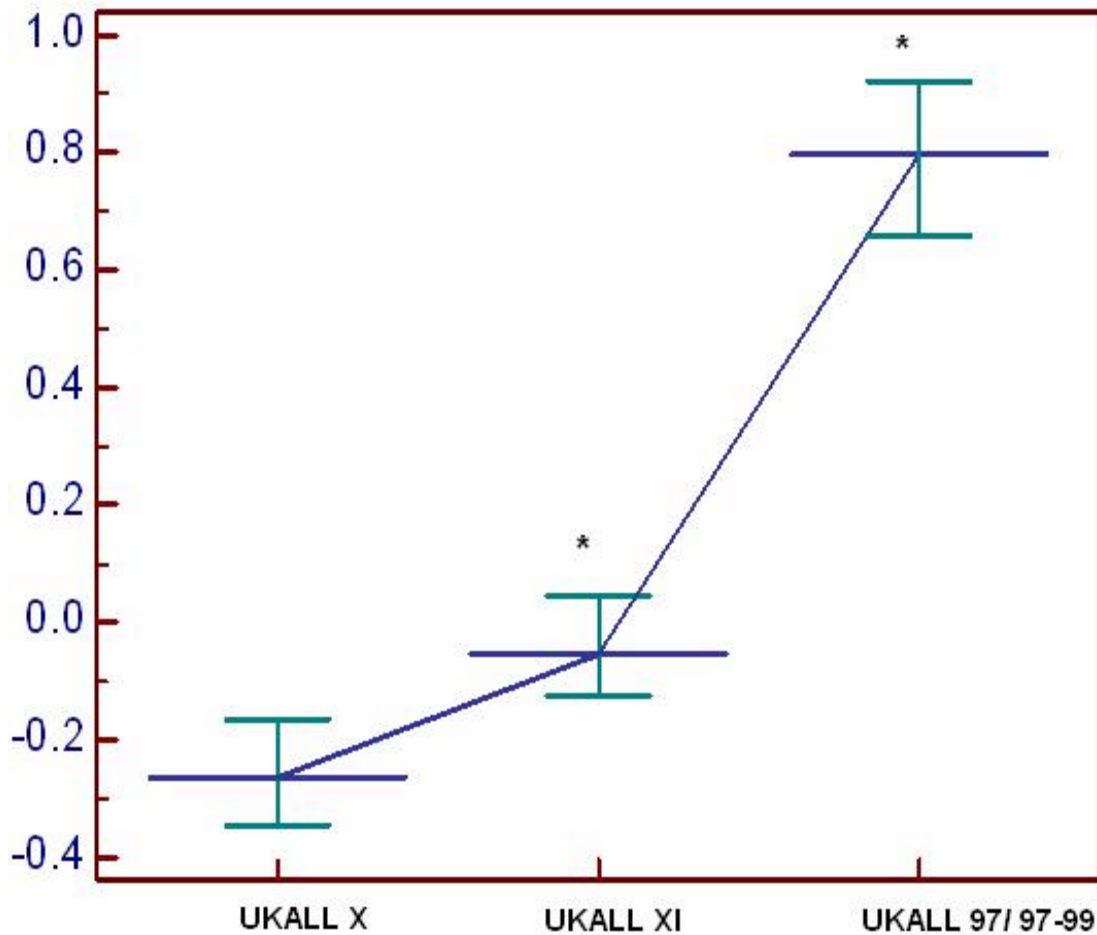
* Significant increase of BMI z score over time between UKALL X and UKALL XI (Mann-Whitney test, p value < 0.0001); * Significant increase of BMI z score over time between UKALL X , UKALL XI and UKALL 97/ 97-99 (kruskall- Wallis test, p value < 0.0001)

4.4.3.5 Agreement between Cole et al. (2007)/ IOTF and UK 1990 definitions on the prevalence of weight status

In terms of the agreement between the Cole et al., (2007) IOTF (Cole et al., 2000) and UK 1990 (Cole et al., 1995) approaches based on BMI for age, applying weighted kappa (k) statistic suggested "almost perfect" agreement in defining overweight and obesity (combined) (k= 0.85; 95% CI: 0.80 - 0.90) in UKALL X, (k= 0.81, 95% CI: 0.78

– 0.85) in UKALL XI and (k= 0.85; 95% CI: 0.82- 0.90) in UKALL 97/97-99. However, the agreement between used definitions was 'moderate' in defining overweight alone amongst the patients: (k= 0.59; 95% CI: 0.50 – 0.69) in UKALL X, (k= 0.49, 95% CI: 0.43 – 0.56) in UKALL XI, (k= 0.42, 95% CI: 0.35 – 0.49) in UKALL 97/97-99. Similarly, 'moderate' agreement was suggested in defining obesity amongst those patients: (k= 0.45, 95% CI: 0.45, 0.29 – 0.6) in UKALL X, (k= 0.47, 95% CI: 0.38 – 0.56) in UKALL XI, (k= 0.51, 95% CI: 0.44 – 0.58) in UKALL 97/97-99(see table 4.4.14).

Table 4.4.14: Agreements between IOTF and UK 1990 definitions to define overweight, obesity and overweight and obesity (combined) by using weighted kappa test

		Kappa	**Confidence Interval**	**Kappa Interpretation**
UKALL X	Overweight	0.59	0.50 – 0.69	Moderate
	Obesity	0.45	0.29 – 0.60	Moderate
	Overweight and obesity	0.85	0.80 – 0.90	Almost perfect
UKALL XI	Overweight	0.49	0.43 – 0.56	Moderate
	Obesity	0.47	0.38 – 0.56	Moderate
	Overweight and obesity	0.81	0.78 – 0.85	Almost perfect
UKALL 97/97-99	Overweight	0.42	0.35 – 0.49	Moderate
	Obesity	0.51	0.44 – 0.58	Moderate
	Overweight and obesity	0.85	0.82 – 0.90	Almost perfect

4.5 Discussion

4.5.1 Main findings and implications:

4.5.1.1 Prevalence of weight status categories in the trials:

This study has described a dramatic alteration in the pattern and prevalence of underweight, overweight and obesity amongst newly diagnosed paediatric ALL patients in the UK. The patient population had a high prevalence of underweight and low prevalence of overweight and obesity in the mid to late 1980s, a picture that had considerably changed by the early 2000s to a lower prevalence of underweight and high prevalence of overweight and obesity. To be more precise, in the trial that ran in the mid to late 1980s, the prevalence of underweight was around 19% according to the Cole et al., (2007) definition. The prevalence had shifted to around 5% by the trial which ended in 2002. In contrast, the rates of overweight and obesity (combined) at the start of the trial (1985- 1990) were around 10% and 13% respectively according to the IOTF (Cole et al., 2000) and UK 1990 (Cole et al., 1995) definitions. However, prevalence of overweight and obesity (combined) substantially increased to around 34% and 40% when both definitions were applied.

Therefore, the present study demonstrates that, in the UK, more than 40% of all patients with ALL were underweight, overweight or obese at diagnosis using the most recent dataset available (from the UKALL 97/ 97-99 trial which ended in 2002). No estimates of the prevalence and trends over time of underweight or overweight and obesity have previously been available from nationally representative samples of patients using the currently recommended definitions of weight status based on BMI for age (Reilly et al., 2010b) so, the present study is the first study in this field.

It is important to note that our prevalence estimates were conservative the prevalence of markedly high fatness would probably have been higher than the prevalence of high BMI for age measured in the present study. The BMI for age has a high

specificity but moderate sensitivity in the general population of children (Reilly et al., 2010b) (in other words, some obese i.e. excessively fat patients may be missed when BMI is used to define obesity, but the risk of wrongly being diagnosed as obese is rare) for diagnosis of excessive weight in both children and adolescents (as mentioned in 1.4.5.1.5). Also, in children with malignancy, Warner et al., (1997) investigated the ability of BMI in predicting excess adiposity against body composition techniques such as DXA and skinfold thickness. They found that BMI in children with malignancy underestimates the prevalence of excessive fatness in patients with ALL. Similarly, this underestimation of excessive body fatness was discovered and discussed in chapter 3 (Aldhafiri et al., 2012).

Additionally, children with ALL in the UK typically experience substantial excessive weight gain during and after therapy (Reilly, 2009). For example, Breene et al., (2011) assessed changes in 134 patients who were treated by using UKALL 97/97-99 from diagnosis up to three years after the end of the therapy. The patient's median age (range) at diagnosis was 4.6 years (1.1- 15.9). It was found that the mean (95% CI) of the BMI z score significantly increased (<0.0001) from diagnosis 0.35 (0.20- 0.50) until three years post-therapy 1.04 (0.85- 1.22). In addition, Reilly et al., (2000b) examined excess weight gain amongst 98 patients in the 1980-1990s who were treated by UKALL XI protocols in Scotland. They found that obesity (defined as BMI z score> 2.0) was significantly (p value < 0.01) increased from < 2.0 % at diagnosis up to 16.0% at 3rd year since diagnosis. Odame et al., (1994) stated that obesity was seen very commonly amongst survivors of ALL (mean age at diagnosis was 3.4 years) who were treated on the UKALL VIII (n= 15 children) and UKALL X protocols (n=25 children) (both trials included CRT at 1800 Gy) than control group. They found that Prevalence of obesity at diagnosis were 5.0 % and 10.0% amongst ALL patients and control group; respectively. However, the prevalence of obesity in fourth year since diagnosis was 39.0% in the ALL group and 22.5% in the control group. In the USA, a recent study (Esbenshade et al., 2011) found that the prevalence of overweight and obesity (defined as CDC: BMI >85th percentile) in 183 children whose

(median age (range)) was 5.7 years (1.2, 20.9) was 55% at diagnosis, which steadily increased to reach 70% by the end of the ALL standard risk therapy (based on Children's Oncology Group protocols) (for more details see the table 1.5.1).

Underweight and obesity at diagnosis might have a role in outcome of the treatment. Institute of medicine recently reported that obesity has a role in incidence, recurrence, progression and death amongst cancer patients (Patlak and Nass, 2012). This thesis will deal with this issue in the following chapter (chapter 5).

4.5.1.2 Using national and international approaches for defining weight status

The present study used the international definitions amongst UK ALL children because the national UK BMI cut-offs are not available for defining underweight. The weighted kappa analysis pointed to some agreement between international and national definitions, but this was not perfect. The reason for the difference between the national (UK 1990) definitions and the Cole/IOTF approach to defining obesity was investigated by Chinn and Rona (2002). They examined 6000 white English healthy children aged 4 – 11 years between 1984 – 1994 by applying UK- specific reference (BMI z score equivalent to BMI 25 and BMI 30 at ages 18, 19.5 and 23) and IOTF (Cole et al., 2000) definitions. They found for example prevalence of overweight by applying UK cut-off in boys was increased from 10.2% in 1984 up to 13.8% in 1994. However, the prevalence increased was 5.4% in 1984 up to 9.0% in 1994 by applying IOTF (Cole et al., 2000) definition. They showed also, that the greatest difference between the national and international definitions is before the age of 5 years old than older children as same as to the present study when the median age in all three used cohorts in the present study was 4.5 years. The varying difference is due to converting each international BMI-cut offs point to overweight (BMI= 25) or obese (BMI= 30) extrapolated back from age18. They concluded that the IOTF definition of obesity is not compatible to UK reference curve for BMI cut-offs because its data comes from different countries, and also because the BMI curves were

modelled through BMI values at age 18 (while adolescents will still be growing) rather than age 21 (when growth should have stopped).

Moreover, the present study showed no difference in weight status between boys and girls using international and national definitions. In contrast, Chinn and Rona (2002) found a substantial difference in the prevalence overweight and obesity in boys than girls who were before age of 5 and so, the international definition would underestimate the prevalence of obesity. Therefore, the present study with a large and representative sample supports the view that there is no reason to believe that girls with ALL are at greater risk of overweight and obesity than boys.

Similar to the present study, some other studies have examined differences between definitions of weight status between national and international approaches. El-Ghaziri et al., (2011) compared the impact of using international approaches (Cole et al., (2007), IOTF, WHO, CDC) for defining weight status in 499 Kuwaiti adolescents (aged 10- 14 years) versus national approaches. They found that the international approaches had almost perfect agreement to each other by using weighted kappa statistic test. However, they showed that there were marked differences in defining weight status categories between the national and international approaches.

Reilly et al., (2010b) in a systematic review of eight studies found that BMI for age based on national reference data was superior (higher sensitivity and higher diagnostic accuracy) for defining obesity than the IOTF approach. The present study similarly showed that obesity prevalence in all three trials was lower (4 – 14%) by using the international definition than when using the national definition.

4.5.2 Comparisons of the present study with ALL studies

4.5.2.1 UKALL X trial

The few studies (shown in table 4.5.1) that have examined weight status at diagnosis of ALL in UK children had a relatively small sample sizes except Weir et al., (1998) study. In the present study, almost the same UKALL X trial patients datasets that used in the present study were also, used and studied by Weir et al., (1998) and Reilly et al., (1999b), but they applied different weight status approach. Weir et al., (1998) examined 1,025 children who median age at diagnosis was 4.4 years. They found that prevalence of overweight and obese combined (defined as BMI z score > 0.5) was 24.3% whereas in the present study they were 13.3% and 10.2% by using UK 1990 and IOTF approaches; respectively. Underweight at diagnosis prevalence were 42.9% by Weir et al., (1998) study who defined underweight as BMI z score < -0.5 but in the present study this was reduced by using Cole et al., (2007) definition (19.4%). Therefore, it seems that the overnutrition and undernutrition definitions used by Weir et al., (1998) overestimated prevalence compared to the current national and international definitions.

Reilly et al., (1999b) studied 1,019 ALL patients at diagnosis who were treated by UKALL X protocols. They found that prevalence of undernutrition (defined as BMI z score < - 2.0) was 7.6 % and 6.7% in boys and girls; respectively. However, by applying Cole et al., (2007) definition in the present study, the prevalence of underweight was highly elevated to 20.3% and 16.4% in boys and girls; respectively. Moreover , in Reilly et al., (1999b) study, the prevalence of overnutrition (BMI z score > 2.0) was 2.6% and 3.2% in boys and girls; respectively. A similar prevalence of obesity was observed in the present study amongst boys (1.4%) and girls (1.9%) by using the IOTF definition of obesity (Cole et al., 2000). However, by applying UK 1990 definition (Cole et al., 1995), the prevalence of obesity was slightly higher in boys (4.7%) and girls (6.6%). Reilly (1999b) used overnutrition definitions which appear to have underestimated prevalence. At the time of these studies, Weir et al., (1998) and

Reilly et al., (1999b), no international definitions of overweight, obesity and underweight based on BMI existed.

In addition, Odame et al., (1994) examined weight status in a small sample compared to the present study. They recruited only 40 children in single centre whose mean age (range) at diagnosis was 3.4 years (2.1- 5.2) with ALL in the first remission treated on the UKALL VIII or X protocols. The prevalence of obesity reported (as BMI z score >2.0) was 5%, similar to that obtained in the present study (5.1%; UKALL X data) using the UK 1990 definition (Cole et al., 1995), with no significant difference between the sexes. Although the prevalence of obesity was similar to the present study as they used same reference data but, it might not support our findings because different cut-offs were applied. However, in the present study, the prevalence of obesity was lower (1.5%) when the IOTF definition was applied.

4.5.2.2 UKALL XI

A similar prevalence of obesity (defined by the IOTF (Cole et al., 2000)) to that observed in the present study (UKALL XI) (2.3%) was reported by Reilly et al., (2000b), who stated that obesity (defined as a BMI z score > 2.0 relative to the UK reference) was 2.0% amongst 98 children with ALL treated on the UKALL XI protocol in Scotland. In contrast, the prevalence changed to 7.2% when the UK 1990 (Cole et al., 1995) definition was used in the present study. However, the Reilly et al., (2000) study had a relatively small sample size from one single centre and used different reference data which likely influenced the prevalence estimates obtained. The present study is likely to have provided a clearer and more informative picture as it used a large representative sample and applied modern and widely accepted definitions of weight status (Cole et al., 2000, Cole et al., 2007, Cole et al., 1995).

Table 4.5.1: Prevalence of overweight and obesity amongst UK children with ALL at diagnosis

Author	Methods	Definition	Prevalence of overweight	Prevalence of obesity
The present study	– UKALL X trial – 1 – 14 years	IOTF (n=917)	8.7	1.5
		UK 1990^ (n= 1033)	8.2	5.1
	– UKALL XI trial – 1 – 14 years	IOTF (n=1877)	10.8	2.3
		UK 1990^(n= 2031)	11.2	7.2
	– UKALL 97/ 97-99 – 1 – 18 years	IOTF(n=848)	25.7	8.8
		UK 1990^ (n= 898)	18.8	22.1
Weir et al., (1998)	– Retrospective study – 0.2 – 14.9 years – UKALL X trial – n= 1025	– BMI z score >0.5	– 24.3	---
Odame et al., (1994)	– Retrospective study – 2 – 8 years – Treated by UKALL VIII or X – n= 40 (♂:21, ♀: 19)	– BMI z score > 2.0 *	---	– 5.0% ♂: 5.0% ♀: 5.0%
Reilly et al., (2000b)	– Longitudinal study – Mean (SD) age: 5.2 years (3.4) – Treated by UKALL XI – n= 98 (♂: 53, ♀: 45) –	– BMI z score > 2.0*	---	– 2.0%
Breene et al., (2011)	– Retrospective study – Median age (range): 4.6 years (1.1- 15.9) – Treated by UKALL 97 – n= 77 (♂:37, ♀:40)	– IOTF	– 27.3%	– 2.6%

♂: Male; ♀: Female; IOTF; International Obesity Force Task; * BMI z score relative to UK reference data; ^ UK 1990 defined weight status overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64) (King et al., 2010)

4.5.2.3 UKALL 97/97-99 trial

Breene et al., (2011) examined weight status changes in 77 paediatric ALL patients who were treated on UKALL 97/97-99. The prevalence of overweight and obesity by

applying IOTF definition (Cole et al., 2000) (combined) was around 30%, a result similar to that obtained in the present study (34.5%) when the same definition was applied IOTF definition (Cole et al., 2000). This would support the present study findings even with large number of excluded patients (discussed later in this chapter).

Conclusions

The prevalence of unhealthy weight status depends on the cut-offs and reference data that have been used and the sample size and the time. Therefore, the prevalence was inconsistent in previous studies that used UKALL X dataset compared to the present study. However, the present study used internationally accepted definitions of being underweight (Cole et al., 2007) or overweight and obesity (Cole et al., 2000) in childhood and adolescence. These international definitions of weight status are widely used in research and are particularly suitable for between-study and international comparisons. Also, UK 1990 cut-offs used in the present study are recommended in the UK by clinicians and other health professionals although no clear evidence-based definition of being underweight exists with the UK 1990 BMI reference data (Reilly et al., 2000).

4.5.3 Comparison of the present study with general UK population of children and adolescents studied of obesity prevalence at around the same time

Overweight and obesity amongst children and adolescents described in the present study may reflect rapid secular trends in the general child population in the UK (Reilly, 2006b) (see table 4.5.2). Reilly and Dorosty (1999) studied 2630 English children aged 6 – 15 years in cross sectional English health survey and a representative sample. This survey was carried out between 1978- 1996. The prevalence of overweight (BMI > 85th centile) and obesity (BMI> 95th centile) relative to UK reference data at age six (n= 298) were 21.8% and 10.4% respectively. These

prevalence estimates were higher than the present UKALL X trial (as it is around the Reilly and Dorosty (1999) period) by using both definitions.

In a review of studies on the general population and using the same reference data and definitions (it is possible to use the same reference data but different cut-points) as the present study, Chinn and Rona (2002) examined 6000 white children aged 4 – 11 years from 1984-1994 in England. They used UK- specific reference (BMI z score equivalent to BMI 25 and BMI 30 at ages 18, 19.5 and 23) and IOTF (Cole et al., 2000) definitions. They found in 1984 that the prevalence of overweight and obesity defined by IOTF (Cole et al., 2000) was 8.4%. In 1994, the prevalence of overweight and obesity increased to 13.5%. In UKALL X data for the present study showed quite similar prevalence of overweight and obesity (10.2%) whereas UKALL XI had similar prevalence of overweight and obesity (13.1%). However, Chinn and Rona (2002) did not present the age group in their study. In addition, Kinra et al., (2000) found a roughly similar obesity prevalence (defined as BMI > 98th centile based on UK curves for children) (5%) in UK children the mid-1990s to the UKALL XI data used in this study (~7%) by using same definition.

Table 4.5.2: Prevalence of overweight and obesity in general population of children in the UK (1985- 1999)

Author	Methods	Definition	Prevalence of overweight	Prevalence of obesity
The present study	− UKALL X trial − 1 – 14 years	IOTF (n=917)	8.7	1.5
		UK 1990^ (n= 1033)	8.2	5.1
	− UKALL XI trial − 1 – 14 years	IOTF (n=1877)	10.8	2.3
		UK 1990^(n= 2031)	11.2	7.2
	− UKALL 97/ 97-99 − 1 – 18 years	IOTF(n=848)	25.7	8.8
		UK 1990^ (n= 898)	18.8	22.1
Reilly and Dorosty (1999)	− Cross-sectional; England (1978-1990) − 2630; 6 – 15 yr	UK reference data Overweight: BMI z score > 85th centile Obesity: BMI z score > 95th centile	At age 6 yr: 21.8%	At age 6 yr: 10.4%
Lobstein et al., (2003)	− 1994 -1998 survey (England) − 2882, M: 51.5%; 17 yr	IOTF	Total: 16%	♂: ~ 2% ♀: ~ 8% Total: 4%
Chinn and Rona (2002)	− Cross-sectional; England (1994) − ~6000; 4 – 11 yr	IOTF	♂: 9.0% ♀: 13.5%	♂: 1.7% ♀: 2.6%
		UK- Overweight: z score equivalent to BMI 25;Obesity: z score equivalent to BMI 30	♂: 13.8% ♀: 13.5%	♂: 2.5% ♀: 2.2%

Kinra et al., (2000)	– Cross-sectional; England (Plymouth) (1994-1996) – 20,973; F: 49%; 5 - 14 yr	UK 1990 Obesity: BMI z score >1.64	n/a	♂: 5.2% ♀: 4.8% Total: 5.0%
Rudolf et al., (2001)	– Longitudinal; England (Leeds) (1998-9999) – 1762; M: 44.6%; 7 - 11 yr	UK 1990 Overweight: BMI z score >1.04 (85th centile) Obesity: BMI z score > 1.64 (95th centile)	♂:22.0% ♀:22.0%	♂: 11.0% ♀: 12.0%

M: Male; F: Female; yr: years; IOTF: International Obesity Force Task; n/a: not available; ^ UK 1990 defined weight status overweight (BMI z score 1.04≤ 1.64) and obese (BMI z score >1.64) (King et al., 2010)

Lobstein et al., (2003) studied overweight and obesity among 2882 (51.5% boys) English children and adolescents aged 5 – 17 years. Their study was carried out in the mid to late 1990s (the period of time covered by the UKALL XI and UKALL 97/97-99 data) and showed that the prevalence of overweight and obesity (based on IOTF definition (Cole et al., 2000)) varied from 20%, while the prevalence of overweight and obesity from the present UKALL X and UKALL 97/97-99 data was higher (34.5%) and lower (13.1%) in UKALL XI by using the same definition (IOTF) (Cole et al., 2000). Also, In a longitudinal English study (in Leeds), 1,762 children in primary school aged 7 – 11 years were examined from 1998 – 1999 (Rudolf et al., 2001). By applying UK 1990 definition of weight status, the prevalence of overweight and obesity were 22.0% and 11.5%; respectively. By using same period data and the same definition, the present UKALL 97/97-99 data shows that the prevalence overweight was similar (18.8%), but the prevalence of obesity (22.1%) was extremely different.

In conclusion, the present study shows the prevalence of unhealthy weight status in children at diagnosis of ALL in UK. Some differences in weight status at diagnosis between the ALL patient population in the present study and the general population are to be expected according to possible nutritional effects of ALL before it is diagnosed and length of time before diagnosis and age at typical diagnosis.

4.5.4 Secular trends in weight status in UK children and adolescents

The childhood overweight and obesity epidemic began in the UK in the mid to late 1980s and developed rapidly at least until the mid to late 2000s as mentioned in some studies above (Reilly and Dorosty, 1999, Reilly, 2006b, Stamatakis et al., 2010). In British surveys of 11-16 year olds, boys (n=1,567) in 1977 and girls (n= 2,217) in 1977 and both sexes (boys n= 389; girls n= 387) in 1997 examined overweight (defined as a BMI z score >1.33 relative to UK 1990 reference) and obesity (defined as BMI z score >2.0 relative to the UK 1990 reference) (McCarthy et al., 2003). The percentage increase overtime between 1977 -1997 was 11- 13% in overweight and 7% in obesity.

It was concluded that over the 10 to 20 years from the late 1980's overweight and obesity in young people has risen. However, it is worth noting that obesity in UK children has tended to level off or decline beyond the mid to late 2000s but not in all age groups especially the more deprived (Stamatakis et al., 2010) . However, the likely prevalence for ALL patients at diagnosis today is not studied yet so, it is not clear whether prevalence is similar to the general population or not. On the other hand, the secular trends over time in underweight children in the UK have not been well addressed and the author could find no published studies on trends in prevalence of underweight in the UK.

Dramatic increases in the prevalence of obesity in newly diagnosed children with ALL in the UK seems to be a reflection of what happened in the general UK childhood population. Obesity can only develop secondary to a chronic state of positive energy balance, a higher energy intake consumed over total energy expenditure or a decline in total energy expenditure (e.g. due to a low level of physical activity). Children and adolescents need for their growth and development a very small daily energy imbalance (the energy spent in deposition of new tissue). Obesity as an energy balance disorder seems to have very simple origins: increased energy (food) intake, reduction in energy expenditure or both. In reality, the aetiology of obesity in general paediatric population is more complex than the simple static model as mentioned because many factors can influence energy intake and energy expenditure. Also, the principal causes of the obesity epidemic in the paediatric population remains inadequately understood for several reasons (Reilly et al., 2009). First of all, measurement issue is one of the big challenges because measurements of energy intake and expenditure have limited accuracy and precision, especially energy intake. The energy imbalance that may cause obesity can be very small and complicated to distinguish. Understanding energy imbalance is also complex because a change in energy (food) intake might produce compensatory modification in the other terms of the energy balance equation (Reilly et al., 2007). Subtle societal effects on energy intake and expenditure are more likely the underlying causes that lead to obesity (Reilly et al., 2007). Children globally may consume a higher energy intake

than they need especially because they and their parents may not be aware of these effects (Cohen, 2008). Finally, causes of obesity may differ between child groups within populations. For all these reasons, it is complex to understand the aetiology of obesity in children.

Nevertheless, there are few well-established behaviours that have contributed to the childhood obesity epidemic, but even these behaviours are contested (Monasta et al., 2010). The well-established behaviours are: formula-feeding in infancy; rapid growth in infancy and early childhood; high consumption of sugar-sweetened drinks; high levels of sedentary behaviours such as TV viewing and forms of screen-time or media use (Monasta et al., 2010). Moreover, some evidence recently shows that both less sleep time and low level of physical activity are considered as causes of childhood obesity (Reilly et al., 2009).

For patients during and after of treatment of childhood cancer a good deal of specific evidence on the aetiology and natural history of obesity is available, particularly in ALL as discussed in details in 1.5.6. Consequently, this evidence should inform strategies for prevention of obesity and reduction in cardiovascular risk.

4.6 Nutritional screening for patients weight status from diagnosis

In the UK there is currently no formal requirement to screen patients with ALL for unhealthy weight status at diagnosis or any stage of treatment, and routine measurement of patient weight and height was abandoned a decade ago when the algorithm to estimate body surface area (to calculate drug dosage) was changed. It seems that no policy responses in terms of changes in clinical management around nutritional assessment and dietetic input for example- to the dramatic secular trends in patient weight status described in the present study. Clinical management appears to have proceeded largely unchanged despite marked changes in weight status of patients. In the absence of formal anthropometric screening for unhealthy weight status, few patients who have unhealthy weight status would be identified, even by

experienced paediatricians, paediatric dietitians, and paediatric nurses (Cross et al., 1995, Smith et al., 2008) or parents (Parry et al., 2008) . Identification of both underweight and overweight/obesity at diagnosis of ALL should be relatively straightforward using the BMI in conjunction with widely available centile charts (Reilly et al., 2010b), but there remains a widespread resistance to using such charts routinely in paediatric practice (Flower et al., 2007). Nonetheless, the present study supports the view that the assessment of weight status should receive a higher priority in the management of childhood ALL in future.

4.7 Weaknesses and strengths of the present study

A number of limitations may have affected the interpretation of the results of this study.

Sample size

In the UKALL X dataset, the number of included girls (25.1%) was much lower than boys (74.9%).The sample size of UKALL X trial was affected by low percentage of girls aged 2 – 9 years old as at that time girls tended to be defined as low risk ALL patients (Weir et al., 1998) unless certain additional criteria were met (e.g. high WBC at diagnosis > 50 x 10^9/ L). Only standard risk data patients were provided for UKALL X by the CTSU and so this limitation could not be avoided. Also, the present study assessed only ~46% of the whole UKALL 97/97-99 trial because of a lot of missing data (n= 1037). However, despite these limitations the present study evaluated very large number of (n= 3962) of ALL patients over different trials for the time period 1985 – 2002.

Design and methods limitations

The measurements used in the present used were collected retrospectively and relied on routine collection of clinical measurements rather than an (ideally) research-based approach. Height and weight were therefore

measured around the time of the diagnosis and no data were excluded because they were implausible data which looked like outliers (by using scatter plot graph (n= 28; in all three trials)) were not excluded. Also, these measurements were taken by many different health professionals, centres, scales and stadiometers . Nevertheless, it was possible to estimate the prevalence of malnutrition using national datasets collected by routine clinical measurements are not usually subject to a high degree of bias. A Scottish study studied data from 15 health boards to examine whether the anthropometric data that are collected routinely by the Scottish Child Health Surveillance System are suitable for monitoring weight status (Armstrong and Reilly, 2003). It was found that anthropometric data extracted from routine collection could be useful in monitoring the prevalence of malnutrition-individual measures might be subject to error but for large groups Armstrong and Reilly (2003) concluded that errors for median or mean values and for prevalence the effect of errors was likely to be quite small.

The present study assessed weight status solely according to BMI for age and sex. The BMI is a conservative tool in predicting overweight and obesity (Reilly et al., 2010b) as noted above, and its predictive validity for outcomes and complications of the underweight definition used in the present study have yet to be addressed and this is also true for the overweight definitions used in the present study. Nonetheless, BMI remains the simplest approach and provides a useful clinical and epidemiological definition of childhood obesity (Reilly et al., 2010b) and this study used two approaches to examine the prevalence of unhealthy weight in order to minimise the limitations of each, and also focused on secular trends in the patient population rather than make assessments of individual patients.

Thirdly, the large amount of missing data in the most recent dataset (UKALL 97/97-99) was a cause for concern. In the UKALL X and UKALL XI trials, the algorithm of chemotherapy dosage relied on the surface area, which was calculated by measuring and recording height and weight (Lilleyman and Lennard, 1994, Chessells et al., 1997b). However, when the algorithm only depended on weight rather than the height measurement after UKALL 97/ 97-

99, the recording of height declined substantially from 0.7%- 2.8% of heights missing out of the total sample in UKALL X and UKALL XI data, up to 53.7% out of the UKALL 97/97-99 total sample. It is not clear whether the missing data (see follow diagram in figures 4.4.1, 4.4.2 and 4.4.3) may have biased the estimation of weight status in the present study, particularly when the prevalence of UK childhood overweight/obesity amongst patients treated on the UKALL 97/79-99 protocols was higher (~40%) relative to the UKALL XI trial as same as to that observed in the smaller study (~30%) (Breene et al., 2011).

Generalising the findings of this study to other patient populations should be approached with caution, though the availability of national trial data in the present study should increase the opportunity to generalise them. Furthermore, the childhood obesity epidemic is a global phenomenon and the increases over time observed in the UKALL trial cohort reflect population changes.

This study assessed weight status as measured by BMI for age and sex, which conceptually refers to a chronic deficit or excess of energy. However, this definition of malnutrition based on weight status used in this thesis could be extended to micronutrient deficiency or excess. A deficiency or excess of micronutrients has a clinical impact on outcomes, particularly important in paediatric haematology and oncology (Rogers and Ladas, 2011) (described in section1.4). However, this issue was beyond the scope of present study since no routinely collected data are available for the nutritional status of other nutrients in the UKALL trials.

4.8 Conclusions

Obesity has reached epidemic proportions in the general child population. The prevalence of underweight, overweight and obesity at diagnosis in UK children with ALL has undergone a remarkable shift over the lifespan of the three trials examined in the present study according to both national and international definitions. Whilst the prevalence of overweight and obesity has

substantially increased over time, the prevalence of underweight has decreased significantly, though it still existed in the most recent trial which had data.

This prevalence over time of an unhealthy weight at diagnosis of childhood ALL has to date probably gone largely unrecognised by clinicians and researchers partly because no study in this field has been published, so the present study is the first study focused on this vital issue.

Generally speaking, it is well-known that underweight, overweight and obesity have short and long- term adverse outcomes for the health of the paediatric population (Reilly and Kelly, 2011, Pelletier and Frongillo, 2003, Reilly et al., 2003) (as discussed in sections 1.2 and 1.3) and could therefore have implications for the treatment outcome.

Finally, unhealthy weight status is sufficiently common at diagnosis in childhood ALL to at least support the consideration of screening of weight status at diagnosis. Therefore, early health interventions are important if long and short term morbidity and mortality arising from underweight, overweight and obesity are to be reduced. However, these interventions should ideally be based on intervention strategies, and should use trained and qualified health professionals, particularly nutrition care services.

Chapter 5

Influence of weight status at diagnosis on survival in UK patients treated for ALL

This chapter describes a study which is now accepted as a paper in Journal of Pediatric Hematology and Oncology

5.1 Introduction

There is some evidence from both developing and developed countries that overweight/obesity and underweight/thinness at diagnosis are adverse prognostic factors amongst ALL patients. Both underweight and overweight/obesity might lead to increased risk of relapse or death as discussed in the chapter (section 1.5.5). Briefly, Butturini et al., (2007) examined 343 obese (BMI > 95th centile relative to US reference data) and 3,971 non-obese US ALL patients at diagnosis. They found that obese patients aged 10 years old and over at diagnosis had increased risk of relapse with adjusted hazard ratio for relapse 1.65 (95% CI: 1.13 – 2.41) relative to the non-obese. A recent Brazilian study also, suggested that obesity at diagnosis of ALL was an adverse prognostic factor (Gelelete et al., 2011). They examined 181 patients with ALL aged < 10 years old. They reported that 35.9% of the sample were overweight or obese (BMI above +1SD relative to WHO reference data) (Gelelete et al., 2011). Furthermore, a critical review of nine papers concluded that undernutrition at diagnosis may be an adverse prognostic factor in ALL patients (Lobato-Mendizabal et al., 2003). If it is confirmed that obesity and /or underweight increase the risk of relapse in ALL that could lead to early intervention and treatment of unhealthy weight status during ALL treatment. Particularly when the Chapter 4, (UKALL 97/97-99) showed that the prevalence of obesity (defined conventionally and using a conservative approach based on BMI for age) suggested that at least 20% of the patients at diagnosis of ALL were obese in the most recent UK trial for which data are available . Also, if unhealthy weight status at diagnosis did influence risk of relapse, therapy might even be tailored to take account of this in future (e.g. more intensive therapy for obese patients for example).

On the other hand, there is some doubt about the question of whether weight status at diagnosis influences relapse risk in ALL patients. Some evidence showed that weight status at diagnosis might not influence weight status in ALL patients; as described in chapter 1 (section 1.5.5). Briefly, Weir et al., (1998), Hijiya et al., (2006) and Baillargeon et al., (2006) all concluded that overweight/obesity at diagnosis of ALL does not change relapse risk in both

developing and developed countries. Also, Pedrosa et al., (2000) in developing countries (El Salvador and North Brazil) found that undernutrition (defined as weight for height, weight for age and height for age z score < - 2.0) did not have an influence on relapse risk in ALL patients at diagnosis.

It is worth noting that Weir et al., (1998) previously studied the same UKALL X data used in the present study and the present study was following Weir et al., (1998) study methods . When the Weir et al., (1998) study was going on in the mid-1990's there was no consensus on the appropriate definitions of underweight, overweight and obesity based on BMI, and so Weir et al. (1998) could not have examined the influence of unhealthy weight status on relapse risk using definitions of unhealthy weight status which are acceptable today. In fact, Weir et al., (1998) focused on the effect of undernutrition at diagnosis of ALL on risk of relapse and defined undernutrition as BMI z scores below - 0.5. Also, inconsistent findings between studies in this field mean that additional evidence would be useful. Therefore, there was a need for a new study which has a fairly homogenous sample, included a large sample size, and used recent modern and accepted weight status definitions.

5.2 Aims

This chapter aimed to test the hypothesis that unhealthy weight status at diagnosis is an independent prognostic factor for relapse in standard risk; because standard risk patients are the largest single group of patients with ALL, they provide a fairly homogenous group of patients, and only these data were provided by the CTSU at Oxford as described (in section 2.2.2). Also, no clear underweight definition according to the UK 1990 reference data (Cole et al., 1995) for BMI exists, and so the present study used the Cole et al., (2007) definition. The present study used more modern evidence based and recommended definitions of underweight, overweight, and obesity based on BMI for age (Reilly et al., 2000a). The present study also aimed to estimate the magnitude of any effect of overweight/obesity and underweight on risk of relapse.

5.3 Methods

5.3.1 Participants

The UKALL X trial from the UK was described in detail in the general methods chapter (section 2.2.4.1). Briefly, UKALL X entered 1,635 patients aged 1 - 14 years old. A number of patients were excluded from the trial as they were misdiagnosed (n= 23). Also, the present study excluded any patients diagnosed with CNS disease at diagnosis (n= 12), those who were defined as high risk (n= 213; high risk defined as presenting WBC > 100 x 10^9/L or having Down's Syndrome) and girls who were defined as low risk (n= 347; low risk being defined as girls with presenting WBC < 20 x 10^9/L). Therefore, 1,040 ALL patients (standard risk defined at the time of study as presenting WBC < 100 x 10^9/L and age less than 15 years old) for which data were provided by CTSU at Oxford were potentially eligible for inclusion in the present study (Weir et al., 1998).

5.3.2 Measures of weight and height

As described in section 2.2.6.1, height and weight were measured to 0.1 cm and 0.1 kg; respectively. These measurements were taken around the time of diagnosis by different nurses at UK treatment centres for ALL for clinical purposes (mainly for estimating drug dosage).

5.3.3 Weight status and other possible prognostic factors at diagnosis

The primary aim of the present study was to test whether the weight status at diagnosis is a prognostic factor in childhood ALL. Weight status in the present study was defined according to IOTF (Cole et al., 2000) and Cole et al., (2007) definitions as described in the methods chapter (section 2.1.3.1.4 and 2.1.3.1.5). This chapter did not use the definition of thinness/underweight using BMI with UK 1990 reference data (Cole et al., 1995) since thinness/ underweight is not defined using BMI with UK 1990 reference data (Cole et al., 1995). However, the present study used BMI z scores expressed relative

to UK 1990 reference data (Cole et al., 1995) only to test the influence of BMI z scores at diagnosis as continuous variable on the time of relapse.

However, the present study also assessed other known or suspected prognostic factors though they were not the primary aim. These other factors were age at diagnosis, gender, white blood count (WBC) count at diagnosis, intensification schedule of treatment, and ethnicity. Assessing these prognostic factors could be essential since any association between weight status and relapse rate might have been caused by artifactual association with one or more of these tested prognostic factors. There is no reason to suspect that the present study had a particularly selected sample as it attempted to include all patients with standard risk ALL as defined at the time of the UKALL trial. Some groups (e.g. girls) might appear to have been under-represented, but that was because girls have been considered to be at lower risk of relapse than boys and they received different treatment as a result.

5.3.4 Statistical analysis

Results are expressed as median (Interquartile: Q1, Q3) unless otherwise stated. Patients who relapsed and did not relapse were used to define the clinical outcome. First relapse was the key outcome variable for analysis. Also, a censored survival time (time since diagnosis to the endpoint of interest) was used in days for patients who had not relapsed. The influence of each individual prognostic factor was assessed by applying log ranks testing (Altman, 1991). It is worth mentioning that the log ranks test is used only for categorical variables, and also that it is a univariable analysis which does not allow for the potential testing of several prognostic factors simultaneously. The Mann-Whitney test was used for non-parametric data to test the significance of any differences in the mean between numerical variables. Differences in the prevalence of an unhealthy weight status between boys and girls were tested for significance using a Pearson's Chi Square and Fisher's exact tests were used for two binary variables to determine whether two population proportions are equal.

The present study categorised the possible prognostic factors into subgroups. Intensification of treatment was categorised into four groups to examine significance of the influence of each group on the outcome of treatment: none, early, late and early and late intensification interventions. Moreover, the present study divided the patients' age to different subgroups: 2.0 – 3.9, 4.0- 9.9 and 10.0- 14.9 years old to examine the impact of age group at diagnosis on the risk of the relapse. These age cut offs were chosen to provide fairly equal numbers of patients in subgroups. Ethnicity as a possible prognostic factor was spilt into European and Non- European ethnicity because the number of non-European origin patients was small. Therefore, this chapter used the log ranks test to examine the individual possible influences of gender, intensification of treatment, age at diagnosis, ethnicity, and weight status (Healthy, thin/underweight and overweight/obese as defined according to IOTF (Cole et al., 2000) and Cole et al., (2007) definitions) using SPSS version 18.0 package.

For individual continuous variables (univariable analysis the Cox proportional hazards model was used to test the influence of possible prognostic factors on the outcome of relapse risk (Altman, 1991) using SPSS version 18.0 package. These variables were WBC count at diagnosis, age and BMI z score. The overall survival probabilities were estimated by the Kaplan- Meier method (Kaplan et al., 1968) using Originpro version 8.5.

To examine the possible influence of combined prognostic factors on the outcome of relapse risk using a multivariable analysis i.e. with several potential prognostic factors considered together, stepwise proportional hazards regression modelling was applied (Altman, 1991) using SPSS version 18.0 package . Intensification treatment in this model was split into two binary variables as a factorial structure: coded to yes and no for early intensification and yes and no for late intensification (Weir et al., 1998).

5.4 Results

5.4.1 Excluded patients

From the potentially eligible patients who met study entry criteria (standard risk patients with ALL) some patients had missing data for weight and height (n= 7). Some ALL patients were ineligible to be included in the present study because they were out of the IOTF (Cole et al., 2000) and Cole et al., (2007) definitions age ranges. Hence, any patients aged less than 2 years old was excluded (n= 116). The characteristic of continuous variables in patients, who were excluded from the present study because they had missing data and/ or they were less than 2 years old at diagnosis (n= 123), is described in table 5.4.1. The median (Q1, Q3) of age at diagnosis, BMI z score at diagnosis and WBC count at diagnosis in excluded patients (n= 123) were 1.6 years (1.3, 1.9), -0.39 (-1.05, 0.59) and 7.2 (x 10^9/L) (3.8, 20.1); respectively. Also, the characteristics for categorical variables (gender, categories intensification, categorised WBC count and ethnicity) in excluded patients (n= 123) at diagnosis and relapse rate is shown in table 5.4.2 and figure 5.4.1.

Table 5.4.1: Characteristics of continuous variables in excluded patients, median (Q1, Q3)

	Boys (n=71)	Girls (n= 52)	Overall sample (n= 123)	P value*
Age at diagnosis (yr)	1.6 (1.3 , 1.8)	1.6 (1.1 , 1.9)	1.6 (1.3 , 1.9)	0.69
BMI z score	- 0.31 (- 1.01 , 0.61)	-0.55 (-1.35 , 0.57)	-0.39 (-1.05, 0.59)	0.62
White blood cell count at diagnosis (x 10^9/L)	6.4 (3.4 , 15.9)	9.8 (4.6, 26.7)	7.2 (3.8 , 20.1)	0.11

* using Mann-Whitney test

5.4.2: Characteristics for categorical variables in excluded patients at diagnosis and relapse rate

		Relapse n (%)	No relapse n (%)	Overall n	P value [⊗]
Gender	Boys	32 (45.1)	39 (54.9)	71	0.31
	Girls	12 (23.1)	40 (76.9)	52	< 0.001
	Total	44	79	123	< 0.001
WBC	0 – 10	24 (35.3)	44 (67.7)	68	0.01
(x 10^9/L)	10 - 20	5 (25.0)	15 (75.0)	20	0.004
	20 – 50	9 (45.0)	11 (55.0)	20	0.75
	50 - 100	4 (44.4)	5 (55.6)	9	1.00
	Total *	42	75	117	< 0.001
Intensification	None	13 (44.8)	16 (55.2)	29	0.60
	Early	14 (43.8)	18 (56.2)	32	0.45
	Late	10 (32.3)	21 (67.6)	31	0.01
	Early and late	7 (22.6)	24 (77.4)	31	< 0.001
	Total	44	79	123	< 0.001
Ethnicity	European	35 (32.7)	72 (67.3)	107	< 0.001
	Non-European	7 (58.3)	5 (41.7)	12	0.68
	Total*	42	77	119	< 0.001

* There are some missing data; [⊗] using fisher's exact test

5.4.2 Included patients

In the included sample, 917 patients were included in the analyses (as shown in table 5.4.3 and figure 5.4.1), the median (Q1, Q3) age at diagnosis was 4.9 years (3.3, 8.8). Also, median (Q1, Q3) BMI z score at diagnosis was – 0.27 (-1.03, 0.45). Finally, median (Q1, Q3) of WBC (x 10^9/ L) at diagnosis was 7.0 x 10^9/ L (3.0, 20.4).

Categorical variables (age at diagnosis, gender, WBC count at diagnosis, intensification treatment and ethnicity) for the included patients and relapse rate is illustrated in table 5.4.5. The 22 patients who did not have a recording of WBC at diagnosis were included because the weight status - the primary aim of the present study- was definable.

Figure 5.4.1: Characteristics of continuous variables for excluded and included patients
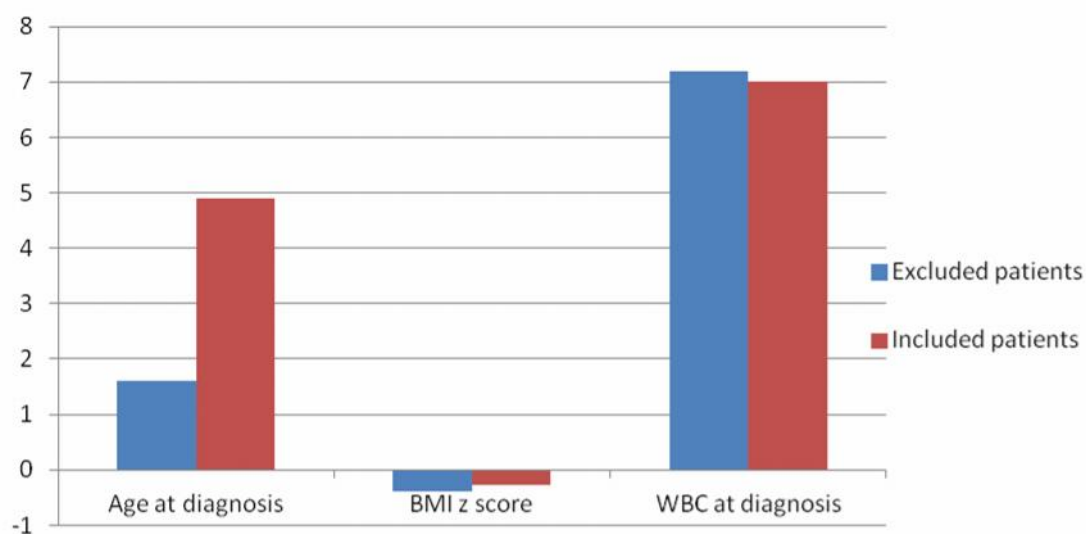
WBC: White blood cell counts

5.4.3: Characteristics of continuous variables in included sample at diagnosis, median (Q1, Q3)

	Boys (n= 710)	Girls (n= 207)	Overall sample (n= 917)	P value *
Age (yr)	4.7 (3.3 , 7.8)	6.2 (3.5 , 11.4)	4.9 (3.3 , 8.8)	< 0.001
BMI z score	- 0.25 (-1.05, 0.43)	- 0.33 (-0.9, 0.50)	- 0.27 (- 1.03 , 0.45)	0.83
White blood cell count (x 10^9 /L)	6.1 (2.9, 15.7)	16.9 (3.5 , 34.5)	7.0 (3.0 , 20.4)	< 0.001

* using Mann-Whitney test

5.4.3 Prevalence of weight status at diagnosis in included patients

Table 5.4.4 gives weight status of those included in the analysis. Percentage of healthy weight was 70.3% whereas 19.4% of the sample was thin according to Cole et al. (2007) and 10.2% of them were either overweight or obese as defined by IOTF (Cole et al., 2000). The prevalence of weight status categories did not differ significantly between genders (Pearson chi-square test; p value=0.53).

5.4.4 Prevalence of weight status at diagnosis in included patients

Weight status	Cole et al., (2007)/ IOTF			
	Boys n (%)	Girls n (%)	Overall sample n	%
Thin/ Underweight	144 (20.3)	34 (16.4)	178	19.4
Healthy	500 (70.4)	45 (70.1)	645	70.3
Overweight/ obesity	66 (9.3)	28 (13.5)	94	10.2

5.4.5: Characteristics of categorical variables of the included patients and relapse rate

		Relapse n (%)	No relapse n (%)	Overall N	P value
Age (yr)	2.0 – 3.9	112 (31.9)	239 (68.1)	351	< 0.001
	4.0 – 9.9	143 (37.8)	235 (62.2)	378	< 0.001
	10.0 –14.9	82 (43.6)	106 (56.4)	188	0.02
	Total	337 (36.8)	580 (63.2)	917	< 0.001
Gender	Boys	277 (39.0)	433 (61.0)	710	< 0.001
	Girls	60 (29.0)	147 (71.0)	207	< 0.001
	Total	337 (36.8)	580 (63.2)	917	< 0.001
WBC	0 – 10	188 (35.3)	344 (64.7)	532	< 0.001
	10 – 20	49 (36.3)	86 (63.7)	135	< 0.001
($x\ 10^9$/L)	20 – 50	66 (39.8)	100 (60.2)	166	< 0.001
	50 – 100	27 (43.5)	35 (56.5)	62	0.21
	Total *	330 (36.9)	565 (63.1)	895	< 0.001
Weight status	Healthy weight	236 (36.6)	409 (63.4)	645	< 0.001
	Underweight	67 (37.6)	111 (62.4)	178	< 0.001
	Overweight/ obese	34 (36.2)	60 (63.8)	94	< 0.001
	Total	337 (36.8)	580 (63.2)	917	< 0.001
Intensification	Non	97 (42.7)	130 (57.3)	227	0.003
	Early	80 (35.2)	147 (64.8)	227	< 0.001
	Late	81 (35.4)	148 (64.6)	229	< 0.001
	Early and late	79 (33.8)	155 (66.2)	234	< 0.001
	Total	337 (36.8)	580 (63.2)	917	< 0.001
Ethnicity	European	310 (37.3)	522 (62.7)	832	< 0.001
	Non-European	26 (32.1)	55 (67.9)	81	< 0.001
	Total*	336 (36.8)	577 (63.2)	913	< 0.001

*Note: there are some missing data as described above; [⊗] using fisher's exact test

5.4.4 Analysis of individual potential prognostic factors

By using the log rank test (for categorical variables), the factors that influenced survival time significantly were as follows: gender (p value= 0.02); age (p value= 0.01). (As shown in figure 5.4.2)

The following potential prognostic factors were not significantly associated with risk of relapse using log ranks tests: Intensification (p value= 0.11); WBC ($x10^9$/L) at diagnosis (p value= 0.19); weight status at diagnosis (p value = 0.90); ethnicity (European versus Non-European) (p value= 0.67) (shown in figure 5.4.2).

Individual proportional hazard ratio analyses (for continuous variables at diagnosis) showed that only one factor was significantly associated with risk of relapse: age (p value = 0.001). Factors which did not have a statistically significant influence on time to relapse were as follows: WBC count at diagnosis (p value = 0.203) and BMI z score at diagnosis (p value = 0.423).

5.4.5 Stepwise proportional hazard modelling

By using stepwise (likelihood ratio) modelling, some explanatory variables had a statistically significant influence on probability of relapse: age (p value < 0.0001), WBC count at diagnosis (p value = 0.005) and gender (p value < 0.0001). In other words, higher relapse risk was found in boys than in girls, in older children at diagnosis, and in patients diagnosed with initial high WBC at diagnosis. Using proportional hazards weight status had no significant impact on risk of relapse (p value = 0.96).

Figure 5.4.2 Kaplan-Meier curves estimate individual potential prognostic factors
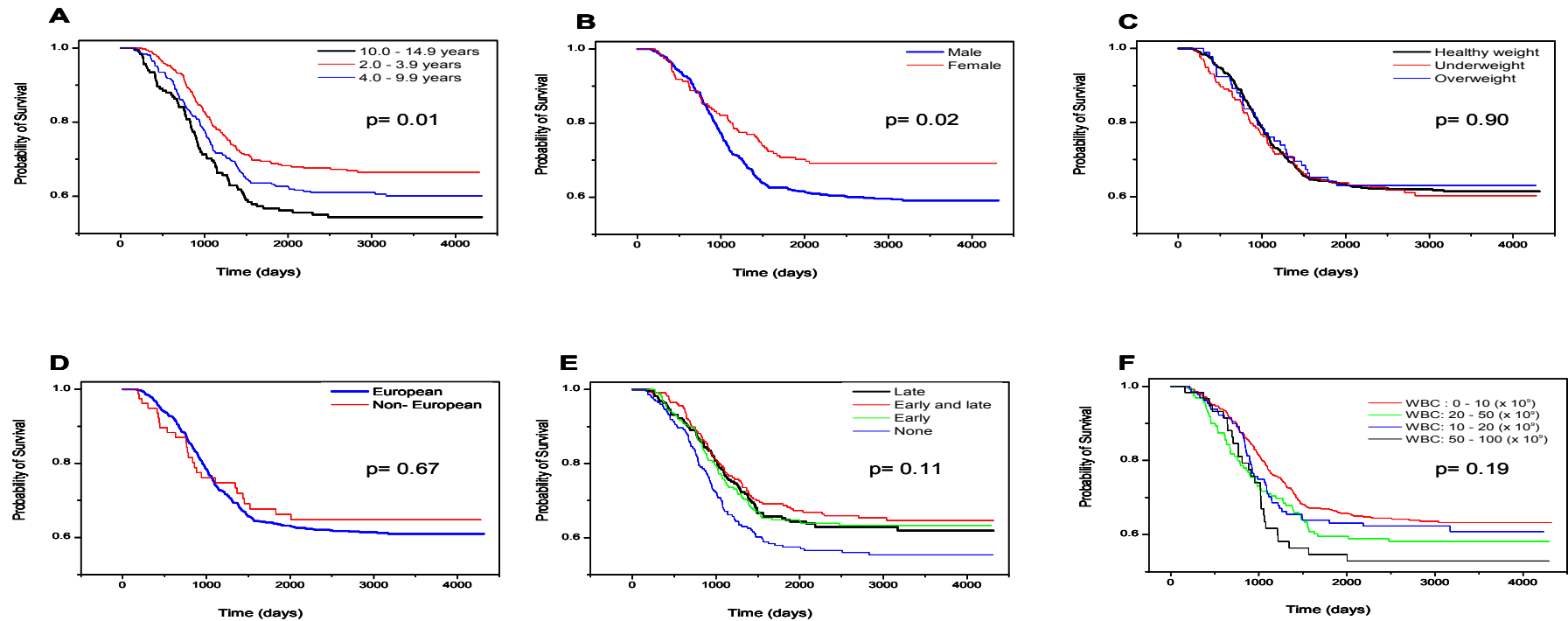
A: The curves were built with patients according only to the age categories at diagnosis; B: The curves were built with patients according only to gender; C: The curves were built with patients according only to weight status at diagnosis using IOTF and Cole al. (2007) definitions; D: The curves were built with patients according only to ethnicity; E: The curves were built with patients according only to intensification; D: The curves were built with patients according only to white blood cells count at diagnosis; p: p value

5.5 Discussion

5.5.1 Main findings and implications

The present study found no evidence that weight status (underweight, overweight and obesity) at diagnosis led to increased risk of relapse in children with standard risk ALL in the UK. The study provides no support for the view that treatment should be stratified in underweight, overweight or obese patients not at high risk of relapse. Despite the present study showing that weight status at diagnosis does not have an impact on outcome of treatment amongst standard risk ALL patients in the UK. On the other hand, the present study is contrary to other studies conclusions when obesity can impair outcome in a number of cancers (Patlak and Nass, 2012), and there is other evidence that underweight, overweight, and obesity at diagnosis can adversely impact outcome of ALL as   discussed below (Gelelete et al., 2011, Butturini et al., 2007, Lobato-Mendizabal et al., 2003, Antillon et al., 2008, Meji´a-Aranguré et al., 1999, Viana et al., 1994, Reilly et al., 1994).

However, the present study confirmed that age at diagnosis, gender and WBC count at presentation are prognostic factors   in the UK. It is well known now that age at diagnosis, gender and WBC count presentation have a strong impact on the outcome. Mitchell et al., (2010) studied 4 clinical trials which have conducted a total of 6516 patients. These trials which conducted in the UK from 1980 – 2001 were UKALL VIII, UKALL X, UKALL XI and UKALL 97/97-99. They reported that female gender, age between 1 and 9 years and WBC count under 50 x10^9/L features were consistently associated with a more favourable prognosis.

Age at diagnosis has strong prognostic significance, reflecting the different underlying biology of ALL in different age subgroups (Moricke et al., 2005). First of all, infants (less than 1 year) with ALL particularly have shown high risk of relapse. Infants less than 6 months, infants with high WBC counts at presentation and infants with poor response to a prednisone therapy prophase are almost adverse prognostic features

(Kosaka et al., 2004 , Hilden et al, 2006). Approximately 80% of infants with ALL have an MLL gene rearrangement. Infants less than 6 months have higher MLL gene translocation than older than 6 months (Pieters et al., 2007). Infants with ALL and precence of MLL gene translocations have so high WBC counts and increased chance to have CNS involvement. Therefore, the survival rate is poor in infants especially who are younger than 6 months old (Pieters et al., 2007). Secondly, young children (aged 1 to 9 years) have a better disease-free survival (DFS) than infants (younger than 1 year), older children and adolescents (aged ≥ 10 years) (Mitchell et al., 2010). The improved prognosis in young children with ALL is to some extent explained by presence of favorable cytogenetic features (Moricke et al., 2005). Thirdly, in patients with ALL who are aged ≥ 10 years (older children, adolescents and young adults), the prognosis is inferior than children aged younger 10 years old even though their outcomes have improved overtime (Nachman et al., 2009).

As noted from the present study WBC count at presentation is a strong prognostic factor since it indicates a more aggressive form of the disease. WBC count under 50 $x10^9$/L at diagnosis is considered as a better cut-off even though the relationship between WBC count and prognosis is not a step function but continues relationship. ALL patients with B-precursor and WBC count at presentation have an increased risk of relapse than patients presenting with low WBC count (Smith et al., 1995). The median WBC count at diagnosis of ALL with B-precursor (<10 $x10^9$/L) is much lower than patient with T-cell ALL (> 50 $x10^9$/L). However, WBC count at diagnosis of ALL with T-cell does not have consistent effect like ALL patients with B-precursor (Goldberg et al., 2003).

The present study showed that girls had significantly better prognosis than boys and other studies showed similar findings (Mitchell et al., 2010 , Pui et al., 1999 , Chessels et al., 1995). The reason for boys having an adverse prognosis is the occurrence of testicular relapses. Also, boys seem to have a higher risk of bone marrow and CNS relapses than girls but, the reason for this is unknown (Pui et al.,

1999 , Chessels et al., 1995). Nevertheless, the recent clinical trials showed that the boys prognosis overall is similar to girls because treatment protocols differ between and girls (Pui et al., 2009, Silverman et al., 2001).

There are a number of biologically plausible mechanisms by which overweight and obesity could increase risk of relapse in ALL and other cancers (Lange et al., 2005, Zuccaro et al., 1991, Patlak and Nass, 2012). Briefly, for instance, consuming a high amount of nutrients daily could lead to energy imbalance. This might cause oxidative stress and fatty acid metabolism malfunction which encourage inflammation and insulin resistance. Consequently, inflammation and insulin resistance could cause a number of processes that might encourage either cancer initiation and promotion including DNA damage, delayed cell death, cell division and cell migration (Patlak and Nass, 2012). On the other hand, adipose tissue can act as an endocrine organ for example by producing some hormones (leptin and adiponectin), growth factors (Insulin growth factor-1) and cytokines (AMP kinase) that can influence cell development (Patlak and Nass, 2012). Behan et al., (2009) suggested that excessive adiposity can encourage cancer cells to be resistant to chemotherapy in leukaemic patients.

Underweight/thinness amongst ALL patients at diagnosis is associated with functional impairment such as immune deficiency that increases risk of relapse (Weir et al., 1998) . Undernutrition can be associated with malabsorption, low drug protein binding and these effects may prevent or reduce oxidative and some other important metabolic process. These effects might reduce glomerular filtration which might increase the toxicity of some chemotherapy (Murry et al., 1998). Moreover, Barr and Gibson (2000) stated that many cancer patients in developing countries also, suffer from protein- energy undernutrition and vitamin and mineral deficiency. Sala et al., (2012) prospectively studied 2,954 children and adolescents with cancer aged 1- 18 years old in 7 countries of Central America. They defined nutritional status using BMI for age expressed relative to CDC reference data, weight for height, mid upper arm

circumference and triceps skin fold thickness. So, severely nutritionally depleted at diagnosis was defined as: albumin < 3.2 g/dl or triceps skin fold thickness < 5th centile or mid upper arm circumference < 5th centile and moderately nutrition depleted as: albumin 3.2- 3.5 g/dl or triceps skinfold thickness 5th – 10th centile or mid upper arm circumference 5th – 10th centile. Prevalence of severe nutritional depletion was 45% and 18% of them had moderately nutrition depletion. They also found a significant difference for (p value < 0.001) EFS between adequately nourished, moderately depleted and severely depleted patients. Also, they reported that 65% of adequately nourished patients were surviving at 2 years from diagnosis compared to 48% of severely depleted patients.

Undernourished patients (defined as weight less than 80% of the weight expected for height) may have poorer tolerance or poor compliance to the planned therapy (Meji´a-Aranguré et al., 1999). Though limited compliance with 6-mercaptopurine (anticancer drug) in developed countries such as USA and UK has been reported (Barr and Gibson, 2000), it is possible that severe undernutrition in developing countries is associated with increased risk of relapse because of poverty and the associated limited access to treatment.

5.5.2 Comparisons with ALL previous studies

As the present study discussed above, the childhood cancer patient who lives in developing countries has sometimes different problems compared to those in the developed world, such as access to treatment and severity of undernutrition (summarised in evidence table 1.5.3 and 1.5.4).

5.5.2.1 Studies from developed countries

In contrast to the present study findings, there is evidence that overweight/obesity at diagnosis might impair prognosis in higher-risk and/or older patients with ALL. In large study, Butturini et al., (2007) studied 4,260 ALL patients in USA and they found that hazard ratio of events and relapses in patients who were older than 10 years and obese at diagnosis were 1.5 (p value= 0.01) and 1.5 (p value= 0.01). Even though they included mixed ALL subgroups (low, standard and high risk groups) and the patients were treated with type of ALL and therapy protocols which are considered as independent prognosis of the disease (not fairly homogenous group like the present study), they did not find an association between weight status and relapse in low risk and/or younger patients, as the present study found.

In contrast, Hijiya et al., (2006) similar to the present study findings examined the association between BMI at diagnosis and pharmacokinetics and outcome of treatment in 621 USA children with ALL aged 2.4 – 16.9 years old. They reported that weight status (defined as underweight BMI ≤ 10th centile, overweight BMI ≥ 85th centile and obesity ≥ 95th centile) according to CDC reference data did not have any effect on both toxicity and outcome of treatment in low, standard and high risk ALL subgroups. It worth noting that they did not find effect of overweight/ obesity (19%) even the prevalence with higher than the present study (10%). One other study from a developed country found evidence that undernutrition at diagnosis is an adverse prognostic factor in ALL. Reilly et al., (1994) with a small number of (n= 78) standard risk ALL patients from UKALL X in the one treatment centre defined the weight status at diagnosis in different method that applied in the present study using weight for height z score < -0.5 for underweight and >0.5 for overweight and obesity. They found that lower weight for height z score significantly (p value= 0.01) influenced relapse risk. On the other hand, Weir et al., (1998) failed similar to the present study to find an association between underweight and relapse risk. Weir et al., (1998) used the same patient data from UKALL X data as the present study explained in the present study

introduction, but they defined weight status using a different approach (BMI z score > 0.5 for overweight and < -0.5 for underweight) because in the mid 1990s there was no consensus of definition of weight status (underweight, overweight and obesity) in childhood. The present study reached the same conclusion as Weir et al., (1998) even though the present study used more modern weight status definitions.

5.5.2.2 Studies from developing countries

Some studies from developing countries as mentioned in table 1.5.3 found evidence that that overweight/obesity at diagnosis might impair prognosis in higher risk patients with ALL rather than low or standard risk ALL patients as it is shown in the present study. The Gelelete et al., (2011) study was conducted on 181 children with ALL (median age 4.8 years) in Brazil and they were treated with different type of ALL and therapy protocols. They reported in this heterogeneous group that obesity in intermediate and/or high risk ALL was a prognostic factor for relapse. However, they recruited a relatively and not representative sample.

 On the other hand, the Baillargeon et al., (2006) study supports the present study findings that there was no evidence that overweight/ obesity at diagnosis of standard risk ALL is associated with adverse prognosis. However, Baillargeon et al., (2006) studied the impact of obesity (BMI > 95th percentile based on CDC reference data) in 322 standard risk ALL children aged 2 – 9 years old at diagnosis. They reported that obesity at diagnosis was not a prognostic factor in their sample.

Undernutrition (including underweight) at diagnosis of ALL was reported to be an adverse prognostic factor in some studies as noted above. Meji´a-Aranguré et al., (1999) in Mexico (17 cases and 76 controls) which was contrary to the present study, however, the study sample size was small. Also, a Brazilian systematic review (Viana et al., 1994), found that relapse risk amongst 128 ALL children and adolescents was 8.2 times higher in undernourished patients (defined as height for

age z score < -2.0) relative to patients who had height for age z score > - 2.0. however, (Viana et al., 1994) study used old weight status definitions and they did not differentiate between ALL subgroups i.e. whether the patient had low, standard and high risk group.

Conversely, Pedrosa et al., (2000) studied two types of cancer (ALL and solid tumour) patients in El Salvador and North Brazil: 283 children were either low risk (defined as WBC count <25.000/ L, no CNS disease, no mediastinal mass and age at diagnosis > 1 years < 10 years old) or high risk ALL patients whereas 160 children had solid tumours. They reported even though they mixed between different ALL subgroups that survival rate was not significantly different for the malnourished patients at diagnosis (defined as weight for age and height for age z score < -2.0 based on WHO reference data) relative to the normally nourished patients.

The reasons for the obvious inconsistencies between the findings of the present study and some other studies (Gelelete et al., 2011, Butturini et al., 2007, Meji´a-Aranguré et al., 1999, Viana et al., 1994, Reilly et al., 1994) to address the question of the role of weight status as a prognostic factor on outcome of treatment in childhood ALL are not totally clear. Nevertheless, amongst patients who were overweight/ obese at diagnosis the most likely explanation may lie in differences in patient characteristics between different studies. The Butturini et al., (2007) and Gelelete et al., (2011) studies found that that relapse rate was significantly increased in higher risk ALL patients group who had overweight/ obesity at diagnosis of ALL. Gelelete et al., (2011) study reported that intermediate and high risk ALL patients (based on BFM-95 protocol (Schrappe et al., 2000)) had significantly (p value= 0.02) lower 5-year EFS amongst only those were overweight/ obese. All five studies to date have found no risk of relapse in lower-risk patient groups or subgroups with ALL (present study plus Baillargeon et al., (2006), Butturini et al., (2007), Gelelete et al., (2011) and Hijiya et al., (2006)), i.e. in younger patients and those without a high WBC at diagnosis.

Moreover, there is a wide difference in sample size between the different studies of the influence of overweight and obesity at diagnosis on relapse risk in ALL in the developed world that might be a cause of different associations of overweight/obesity with outcome between different studies. For instance, Hijiya et al., (2006) recruited 468 standard risk and 153 high risk ALL patients while 797 low and standard risk ALL patients were included by Butturini et al., (2007) while the number of high risk ALL patients was 263. In addition, some studies (Baillargeon et al., 2006, Pedrosa et al., 2000) may have been too small, and in particular, obese and underweight percentages have been relatively low in the sample to detect association between weight status and relapse in ALL patients: for example, Baillargeon et al., (2006) may have been small (n= 322 standard risk ALL patients) to detect on association between overweight/ obesity (prevalence of overweight/ obesity combined was 26%) and relapse risk. Also, Pedrosa et al., (2000) recruited 443 (23% were undernourished) of cancer patients only 252 were with ALL (the risk grade was not reported) and they concluded that undernutrition does not have impact on the survival rate.

Most of the reviewed studies used different types of ALL and therapy protocols which are considered as independent prognostic factors. Also, in some studies in the developing world as motioned in table 1.5.4, undernutrition and relapse may be confounded by factors related to socio-economic status for instance ability to access treatment i.e. cost of drugs and availability of quality care. Generally, patient who are undernourished may be poorer than those adequately nourished and consequently they may not have the same access to the good quality care and treatment as noted above.

Although the present study did not find an association between weight status at diagnosis and influence risk of relapse, it is worth noting that systematic reviews have found important short and long-term adverse consequences of childhood underweight and obesity (Zuccaro et al., 1991, Reilly and Kelly, 2011, Black et al., 2008) as

explained in detail in section 1.2 and 1.3, and the lack of associations with relapse in typical patients with ALL does not mean that underweight, overweight, obesity are not cause for concern. In addition, obesity increases markedly during and after ALL therapy, and results largely from marked lifestyle changes such as high sedentary behaviour and low physical activity which are presumably preventable to some degree (Reilly, 2009).

5.5.3 Strengths and weaknesses of the present study

Sample size

As this thesis discussed in chapter 4.6.1, the number of included girls (n= 207; 22.6%) was much lower than number of boys (n=710; 77.4%), however, this limitation was unavoidable according to study design. The definition of standard risk, low risk, and high risk, as it was applied back at the time of UKALL X meant that many more girls than boys were defined as low risk and so did not meet our entry criterion of standard risk ALL at diagnosis. Therefore, in the present study presumably it would have been useful to do the same survival analysis for low and high risk patients as but we did not have the data to do so.

The present study had a relatively large sample size for studies of this kind, and the inclusion of a relatively homogenous group of patients (only standard risk ALL patients) from a national trial, all treated according to the same protocol in the UK. To be more precise, Butturini et al., (2007) was one of the largest sample size studies amongst children with ALL. However, they enrolled a heterogeneous group of patients when they included different risk groups of ALL and patients treated on different treatment protocols (CCG 1881, CCG 1922 and CCG 1891).

The present study design

Limitations of collection method of the present study data and the limitations of using BMI for age and sex were argued in details in section 2.2.4.1. Briefly, the present study data were collected in routine clinical practice for the purposes of calculating body surface area in order to prescribe drug dosage not in a research-based approach, so, height and weight were collected by many health professionals and measures were made using a variety of stadiometers and scales which could lead to some errors. However, anthropometric data collection errors in epidemiological studies with large samples are more likely to have quite small biases (i.e. small mean or median value errors), though errors can be quite large for individual children (Armstrong and Reilly, 2003). Moreover, a high BMI for age provides a good indicator of children with excessive fat mass (Reilly et al., 2010b), but it is imperfect both in healthy children and those with malignancy (Warner et al., 1997b, Aldhafiri et al., 2012). However, BMI for age and sex is considered both reasonably valid as an indicator of high fat mass and the simplest epidemiological tool nowadays (Reilly et al., 2010b). Also, BMI for age and sex has high specificity, but moderate sensitivity in detecting obesity in children and adolescents (Reilly et al., 2010b) . However, whether or not the Cole et al. (2007) definition of thinness successfully predicts health outcome and complications was not addressed yet by any studies that the author is aware of.

In addition, the present study in common with previous studies to test for an impact of underweight and overweight/obesity and outcome of ALL, we excluded patients where obvious confounders were present (e.g. Downs Syndrome, which affects both risk of obesity and risk of relapse from ALL), and the present study considered the main established prognostic factors in our analyses. However, data on other potential confounders, such as socio-economic status, (Lightfoot et al., 2012) were not available, as in other studies (Baillargeon et al., 2006, Butturini et al., 2007, Gelelete et al., 2011, Hijiya et al., 2006): for example, it is possible that consideration of socio-

economic status might attenuate any associations between obesity and outcome of childhood ALL for those studies which find associations (Lightfoot et al., 2012).

The dataset used in the present study was from a treatment trial which ended more than 20 years ago, though for more than 10 years weight and height have not been measured and recorded routinely in patients with ALL in the UK and so such studies have not been possible for some time as discussed in 4.6.2. It is true that ALL treatment protocols have changed since that time (Jeha and Pui, 2009), though not radically (Jeha and Pui, 2009), and prevalence of overweight and obesity have increased markedly (Reilly, 2006b). However, some studies (Whitaker et al., 2011) showed that the prevalence of underweight in the UK children and adolescents was lower than the present study findings by using UKALL 97/ 97-99 trial data. examined underweight/thinness (defined by Cole et al., (2007)) in 7078 English children and adolescents (aged 2 – 15 years old) from 2001 – 2006. They reported that the prevalence of underweight/thinness in the total sample was 5.7%, much lower than the present study findings (19.4%) using same definitions.

Nonetheless, the strengths of the present study, noted above, combined with the consistency with the other studies-also noted above- enhances confidence in our conclusions.

5.6 Conclusion

The present study concludes that it is unlikely that weight status based on BMI for sex and age at diagnosis has an adverse impact on outcome of childhood ALL for patients not deemed to be at high risk of relapse. However, the present study confirmed that age at diagnosis, gender, WBC at presentation can be regarded as prognostic factors for standard risk ALL childhood patients in the UK, and these findings are consistent with current treatment of ALL in the UK where all of these factors are considered to influence risk of relapse.

Chapter 6

Importance of adjusting dual energy X-ray output for body size when assessing bone health: an example from survivors of childhood acute lymphoblastic Leukaemia

This chapter describes a study which is now published, publication details as follows:

6.1 Introduction

An adverse effect of childhood malignancy or its treatment on bone is a widespread concern (Elmantaser et al., 2011, Elmantaser et al., 2010, van der Sluis and van den Heuvel-Eibrink, 2008, Warner et al., 1998b, White et al., 2005), and there is increasing evidence that skeletal morbidity is common in patients with ALL during and after therapy as noted in section 1.5.7.5. DXA is used widely as a clinical indicator of bone health.

The present study was originally not in the thesis plan until the author found results from DXA measures of bone health of the ALL survivors described in chapter 2. These data combined with literature searching by the author and a discussion with experts in bone health at Yorkhill hospital (Professor Faisal Ahmed and Dr. Sheila Khana) led to the present study. The literature found by the author suggested that many authors did not use the adjustment to DXA output for body size described in chapter 2 (section 2.1.8.2.1). In some specialties it has been well known for some time that there is a need to correct DXA derived BMD data for body size, particularly in children and adolescents with chronic disease, including malignancy (Warner et al., 1998b, Ahmed et al., 2004). Such corrections are not universal in the literature in other specialties though, and a number of recent reports on bone health in patients with childhood cancer have been based on BMD data with no formal correction for body size, but just an adjustment for age and sex (Al-Tonbary et al., 2011, Muszynska-Roslan et al., 2009). For instance, Muszynska-Roslan et al., (2012) assessed BMD recently for 69 children and adolescent survivors of ALL by using DXA. However, even though they acknowledged the guidelines of the ISCD 2007 (Baim et al., 2008) to calculate z scores for sex and age, they used the unadjusted BMD approach (using DXA manufacturer reference data, apparently adjusted for age and sex only) to assess BMD. They concluded that ALL survivors were not at risk of low BMD. In addition, a recent study of BMD in patients with Neuroblastoma used BMD data, without formal correction for body size, to conclude that impaired bone

health was very common (Al-Tonbary et al., 2011). Also, Rayar et al., (2012) more recently examined 124 patients with ALL aged less than 18 years old using DXA. However, they reported that prevalence of osteoporosis (defined as BMD z score -2.0 and below) was 11% among those patients, but without using adjustment for body size which it is recommended by the ISCD 2007 (Baim et al., 2008) as mentioned in chapter 2 (section 2.1.8.2). In summary, in some paediatric specialties it has become fairly common in both clinical practice and research to present DXA bone health data after an adjustment for body size. In other specialities, including Paediatric Haematology and Oncology, this is not the norm and the need to make adjustments of this sort is not well known. In addition, it is not clear which adjustment is best to make, or how big a difference the choice of body size adjustment will make. The present study was prompted by a series of recent publications in the Paediatric Haematology and Oncology literature which did not report any adjustments to DXA data for body size.

6.2 Aims

Adjusting DXA output for body size is regarded by specialists in bone health essential to avoid misinterpretation in children and adolescents bone health status (Baim et al., 2008). It is considered especially important in more vulnerable groups likely to have suffered from growth or body composition abnormalities such as survivors of ALL. Therefore, the aim of the present study was to examine the effect of using different approaches to identify low bone mass and to examine the agreement between them: manufacturers software (DXA Lunar Prodigy, software version 9.15), Warner et al., (1998b) and $BMAD_{LS}$ (Kroger et al., 1995) approaches.

6.3 Methods

Briefly, 51 standard risk ALL Saudi survivors treated according to CCG 1891 (those described in chapter 2, section 2.1.1) were scanned by using DXA (Lunar Prodigy,

software version 9.15). No study was found which examined how relevant the DXA device was to the Saudi population as described above in section 2.1.5.2. There is currently no consensus as to how best to make the adjustment of DXA derived BMD data for body size. For the present study we used the approach described by Warner et al., (1998b), based on calculation of BMC z scores, $BMAD_{LS}$ (Kroger et al., 1995) and manufacturer's reference data approach as described in details in the section 2.1.6.

The ISCD 2007 (Baim et al., 2008) recommended that the terms of osteopenia and osteoporosis should not be used in children and adolescent except in some certain conditions as mentioned in section 2.1.8.2. The present study therefore considered low bone mass in survivors below z score -1.0 (Rayar et al., 2012). Finally, unhealthy weight status defined according to Cole et al., (2007) and IOTF (Cole et al., 2000) as described in chapter 2 (section 2.1.3.1.4 and 2.1.3.1.5).

6.3.1 Statistical analysis, power and sample size

Power of the present study was fixed by the size of the cohort of patients available to us and so no formal power calculation was carried out, but paired comparisons of preliminary corrected and uncorrected DXA data showed that the study was powered adequately to compare between corrected and uncorrected data.

Means and standard deviations (SD) are presented in the results unless otherwise stated. Normality of data was tested by using formal Normality tests in Minitab (Version 15.1.30.1). A two-sample t-test (when data followed a normal distribution) was used to test the significance of the difference in the means between the numerical variables in two different groups and to for three and more different groups a one-way ANOVA was used. Also, the Mann-Whitney test was used for non-parametric data to test the significance of the difference in the median between numerical variables. A k analysis was carried out using MedCalc software version

11.5. We used the weighted Kappa statistic (k) and 95% CI for this statistic to assess the degree of agreement between BMD and BMC z score categories, with the descriptors which summarise agreement proposed by (Landis and Koch, 1977) (as described in figure 3.3.1).

6.4 Results

6.4.1 Characteristics of study participants

The number of consented survivors was 51 (33 males, 18 females) as it is clarified in table 6.4.1.

Table 6.4.1: Characteristics of study participants mean (SD)

	Males (n= 33)	Females (n= 18)	Total sample (n= 51)	P value
Age (yr)	13.2 (4.6)	14.0 (3.1)	13.5 (4.1)	0.40
Height (m)	1.49 (0.19)	1.51 (0.11)	1.50 (0.17)	0.90
Weight (kg)	45.7 (16.8)	48.9 (17.6)	46.8 (16.9)	0.50
Time from diagnosis (yr)	9.2 (4.7)	9.0 (3.6)	9.1 (4.3)	0.90
Time since completion of therapy (yr)	6.6 (4.4)	5.6 (3.5)	6.3 (4.1)	0.40
% Total body fat by DXA*	24.7 (10.6)	37.6 (8.8)	29.2 (11.7)	>0.001
CDC[†] BMI z score	- 0.16 (1.6)	0.12 (1.3)	- 0.06 (1.5)	0.50

[†] CDC US Centres for Disease Control and Prevention; *Dual X-ray Absorptiometry

The mean (SD) of age for total sample was 13.5 years (4.1) without any significant difference between the gender (p value= 0.4; (2 sample t test)). Mean (SD) of BMI z score (based on CDC approach (Kuczmarski et al., 2000)) of the sample was - 0.06 (1.5) no significant difference between the gender (p value = 0.5 (2 sample t-test)). However, there was a significant difference between male and females (p value > 0.001) in % total body fat by DXA and the mean (SD) for the sample was 29.2% (11.7). Mean (SD) time from diagnosis was 9.1 year (4.3) and it was 6.3 year (4.1) for time since completion of the therapy course; for more details see table 6.4.1.

6.4.2 Comparison of DXA data: corrected BMC versus BMAD$_{LS}$ versus uncorrected BMD data

6.4.2.1 Bone health assessment by applying DXA manufactures' software approach versus corrections for body size

The Mean (SD) of the sample for total body and lumbar spine aBMD z score that produced by DXA manufacture's software was – 0.8 (1.1) and – 1.2 (0.9); respectively (table 6.4.2). No significant difference was found between the genders in both total body (p value= 0.2) and lumbar spine aBMD z score (p value= 0.9) (table 6.4.3).

Table 6.4.2: Bone health z scores derived from DXA (mean and SD or median and Q1, Q3 as appropriate) using three different approaches

Approaches	Lumbar spine	Total body
Manufacturer's software	- 1.2 (0.9)	- 0.8 (1.1)
Adjusted BMC for BA* (Warner et al., 1998b)	- 0.4 (0.6)	- 0.3 (-0.5, 0.2)
BMAD$_{LS}$ $^{\Theta}$ (Kroger et al., 1995)	- 0.9 (0.9)	----
P value	<0.001^	0.003$^{\otimes}$

* Bone mineral content for bone area; $^{\Theta}$ Bone mineral apparent density of lumber spine
  BMAD$_{LS}$ is only based on lumbar spine rather than total body; using one-way ANOVA test; $\otimes$ using two-sample t-test

Table 6.4.3: Bone health z scores derived from DXA (mean and SD or median (Q1, Q3) as appropriate) using three different approaches based on gender

	Approach	Males (n 33)	Females (n 18)	Total sample (n 51)	P value
Manufacturer's software	**TB aBMD z score**	- 0.7 (11)	- 1.0 (1.2)	- 0.8 (1.1)	0.20
	LS aBMD z score	- 1.2 (0.9)	- 1.2 (1.0)	- 1.2 (0.9)	0.90
Warner et al., (1998b)	**TB BMC for BA z score (median)**	- 0.1 (- 0.4, 0.3)	- 0.5 (- 0.7, 0.1)	- 0.3 (- 0.5, 0.2)	0.06[a]
	LS BMC for BA$^\Delta$ z score	- 0.4 (0.6)	- 0.4 (0.6)	-0.4 (0.6)	0.80
BMAD$_{LS}$ (Kroger et al., 1995)	**BMAD$_{LS}$ z score**	- 0.8 (0.8)	- 1.1 (0.9)	- 0.9 (0.9)	0.20

[a] Using Mann-Whitney test; TB aBMD: Total body areal bone mineral density; LS aBMD: Lumbar spine areal bone mineral density; ө TB BMC for BA : Total body bone mineral density for bone area; LS BMC for BA: Lumbar spine bone mineral density for bone area; BMAD$_{LS}$: Bone mineral apparent density of lumber spine

The number of survivors who had lumbar spine aBMD and total body aBMD z score between -1.0 to -2.0 was 18 (35.3 %) and 13 (25.5%); respectively. In addition, 21.6 % (11 survivors) and 15.7 (8 survivors) had lumbar spine and total body aBMD z score below – 2.0; respectively. Therefore, If a z score below –1.0 was considered to be of potential concern (Rayar et al., 2012), this would apply to 29 (56.9%) of the survivors at the lumbar spine, and 21 (41.2%) for the total body using BMD derived directly from DXA output, with no correction for body size (table 6.4.4).

Table 6.4.4: Summary data for bone health cases and prevalence of potential concern (defined as z score > -1.0 to -2.0 or < -2.0) of low bone mass by using three different approaches

Z score	aBMD n= 51		BMC for BA n= 51		BMAD$_{LS}$ n= 51
	LS	TB	LS	TB	LS
-1.0 > to -2.0 n, (%)	18 (35.3)	13 (25.5)	6 (11.8)*	3 (5.9)*	18 (35.3)
<-2.0 n, (%)	11 (21.6)	8 (15.7)	0 (0.0)*	1 (2.0)*	6 (11.8)
Total (%)	56.9%	41.2%	11.8%	7.9%	47.1%

aBMD: Body areal bone mineral density; BMC for BA: Body mass content for bone area; BMAD$_{LS}$: Bone mineral apparent density for lumber spine; LS: Lumbar spine; TB: Total body; * p value > 0.05 using 2 proportions test compared the used methods with manufacture's software reference data

6.4.2.2 Bone health assessment by applying adjusted BMC for BA (Warner et al. 1998 approach)

As shown in table 6.4.2, the median (Q1, Q3) of the sample of total body BMC for BA was - 0.3 (-0.5, 0.2) and the mean (SD) of lumbar spine BMC for BA for the sample was – 0.4 (0.6). Table 6.4.3 illustrated that, the difference between total body BMC for BA and lumbar spine BMC for BA in both boys and girls was not significant (p value= 0.06 and 0.8; respectively).

Only 6 (11.8%) survivors had lumbar spine BMC z scores between –1.0 and –2.0, and none had a z score below –2.0. For the total body BMC, only 3 survivors (5.9%) had BMC z scores between –1.0 and –2.0, with 1 (2%) below –2.0. If a z score – 1.0 and below was considered to be potential concern (Rayar et al., 2012), this would apply to 6 (11.8%) of the survivors at lumbar spine, and 4 (7.9%) for the total body BMC (table 6.4.4).

Mean (SD) % predicted BA for age for lumbar spine and total body was 90% (11) and 87% (12); respectively. Mean (SD) % predicted BMC for BA was 93% (11) for lumbar spine and 97% (11) for the total body.

6.4.2.3 Bone health assessment by applying BMAD$_{LS}$ (Kroger et al., 1995) approach

The mean (SD) of the sample was -0.9 (0.9) with no significant difference between genders (p value= 0.2 (2 sample t-test)) as stated in table 6.4.2 and 6.4.3. Table 6.4.4 shown that number of survivors who had z scores between – 1.0 and – 2.0 was 18 (35.3%), while 6 (11.8%) of them had lumbar spine z scores below – 2.0. If a z scores – 1.0 and below was considered to be potential concern (Rayar et al., 2012), this would apply to 24 (47.1%) of the survivors at the lumbar spine.

6.4.3 Comparison of bone health status and weight status

The Cole et al., (2007) and IOTF (Cole et al., 2000) definitions of underweight, overweight and obesity were used in the three used approaches (described in table 6.4.5 and figure 6.4.1). Using uncorrected BMD z scores (DXA manufactures' software) for total body and lumbar spine found an excess of low BMD (defined as z score > - 1.0) values in the underweight survivors: prevalence of low bone status amongst the 9 underweight patients was 78% (7/9) and 89% (8/9); respectively. In overweight/obese survivors: prevalence of low bone mass was 13% (2/16) and 31% (5/16).

Once adjusted using the BMC for BA approach (using method of Warner et al., (1998b)), only 1/9 (11%) of the underweight survivors and 0/9 had low total body and lumbar spine BMC; respectively. Similarly, amongst those who were overweight/ obese: 13% (2/16) had low total body BMC. Overweight/obese survivors who had low lumbar spine BMC were 19% (3/16) of the overweight/ obese sample.
Using the BMAD$_{LS}$ approach (Kroger et al., 1995), almost half of the underweight survivors (56%, n= 5/9) had low bone density. One third (31%; n= 5/16) of the overweight/ obese survivors had low bone density.

Table 6.4.5: Prevalence of low bone status (defined by z score below -1.0) based on weight status defined by Cole et al., (2007) and IOTF definitions

	Approach	Healthy weight* (26/51 patients) (n, %)	Underweight * (9/51 patients) (n, %)	Overweight/ Obese* (16/51 patients) (n, %)
Manufacturer's software	**TB aBMD**	12 (46.2)	7 (77.8)	2 (12.5)
	LS aBMD	16 (61.5)	8 (88.9)	5 (31.3)
Warner et al., (1998b)	**TB BMC for BA**	1 (3.8)$^{\otimes}$	1 (11.1)$^{\otimes}$	2 (12.5)
	LS BMC for BA	3 (11.5)$^{\otimes}$	0 (0.0)$^{\otimes}$	3 (18.8)
$BMAD_{LS}$ (Kroger et al., 1995)	**$BMAD_{LS}$**	14 (53.8)	5 (55.6)	5 (31.3)

TB aBMD: Total body areal bone mineral density; LS aBMD: Lumbar spine areal bone mineral density; TB BMC for BA: Total body bone mineral content for bone area; LS BMC for BA: Lumbar spine bone mineral content for bone area; $BMAD_{LS}$: Bone mineral apparent density for Lumbar Spine;
* Underweight, overweight and obesity were defined based on Cole et al., (2007) and IOTF (Cole et al., 2000); $^{\otimes}$ p value > 0.05 using 2 proportions test compared the used methods with manufacture's software reference data

Figure 6.4.1: Prevalence of low bone status defined by z score less than – 1.0 based on weight status by IOTF
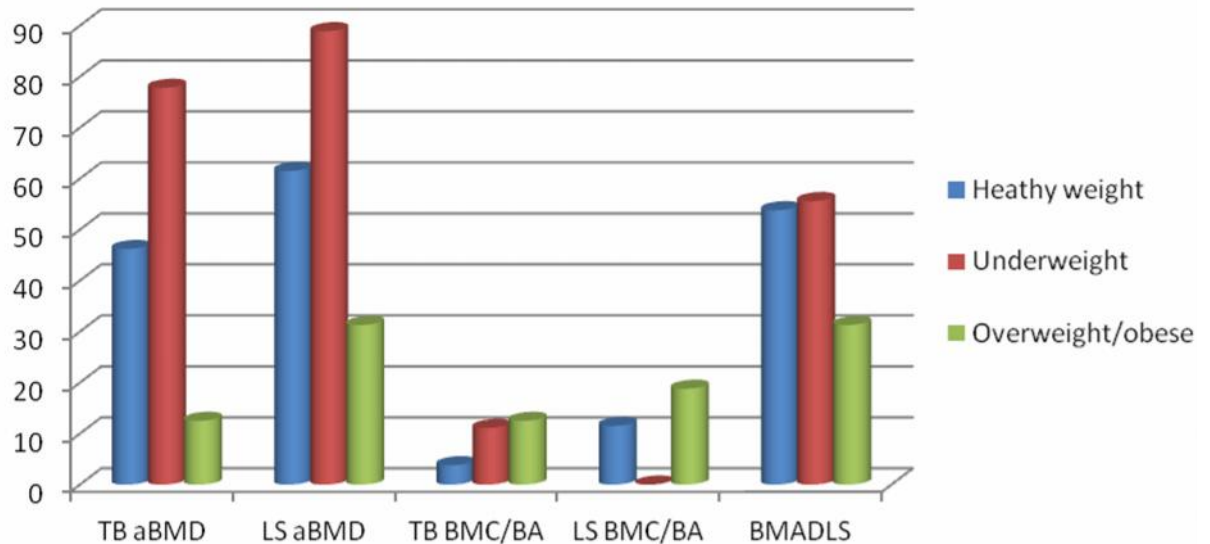
IOTF: International Obesity Task Force; TB aBMD: total areal bone mineral density; LS aBMD: lumbar spine areal bone mineral density; TB BMC: total body bone mineral content; LS BMC: lumbar spine bone mineral content; BMAD$_{LS}$: Bone mineral apparent density for lumbar spine

6.4.4 Extent of agreement between three approaches for assessing bone health using DXA

Agreement between BMD (uncorrected) and BMC (corrected) categories of possible low bone mass (Z scores below –1) was 'poor' as defined by (Landis and Koch, 1977) at the lumbar spine (k =0.18; 95% CI: 0.04 – 0.33) and for the total body (k= 0.13; 95% CI: 0.06 – 0.31). Also, the agreement between BMC (corrected) and BMAD$_{LS}$ (Kroger et al., 1995) was 'fair' (k= 0.26; 95% CI: 0.08 – 0.45). A 'Substantial' level of agreement was found between uncorrected lumbar spine BMD and BMAD$_{LS}$ (Kroger et al., 1995) approaches (k= 0.65; 95% CI: 0.45 – 0.85). (See table 6.4.6)

Table 6.4.6: Extent of agreement (weighted Kappa statistic) between three different approaches to assess bone health using DXA

	Approach	Weighted Kappa	95% CI	Level of agreement (Landis and Koch, 1977)
Manufacture's software vs. Warner et al., (1998b)	**TB aBMD vs. TB BMC**	0.13	-0.06 – 0.31	Poor
	LS aBMD vs. LS BMC	0.18	0.04 – 0.33	Poor
Manufacture's software vs. BMAD$_{LS}$	**LS aBMD vs. BMAD$_{LS}$**	0.65	0.45 – 0.85	Substantial
Warner et al., (1998b) vs. BMAD$_{LS}$	**LS BMC vs. BMAD$_{LS}$**	0.26	0.08 – 0.45	Fair

TB aBMD: total body areal bone mineral density; TB BMC: total body bone mineral content; LS aBMD: lumbar spine areal bone mineral density; LS BMC: lumbar spine bone mineral content; BMAD$_{LS}$: lumbar spine bone mineral apparent density

6.5 Discussion

6.5.1 Main findings and implications

In the present study, a very high prevalence of low BMD z scores in both lumbar spine and total body was observed when the standard approach recommended by the DXA manufacturer's software was used. Likewise, almost half of the sample had a concerning bone mass (defined as z score > -1.0) when the BMAD$_{LS}$ approach (Kroger et al., 1995) was applied. Therefore, the extent of agreement level between these approaches was "substantial" according to (Landis and Koch, 1977) definitions. The conclusion that poor bone health was common among the patients might have

been reached on the basis of these findings, particularly in view of the background supplied by recent evidence that skeletal morbidity is common among patients with ALL, and that there are more general concerns over poor bone health in patients with ALL (Elmantaser et al., 2010, Elmantaser et al., 2011, van der Sluis and van den Heuvel-Eibrink, 2008, White et al., 2005).

In contrast, this conclusion would not be appreciable when BMD is corrected for body size particularly using the approach described by Warner et al., (1998b); due to the relatively low prevalence of low BMC z scores of lumbar spine and total body being found. The corrected data suggested an alternative conclusion in relation to the bone health of these survivors i.e. that poor bone health was uncommon as shown in figure 6.5.1.

However, even though the present study provides evidence that using an adjusted approach for body size does make a difference to the apparent bone health data from DXA, it was not able to distinguish which is the best one as both of the approaches led to different conclusions and the present study had no access to a gold standard measure of none health. Other measures might have been available (e.g. blood based markers of bone health) and would have been useful had the present study been funded to include them. In addition, the relatively small sample made it difficult to justify a more detailed analysis of the characteristics of the children and adolescent survivors who were classified differently by the three different approaches. Further studies which use larger sample sizes and have bone health as a primary aim would be needed to provide a greater understanding of the reasons for differences in bone health classifications between the different approaches.

One universal adjusted approach for body size would be more useful rather than general recommendation of adjustment for bone size. Moreover, the present study highlights to non specialists in bone health the need to pay more attention in

interpreting the outcome data from DXA manufacturer's software. Also, researchers and health professionals should be more cautious in dealing with studies that report low bone density in children or adolescents without making any adjustments for body size.

Figure 6.5.1: Prevalence of low bone status (defined as z score -1.0)
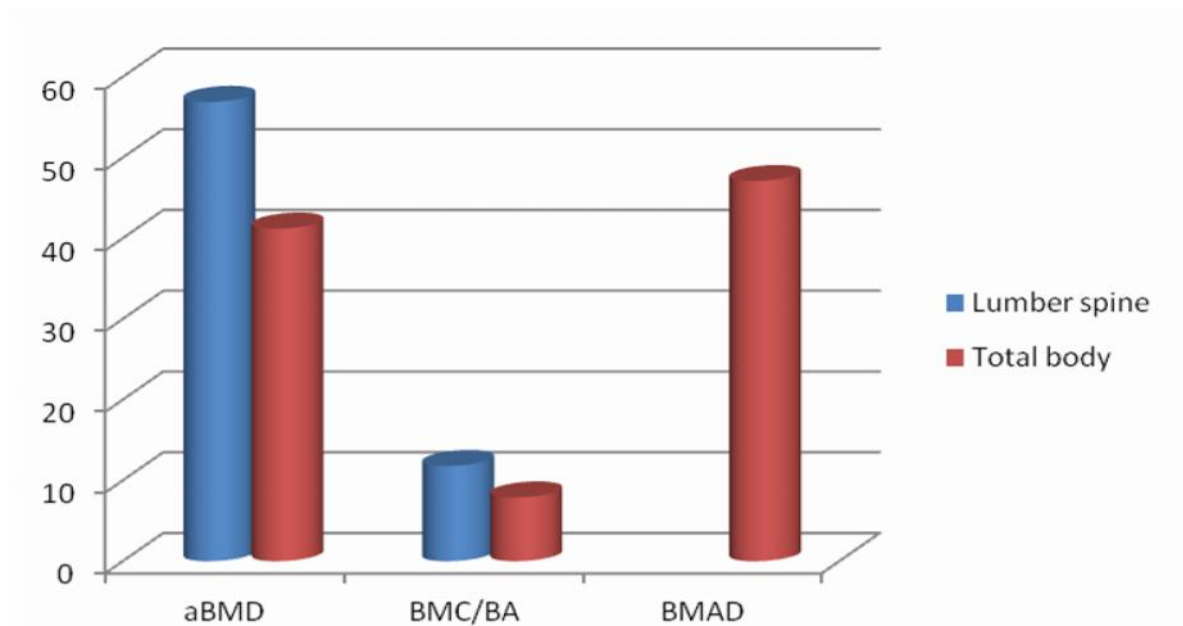
LS: lumbar spine; aBMD: areal bone mineral density (DXA manufacture's software method); BMC for BA: bone mineral content for bone area for bone area (Warner et al., 1998 method); $BMAD_{LS}$: Bone mineral apparent density for lumbar spine method

Nevertheless, using all the three different approaches to define low bone mass clarified the persistence of some apparent bone mass deficits, even after adjustment for body size. This provides confidence that an apparently increased risk of impaired bone health was real, rather than completely an artifact of the poor growth, delayed puberty, or abnormal body composition, which characterizes many populations of children and adolescents with chronic diseases (Ahmed et al., 2004, Buison et al., 2005).

The issue of whether or not to correct DXA BMD data in relation to body size might have implications beyond the simple assessment of the prevalence of low bone mass. Failure to adjust DXA BMD values for body size might also bias studies determining correlations and the aetiology of low bone mass. As illustrated in Chapter 3 , the high prevalence of high underweight subjects, where underweight is defined based on the Cole et al., (2007) definition was observed. The present study intended to test an *a priori* hypothesis that bone health would be poorer in underweight survivors compared to other survivors. However, after correction, low total BMC for body size was apparent in only 1 out of 9 (11%) of the underweight survivors and none had a low lumbar spine BMC respectively. when $BMAD_{LS}$ approach (Kroger et al., 1995) for correction was used, the prevalence of low bone mass amongst underweight survivors was sharply increased (56%). Consequently, this example illustrates that the consequences of misinterpreting BMD data obtained from DXA go beyond simple conclusions about the prevalence of impaired bone health in a particular patient group.

6.5.2 Comparison of the findings with other studies

BMD correction for body size is recommended widely (Lewiecki et al., 2008, Fewtrell, 2003); as similar conflicts reportedly arise with findings when investigating other chronic diseases and also in general paediatric studies. For instance, Ahmed et al., (2004) made a similar conclusion to the present study when they used two different methods amongst children with chronic disease. Moreover, they examined BMD in 26 children aged 5.5 -18.2 years with inflammatory bowel disease, using DXA. They interpreted the data on the basis of two different approaches: the manufactures' software based reference approach; by adjusting BMC for BA (Warner et al. 1988) as in the present study. The prevalence of osteopenia defined by Ahmed et al., (2004) (BMD z scores below -1.0) in the sample based on the first approach was about 65%, however, after adjustment the prevalence was greatly decreased to 22%.

It is now common to use unadjusted BMD to make conclusions about bone health in some specialties; this is not universal in general paediatric practice, in the paediatric research literature, or in other childhood cancer literature. For example, van der Sluis et al., (2002b) evaluated 61 children with ALL aged 1.6 – 16.8 years old. Out of the 61 (median age was 5.5 years) patients, 43 were classified as standard risk ALL. They assessed the patients over 5 different periods from the point of diagnosis until the third year of the therapy. They used the $BMAD_{LS}$ approach (Kroger et al., 1995) to correct BMD for bone size and the manufacture's reference data approach. They found that the BMD of lumbar spine was decreased significantly (p value= 0.01) from diagnosis, but that the BMD of total body was normal. However, different findings were produced using the $BMAD_{LS}$ approach (Kroger et al., 1995) similar to the present study findings. There was a lowering in $BMAD_{LS}$ (Kroger et al., 1995), but no significant difference shown between the point of diagnosis and the three years after off-therapy. van der Sluis et al., (2002b) therefore demonstrated that children with ALL were categorised as at risk of osteopenia, but there were conflicting conclusions according to the different findings obtained using the different approaches. However, they stated that ALL survivors are at risk of low bone mass even though there is no consensus as to how best to adjust, as stated in the present study.

Moreover, in general paediatric practice, some of researchers in recent literature do not use any adjusted method for bone size as recommended by ISCD 2007 (Baim et al., 2008) and they consistently report a concern over low bone mass. For instance, Ibrahim et al., (2011) in a recent study assessed the BMD in a national survey amongst adolescents (n=4002) in Egypt with short stature aged 10 – 18 years. They used DXA as a diagnostic tool but they did not correct BMD for bone size. Thus, they used BMD z scores for children and defined osteopenia as BMD z score -1.0 – 2.5, and osteoporosis as BMD z ≥ -2.5. They also defined osteoporotic subjects as those who had experienced 1 or more low- trauma fractures regardless of BMD measurement. They reported that amongst stunted boys, 31.1% and 44.7% had

osteopenia and osteoporosis; respectively. Amongst stunted girls, 26.5% had osteopenia and 5.4% had osteoporosis. They reported a high of prevalence of low BMD in adolescents.

Also, in a recent study in childhood cancer, Al-Tonbary et al., (2011) reported BMD using DXA at diagnosis in 27 children and adolescents (aged 1- 16 years) with neuroblastoma. They defined low bone mass as a BMD z score < -1.0. They found 25.9% of the total sample had a low bone mass. However, they raised this issue without correction of BMD for body size.

6.5.3 Bone density in children with ALL at diagnosis and during therapy

There are several studies that have examined BMD in children with ALL during therapy and found deficits in bone turnover or other indicators of bone health. For example, Halton et al., (1996) assessed BMD by DXA in 40 children consecutively admitted (aged 0.3 – 14 years), all with ALL (standard risk: n= 18) at diagnosis, then again after periods of 12 months and 24 months. They used the manufacturers DXA reference data approach which is not recommended by ISCD 2007 (Baim et al., 2008) to assess low BMD (osteopenia defined here as BMD and BMC z score below -1.0). They reported that the prevalence of osteopenia was 10% at diagnosis and that it reached up to 76% of the sample at 24 months. However, they recruited a mixed group of ALL patients treated with different therapy protocols in contrast to the present study which had a fairly homogenous sample. Also, they used the term of osteopenia with disregard to the history of bone fractures (Baim et al., 2008).

In addition, in a Canadian study by Rayar et al., (2012) 124 children with ALL were assessed at diagnosis and during therapy, they defined osteopenia and osteoporosis by using unadjusted BMD of lumbar spine z scores as -1.0 – 1.99 and -2.0 and below; respectively. Even though it is unacceptable from an ISCD 2007 (Baim et al., 2008) perspective to define osteopenia and osteoporosis without considering the history of

bone fractures and without corrections of BMC for body size, the prevalence of osteopenia and osteoporosis was recorded as 30% and 11% at diagnosis. Prevalence of patients with ALL who had osteopenia (defined as lumbar spine BMD z score below -1.0) and osteoporosis (defined as lumbar spine BMD z score below -2.0) were 39.5% and 8%; respectively, during maintenance therapy for ALL (Rayar et al., 2012).

6.5.4 Comparison with previous studies amongst survivors of ALL

There are arguments as to whether or not survivors with childhood ALL are at risk of low bone mass. Some studies (as summarised in table 6.5.1) have concluded that ALL survivors are at risk of low bone mass in the medium-term (up to 5 yrs after end treatment) using either adjusted or unadjusted BMD approaches. For instance, in a relatively recent Turkish study, Gunes et al. (2010) examined 70 (aged 3.4 – 17.5 years) survivors of ALL; however, the ALL treatment protocol used included CRT and the sample had only 23% (n= 16) classified as standard risk. Therefore, some of the sample was exposed to very different therapy protocols (i.e. this study did not have a homogeneous group). After using the DXA manufacturers reference data as an approach, they reported that 44% and 41% of the sample were either osteopenic (defined as BMD z score below -1.0) or osteoporotic (defined as BMD z score below -2.0); respectively which is higher than found in the present study using the same approach. Gunes et al., (2010) did not use an adjusted method as recommended (Baim et al., 2008) and they reported about the prevalence of osteoporosis and osteopenia amongst survivors without considering ISCD 2007 (Baim et al., 2008) recommendations about both adjustments and terminology.

Moreover, Kelly et al., (2009) in a cross-sectional study examined patients (fewer than in the present study) who were under- therapy (n= 21) and patient who were off-therapy (n= 21). DXA was performed and the data interpreted using algorithm adjusted BMD and BMC. They found adjusted BMC, BA and BMD z scores were less

than 0.0 across the whole sample, and so were similar to the present study findings when using all approaches. A similar conclusion was reported by Brennan et al., (1999a) when they examined 31 ALL patients (aged 6.8 – 28.6 years) who had been treated with CRT, compared to 35 healthy adults (aged 21 – 25 years). However, they used DXA manufacture's reference data for assessing BMD which is not recommended by ISCD 2007 (Baim et al., 2008). They found a low lumbar spine BMD and low femoral neck BMD with a median score of – 0.74 and -0.43; respectively.

Nonetheless, other researchers have conducted investigations on medium-term ALL survivors and reported that bone mass does not seem to be affected amongst those patients when using either adjusted or unadjusted BMD. Using a larger sample size (n= 69) for a recent cross sectional study (Muszynska-Roslan et al., 2012) had a similar number of standard risk ALL (n=53) to the present study. They recruited survivors of ALL mean (SD) ages 12.2 years (0.5), at least 5 years off-therapy. They used an unadjusted BMD approach (using manufacture's reference data approach) to calculate z scores to define a low bone mass for total body and lumbar spine BMD z scores below -2.0. They reported no significant difference in BMD z scores in both total body BMD and lumbar spine BMD in survivors who were off-therapy for less than or more than 2 years. Thus, it was suggested ALL survivors are not at risk of low BMD by the authors of the study (Muszynska-Roslan et al., 2012).

Some other studies did not support other evidence suggesting that ALL survivors are at risk of low bone mass. Kadan-Lottick et al., (2001) examined 75 (standard risk survivors numbered 69) ALL survivors who had been off-therapy for 0.8 – 6.8 years. By using an unadjusted BMD approach with z scores calculated relative to the reference population based on age and sex, osteopenia (defined as total body BMD z score below – 1.0) prevalence was found to be 11% which was less than the present study findings (41.2%) with BMD z score below -1.0. They reported that none had

osteoporosis (defined in this study as BMD z score below – 2.0) whereas 16% of Saudi survivors had BMD less than -2.0. Other than according to the ISCD 2007 (Baim et al., 2008) recommendation an adjusted method and, ideally a history of bone fractures should be used to define either osteoporosis or osteopenia.

Marinovic et al., (2005) examined 37 survivors of ALL, a relatively small sample size, in a longitudinal study for one year. They compared the survivors with healthy children (n= 74) and used the $BMAD_{LS}$ approach to adjust the BMD for body size. They found a slight reduction in total body BMD after 2.2 years off-therapy. Brennan et al., (2005) similarly examined 53 survivors of ALL aged 6 – 17 years who had been treated by a more modern protocol (without CRT) compared to healthy children (n= 187) aged 5 – 19 years old. They adjusted BMD using a $BMAD_{LS}$ approach (Kroger et al., 1995). Brennan et al., (2005) found that after adjustment total body BMD and total body BMD were no different between survivors and controls and so adverse effects of ALL on bone mass were not reported.

In longer -term (more than 5 yrs after end treatment) studies (as they are summarised in table 6.5.2), it was uniformly found that bone mass seems to be adversely affected as result of ALL or its treatment. Warner et al., (1999), using a relatively small sample size (n= 35), examined survivors with childhood ALL. After adjusting BMC for BA, they reported lumbar spine percentage predicted BMC at 92%, which was similar to the present study at 93%. Percentage predicted BMC was decreased significantly compared to the healthy children control group and lumbar spine percentage predicted BMC in ALL group was low compared to other malignancies.

Table 6.5.1: Some studies on bone mass of ALL survivors a medium-term period after therapy

Author Place	Sample size Gender Age	Main methods	Main results
Medium-term studies that supported ALL survivors at risk of low bone mass			
Gunes et al. (2010) Turkey	70 M: 41; F: 29 3.4 – 17.5 yr	• Used unadjusted BMD for BA approach • Osteopenia: BMD z scores -1.0 to -2.0 • Osteoporosis: BMD z scores < -2.0 • Treatment protocol had CRT, while SR patients were 23%	• Osteopenic: 44%; Osteoporotic: 41% • During 2 years since off-therapy, BMD z score was significantly decreased • Fracture history: 12% • No significant difference showed between patients who treated with CRT and non-CRT (P> 0.05)
Kelly et al (2009) USA	41 M: 25; F: 16 3 – 18 years	• Subjects: 21 patients (during therapy) and 20 patients (off-therapy) • CRT: 9 patients • Included 4 had history of fractures • Using algorithm adjusted BMD and BMC to age, ethnicity, body size and BA	• BMC, BMD and BA z scores significantly below 0.0
Brenan et al (1999) UK	31 M: 16; F: 15 6.8 – 28.6 yr	• All patients received CRT • Patients were at least 2 years of therapy • BMD unadjusted to BA • Controls: 35 healthy children (21 – 25 years)	• LS BMD was highly significantly reduced in ALL patients: median z score was – 0.74 (p=0.01) • Femoral BMD was also significantly reduced: median z score was -0.43 (p= 0.03)
Medium-term studies that did not supported ALL survivors at risk of low bone mass			
Muzynska-Roslan et al. (2012) Poland	69 M: 46; F: 23 12.2 (0.5) yr	• SR ALL were 53 • 25 of survivors had CRT • Off-therapy within 5 years • Used unadjusted BMD; Low bone mass: defined as BMD below -2.0	• BMC z scores, TB BMD and LS BMD were not significant between survivors who were off-therapy more or less than 2 years
Marinovic et al (2005) France	37 M: 20; F: 17 4.7 – 20.6 yr	• Longitudinal study for 1 year • measured controls healthy children twice (n= 74) • Adjusted BMD using BMAD$_{LS}$ approach • Median times was 2.2 years off-therapy	• Slight reducing (p= 0.6) in TB BMD after median times 2.2 years off-therapy. • A significant elevate in median TB BMD in baseline (p= 0.03) and after one year (p= 0.01) when compare > 1.5 year with < 1.5 year since off-therapy
Brenan et al (2005) UK	53 6- 17 yr M: 22; F: 31	• CRT did not use; at least 2 years since off-therapy • 187 Healthy children as a control (aged 5- 19 years) Adjusted BMD using BMAD$_{LS}$ approach	• The median of TB BMC, TB BMD was not differ from survivors and controls

M: Male; F: Female; LS: lumbar spine; TB: total body; BMD: Bone mineral density; BMC: bone mineral content; BMAD$_{LS}$: Bone mineral apparent density for lumbar spine; SR: standard risk; CRT: Cranial radiation therapy; BA: Bone area

In addition, Arikoski et al., (1998), by using $BMAD_{LS}$ (Kroger et al., 1995) in a small sample of survivors (n= 29; 55% treated with CRT), found that lumbar spine BMD was significantly decreased compared to healthy children in the control group (n= 273). Jarfelt et al., (2006) they examined small size (n= 35) survivors aged 20 – 30 years with childhood ALL where half of them had been treated with CRT (quite a heterogeneous ALL sample). They used two BMD adjusted approaches: DXA manufacture's reference data and $BMAD_{LS}$ (Kroger et al., 1995) approaches. Osteopenia was defined as BMD z scores below –2.5, and osteoporosis was defined as BMD z score below – 2.5. They reported that based on following the manufacture's reference data approach, 1, 4 and 8 survivors had osteopenia in total body BMD, lumbar spine and the femoral neck; respectively, with no significant differences between survivors who had been treated or not by CRT. However, they used a non recommended approach by not adjusting for bone size (Baim et al., 2008) and reported the concern over low bone mass in ALL long-term survivors based on unadjusted data. $BMAD_{LS}$ (Kroger et al., 1995) was only used to assess survivors who had been treated (or not) by CRT, and they found no significant difference between who treated or not treated by CRT patients in total body, lumbar spine and femoral neck BMD.

To sum up, inconsistent findings were found on bone mass, and inconsistency probably occurred because of applying different approaches to adjust the BMD. However, the findings relating to ALL survivors in long-term, suggest that low bone mass may be an issue of concern and there are also studies of fracture risk which suggest a cause for concern (Warner et al., 1999, Arikoski et al., 1999).

Table 6.5.2: Some studies on bone mass ALL survivors a long-term period after therapy

Author Place	Sample size Gender Age	Main method	Main results
Long-term studies that supported ALL survivors at risk of low bone mass			
Jarfelt et al (2006) Sweden	35 M: 17 F: 18 20 – 30 years	• 19 survivors had CRT • Using DXA manufacture's reference data and $BMAD_{LS}$ • Osteopenia: BMD z scre above – 2.5 • Osteoporosis: BMD z score below -2.5	• Median LS BMD z score – 0.4 • One, 4 and 8 survivors had Osteopenia in TB BMD, LS and femoral neck; respectively. • $BMAD_{LS}$ showed no significant difference between who had or had not have CRT
Warner et al (1999) UK	35 M: 14 F: 21 7 – 19 years	• Compare with other malignancies group (n= 20) and healthy children as a control group (n= 31) Adjusted BMD using Warner et al (1998) approach	• PP BMC was reduced significantly (P< 0.05) ALL group (92.4%) compare to control group (100.4%) • LS PP BMC had slower improving in ALL compare to other malignancies group
Arikoski et al (1998) Finland	29 M: 16 F: 13 12 – 30 years	• CRT group: (n= 20) • Non-CRT group: (n= 9) • BMD adjusted by $BMAD_{LS}$ approach • Healthy children as control group (n= 273) aged 12 – 30 years	• LS BMD was significantly decreased in ALL patients (95.6%; p= 0.03) compare to controls • Male who treated with CRT had significant low LS and femoral BMD • High dose of MTX was significantly associated with low LS BMD

M: Male; F: Female; LS: lumbar spine; TB: total body; BMD: Bone mineral density; BMC: bone mineral content; $BMAD_{LS}$: Bone mineral apparent density for lumbar spine; CRT: Cranial radiation therapy; PP: Percentage predicted; MTX: methotrexate

6.6 Strengths and limitations of the present study

The main strengths in the present study were the homogenous sample of survivors (n= 51) treated for standard risk ALL, the most common childhood malignancy. Another strength of the study was the sample size was either larger than many previous studies (Kelly et al., 2009, Warner et al., 1999, Arikoski et al., 1998, Brennan et al., 1999a, Jarfelt et al., 2006, Marinovic et al., 2005) or quite similar to others (Muszynska-Roslan et al., 2012, Brennan et al., 2005). In addition, the present study aimed to test the influence of adjusting or not adjusting DXA data for body size.

On the other hand, the present study had a number of limitations. It was not intended to provide definitive conclusions in relation to the bone health of survivors of ALL-issues of the prevalence, nature, and aetiology of bone health impairments in ALL were beyond the scope of the present small study. The present study was methodological, aimed solely at examining the impact of correction of BMD for size, and it was adequate for this purpose. It should also be noted that, whilst serial measurement using DXA is a helpful tool for assessing longitudinal changes in bone health, it is insufficient on its own as a measure of bone health: the role of DXA in diagnosing impaired bone health in children with chronic disease is complex and remains unclear (Wong et al., 2008). Data not included in the present study (e.g. fracture history) would provide clinically important information on bone health but collecting such data was beyond the scope of the present study. Alternative means of correcting DXA data are available (Fewtrell, 2003) but these were also beyond the scope of the present study which aimed to provide a simple empirical demonstration of the impact of using corrected versus uncorrected DXA BMD data.

6.7 Conclusions

Bone health remains a concern during and after treatment for childhood malignancy. This study provides empirical evidence which strongly supports the recommendation that BMD data from DXA should be interpreted cautiously, particularly in children and

adolescents with malignancy. The use of DXA as a measure of bone health requires an adjustment for body size. This is well known from studies of some specialities in paediatrics (especially endocrinology), but is not widely used in studies of childhood malignancy cited earlier (Kadan-Lottick et al., 2001, Rayar et al., 2012, Al-Tonbary et al., 2011, Muszynska-Roslan et al., 2012, Halton et al., 1996, Brennan et al., 1999a) in which DXA data produced bone health z scores based on age and sex reference data, but not corrected for body size. Bone status of ALL survivors should be screened regularly for clinical signs and fracture history. They should be referred to be evaluated by a bone density specialist if there is a cause concern, and bone health is one of a number of issues which could be dealt with by "Late Effects Clinics" in ALL.

Chapter 7
General discussion

This final chapter synthesises the main findings of the thesis studies and considers the implications of the studies in human nutrition for ALL patients in future. Also, future research which improves on the limitations of this thesis will be considered and discussed. Finally, general recommendations arising from this thesis studies will be outlined.

7.1 Brief Summary of Main findings

This thesis studied weight status (underweight, overweight and obesity) during and post- therapy for ALL child patients in the UK, Saudi survivors and its status at diagnosis on the prognosis of treatment. The thesis also considered bone health in survivors of ALL and highlighted methodological issues related to concerns regarding low bone mineralisation as it is one of the main "late effects of ALL" hot topics.

The thesis dealt with the prevalence of unhealthy weight status over time and at diagnosis of ALL in UK children who had been treated according to UKALL protocols between 1985 and 2002 (Mitchell et al., 2010). The thesis included a large representative sample size and used modern and widely accepted definitions of weight status (Cole et al., 1995, Cole et al., 2000, Cole et al., 2007) which had not previously been available when estimates of the prevalence of unhealthy weight status had been made in UK patients with ALL. Prevalence of overweight and obesity increased remarkably over the three trials, whilst prevalence of underweight reduced over time. As the first study in this field this provides an obvious message to clinicians and other health professionals as to just how common unhealthy weight status is at diagnosis in ALL. This is valuable, because, although this is sometimes expressed as a concern in the management of ALL no published evidence has previously been provided estimating the prevalence of unhealthy weight status at diagnosis of ALL. Also, while there were strong secular trends towards overweight and obesity in UK children and adolescents (McCarthy et al., 2003), it seems that unhealthy weight

status at diagnosis in ALL patients reflects exposure in the general population to an obesity contaminated environment.

This thesis did not support the hypothesis that unhealthy weight status is an independent prognostic factor for relapse risk amongst standard risk ALL patients. Unhealthy weight status increases risk of several adverse consequences as discussed in the introduction to this study (sections: 1.3 and 1.2) even if it is not predictive of relapse risk in UK patients with ALL. The thesis supports using anthropometric methods to identify unhealthy weight status, as these are simple and practical even if they are imperfect. It is worth noting that there is no evidence available that focuses on what is an appropriate time to intervene and identify unhealthy weight status in ALL patients or when to intervene nutritionally in patients with ALL, e.g. whether this should be during or post-therapy. However, there are evidence based child obesity prevention and treatment guidelines which could be used, such as SIGN (Scottish Intercollegiate Guidelines Network, 2010) (as summarised in appendix F).

There is increasing evidence that paediatric nutritional screening tools are valid, reliable and practical (Gerasimidis et al., 2010, Secker and Jeejeebhoy 2007, Hulst et al., 2010). Currently, there is no consensus as to the ideal approach with which to assess children on admission as at risk of developing malnutrition during their hospital stay. Such a screening tool differs from measuring actual nutritional status in conjunction with weight and height. For instance, Gerasimidis et al., (2010) developed the Paediatric Yorkhill Malnutrition Score, which is a four-stage evaluation based on four questions considering the BMI for age, recent weight loss, decreased nutrient intake the previous week, and expected altered nutrition over the course of the next week. The validity of using this tool was evaluated in comparison with a full dietetic assessment (dietary history, anthropometric measurements, nutrition associated physical examination, the ability to maintain age appropriate energy levels, and a

review of medical notes). The patients (n= 247) were aged 1 -16 years old and there were three classification risks: low, medium and high malnutrition risk. The nurse-rated Paediatric Yorkhill Malnutrition Score found 59% of those to be admitted were classified as high risk when using the four dietetic assessment tools. Also, according to the nursing Paediatric Yorkhill Malnutrition Score; of those classified as at high risk of malnutrition, 47% were confirmed as being high risk when given full dietetic assessment. There is as yet no evidence as to whether and how nutritional screening tools such as these should be used in the management of ALL, but they would seem to be potentially very useful and could be tested in future studies in this patient population.

The thesis also assessed weight status, over-fatness and MS amongst Saudi adolescent survivors of ALL drawn from a fairly homogenous group. It showed that the prevalence of excess weight and obesity in survivors of ALL was quite high, even though obesity prevalence is extremely high in the general population of Saudi children and adolescents. We found that MS amongst ALL standard risk patients was confined to those who were either overweight or obese. These findings might support early intervention to provide weight management to patients with ALL. Other evidence has shown that UK ALL patients experience excessive weight gain both during and after therapy (Reilly, 2009).

BMI for age and sex in children and adolescents provides an effective and simple indicator of body fatness (Reilly et al., 2010b); however, it is important to note that the BMI-based estimates of the prevalence of overweight and obesity throughout the whole thesis were conservative. BMI-based definitions of obesity, at best, have moderate sensitivity for the detection of excessively fat individuals, with a low false positive rate and a moderate high negative rate, both in the general child population (Reilly, 2010) and in those with malignancy (Warner et al., 1997, Aldhafiri et al.,

2012). Amongst Saudi ALL survivors, by using DXA and BIA high adiposity was more prevalent than when defined using BMI-based definitions.

However, giving estimates of the prevalence of overweight and obesity in ALL children and adolescents, using national or international definitions is debatable. Studies carried out for the thesis found that the Saudi national definition more conservatively estimated the prevalence of overweight and obesity compared with the other widely used international definitions. This might be because the Saudi reference data has been "contaminated" by an obesity epidemic, and so, caution is recommended when the Saudi definition is used in public health surveillance or in clinical practice. Wright et al., (2002) recommended 'fixing' UK national reference data for BMI in 1990, and not updating them, so that future national reference data would not become contaminated by the obesity epidemic.

Survivors of childhood ALL suffer increased risk of several 'late effects' including deterioration of bone health. The author noted, while carrying out the study described in chapter 3, that DXA measures of bone health showed what seemed to be a high prevalence of unhealthy bone results amongst Saudi survivors of childhood standard risk ALL. Since there was already some concern over the bone health of patients with ALL both during treatment and in long term survivors (Rayar et al., 2012, Warner et al., 1999) it seemed worth considering this issue more extensively within this work. In addition, following literature searches and discussions with child bone health experts in Yorkhill hospital, determining the bone health of survivors of ALL as measured by DXA became one of the aims of this thesis. The chapter concluded that bone health remains a potential concern for survivors of ALL, even though the extent to which this is a concern based on DXA measures depends very much on how DXA data are treated. The chapter supports the ISCD 2007 recommendations (Baim et al., 2008) which emphasise that bone health data produced using DXA devices should be carefully interpreted with adjustments to correct for body size.

7.2 Future research suggestions arising from this thesis

It is well-recognised that obesity is epidemic now in Saudi Arabia (El Mouzan et al., 2010) and it has several complications (discussed further in chapter 1), but unfortunately there is no evidence-based treatment protocol for obesity in the general Saudi population of children, or for the management of unhealthy weight in Saudi children with malignancies. Evidence based guidelines from other countries might be a useful starting point in the prevention and treatment of obesity in ALL patients and survivors. So, the author discussed with Professor John Reilly a possible future randomised controlled trial of the treatment of obesity and metabolic syndrome in childhood. Then suggestion was discussed with the head of dietetic department in the KFSH&RC and the initial approval was provided.

In this thesis, unhealthy weight status at diagnosis was not an independent prognostic factor for relapse risk. It is possible that unhealthy weight status might have an adverse impact on risk of relapse in other populations and settings as shown by other studies (Gelelete et al., 2011, Butturini et al., 2007, Lobato-Mendizabal et al., 2003, Antillon et al., 2008, Meji´a-Aranguré et al., 1999, Viana et al., 1994, Reilly et al., 1994).The author and Prof. John Reilly, in collaboration with KFSH&RC staff have proposed to test this hypothesis again using a large and fairly homogenous sample which is already available in KFSH&RC.

7.2.1 Chapter 3: further research suggestions

The present study was carried out in only one centre in Saudi Arabia in a fixed and limited number of survivors. The study used a cross sectional design and this has some limitations, e.g. it can not measure change in variables over time, or confirm causal relationships and researchers may be unable to rule out alternative explanations. Therefore, more prospective studies on the weight status of Long term standard risk ALL Saudi survivors would helpful, with a larger sample sizes. Recruiting the survivors from multicentre rather than one centre would produce a

larger and more representative sample. Also, sophisticated methods for examining over-fatness in ALL survivors should be used in future research.

The inclusion of nutritional status assessment (e.g. using BMI, DXA and/or BIA) should be considered in follow up clinics for survivors of ALL. The prevalence of unhealthy weight status in ALL survivors might not be as high as in the general population of children and adolescents in Saudi Arabia, but that is still a high prevalence of unhealthy weight status and so monitoring of weight status is indicated along with considering options for treatment of unhealthy weight status.

7.2.2 Chapter 4: further research

Although the chapter 4 study had a very large sample size of ALL patients at diagnosis, weight status was assessed retrospectively. A prospective cohort study that uses research-based measurement of height and weight (and possibly even body composition) is recommended to minimise the error in measuring weight status, and test the link between unhealthy weight status and outcomes. It is therefore recommended that malnutrition and any adverse outcomes be studied at diagnosis, during and after therapy in groups of patients with an acceptable sample size- the chapter 4 study stopped at the end of UKALL 97/ 97-99 because that was when weight and height data were no longer being measured at diagnosis of ALL in the UK, and were no longer being recorded in the UKALL datasets. No national UKALL height and weight data were therefore available for the past 10 years. The big question is 'What would the prevalence of different weight status categories at diagnosis of ALL be now?' Prevalence of overweight and obesity appear to have levelled off in the general population of UK children and adolescents in the 2000's (Stamatakis et al., 2010).

7.2.3 Chapter 5: further research

As noted from study of chapter 5, height and weight which are essential for calculating BMI for age and sex were collected for routine clinical purposes rather than research purposes. Also, the UKALL dataset that used ended more than 20 years ago. Therefore, to avoid some of these limitations for future studies, research-based measurements of weight and height collected prospectively would be advised. Also, as noted above, the BMI for age provides limited information. Further studies to investigate total body fat or body fat distribution using DXA or BIA may afford a better insight into relationships between body fatness at diagnosis and outcome of treatment for ALL (Rogers et al., 2005, Goodpaster, 2002).

Furthermore, there are some other potential variables that possibly attenuate any associations between weight status and outcome of the treatment of ALL such as socio-economic status (Lightfoot et al., 2012). Therefore, socio-economic status should be included in future studies of the relationship between unhealthy weight and outcome in ALL as it might be a confounder. However, socio-economic status has not been included in previous ALL survival analyses and was not available from UKALL trial databases for the work described in the present thesis.

7.2.4 Chapter 6: further research

There is currently no consensus as to the best approach to correct DXA bone health data for body size. Chapter 6 showed that it not easy to reach a conclusion about low bone mass in the survivors of ALL because different corrections for body size gave fairly different conclusions. However, irrespective of the issue of how to correct DXA data for body size, serial measurement using DXA is a helpful tool for assessing longitudinal changes in bone health within individual children and groups of children (Fewtrell, 2003). For further research in bone health, it would be advisable to use DXA in assessing bone health of children and adolescents with ALL in a large and longitudinal prospective study. The data that are produced from DXA should be

interpreted based on some correction for body size approach as described by chapter 6.

A number of recently published studies in childhood malignancies have not taken any body size correction approach to interpreting DXA bone health data (e.g. Muszynska-Roslan et al., 2012, Al-Tonbary et al., 2011, Rayar et al., 2012). In addition, measures other than just DXA are helpful to understanding bone health- for example a fracture history would provide clinically significant information on bone health (Baim et al., 2008).

7.3 Clinical recommendations arising from this thesis

- Height measurement seems not to have been recorded in the most recent UKALL trials as it is no longer needed to calculate the surface area in algorithms required for chemotherapy. This study highlights the importance of height in calculating a BMI z score and the ease with which this can be used to diagnose the patient's weight status; without recording of height and weight it has become impossible to carry out surveillance on weight status of ALL patients at diagnosis in the UK- this became impossible after around the end of the UKALL 97/97-99 trial in 2002. Routine measurement and recording of height and weight should possibly be restored in future UKALL trials, both to help identify and manage unhealthy weight status and also for population surveillance of unhealthy weight status.

- It would be useful if health professionals were to consider including more sophisticated approaches to assessing fatness alongside the use of BMI; techniques such as such as BIA or DXA might be most useful as they are the most practical in clinical settings.

291

- Establishing childhood underweight, overweight and obesity intervention strategies from diagnosis could be considered in ALL. There are evidence based clinical guidelines which could be used e.g. SIGN (Scottish Intercollegiate Guidelines Network, 2010) (shown in Appendix F), AAP (Spear et al., 2007) and NICE (National Institute for Health and Clinical Excellence, 2010) to help ALL patients and survivors achieve improved lifestyles and weight status. However, no specific guideline is available nowadays for weight status of children with ALL.

- Trained and qualified health professionals are vital for the diagnosis, monitoring and treatment of unhealthy weight in childhood cancer. Health professionals such as dietitians have to be more aware of the need to evaluate nutritional status and how to evaluate nutritional status in childhood cancer management, and how to implement interventions.

- Finally, (Van Eys, 1998) stated that "Nutrition should be viewed for what it is: supplying the most basic needs of children. No child has died from being fed appropriately, but many die of starvation. The practice of paediatric oncology should not contribute to that statistic".

Appendix A
Published and accepted papers

Obesity and Metabolic Syndrome in Adolescent Survivors of Standard Risk Childhood Acute Lymphoblastic Leukemia in Saudi Arabia

Fahad Aldhafiri, Msc,[1] Abdullah Al-Nasser, MB, ChB,[2] Abdulaziz Al-Sugair, MB, ChB A,[2] Hanan Al-Mutairi, RD,[2] David Young, PhD,[3] and John J Reilly, PhD[1,4]*

Background. This study estimated prevalence of unhealthy weight status and metabolic syndrome (MS) amongst Saudi survivors of standard risk ALL. **Procedure.** We recruited 56 survivors, mean age 13.4 years (SD 4.1), a mean of 9.1 years (SD 4.1) post-diagnosis. The BMI for age was used to define weight status relative to national (Saudi) and International (Cole et al., Cole-IOTF, WHO, and CDC) reference data. We measured body composition by dual-energy X-ray absorptiometry (DXA), waist circumference, blood pressure, lipid profile (HDL-C, Triglycerides), fasting glucose and insulin. **Results.** According to international definitions based on BMI for age, around half of the sample had unhealthy weight status. All of the approaches based on BMI for age underestimated over-fatness, present in 27/51 (53%) of the sample according to DXA. Prevalence of MS was 7.1% (3/42 of those over 9-years old) and 5.4% (3/56) by applying the International Diabetes Federation (IDF) definition and National Cholesterol Education Program Third Adult Treatment panel Guidelines (NCEP III), respectively. However, MS by the NCEP III definition was present in 19% of the overweight and obese survivors and 7.1% of the sample had at least two of the components of MS. **Conclusion.** Unhealthy body weight and over-fatness may be common amongst adolescent Saudi survivors of standard risk ALL, though overweight and obesity may be no more common than in the general Saudi adolescent population. Defining weight status using BMI underestimates overfatness. Ideally, body composition and cardiometabolic risk factors should be monitored at late effects clinics. Pediatr Blood Cancer 2012;59:133–137. © 2011 Wiley Periodicals, Inc.

Key words: acute lymphoblastic leukemia; late effects; metabolic syndrome; obesity

INTRODUCTION

Underweight, overweight, and obesity in childhood and adolescence have adverse consequences for health [1–4]. Obesity during and after treatment of ALL may be very common, even in patients treated on modern protocols, which do not involve cranial radiotherapy [5]. Metabolic syndrome (MS) may also be more common than might be expected in survivors of ALL [6,7]. A particular concern for obesity in ALL is the possibility that it might be associated with increased risk of relapse [8]. Underweight is also present in patients with ALL [9,10], and it may also increase risk of relapse [10,11].

Several major problems exist in the literature on weight status and MS in ALL: most studies have taken place during therapy, with limited evidence on survivors of ALL [12–15]; almost no evidence has been published outside the western world [6]; published studies have generally used older definitions of under-weight, overweight, obesity, and MS-few have used recent international consensus definitions of unhealthy weight status and MS.

The primary aim of the present study was therefore to examine the prevalence of unhealthy weight status and MS in a relatively homogenous group of survivors-in first remission from standard risk ALL-in Saudi Arabia. A secondary aim was to examine whether BMI for age-based estimates of overweight and obesity agreed with measures of over-fatness from dual-energy X ray absorptiometry (DXA).

METHODS

Study Participants

The present study recruited standard risk patients with ALL in first remission, and who had been treated at King Faisal Specialist Hospital and Research Centre on treatment Protocol Cancer Study Group (CCG) 1891 and 1881, during the period 1994–2009. Standard risk ALL was defined as: age >1 and <10 years, initial white blood cell count <50 × 10^9/L, DNA index ≥1.16 or ≤1.60, lack of adverse cytogenetics/molecular genetic studies (t(9;22)/BCR-ABL; t(1;19)/ E2A-PBX1; t (4; 11)/AF4-MLL) and negative for central nervous system or testicular involvement. Patients were potentially eligible if they had been treated on CCG 1891 and 1881 and were in first remission (n = 77). This treatment protocol did not involve cranial radiotherapy. Patients were ineligible if they had relapsed (n = 3), were pregnant (n = 2), had pre-existing type 1 diabetes (before diagnosis of ALL) (n = 1) or had a longbone fracture in plaster (n = 2), leaving 69 potentially eligible survivors. The rationale for the exclusions was to leave a sample to which abnormalities in weight status or body composition might be attributable to ALL or its treatment. All 69 eligible survivors were invited to participate, but 56 (81%) agreed to take part in the present study. The sample of 56 patients was similar to the sample of 69 eligible for age at diagnosis, and for sex distribution, though the small number of those who did not consent precluded statistical analysis.

Ethics committee approval was provided by the Research Advisory Council (RAC) at King Faisal Specialist Hospital and Research Centre on 26 October 2009. Study participants provided informed written consent to their participation.

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Conflict of interest: nothing to report.

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134   Aldhafiri et al.

Anthropometric Data

Height and weight were measured to 0.1 cm and 0.1 kg, respectively, using a Scale-Tronix 5002 stand on scale while patients removed shoes and outdoor clothes. The BMI was calculated and expressed as an age and sex specific z-score or centile.

Classification of Weight Status

In the present study, we used the most modern, recommended definitions of body weight status based on BMI for age. Saudi BMI reference data are available [16] in the form of centile charts for boys and girls and so these were used in the present study. Various international BMI for age reference data are also available, the most widely used probably those provided by WHO [17] and the US Centers for Disease Control and Prevention (CDC) [18], so both of these were also used in the present study. BMI z-scores were calculated from WHO 2007 reference data using WHO Anthro version 3.2.2, January 2011 software [19]. BMI z-scores were calculated relative to US CDC reference data [18]. When using Saudi, WHO, and US CDC BMI for age reference data obesity was defined conventionally, as ≥95th centile, overweight as 85th to 94th centile, and underweight as <5th percentile [18,20,21].

In recent years, the Cole-International Obesity Task Force (IOTF) BMI [22] based definitions of pediatric overweight and obesity have become popular [23]: these facilitate international comparisons of obesity prevalence and use age and sex specific cut-offs for absolute BMI. We therefore also defined overweight and obesity in participants in the present study using the Cole-IOTF approach. More recently, Cole et al. [24] proposed an international definition of pediatric underweight based on BMI for age and so we used this to define underweight [24].

Body Composition Measures

A recent systematic review [23] concluded that the BMI for age is a helpful simple proxy for excessive body fatness. However, the BMI may not be as informative as measurement of body composition in pediatrics in general, including studies of survivors of childhood cancer [25,26]. In addition, body composition is recommended by the International Diabetes Federation (IDF) as a useful research measure, which is relevant to defining MS [27]. In the present study, we therefore measured body composition (% body fat) in participants by DXA as recommended by Warner et al. [25] using DXA Lunar Prodigy software version 9.15.

Levels of total body fat % which are excessive (because of associations with adverse cardiometabolic risk profiles) have been established by previous studies as: >25% fat for males and >30% for females age 5–18 years, >25% and >32% in males and females aged over 18 years [28] and so these definitions were applied in the present study.

Metabolic Syndrome: Definitions and Measurements

We defined the presence or absence of the MS in all participants using two modern and widely accepted definitions: the IDF approach [29] and the approach of The National Cholesterol Education Program Third Adult Treatment Panel guidelines (NCEP III) modified by Cook et al. [30].

MS in 10–15 years was defined by the IDF as having central obesity assessed by Waist circumference (WC) ≥90th centile plus two or more of the following criteria: triglycerides ≥150 mg/dl; HDL-cholesterol < 40 mg/dl blood pressure ≥130/85 mm Hg; fasting glucose ≥100 mg/dl. For those age ≥16 years, MS was defined by the IDF as having central obesity assessed by WC ≥94 cm for men and WC ≥80 cm for women plus two or more of the following criteria: triglycerides ≥150 mg/dl; HDL-cholesterol < 40 mg/dl in males and <50 mg/dl for females; Blood pressure ≥130/85 mm Hg; fasting glucose ≥100 mg/dl.

The NCEP III approach to defining MS for those aged 10–19 years requires at least three of the following five criteria: (i) central obesity, WC ≥90th centile; (ii) triglycerides ≥110 mg/dl; (iii) HDL-cholesterol ≤40 mg/dl; (iv) blood pressure ≥90th centile; (v) fasting glucose ≥ 110 mg/dl. For those ≥19 years three criteria are required from the following: (i) central obesity assessed by WC ≥102 cm for men and WC ≥88 cm for women; (ii) triglycerides ≥150 mg/dl; (iii) HDL-cholesterol ≤ 40 mg/dl for men and HDL-cholesterol ≤50 mg/dl for women; (iv) blood pressure ≥130/85 mm Hg; (v) fasting glucose ≥110 mg/dl.

In order to apply these two approaches to defining the MS a single trained observer measured abdominal obesity by WC at 4 cm above the umbilicus [31], blood pressure, triglycerides, fasting glucose. We interpreted these in the age and sex specific ways recommended by the IDF [29] and by the NCEP [30]. In addition, we calculated the prevalence of 1 and 2 components of the MS by both definitions.

Statistical Analysis, Power, and Sample Size

Power of the present study was fixed by the size of the cohort of patients available to us, who had been treated on protocol CCG 1891. The sample size was similar to or larger than many previous studies of weight status in ALL [6,32–34].

Means and standard deviations are presented in the results unless otherwise stated. Normality of data was tested by using formal Normality tests. A P-value of < 0.05 was considered as significant. Minitab 15.1.30.0 software was used for all statistical analyses except for the weighted kappa analysis, which used Medcalc software version 11.5.0.0. Differences between groups were tested for statistical significance by using two sample t-tests. Two proportion tests were applied to test the significance of differences between two proportions.

The weighted Kappa statistic (k) with 95% CI was used to assess the degree of agreement between the different approaches to defining underweight, healthy weight, overweight, obesity, and overfatness. We also used the weighted kappa analysis as a preliminary test of agreement between the two definitions of pediatric MS. The k statistics were interpreted as recommended by Landis and Koch [35]: "slight agreement" 0.0–0.20; "fair agreement" 0.21–0.40; "moderate agreement" 0.41–0.60; "substantial agreement" 0.61–0.80; "almost perfect agreement" 0.81–1.00.

RESULTS

Characteristics of Study Participants

The sample of 56 consented to all measures, though five did not attend for DXA measurements. Mean (SD) time from

diagnosis was 9.1 (4.1) years, and mean time from end of therapy was 6.2 (3.9) years. Characteristics of study participants are shown in Table I.

Weight Status of the Sample

Weight status of the sample is illustrated in Table II. Approximately half of the sample was of unhealthy weight status (underweight, overweight, obese) by most of the approaches used to define weight status, though prevalence of unhealthy weight status varied by the approach taken. In particular, the prevalence of overweight and obesity was lower when using the local Saudi BMI reference data (prevalence 21.4%; 12/56 participants) than when using the alternative definitions (prevalence of combined overweight and obesity varied between 28.6% and 32.1% for the other definitions). Underweight was present in the sample, with prevalence varying differing slightly between the different definitions, as illustrated in Table II.

Agreement Between Different Approaches to Defining Weight Status

Agreement between the different definitions based on BMI for age, using weighted Kappa (k) statistics, was "moderate-substantial" between use of the Saudi reference data and definitions versus those from the US CDC (k = 0.70) and WHO (k = 0.67). There was poorer agreement between the Saudi approach and the Cole et al. [24] and Cole-IOTF [22] approaches to defining weight status (k = 0.47).

Body Composition of the Sample

According to DXA estimates of body fatness, more than half of the sample (52.9%, 27 out of 51 survivors) had over-fatness.

Mean (SD) body fat % by using DXA was 24.7% (SD 10.6) for males and 37.6% (SD 8.8) for females (P <0.001).

When the ability of the various anthropometric approaches (with reference data from Saudi Arabia, the US CDC, the WHO and the Cole-IOTF approach) to defining overweight and obesity based on BMI for age was compared against the measures of overfatness by DXA (Table III), agreement was only fair [35].

Metabolic Syndrome

Prevalence of MS was 7.1% (3/42 survivors aged ≥10 years) by the IDF definition [29] and 5.4% (3 out of 56) by the NCEP approach [30]. Of the three survivors defined as having MS by the IDF definition, two survivors were also defined as having MS using the NCEP definition. The weighted kappa statistic for agreement between the two methods was 0.65, indicating "substantial agreement", but with a wide confidence interval (95% CI: 0.19–1.00). In those survivors who were overweight or obese (BMI at or above the 85th centile relative to CDC reference data) prevalence of MS was much higher (19% by the NCEP III criteria).

Prevalence of 1 MS component was 35.7% (15/42) using the IDF criteria, and 37.5% (21/56) using the NCEP III criteria. Prevalence of 2 MS components was 11.9% (5 /42) using the IDF criteria and 7.1% (4/56) using the NCEPIII criteria.

DISCUSSION

In the present study, around half of the adolescent survivors of standard risk ALL had unhealthy weight status (underweight, overweight, or obesity) by applying the international approaches based on BMI, an average of 6 years after completion of chemotherapy. Prevalence of excessive body fatness measured by DXA was very high, and much higher than the BMI for age-based definitions of overweight and obesity suggested. It is likely that

TABLE I. Characteristics of Study Participants Mean (SD)

	Males (n = 34)	Females (n = 22)	Total sample (n = 56)
Age (years)	13.0 (4.6)	14.0 (3.1)	13.4 (4.1)
Height (m)	1.49 (0.20)	1.51 (0.11)	1.50 (0.17)
Weight (kg)	42.0 (16.9)	49.3 (18.4)	46.7 (17.5)
Time from diagnosis (years)	9.1 (4.5)	9.1 (3.2)	9.1 (3.2)
Time since completion of therapy (years)	5.9 (4.5)	6.7 (3.1)	6.2 (3.9)
CDC[a] BMI-z score	−0.17 (1.6)	0.16 (1.3)	−0.04 (1.48)
WHO[b] BMI-z score	0.14 (2.0)	0.31 (1.5)	0.21 (1.77)
% body fat by DXA[c]	24.7 (10.6)	37.6 (8.8)	29.2 (11.7)

[a]CDC, US Centers for Disease Control and Prevention. [b]WHO, World Health Organisation. [c]DXA, dual-energy X-ray absorptiometry.

TABLE II. Prevalence of Obesity, Overweight, and Underweight by Four Methods

Reference approaches	Obesity (n), %	Overweight (n) %	Underweight (n), %
Saudi reference data [16]	(4) 7.1	(8) 14.3	(5) 8.9
Cole et al. and Cole-IOTF[a]; [22,24]	(5) 8.9	(13) 23.2	(12) 21.4
CDC[b] [18]	(6) 10.7	(10) 17.9	(10) 17.9
WHO[c] [17]	(6) 10.7	(12) 21.4	(7) 12.5

[a]Cole-IOTF, Cole-International Obesity Task Force. [b]CDC, US Centers for Disease Control and Prevention. [c]WHO, World Health Organisation.

136   Aldhafiri et al.

TABLE III. Extent of Agreement (Weighted Kappa Statistic With 95%CI) Between Different BMI-Based Approaches for Defining Overweight and Obesity Compared to Over-Fatness Defined as Excessive[a] Body Fat % From Dual-Energy X-ray Absorptiometry

Comparisons	Weighted kappa	95% Confidence interval	Level of agreement [35]
DXA vs. Saudi reference data [16]	0.24	0.08–0.39	Fair
DXA vs. CDC[b] reference data [18]	0.34	0.16–0.51	Fair
DXA vs. Cole-IOTF[c] approach [22,24]	0.22	0.03–0.41	Fair
DXA vs. WHO[d] reference data [17]	0.39	0.21–0.57	Fair

[a]Excessive defined as: >25% fat for males and >30% for females age 5–18 years, >25% and >32% in males and females age over 18 years.
[b]CDC, US Centers for Disease Control and Prevention. [c]Cole-IOTF, Cole-International Obesity Task Force. [d]WHO, World Health Organisation.

BMI-based approaches to defining overweight and obesity will underestimate the scale of the problem in survivors of ALL.

The optimal population reference data (for BMI for age or for body fatness) on which to base estimates of unhealthy body weight is unclear, though one common view is that such reference data should have been collected prior to the obesity epidemic. Data collected prior to the obesity epidemic might represent "standards". More recently collected data might describe norms characterised by a higher prevalence of unhealthy weight status [36].

While prevalence of underweight, overfatness, overweight, and obesity seemed high in the present study, comparison with recent Saudi population data is necessary to establish if this as an ALL-specific problem or if it simply reflects the nutritional status of contemporary Saudi adolescents. El Mouzan et al. [20] provide a healthy population-based comparison group for the present study. This survey of 19,317 Saudi children and adolescents, which defined overweight and obesity as BMI for age >85th and > 95th centiles, respectively relative to Saudi reference data for BMI for age [16], found that 34.4% of the children and adolescents were overweight or obese (combined). The prevalence of BMI for age defined overweight and obesity in the adolescent survivors of ALL in the present study (combined 28.5%) was actually lower than in the general population in Saudi Arabia, suggesting that overweight and obesity observed is probably not an ALL specific problem. Further research on the causes of obesity in ALL and the general population in Saudi Arabia would be desirable. We are not aware of any etiological studies of adolescent obesity in Saudi Arabia-studies to date have focused on describing the rapid recent increases in obesity prevalence [20,21].

While MS was not common in the present study, prevalence of 1 and 2 components of MS were higher. We are not aware of any comparable studies of prevalence of MS for the general adolescent population in Saudi Arabia, and so further research would be required to establish whether or not the prevalence estimates observed in the present sample were high or low.

Relatively few other studies have focused on medium term survivors of ALL and we have been unable to find any reports of weight status, body composition, or MS (with modern definitions) in survivors of ALL treated on modern protocols outside western countries [12,34].Warner et al. [25] found that the BMI for age provided a poor indicator of excess adiposity in patients with childhood cancer and other chronic diseases, consistent with the findings of the present study.

The present study was limited by small sample size, but the sample recruited was similar to or larger than a number of

previous studies in this area [6,32–34] and was fairly homogenous, in that all participants were survivors of standard risk childhood ALL on the same treatment protocol. Another limitation was the short time between end of the therapy and the present study. Longer-term follow-up studies would be useful, and the high prevalence of both overfatness and unhealthy body weight status observed in the present study indicates that longer-term follow-up studies of survivors of ALL outside the Western world are indicated. While contemporary Saudi data were available on prevalence of overweight and obesity using the BMI for age, no Saudi data were available for body fatness measured by DXA and so a population comparison group was not available for body fatness.

CONCLUSIONS

Unhealthy body weight status and unhealthy body composition appear to be quite common among the medium-term survivors of standard-risk ALL in Saudi Arabia, though overweight and obesity may be no more common than in the general population. Use of BMI for age-based definitions of overweight and obesity will underestimate the prevalence of overfatness, and so body composition measurement should be considered. Future care of long-term survivors of ALL should include assessment of weight status, should consider body composition measurement rather than just measures of BMI, and should consider cardiometabolic health.

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RESEARCH PAPER

Prevalence of being underweight and overweight and obesity at diagnosis in UK patients with childhood acute lymphoblastic leukaemia 1985–2002

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Abstract

Background: Being underweight or overweight and obesity at diagnosis may all worsen prognosis in childhood acute lymphoblastic leukaemia (ALL), although no studies have estimated the prevalence of an unhealthy weight status at diagnosis in large representative samples using contemporary definitions of weight status based on body mass index (BMI) for age.
Methods: The present study comprised a retrospective study that aimed to estimate prevalence of being underweight and overweight and obesity at diagnosis for patients with childhood ALL on three successive UK treatment trials: UKALL X (1985–1990; $n = 1033$), UKALL XI (1990–1997; $n = 2031$), UKALL 97/99 (1997–2002; $n = 898$).The BMI for age was used to define weight status with both UK 1990 BMI for age reference data and the Cole-International Obesity Task Force (IOTF) definitions.
Results: The prevalence of being underweight was 6% in the most recent trial for which data were available. The prevalence of being overweight and obesity was 35% in the most recent trial when expressed using Cole-IOTF definitions and 41% when expressed relative to UK 1990 reference data.
Conclusions: Even with highly conservative estimates, >40% of all UK patients with ALL were underweight, overweight or obese at diagnosis in the most recent trial for which UK data are available (UKALL 97/99, 1997–2002).

Introduction

Being underweight or overweight and obesity have adverse short and long-term health effects for children and adolescents (Pelletier & Frongillo, 2003; Reilly et al., 2003; Reilly & Kelly, 2011). Moreover, both being underweight and obesity at diagnosis of childhood acute lymphoblastic leukaemia (ALL) appear to have disease-specific adverse effects in that they can increase the risk of relapse (Lobato-Mendizabal et al., 2003; Butturini et al., 2007; Gelelete et al., 2011), with similar findings in some other childhood malignancies (Lange et al., 2005). In addition, in a number of childhood malignancies, including ALL, obesity is a common consequence of the disease or its treatment (Reilly, 2009).

Despite the clinical importance of weight status during and after a diagnosis of ALL, prevalence estimates of weight status at diagnosis have usually been made with small samples, typically obtained from samples of patients from single centres. Prevalence estimates for being underweight or overweight and obesity are not available for large nationally representative samples of patients. In addition, older studies generally did not base their prevalence estimates on well-established definitions of weight status (Reilly, 2010) using the body mass index (BMI) for age (Cole et al., 1995, 2000, 2007; Reilly et al., 2010), some of which became available only recently, such as the definition of underweight from Cole et al. (2007). Anonymised national trial data are available for patients with childhood ALL in the UK, and almost all patients enter

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these trials, so that the trials provide an excellent opportunity for estimating the prevalence of being underweight or overweight and obesity for the entire patient population. The primary aim of the present study was to describe weight status at diagnosis of ALL (typical age of diagnosis is approximately age 4 years) using contemporary and recently established definitions.

Materials and methods

Study participants

The present study was based on clinical measures of weight and height of all patients at entry onto the trial protocol from successive UKALL national treatment trials, which covered the period 1985–2002: UKALL X (1985–1990), UKALL XI (1990–1997) and UKALL 97/99 (1997–2002). Since 2002, patient weight and height have no longer been routinely measured and recorded at diagnosis of ALL in the UK: no national estimates of the prevalence of an unhealthy weight status are possible beyond 2002. The Clinical Trials Service Unit, Oxford, provided the data used in the present study, in anonymised form.

Definitions of weight status categories

Clinical measures of weight and height were recorded to 0.1 kg and 0.1 cm, respectively. These measures were used to calculate the BMI. Internationally accepted definitions of being underweight ('thinness'; Cole et al., 2007) or overweight and obesity (Cole et al., 2000) in childhood and adolescence were used: these are conceptually equivalent to adult BMI cut-offs for being underweight or overweight and obesity. International definitions of weight status were chosen for the present study because they are widely used in research, and are particularly suitable for between-study and international comparisons. Prevalence estimates for being overweight and obesity were also generated using UK BMI population reference data from 1990 (Cole et al., 1995; Reilly, 2010), with overweight defined as a BMI between the 85th and 94th percentiles and obesity ≥95th percentile. The BMI for age defini-

tions of being overweight and obesity based on UK 1990 population reference data are used widely in the UK, and can be applied to a wider age range than the definitions of Cole et al., 2000 based on BMI for age, although no clear, evidence-based definition of being underweight exists with the UK 1990 BMI reference data. The use of UK national reference data for BMI has a higher diagnostic accuracy for obesity (i.e. a higher sensitivity for the detection of excessively fat children) than the use of the international definitions (Reilly et al., 2000, 2010), and has equal sensitivity for the detection of excessive fatness in boys and girls (in contrast to using the definitions of Cole et al., 2000 in UK children; Reilly et al., 2000).

Statistical analysis

Distributions of weight status variables were not normal, and so nonparametric tests were used and nonparametric summary statistics are provided. Differences in the prevalence of being underweight or overweight and obesity between boys and girls were not significant, and so prevalence estimates are presented with the data combined. Secular trends in median BMI Z-score across the three trials were tested for significance using the Kruskal–Wallis test. Secular trends in the prevalence of being underweight or overweight and obesity across the three trials were tested for significance using a chi-square test for trend. MINITAB software, version 16.1.1 (Minitab Inc., State College, PA, USA) and MEDCALC software, version 11.5.0.0 (MedCalc Software, Ostend, Belgium) were used for the statistical analyses.

Results

The characteristics of the study samples are shown in Table 1.

The prevalence of being underweight was 19.4% in UKALL X (1985–1990), 16.0% in UKALL XI (1990–1997) and 5.8% in UKALL 97/99 (1997–2002). The secular trend in the prevalence of being underweight between the three trials was statistically significant ($P < 0.0001$). The

Table 1 Characteristics of study participants at diagnosis in three UK acute lymphoblastic leukaemia (ALL) trials, 1985–2002, median (interquartile range)

	UKALL X (n = 1033) (774 boys)	UKALL XI (n = 2031) (1153 boys)	UKALL 97/99 (n = 898) (488 boys)
Age (years)	4.5 (2.9, 8.1)	4.5 (2.5, 7.5)	4.5 (3.5, 7.5)
BMI Z-score*	−0.28 (−1.06, 0.47)	−0.10 (−0.82, 0.77)	0.78 (−0.18, 1.52)[†]
Height Z-score*	0.10 (−0.67, 0.78)	0.17 (−0.66, 1.01)	0.24 (−0.66, 1.02)

*Z-scores expressed relative to UK 1990 reference data using open access software.
[†]Significant difference in median body mass index Z-score across the three trials (Kruskal-Wallis test, $P < 0.0001$).
BMI, body mass index; UKALL, UK acute lymphoblastic leukaemia.

Table 2 Prevalence of weight status categories at diagnosis in three UK acute lymphoblastic leukaemia (ALL) trials, 1985–2002

Definition and reference data	Weight status	UKALL X, % (n)	UKALL XI, % (n)	UKALL 97/99, % (n)
Cole et al. (2000, 2007)/International Obesity Task Force Definitions	Underweight*	19.4 (178)	16.0 (301)	5.8 (49)
	Healthy weight*	70.3 (645)	70.9 (1330)	59.7 (506)
	Overweight and obese*	10.2 (94)	13.1 (246)	34.5 (293)
Definition based on national reference data				
UK, 1990	Healthy weight*	86.6 (895)	81.6 (1657)	59.1 (531)
	Overweight and obese*	13.3 (138)	18.2 (374)	40.9 (367)

*Test for secular trend across the three trials significant ($P < 0.0001$).
UKALL, UK acute lymphoblastic leukaemia.

prevalence of being overweight and obesity (combined) using the Cole-International Obesity Task Force (IOTF) definitions (Table 2) was 10.2% in UKALL X, 13.1% in UKALL XI and 34.5% in UKALL 97/99. The secular trend in the prevalence of being overweight and obesity between the three trials was statistically significant ($P < 0.0001$).

The prevalence of being overweight and obesity (combined) using UK population reference data was 13.3% in UKALL X, 18.2% in UKALL XI and 40.9% in UKALL 97/99 (Table 2). The secular trend in the prevalence of being overweight and obesity between the three trials was statistically significant ($P < 0.0001$).

Discussion

The present study demonstrates that, in the UK, >40% of all patients with ALL were underweight, overweight or obese at diagnosis using the most recent UK dataset available (from the trial which ended in 2002). No estimates of the prevalence of being underweight or overweight and obesity have previously been available from nationally representative samples of patients using the currently recommended definitions of weight status based on BMI for age. It is important to note that our prevalence estimates were conservative. The BMI-based definitions of obesity, at best, have moderate sensitivity for detection of excessively fat individuals, with a low false positive rate but a moderately high false negative rate, both in the general population of children (Reilly, 2010) and in those with malignancy (Warner et al., 1997; Aldhafiri et al., 2012). The Cole-IOTF definitions are particularly conservative (Reilly, 2010; Reilly et al., 2010). In addition, children with ALL in the UK experience substantial excessive weight gain during and after therapy (Reilly, 2009), and so the estimates of prevalence of obesity made in the present study are also conservative because they are based on measures made at diagnosis rather than after therapy.

The implications of the age of the data available to the present study are worth considering. The most recent data used in this retrospective study are now 10 years

old, and routine measurement and recording of patient weight and height at diagnosis (before induction therapy) in the UK was abandoned a decade ago when the algorithm to estimate body surface area (i.e. to calculate drug dosage) was changed. This means that no more recent prevalence data from national samples are available in the UK. Continued national surveillance of weight status of patients with ALL, with anonymised central data collection as used in the present study, has become impractical. The extent to which the prevalence estimates from the present study 'matter' today will depend to a large extent on secular trends in being underweight or overweight and obesity in the last 10 years. A dramatic increase in the prevalence of childhood obesity occurred in the general population in the UK between the mid- 1980s until the late 1990s (Reilly and Dorosty 1999), and the findings of the present study were consistent with these population-wide trends. The prevalence of childhood obesity in the UK has continued to increase over the past 10 years, although the rate of increase appears to have slowed recently (Stamatakis et al., 2010). It is probable that the prevalence of obesity from more contemporary samples of patients with ALL at diagnosis would be at least as high as those reported in the present study. Secular trends in being underweight are not available for the UK as far as we are aware, and the definition of being underweight used in the present study has emerged only relatively recently (Cole et al., 2007).

In the absence of formal anthropometric screening for unhealthy weight status, few patients who have an unhealthy weight status are identified by experienced paediatricians, paediatric dietitians, paediatric nurses (Cross et al., 1995; Smith et al., 2008) and parents (Parry et al., 2008). The identification of being underweight or overweight/obesity at diagnosis of ALL should be relatively straightforward using the BMI in conjunction with widely available centile charts (Reilly, 2010), although there remains resistance to using such charts routinely in paediatric practice, for reasons which have not been explored fully (Flower et al., 2007). There is increasing evidence that paediatric nutritional screening tools are valid, reli-

able and practical (Gerasimidis *et al.* 2010; Secker and Jeejeebhoy 2007; Hulst *et al.* 2010) and these could also be considered in future management of ALL. Further research will be required to identify how and whether to establish nutritional assessment within routine management of childhood ALL.

In summary, the findings of the present study suggest that being underweight or overweight and obesity are likely to be very common at diagnosis in childhood ALL in the UK.

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CLINICAL AND LABORATORY OBSERVATIONS

Importance of Adjusting Dual-energy X-Ray Output for Body Size: An Example From Survivors of Childhood Acute Lymphoblastic Leukemia

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Summary: We compared DXA whole body and lumbar spine bone mineral density (BMD) using manufacturers software with a body size correction which derived bone mineral content (BMC) for bone area in survivors of acute lymphoblastic leukemia in Saudi Arabia (n = 51, mean age 13.5 y). With no corrections, 29 patients (57%) had lumbar spine BMD Z score < -1.0 and 21 (41%) had whole body BMD Z score < -2. After correction, only 6 (12%) had lumbar spine BMC Z score < -1.0 and 4 (8%) had whole body BMC Z score < -2. Agreement between the methods was "poor" by weighted κ analysis.

Key Words: bone health, dual-energy x-ray absorptiometry, acute lymphoblastic leukemia

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An adverse effect of childhood malignancy or its treatment on bone is a widespread concern,[1–5] and there is increasing evidence that skeletal morbidity is common in patients with acute lymphoblastic leukemia (ALL) during and after therapy.[1,2] Dual-energy x-ray absorptiometry (DXA) is used widely as a clinical indicator of bone health. In some specialties it has been well known for some time that there is a need to correct DXA-derived bone mineral density (BMD) data for body size, particularly in children and adolescents with chronic disease, including malignancy.[4,6] Such corrections are not universal in the literature in other specialties though, and a number of recent reports on bone health in patients with childhood cancer have been based on BMD data with no formal correction for body size.[7,8] For example, a recent study of BMD in patients with neuroblastoma used BMD data, without formal correction for body size, to conclude that impaired bone health was very common.[7] Since the need to correct DXA-derived data for body size is not universally appreciated in pediatric oncology and hematology it is likely that future studies and clinical observations may therefore misinterpret DXA output by not correcting BMD data for body size. The aim of the present study was therefore to examine the impact on apparent bone health of using uncorrected versus corrected DXA-data in a relatively homogenous group of survivors in first remission from standard risk ALL in Saudi Arabia.

METHODS

Study Participants

We recruited standard risk patients with ALL in first remission who had completed therapy at the King Faisal Specialist Hospital & Research Centre, Saudi Arabia, on treatment Protocol Cancer Study Group (CCG) 1881 and 1891. Standard risk was defined as: age > 1 and < 10 years, initial white blood cell count $< 50 \times 10^9$/L, DNA index > 1.16 or ≤ 1.60. Patients were considered potentially eligible if they had been treated on CCG 1881 or 1891, had completed therapy, and were in first remission: 77 survivors were potentially available. Patients were ineligible if they had relapsed, were pregnant, had chronic disease (eg, diabetes) before the diagnosis of ALL which might influence bone health, or had a longbone fracture in plaster. A total of 8 patients were excluded, leaving 69 potentially eligible survivors. All 69 were invited to participate and 51 (74%) agreed to take part. Ethics committee approval was provided by the Research Advisory Council (RAC), and participants provided informed written consent.

Bone Health Measurements by DXA

In all participants DXA driven by Lunar Prodigy software version 9.15 was used. Although adjustment of BMD for body size is recommended widely,[4,6,9] there is currently no consensus as to how best to make the adjustment of DXA-derived BMD data for body size. For the present study we used the approach described by Warner et al,[4] based on calculation of bone mineral content (BMC) Z scores, adjusted for age, sex, and bone size. This approach provides a percentage predicted bone area for age and a percentage predicted BMC for bone area.[4] Moreover, by using linear interpolation, these data give predicted and percentage predicted bone area for age and sex.[4] As indicators of possible concern over bone health we used the cut-offs for BMD and BMC Z scores of -1.0 and -2.0.

Statistical Analysis, Power, and Sample Size

Power of the present study was fixed by the size of the cohort of patients available to us and so no formal power calculation was carried out, but paired comparisons of preliminary corrected and uncorrected DXA data showed

that the study was powered adequately to compare between corrected and uncorrected data. Means and SDs are presented in the results unless otherwise stated. Normality of data was tested by using formal normality tests in Minitab. A weighted κ analysis was carried out using MedCalc software version 11.5. We used the weighted κ statistic (k) and 95% confidence intervals (CI) for this statistic to assess the degree of agreement between BMD and BMC Z score categories, with the descriptors which summarizes agreement proposed by Landis and Koch[10]:

"slight agreement" 0.0 to 0.20; "fair agreement" 0.21 to 0.40; "moderate agreement" 0.41 to 0.60; "substantial agreement" 0.61 to 0.80; "almost perfect agreement" 0.81 to 1.00.

RESULTS

Characteristics of Study Participants

Mean (SD) time from diagnosis was 9.1 (4.3) years, and mean time from end of therapy was 6.3 (4.1) years. Characteristics of study participants are shown in Table 1.

Comparisons of DXA Data: Corrected BMC Versus Uncorrected BMD Data

Table 2 summarizes uncorrected BMD Z scores from manufacturer's hardware and software: 18 (35%) and 13 survivors (26%) had lumbar spine and whole body BMD Z scores between −1.0 and −2.0; 11 (22%) and 8 (16%) had lumbar spine and whole body BMD Z scores < −2.0. If a Z score of −1.0 was considered to be of potential concern, this would apply to 29 (57%) of the survivors at the lumbar spine, and 21 (41%) for the whole body, using BMD derived directly from DXA output, with no correction for body size.

Using BMC corrected for body size with the approach described by Warner et al[10] only 6 (12%) survivors had lumbar spine BMC Z scores between −1.0 and −2.0, and none had a Z score < −2.0. For the whole body BMC, only 3 survivors (6%) had BMC Z scores between −1.0 and −2.0, with 1 (2%) < −2.0. Mean percentage predicted bone area for age[10] was 89% for the lumbar spine and 87% for the whole body. Mean percentage predicted BMC for bone area[10] was 93% for lumbar spine and 97% for the whole body.

Agreement between BMD (uncorrected) and BMC (corrected) categories of possible low bone mass (Z scores < −1) was "poor" as defined by Landis and Koch[10] at the lumbar spine ($k = 0.18$; 95% CI, 0.04-0.33) and for the whole body ($k = 0.13$; 95% CI, 0.06-0.31).

TABLE 1. Characteristics of Study Participants [Mean (SD)]

	Males (n = 33)	Females (n = 18)	Total sample (n = 51)
Age (y)	13.2 (4.6)	14.0 (3.1)	13.5 (4.1)
Height (m)	1.49 (0.19)	1.51 (0.11)	1.50 (0.17)
Weight (kg)	45.7 (16.8)	48.9 (17.6)	46.8 (16.9)
Time from diagnosis (y)	9.2 (4.7)	9.0 (3.6)	9.1 (4.3)
Time since completion of therapy (y)	6.6 (4.4)	5.6 (3.5)	6.3 (4.1)
CDC BMI Z score	−0.16 (1.6)	0.12 (1.3)	−0.06 (1.5)

BMI indicates body mass index; CDC, US Centers for Disease Control and Prevention.

TABLE 2. DXA-derived Bone Mineral Density (BMD) and Corrected Bone Mineral Content (BMC) Z scores [Mean (SD) or Median (Range)]*

Approaches	Lumbar Spine	Whole Body
BMD, uncorrected	−1.2 (0.9)	−0.8 (1.1)
BMC for bone area, corrected using the method of Warner et al[8]	−0.4 (0.6)	−0.3 (−0.5, 0.2)*

DXA indicates dual-energy x-ray absorptiometry.

DISCUSSION

In this study when standard DXA manufacturer's software was used to calculate BMD Z scores for lumbar spine and whole body, the prevalence of low Z scores was very high. The conclusion that poor bone health was common among the patients might have been reached on the basis of these findings, particularly with a background of recent evidence that skeletal morbidity is common among patients with ALL, and more general concerns over poor bone health in patients with ALL.[1 5] However, such a conclusion would be inappropriate since, when BMD was corrected for body size, the prevalence of low BMC at lumbar spine and for the whole body was very much lower. Corrected data suggested an alternative conclusion in relation to the bone health of these patients. Although correction for body size is recommended widely,[9,11] and is now common in some specialties, this is not universal in pediatric practice, in the pediatric research literature, or in the childhood cancer literature specifically.[7,8] Persistence of apparent bone mass deficits from DXA-derived BMD data after adjustment for body size would provide confidence that an apparently increased risk of impaired bone health was real, rather than an artifact of the poor growth, delayed puberty, and abnormal body composition which characterizes many populations of children and adolescents with chronic diseases.[6,12]

The issue of whether or not to correct DXA BMD data for body size might have implications beyond simple assessments of the prevalence of low bone mass. Failure to adjust DXA BMD values for body size might also bias studies of the correlates and etiology of low bone mass. For example, in a separate report from the present study but based on the same sample[13] we noted a relatively high prevalence of underweight, with underweight being defined on the basis of a low body mass index for age and sex using the definition of Cole et al.[14] For the present study, as a secondary aim, we intended to test the a priori hypothesis that bone health would be poorer in the underweight patients compared with the other patients. Using uncorrected BMD Z scores for whole body and lumbar spine we found an excess of low BMD values in the underweight patients: prevalence of low bone status amongst the 9 underweight patients was 78% (7/9) and 89% (8/9), respectively. However, after correction for body size only 1/9 (11%) of the underweight patients and 0/9 had low whole body and lumbar spine BMC, respectively. This example illustrates that the consequences of misinterpreting BMD data from DXA go beyond simple conclusions about the prevalence of impaired bone health in a patient group.

The present study had a number of limitations. It was not intended to provide definitive conclusions in relation to the bone health of survivors of ALL—issues of the

prevalence, nature, and etiology of bone health impairments in ALL were beyond the scope of the present study. The present study was methodological, aimed solely at examining the impact of correction of BMD for size, and was adequate for this purpose. It should also be noted that, while serial measurement using DXA is a helpful tool for assessing longitudinal changes in bone health, it is insufficient on its own as a measure of bone health: the role of DXA in diagnosing impaired bone health in children with chronic disease is complex and remains unclear.[15] Data not included in the present study (eg, fracture history) would provide clinically important information on bone health but collecting such data was beyond the scope of the present study. Alternative means of correcting DXA data are available [9] but these were also beyond the scope of the present study which aimed to provide a simple empirical demonstration of the impact of using uncorrected DXA BMD data in a relatively homogenous sample of survivors of childhood ALL, the most common childhood malignancy.

CONCLUSIONS

Bone health remains a concern during and after treatment for childhood malignancy. This study provides empirical evidence which strongly supports the recommendation that BMD data from DXA should be interpreted cautiously, particularly in children and adolescents with malignancy. The use of DXA as a measure of bone health requires an adjustment for body size.

ACKNOWLEDGMENTS

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CLINICAL AND LABORATORY OBSERVATIONS

PROGNOSTIC SIGNIFICANCE OF BEING OVERWEIGHT AND OBESE AT DIAGNOSIS IN

CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Running Head: Obesity and survival in childhood ALL

ABSTRACT

This study tested the hypothesis that being overweight/obese at diagnosis of childhood ALL was related to risk of relapse. In a national cohort of 1033 patients from the UK there was no evidence that weight status at diagnosis was related significantly to risk of relapse: log ranks test (p 0.90) with overweight and obesity as the exposure (n 917); individual (p 0.42) and stepwise (p 0.96) proportional hazards models, with BMI Z score as the exposure. The study does not support the hypothesis that being overweight/obese at diagnosis impairs prognosis in childhood ALL in the UK.

INTRODUCTION

For at least some cancers, obesity impairs prognosis [1]. Treatment of ALL has improved [2] but the influence of obesity on treatment outcomes is unclear: some evidence that overweight and obesity at diagnosis both does [3,4] and does not [5,6] increase risk of relapse. Butturini et al [3] found that impairment of prognosis was restricted to older obese patients (over the age of 10), yet most patients with ALL are much younger than this at diagnosis. Gelelete et al [4] recently suggested that overweight/obesity impaired prognosis of ALL for intermediate and high-risk subgroups (n 127), but not for standard risk patients (n 44). Around 15% of children in the UK are obese (BMI$\geq$95th centile relative to UK 1990 reference data) at the typical age at diagnosis of ALL [7]. Moreover, prevalence of obesity in UK patients with ALL increases dramatically during treatment [8] and, if obesity does impair prognosis in childhood ALL, these changes in weight status might also be important to risk of relapse.

Since the issue of whether overweight and obesity impair prognosis in childhood ALL is inconclusive [3-6], the present study aimed to test the hypothesis that being overweight/obese is related to the risk of relapse of childhood ALL.

METHODS AND PROCEDURES

Dataset

The present study was based on secondary analysis of anonymised patient data from the UKALL X treatment trial in the UK (1985-1990). In the UK the vast majority of patients diagnosed with ALL have entered national trials for many years. The sample for the present study is described in detail elsewhere [9], but in brief, 1635 patients were entered onto the trial. We excluded patients who were incorrectly diagnosed or randomised (n 23). We also excluded those considered as high risk at the time the trial took place (central nervous system disease at diagnosis and/or presenting white blood cell count $> 100 \times 10^9$/L; n 225), those considered low risk at that time (girls age 2-9 years with presenting white blood cell count $< 20 \times 10^9$/L; n 347). Exclusion of both high and low risk patients was done in part to retain a relatively large and homogenous sample for analyses, but was also a pragmatic decision based on the fact that electronic patient data were more available for standard risk patients. In addition, those patients with no height or weight recorded (n 7) had to be excluded because their weight status could not be assessed, leaving 1033 potentially eligible patients.

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Exposure and Outcome Measures

In the present study BMI Z score at diagnosis, and being overweight and obese at diagnosis, the latter defined using 6-monthly age and sex-specific cut-offs which are conceptually equivalent to adult BMI based definitions of overweight (BMI of 25 kg/m^2) and obesity (BMI of 30kg/m^2) [10], were the main exposures. The exposure variables were derived from routine clinic measures of weight and height at diagnosis, for the purposes of calculating body surface area for drug dosage. The established and potential prognostic factors were also included in the analyses: age, sex, white blood cell count at diagnosis, randomisation allocation to intensive therapy (no intensification; early intensification; late

intensification; both early and late intensification; the treatment protocol in the UK at the time),

ethnicity (defined as European origin or other). The outcome measure was time to first relapse; in

children who did not relapse during the follow-up period, this time was censored at the last date seen in

clinic, based on information held on trial records [9].

Statistical Analyses

The influence of individual known and potential prognostic factors was first tested in a univariate

manner using log ranks tests with patients categorised based on BMI for age and sex as underweight

[10]; healthy weight; overweight and obese combined [10]. In order to categorise subjects in this way,

we had to exclude those patients who were too young to have their weight status defined by the Cole-

IOTF method (all those under the age of two years, n 116).

To examine the possible independent influence of weight status on risk of relapse we used stepwise

proportional hazards models with known and potential prognostic factors considered together [9],

including BMI Z score as a continuous variable (n 1033).

RESULTS

Characteristics of Study Participants at Diagnosis of ALL

At diagnosis median (IQR) age of patients was 4.9y (3.3, 8.8) and median (IQR) BMI Z score –0.27 (-1.03, 0.45).

Being Overweight and Obese as Possible Prognostic Factors

Table 1 shows risk of relapse in relation to the various prognostic factors, known and potential.

From the univariate analysis of individual factors, using log ranks tests, those which influenced risk of relapse were gender (p 0.02) and age (p 0.01). Being overweight/obese at diagnosis was not significantly associated with risk of relapse (p 0.90). Kaplan Meier survival plots are shown in Figure 1.

Univariate proportional hazards ratio analysis with BMI Z score at diagnosis as a continuous variable showed that this was not significantly associated with risk of relapse (p 0.42). From the stepwise (likelihood ratio) modelling age (p<0.0001); white blood cell count at diagnosis (p 0.005); gender (p<0.0001) were all significantly associated with risk of relapse in the expected directions, but weight status was not significant after those variables had entered into the proportional hazards model (p 0.96).

DISCUSSION

The present study found no evidence that being overweight/obese at diagnosis led to increased risk of relapse in typical patients treated for childhood ALL in the UK. There are a number of plausible mechanisms by which overweight and obesity could increase risk of relapse [1,11,12], and evidence that being overweight/obese at diagnosis might impair prognosis in higher-risk and/or older patients with ALL [3,4]. However, there are important short and long-term adverse consequences of childhood obesity [13,14], and an absence of associations with relapse in typical patients with ALL does not mean that obesity is not a cause for clinical concern.

The reasons for the different conclusions between the studies to address the question of the impact of overweight and/or obesity on risk of relapse in childhood ALL are not entirely clear. It is possible, but unconfirmed, that the age and risk status of patients might be important to any association of obesity at diagnosis with adverse outcome in ALL.

Two studies which reported increased risk of relapse associated with being overweight/obese at diagnosis did so in older and/or higher risk patients [3,4], but one small recent study found increased risk of relapse among all patients [15]; five studies to date have found no risk of relapse in lower-risk patient groups or subgroups (present study plus [3-6]). A recent study in adults [16] found that obesity was associated with significantly increased risk of mortality.

The present study had a number of strengths, in particular the relatively large sample size, and the inclusion of a relatively homogenous group of patients from a national trial. The present study had a number of limitations. Since the present study was restricted to patients considered to be standard risk at the time (1985-1990) we cannot draw conclusions about the possible impact of obesity on relapse among patients at higher or lower risk of relapse. It is possible that subtle associations between weight

status and outcome (e.g. in ability to tolerate chemotherapy , or in drug pharmacokinetics) are masked in standard risk patients but manifest in higher risk patients. The algorithm used for determining chemotherapy doses in patients in the present study was based, in the main, on their actual body surface area. There was no trial record of adjustment of doses in obese patients and we believe that this was very rare. Differences in the algorithms used to calculate body surface area, and in the adjustment, or lack of adjustment, for obesity may explain some of the inconsistencies between studies discussed above.

 The Data on some potential confounders, such as socio-economic status [17] were not available. A high BMI for age and sex provides an acceptable diagnostic method for identifying children with excessive fat mass [18], but it is imperfect both in healthy children and those with malignancy [19,20]. Patient categorisations used in the present study (e.g. exclusion of high and low risk patient groups) were those which applied at the time of the trial and are not identical to those which apply today. Clinical trial data used in the present study are from older protocols, but since 2002 height and weight have not been measured and recorded routinely in patients with ALL in the UK, and so the hypothesis tested in the present study is not testable with recent national UK trial data. The strengths of the present study, combined with a degree of consistency of findings with the other studies of non-high risk patients, enhances confidence in our conclusions that for typical patients with ALL overweight/obesity at diagnosis is unlikely to impair prognosis markedly.

ACKNOWLEDGEMENTS

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FIGURE 1. Kaplan-Meier Survival Plot: Relapse Risk in Relation to Weight Status.

Weight status definitions
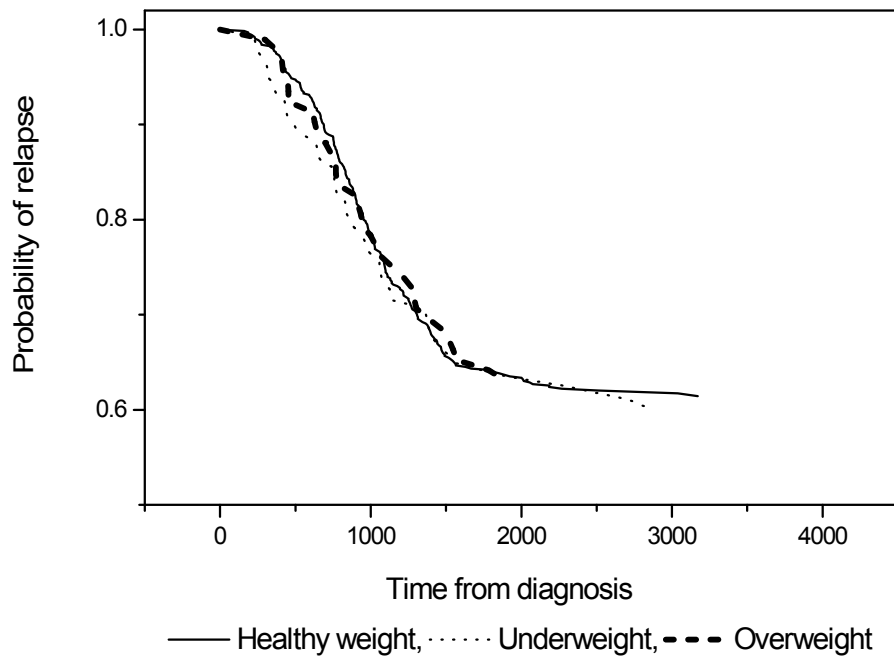
Table 1 Eligible patient characteristics at diagnosis and risk of relapse n (%)

		Relapsed n (%)	No relapse n (%)	Overall n
Age (years)	2.0 – 3.9	112 (31.9)	239 (68.1)	351
	4.0 – 9.9	143 (37.8)	235 (62.2)	378
	10.0 –14.9	82 (43.6)	106 (56.4)	188
	Total	337 (36.8)	580 (63.2)	917
Gender	Boys	277 (39.0)	433 (61.0)	710
	Girls	60 (29.0)	147 (71.0)	207
	Total	337 (36.8)	580 (63.2)	917
White Blood Cell Count (x 10^9)	0 - 10	188 (35.3)	344 (64.7)	532
	10 - 20	49 (36.3)	86 (63.7)	135
	20 – 50	66 (39.8)	100 (60.2)	166
	50 - 100	27 (43.5)	35 (56.5)	62
	Total	330 (36.9)	565 (63.1)	895
Weight status	Healthy weight	236 (36.6)	409 (63.4)	645
	Underweight	67 (37.6)	111 (62.4)	178

317

	Overweight/ obese	34 (36.2)	60 (63.8)	94
	Total	337 (36.8)	580 (63.2)	917
Intensification	Non	97 (42.7)	130 (57.3)	227
	Early	80 (35.2)	147 (64.8)	227
	Late	81 (35.4)	148 (64.6)	229
	Early and late	79 (33.8)	155 (66.2)	234
	Total	337 (36.8)	580 (63.2)	917

Appendix B

Ethical approval
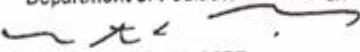
King Faisal Specialist Hospital & Research Centre
Gen. Org.

OFFICE OF RESEARCH AFFAIRS
MBC: 03 | Ext: 32939 | Fax: 27894

INTERNAL MEMORANDUM

TO: Abdullah Al Nasser, MD   DATE: 09 Dhul Qedda 1430
        Consultant   27 October 2009
        Department of Pediatric Hematology/ Oncology

FROM: Mohamed Al Turki, CCRP   REF: ORA/1419/30
        Co-Director
        Office of Research Affairs

SUBJECT: Proposal # 2091 043
         Metabolic Syndrome Prevalence Among Children Acute Lymphoblastic Leukemia
         (ALL) Patients After the End of Treatment

Further to the Office of Research Affairs memo, ORA/1217/30, the revised proposal, Consent Form and Assent Form (received on 21 October 2009) were reviewed and approved by the Research Advisory Council (RAC) on 26 October 2009; and I would like to take this opportunity to congratulate you on behalf of the RAC.

Please be informed that in conducting this study, the investigators are required to abide by the rules and regulations of the Government of Saudi Arabia, KFSH&RC, and the Research Advisory Council. Further, *you are required to submit a Final report by 18 September 2010. The approval of this proposal will automatically be suspended on 18 October 2010* pending the acceptance of the report. You also need to notify the ORA as soon as possible in the case of:
  1 Any amendments to the project;
  2 Termination of the study;
  3 Any new information that may affect the benefit/risk ratio of the proposal.

Please observe the following:
  1 Personally identifying data should only be collected when necessary for research;
  2 The data collected should only be used for this proposal;
  3 Data should be stored securely so that only a few authorised users are permitted access to the database;
  4 Secondary disclosures of personally identifiable data are not allowed;
  5 Copies of the signed Consent Forms should be kept in the research subjects' Medical Records and the Consenting Process should be documented in the Medical Records

We wish you every success in your research endeavours.

Appendix C

CCG 1891 protocol modified by KFSH&RC

OUTLINE OF MANAGEMENT

ACUTE LYMPHOBLASTIC LEUKEM[ ] (STANDARD RISK)

MODIFIED CCG-1891

SECTION OF PEDIATRIC HEMATOLOGY/ONCOLOGY
DEPARTMENT OF ONCOLOGY
King Faisal Specialist Hospital & Research Center

CCG 1891

Phase I – Induction (4 weeks)

Begin after overnight IV hydration, alkalinization and Allupurinol therapy. During induction, no dose will be reduced or delayed solely because of myelosuppression. Induction lasts four (4) weeks.

Dexamethasone, 6 mg/m^2/d P.O. t.i.d., days 0-27, then taper over 14 days
Hyperglycemia: Do not modify; use insulin if necessary.
Grade 4 Hypertension: Reduce dose by 33%. Sodium restriction &
anti-hypertensive drugs may be utilized.
Pancreatitis: Do not modify dose.
Psychosis: Administer half dosage and appropriate antidotes (Benadryl, Haldol).

Vincristine, 1.5 mg/m^2 (2 mg maximum) IV weekly x 4 doses, Days 0, 7, 14, 21.
Seizures: Hold one (1) dose then reinstitute.
Severe foot drop, paresis or ileus:
Hold dose(s); when symptoms abate, resume at
1.0 mg/m^2; escalate to full dose as tolerated.
Jaw pain: Treat with analgesics; do not modify VCR dose.
Hyperbilirubinemia: Withhold if total bilirubin is >32 μmol/l (Grade 3 or 4 toxicity).
Administer ½ dose if total bilirubin is 25-32 μmol/l (Grade 2 toxicity).

L'Asparaginase, 6000 U/m^2 IM x 9 Sat-Mon-Wed Days 3-24.
Pancreatitis, documented by hyperamylasemia, ultrasound or surgery (grade 2-4 toxicity):
Terminate and do not restart.
Symptoms of coagulopathy causing significant bleeding or thrombosis:
Withhold until resolved.
Abnormal coagulation tests without bleeding are not an indication to withhold Asparaginase (ASP).
Hyperglycemia: Do not modify; use insulin if necessary.
Anaphylaxis or anaphylactoid reactions: Initially only E. coli ASP will be used. If an objective hypersensitivity reaction occurs (urticaria, wheezing, hypotension, etc), Erwina ASP will be used as substitute at same dose. Do not switch for pain or non-allergic inflammation at the injection site. If anaphylactic symptoms recur with Erwina ASP, discontinue all ASP therapy.

IT Methotrexate, 8 mg for age 1-2 yr.;

IT MTX should be given on Days 0 and 14.

Hydrocephalus, microcephaly, or known abnormality of CSF flow:
Discuss case with Leukemia Team.

Uric Acid >416 µmol/l, Phosphorous >2.26mmol/l, or Creatinine >88.4µmol/l:
Omit MTX and substitute with Ara-C 30, 50, 70 mg for ages 1-2, 2-3, ≥3 yr. respectively.

Viral, bacterial or fungal meningitis: Omit dose until resolved.

Grade 3 stomatitis: Substitute with Ara-C (see above).

Seizure, paresis, or organic brain syndrome attributed to MTX:
Omit MTX and substitute with Ara-C. Discuss details and indications for CSF drug or myelin basic protein monitoring, etc., with Leukemia Team.

Systemic toxicity:
The dosage of IT MTX will not be reduced for systemic toxicity (myelosuppression, mucositis, etc). Instead, Citrovorum Factor, 10 mg P.O. will be administered 24-36 hours after IT MTX.

Phase II– Consolidation (4 weeks)

For all patients M1 on Day 28 of Induction, Day 0 of consolidation will be Day 28 of Induction or when peripheral counts recover with absolute neutrophil count (ANC) >500/µl and platelet count >100,000/µl. Begin tapering DEX on Day 28 of induction and taper over 14 days.

Once consolidation had begun it may be interrupted for myelosuppression (ANC <500/µl or platelets <100,000) on Day 14 only. Therapy must be interrupted in patients who are neutropenic and febrile with presumed or proven infection; therapy is resumed when the signs of infection have abated. Patients who have discontinued Dexamethasone may require stress doses of hydrocortisone if infection occurs.

Dexamethasone
Taper: 3.0 mg/m²/d P.O. (days 0-2),
1.5 mg/m²/d P. O. (days 3-5),
1 mg/m²/d P.O. (days 6-9),
0.5 mg/m²/d P.O. (days 10-13).

Divide daily into three equal doses to the nearest 0.5 mg.

Hyperglycemia: Do not modify; use insulin if necessary.

Grade 4 Hypertension: Reduce dose by 33%. Sodium restriction & anti-hypertensive drugs may be utilized.

Vincristine, 1.5 mg/m² (2.0 mg maximum single dose) day 0.

6-Mercaptopurine, 75 mg/m²/d P. O. days 0-27, in the evening.

Absolute Neutrophil Count (ANC) >500 and <750: If the absolute neutrophil count falls between 500 and 750, 6-Mercaptopurine should be reduced to 50% of the original dose until the ANC recovers to ≥750 at which time 6-MP should be increased to 75% of the original dose and gradually increased to 75% and then 100% of the original dose at weekly intervals should the ANC remain ≥750.

If the ANC drops below 500, 6-MP should be stopped until the neutrophil count returns to ≥ 750. At this time, the 6-MP should be started at a dosage 50% of the original dose and gradually increased to 75% and then 100% of the original dose at weekly intervals should the ANC remain ≥ 750.

Platelet count <50,000 or <100,000: The same modifications apply if the platelet count falls below 100,000 and 50,000 respectively, as apply to ANC <750 or <500.

ANC <750 or platelets <100,000 for 2 weeks: If the ANC do not rise to ≥750 or platelet count does not rise to ≥100,000 within 2 weeks, a bone marrow should be done.

Hepatotoxicity Grades 3-4: Withhold until etiology is determined. If 6-MP is not the cause, then resume. If it is the cause, resume at half dose when toxicity decreases to grade 0-2; escalate to full dose as tolerated.

Herpes Zoster/Varicella Exposure: Exposure of susceptible patients to varicella or to zoster will not require discontinuation of 6-MP during the incubation period. If disease does occur, 6-MP should be stopped and anti-viral therapy initiated. Re-institute 6-MP when no new lesions appear and old lesions are healing.

Infection: Discontinue 6-MP for serious infection until resolved.

IT Methotrexate, 8 mg for age 1-2 yr.;
   10 mg, age 2-3 yr;
   12 mg, age ≥3 yr.   given days 0, 7, 14, 21.
Grades 3 & 4 stomatitis: Citrovorum 12 mg. IV or P.O. q 6 hr. beginning 36-42 hours after IT MTX and continued until plasma MTX concentration 0.1 micromolar. *Do not hold IT MTX.*

Do not administer Citrovorum solely for myelosuppression.

Phase III – Interim maintenance I (8 weeks)

For all patients in remission upon completion of Phase II, day 0 of Phase III will be day 28 of Phase II or when peripheral counts recover with ANC ≥1000/µl and platelet count ≥100,000/µl, whichever occurs last. During Phase III, therapy should be interrupted for serious infection such as varicella or pneumocystis carinii pneumonia or for ANC ≤1000/µl or platelets <100,000/µl and resumed at full dose when interrupted for infection and at 75% dose when interrupted for low blood counts when counts recover. If counts do not recover within 14 days, bone marrow aspiration should be performed, and if not, M3, repeated at 14-day intervals until counts recover or M3 occurs. Whether or not the scheduled therapy has been completed, Phase III will last no longer than 56 days.

6-Mercaptopurine, 75 mg/m^2/d P.O. days 0-56, in the evening

Methotrexate, 20 mg/m^2/wk P.O. days 7,14,21,28,35,42, & 49 in the evening.

Absolute Neutrophil Count (ANC) >500 and <750: Methotrexate should be reduced to 50% of the original dose when the absolute neutrophil count drops below 750 but remains above 500 until the ANC recovers to ≥750. Methotrexate should then be increased to 75% of the original dose and, if the ANC remains >750 for one week, the full dose should be resumed.

If the ANC falls below 500, Methotrexate should be discontinued until the ANC rises to ≥1000. Methotrexate should then be restarted at 50% of the original dose and follow increases noted above.

Platelet count <50,000 or <100,000: The same modifications apply to platelet count of <50,000 and <100,000 respectively as apply to neutrophil count of <500 or <750.

ANC <750 or platelets <100,000 for 2 weeks: If the ANC does not rise to ≥1000 or platelet count does not rise to ≥100,000 within 2 weeks, a bone marrow examination should be done.

Severe diarrhea &/or Persistent Vomiting: If either develops, MTX should be discontinued. Restart at 50% of the original dose when symptoms remain absent for 1 week and escalate as appropriate. If symptoms recur, adjust the maximum tolerated dose to prevent recurrence of symptoms.

Mouth Ulcers: Methotrexate should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity ulcers until there is resolution and then resume at 50% of original dose with gradual dose escalation.

Liver Dysfunction: Should Grade 3 or 4 liver toxicity develop, discontinue oral MTX until improvement occurs. Restart at 50% of the original dose and escalate as appropriate. If improvement does not occur or recurrent liver dysfunction develops, discuss further modifications with Leukemia Team.

Herpes Zoster/Varicella Exposure: Exposure of susceptible patients to varicella or to zoster will not require discontinuation of MTX during the incubation period. If disease does occur, MTX should be stopped and anti-viral therapy initiated. Re-institute MTX when no new lesions appear and old lesions are healing.

Stomatitis Grade 2 of >3 days duration: Decrease dose by 30%.

Stomatitis Grade 3-4: Withhold dose until resolved; resume dose at 50%.

Vincristine, 1.5 mg/m^2 (2.0 mg maximum) IV monthly, days 0 & 28.

Seizures: Hold one (1) dose then reinstitute.

Severe foot drop, paresis or ileus: Hold dose(s); when symptoms abate, resume at 1.0 mg/m^2; escalate to full dose as tolerated.

Jaw pain: Treat with analgesics; do not modify VCR dose.

Hyperbilirubinemia: Withhold if total bilirubin is >32 µmol/l (Grade 3 or 4 toxicity). Administer ½ dose of total bilirubin is 25-32 µmol/l (Grade 2 toxicity).

Dexamethasone, 6 mg/m^2/d P.O. t.i.d., monthly x 5 days on days 0-4 & 28-32 & days 56-60.
Hyperglycemia: Do not modify; use insulin if necessary.
Grade 4 Hypertension: Reduce dose by 33%. Sodium restriction & anti-hypertensive drugs may be utilized.
Pancreatitis: Do not modify dose.
Psychosis: Administer half dosage and appropriate antidotes (Benadryl, Haldol).
Varicella Exposure/Varicella: Withhold dose.

IT Methotrexate, 8 mg for 1-2 yr. of age, 10 mg for 2-3 yr. of age, 12 mg for ≥3 yr. of age. Give once on day 0.

Phase IV - Delayed Intensification I

This phase consists of reinduction and reconsolidation therapies. For all patients in remission upon completion of Phase III, day 0 of Phase IV is day 56 of Phase III or when ANC is ≥1000/µl and the platelets ≥100,000/µl. Once begun, the reinduction therapy is not interrupted for myelosuppression alone. Reconsolidation therapy is scheduled to begin on day 28 but should be delayed until the ANC is ≥1000/µl and platelets ≥100,000/µl. Once begun, reconsolidation therapy is also not to be interrupted solely for myelosuppresion. Any serious infection such as varicella or pneumocystis pneumonia, presumed or proven infection in a patient with neutropenia and fever warrants chemotherapy interruption at any time during Phase IV. Bone marrows are often difficult to interpret during this phase. Pancytopenia is inevitable and M2 recovery marrows are not uncommon.

Reinduction (Days 0-27)

Dexamethasone, 10 mg/m^2 P.O. tid x 21 days 0-20.
Then taper over 7 days: 5 mg/m^2/d x 3 days
                      2.5 mg/m^2/d x 3 days
                      1.25 mg/m^2/d x 1 day.

Vincristine, 1.5 mg/m^2 (2.0 mg maximum) IV weekly x 3 doses, days 0, 7, & 14.
Adriamycin, 25 mg/m^2 IV bolus over less than 30 minutes weekly x 3, days 0, 7, & 14.

Congestive heart failure: contraindicated.
Total bilirubin <17, 19-24, 25-32 and >32 µmol/l
                      Administer 25, 12.5, 6.25 and 0 mg/m^2, respectively (Grade 0-4 toxicity, respectively).

L'Asparaginase, 6000 U/m^2 IM x 6 doses, Sat, Mon, Wed days 3-17.

Ketoacidosis: Terminate.
History of L'Asp-induced pancreatitis: Omit.

Pancreatitis, documented by hyperamylasemia, ultrasound or surgery (grade 2-4 toxicity):

Terminate and do not restart.

Symptoms of coagulopathy causing significant bleeding or thrombosis:

Withhold until resolved.

Abnormal coagulation tests without bleeding are not an indication to withhold Asparaginase (ASP).

Hyperglycemia: Do not modify; use insulin if necessary.

Anaphylaxis or anaphylactic reactions: Initially only E. coli ASP will be used. If an objective hypersensitivity reaction occurs (urticaria, wheezing, hypotension, etc), Erwina ASP will be used as substitute at same dose. Do not switch for pain or non-allergic inflammation at the injection site. If anaphylactic symptoms recur with Erwina ASP, discontinue all ASP therapy.

Reconsolidation   (Days 28-49)

Dexamethasone.
Complete taper.

Cyclophosphamide. 1000 mg/m^2 IV, day 28.

Reduce urine SpG to <1.010 with IV fluids before and for at least 3hrs. after dose.

Gross hematuria >24 hours: Delete subsequent dose.

Gross hematuria <24 hours or microscopic hematuria: For next dose, prehydrate to urine SpG <1.005 and continue IV fluids for at least 24 hours after CPM; do not withhold for prior microscopic hematuria.

Acute fluid retention: Treat with Furosemide (Lasix) and Saline; Do not modify CPM.

6-Thioguanine, 60 mg/m^2/d P.O. x 14, days 28-41 in the evening.

Cytosine Arabinoside, 75 mg/m^2/d IV or SC x 8 on days 29-32 and 36-39.

Withhold if total bilirubin >32 µmol/l or transaminase >4.9 times normal (Grade 3 hepatotxicity).

Do not modify for rash unless Grade 4.

IT Methotrexate 8, 10, 12 mg for 1-2 yr, 2-3 yr, and ≥3 year olds, respectively, on days 28 and 35.

Phase V – Interim Maintenance II

Interim maintenance II will start on day 49 of delayed intensification I, or when ANC ≥1000/μl and platelets ≥100,000/μl, whichever occurs last.

6-Mercaptopurine. 75 mg/m²/d P.O., days 0-56 in the evening.

Absolute Neutrophil Count (ANC) >500 and <750: If the ANC falls to between 500-750, 6-Mercaptopurine should be reduced to 50% of the original dose until the ANC recovers to ≥750 at which time 6-MP should be increased to 75% of the original dose and then to full dose one week later, should the ANC remain above 750.

If the ANC drops below 500, 6-MP should be discontinued until the neutrophil count returns to ≥750. At this time, the 6-MP should be started at a dosage of 50% of the original drops and gradually increased to 75% and then 100% of the original dose at weekly intervals should the ANC remain ≥750.

Platelet count <50,000 or < 100,000: The same modifications apply if the platelet count falls below 100,000 and 50,000, respectively, as apply to ANC <750 or <500.

ANC <750 or platelets <100,000 for two (2) weeks: If the ANC does not rise to ≥1000 or platelet count does not rise to ≥100,000 within 2 weeks, a bone marrow examination should be done.

Hepatotoxicity Grades 3-4: Withhold until etiology is determined. If 6-MP is not the cause, then resume at half-dose when toxicity decreases to Grade 0-2; escalate to full dose as tolerated.

Herpes Zoster/Varicella Exposure: Exposure of susceptible patients to varicella or to zoster will not require discontinuation of 6-MP during the incubation period. If disease does occur, 6-MP should be stopped and anti-viral therapy initiated. Reinstitute 6-MP when no new lesions appear and old lesions are healing.

Infection: Discontinue 6-MP for serious infection until infection is resolved.

Methotrexate. 20 mg/m²/wk P.O., days 7, 14, 21, 28, 35, 42, & 49 in the evening.
Absolute Neutrophil Count (ANC) >500 and <750: MTX should be reduced to 50% of the original dose when the ANC drops below 750 but remains above 500 until the ANC recovers to ≥750. MTX should then be increased to 75% of the original dose and, if the ANC remains above 750 for one week, the full dose should be resumed.

If the ANC falls below 500, MTX should be discontinued until the ANC rises to ≥750. MTX should then be restarted at 50% of the original dose and follow increases noted above.
Platelet Count <50,000 or < 100,000: The same modifications apply to platelet count of <50,000 and <100,000 respectively as apply to neutrophil count of <500 or <750.

ANC <1000 or platelets <1000,000 for two (2) weeks: If the ANC does not rise to ≥100,000 within 2 weeks, a bone marrow examination should be done.

Severe diarrhea or persistent vomiting: If either develops, MTX should be discontinued. Restart at 50% of the original dose when symptoms remain absent for one week and escalate as appropriate. If symptoms recur, adjust the maximum tolerated dose to prevent recurrent symptoms.

Mouth Ulcers: MTX should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity ulcers until there is resolution and then resume at 50% of original dose with gradual dose escalation.

Stomatitis Grade 2 of >3 days duration: Decrease dose by 30%.
Stomatitis Grade 3-4: Withhold until resolved; resume dose at 50%.

Liver Dysfunctions: Should Grade 3 or 4 liver toxicity develop, discontinue oral MTX until improvement occurs. Restart at 50% of the original dose and escalate as appropriate. If improvement does not occur, or recurrent liver dysfunction develops, discuss further modifications with Leukemia Team.

Herpes Zoster/Varicella Exposure: Exposure to susceptible patients to varicella or to zoster will not require discontinuation of MTX during the incubation period. If disease does occur, MTX should be stopped and anti-viral therapy initiated. Reinstitute MTX when no new lesions appear and old lesions are healing.

Vincristine, 1.5 mg/m^2 (2.0 mg maximum) IV monthly, days 0 and 28.

Severe foot drop, paresis or ileus: Hold high dose(s); when symptoms abate, resume at 1.0 mg/m^2; escalate to full dose as tolerated.
Jaw Pain: Treat with analgesics; do not modify VCR dose.
Hyperbilirubinemia: Withhold if total bilirubin >32 μmol/l (Grade 3 or 4 toxicity). Administer ½ dose if total bilirubin 25-32 μmol/l (Grade 2 toxicity).

Dexamethasone, 6 mg/m^2/day P.O. (divided tid) monthly x 5 days, on days 0-4 and 28-32.

Hyperglycemia: Do not modify; use insulin if necessary.
Grade 4 Hypertension: Reduce dose by 33%. Sodium restriction &
anti-hypertensive drugs may be utilized.
Pancreatitis: Do not modify dose.
Psychosis: Administer half dosage and appropriate antidotes (Benadryl, Haldol).

IT Methotrexate,   8 mg, for age 1-2 yr.;
                  10 mg, age 2-3 yr;
                  12 mg, age ≥3 yr.

Give once on day 0.

Hydrocephalus, microcephaly, or known abnormality of CSF flow: Discuss case with the Leukemia Team.

Uric acid > 416 µmol/l, Phosphorous > 2.26 mmol/l, or Creatinine > 88.4 µmol/l.: Omit MTX and substitute with Ara-C 30, 50, 70 mg for ages 1-2, 2-3, ≥3 yr respectively.

Viral, bacterial or fungal meningitis: Omit until resolved.,

Grade 3 stomatitis: Substitute with Ara-C. See above.

Seizure, paresis, or organic brain syndrome attributed to MTX: Omit MTX and substitute with Ara-C. Discuss details and indications for CSF drug or myelin basic protein monitoring, etc., with Leukemia Team.

Systemic toxicity: The dosage of IT MTX *will not* be reduced for systemic toxicity. (myelosuppression, mucositis, etc). Instead, Leucovorin Factor 10 mg/m² P.O. will be administered 24-36 hours after IT MTX.

Phase VI – Delayed Intensification II

The second delayed intensification will begin on day 56 of Interim Maintenance II or when ANC ≥1000/µl and platelets ≥100,000/µl.

Reinduction – (Day 0-27)

Dexamethasone, 10 mg/m² P.O. tid x 21, days 0-20.
Then taper over 7 days: 5   mg/m²/d x 3 days, then
                  2.5   mg/m²/d x 3 days, then
                  1.25 mg/m²/d x 1 day.

Vincristine, 1.5 mg/m² ((2.0 mg maximum) IV weekly x 3 doses, days 0, 7, and 14.

Adriamycin, 25 mg/m² IV bolus over less than 30 minutes weekly x 3, days 0, 7, & 14.
Congestive Heart Failure: Contraindicated.
Total bilirubin <17, 19-24, 25-32, and >32 µmol/l: Administer 25, 12.5, 6.25 and 0 mg/m², respectively (Grade 0-4 toxicity, respectively).

L'Asparaginase, 6000 U/M² X 6, Mon-Wed-Fri, days 3-17.
Hyperglycemia without ketoacidosis: Do not modify.
Ketoacidosis: Terminate.
History of L-Asp-induced pancreatitis: Omit..
Pancreatitis, documented by hyperamylasemia, ultrasound or surgery (Grade 2-4 toxicity): Terminate and do not re-start.

Hyperammonemia & symptoms of coagulopathy causing significant bleeding or thrombosis: withhold until resolved. Abnormal coagulation tests without bleeding are not an indication to withhold ASP.

Hyperglycemia: Do not modify; use insulin if necessary.

Anaphylaxis or anaphylactic reactions: Initially only E. coli ASP will be used. If an objective hypersensitivity reaction occurs (urticaria, wheezing, hypotension, etc.), Erwina ASP will be used as substitute using same dose. Do not switch for pain or non-allergic inflammation at the injection site. If anaphylactic symptoms recur with Erwina ASP, discontinue all SP therapy.

Liver Dysfunctions: Should Grade 3 or 4 liver toxicity develop, discontinue oral MTX until improvement occurs. Restart at 50% of the original dose and escalate as appropriate. If improvement does not occur, or recurrent liver dysfunction develops, discuss further modifications with Leukemia Team.

Herpes Zoster/Varicella Exposure: Exposure to susceptible patients to varicella or to zoster will not require discontinuation of MTX during the incubation period. If disease does occur, MTX should be stopped and anti-viral therapy initiated. Reinstitute MTX when no new lesions appear and old lesions are healing.

Stomatitis Grade 2 of >3 days duration: Decrease dose by 30%.
Stomatitis Grade 3-4: Withhold until resolved; resume dose at 50%.

Bone Marrow Aspiration

Bone marrow aspirate is required when clinically indicated by:

1. circulating blast cells;
2. unexplained organomegaly or lymphadenopathy;
3. unexplained bone pain;
4. suspected or documented extramedullary leukemia OR
5. two weeks after stopping chemotherapy because of low ANC or platelet count, if the ANC is still <750/μl or the platelet count is <100,000/μl.

Patients are off-protocol therapy if they develop on M2 or M3 marrow or extramedullary disease before or at the end of scheduled maintenance therapy. For additional specifications regarding the management of relapse, discuss with Leukemia Team.

Maintenance Duration

Therapy will end for patients as follows:
1. Girls will end therapy two years from the beginning of Interim Maintenance I
2. Boys will end therapy three years from the beginning of Interim Maintenance I
3. Therapy will end on the anniversary date and the maintenance course in progress is not to be completed.

Reconsolidation – (Days 28-49)

Dexamethasone.
Complete taper.

Cyclophosphamide, 1000 mg/m² IV, day 28.
Reduce urine SpG to <1.010 with IV fluids before and for at least 3 hours after dose.
Gross hematuria <24 hrs or microscopic hematuria: For next dose, prehydrate to urine
   SpG <1.005 and continue IV fluids for at least 24 hours after CPM; do not
   withhold for prior microscopic hematuria.
Acute fluid retention: Treat with Furosemide & Saline; Do not modify CPM.

6-Thioguanine, 60 mg/m²/d P.O. x 14, days 28-41 in the evening.
Hepatotoxicty Grade 3-4: Withhold until etiology is determined. If 6-TG is not the cause,
   resume it. If 6-TG is the cause, resume at half-dose when toxicity grade is 0-2.
   Escalate to full dose as tolerated.

Cytosine Arabinoside, 75 mg/m²/d IV or SC x 8, days 29-32 and 36-39.
Withhold if total bilirubin is >32 µmol/l or transaminases >4.9 times normal (Grade3
   hepatotoxicity).
Do not modify for rash unless Grade 4.

IT Methotrexate, 8, 10, 12 mg for 1, 2, ≥3 year olds, respectively, on days 28 & 35.

Phase VII - Maintenance

Phase VII begins day 49 of Delayed intensification II (Phase VI) or when peripheral counts recover with ANC ≥750/µl and platelets ≥100,000/µl, whichever occurs last. Duration of therapy will be measured from the beginning of Interim Maintenance I. For girls, the duration of therapy will be two calendar years from the beginning of interim maintenance I. For boys, the duration of therapy will be three calendar years from the beginning of interim maintenance I. The course in progress is stopped when the end of therapy is reached.

Routine blood counts are obtained q 28 days unless there is a clinical indication for more frequent monitoring.

Courses will be limited to 12 weeks (days 0-83) Myelosuppression therapy will be interrupted for ANC <750/µl and platelets <100,000/µl and not made up. Oral medications are resumed at 50% of the previous dose when the counts recover. If a patient is due for a VCR/DEX pulse and the counts are too low, the pulse may be given if the therapy is delayed less than two (2) weeks and omitted if the delay is longer. The oral doses of 6-MP and MTX should be adjusted to maintain the ANC between 750/µl and 1500/µl, and the platelet count >100,000/µl.

Days off-therapy due to varicella, rubeola or other infections not associated with neutropenia are not counted as days of maintenance (i.e., if the child stops treatment for varicella, the day that therapy resumes is counted as the next day after treatment stopped.

IT Methotrexate. To be given on day 0 of each 12-week course. 8, 10, 12 mg for 1-2, 2-3, ≥3 year olds respectively.

Hydrocephalus, microcephaly, or known abnormality of CSF flow: Discuss with Leukemia Team.

Uric acid > 416 μmol/l, Phosphorus > 2.26 mmol/l, or Creatinine > 88.4 μmol/l: Omit and substitute with Ara-C 30, 50, 70 mg for 1-2, 2-3 and ≥ 3 year olds, respectively.

Viral, bacterial or fungal meningitis: Omit dose until resolved.

Grade 3 stomatitis: Substitute with Ara-C (see above).

Seizure, paresis, or organic brain syndrome attributed to MTX:
Omit MTX and substitute with Ara-C. Discuss details and indications for CSF drug or myelin basic protein monitoring, etc., with Leukemia Team.

Systemic toxicity: The dosage of IT MTX will not be reduced for systemic toxicity (myelosuppression, mucositis, etc). Instead, Citrovorum Factor, 10 mg P.O. will be administered 24-36 hours after IT MTX.

Vincristine, 1.5 mg/m^2 ((2.0 mg maximum) IV monthly on days 0, 28, & 56
Seizures: Hold one dose, then reinstitute.
Severe foot drop, paresis or ileus: Hold high dose(s); when symptoms abate, resume at 1.0 mg/m^2; escalate to full dose as tolerated.
Jaw Pain: Treat with analgesics; do not modify VCR dose.
Hyperbilirubinemia: Withhold if total bilirubin >32 μmol/l (Grade 3 or 4 toxicity). Administer ½ dose if total bilirubin 25-32 μmol/l (Grade 2 toxicity).

Dexamethasone, 6 mg/m^2/day P.O. (divided tid) monthly x 5 days, on days 0-4 and 28-32, & 56-60.
Hyperglycemia: Do not modify; use insulin if necessary.
Grade 4 Hypertension: Reduce dose by 33%. Sodium restriction & anti-hypertensive drugs may be utilized.
Pancreatitis: Do not modify dose.
Psychosis: Administer half dosage and appropriate antidotes (Benadryl, Haldol).

6-Mercaptopurine, 75 mg/m^2/d P.O., days 0-83 in the evening.
Absolute Neutrophil Count (ANC) >500 and <750: If the ANC falls to between 500-750, 6-Mercaptopurine should be reduced to 50% of the original dose until the ANC recovers to ≥750 at which time 6-MP should be increased to 75% of the original dose and then to full dose one week later, should the ANC remain above 750.

If the ANC drops below 500, 6-MP should be discontinued until the neutrophil count returns to ≥750. At this time, the 6-MP should be started at a dosage of 50% of the original drops and gradually increased to 75% and then 100% of the original dose at weekly intervals should the ANC remain ≥750.

Platelet count <50,000 or < 100,000: The same modifications apply if the platelet count falls below 100,000 and 50,000, respectively, as apply to ANC <1000 or <500.

ANC <1000 or platelets <100,000 for two (2) weeks: If the ANC does not rise to ≥1000 or platelet count does not rise to ≥100,000 within 2 weeks, a bone marrow examination should be done.

Hepatotoxicity Grades 3-4: Withhold until etiology is determined. If 6-MP is not the cause, then resume at half-dose when toxicity decreases to Grade 0-2; escalate to full dose as tolerated.

Herpes Zoster/Varicella Exposure: Exposure of susceptible patients to varicella or to zoster will not require discontinuation of 6-MP during the incubation period. If disease does occur, 6-MP should be stopped and anti-viral therapy initiated. Reinstitute 6-MP when no new lesions appear and old lesions are healing.

Infection: Discoptinue 6-MP for serious infection until infection is resolved.

Methotrexate. 20 mg/m²/wk P.O., days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, & 77 in the evening.
Absolute Neutrophil Count (ANC) >500 and <750: MTX should be reduced to 50% of the original dose when the ANC drops below 750 but remains above 500 until the ANC recovers to ≥750. MTX should then be increased to 75% of the original dose and, if the ANC remains above 750 for one week, the full dose should be resumed.

If the ANC falls below 500, MTX should be discontinued until the ANC rises to ≥1000 MTX should then be restarted at 50% of the original dose and follow increases noted above.

Platelet Count <50,000 or < 100,000: The same modifications apply to platelet count of <50,000 and <100,000 respectively as apply to neutrophil count of <500 or <750.

ANC <750 or platelets <1000,000 for two (2) weeks: If the ANC does not rise to ≥100,000 within 2 weeks, a bone marrow examination should be done.

Severe diarrhea or persistent vomiting: If either develops, MTX should be discontinued. Restart at 50% of the original dose when symptoms remain absent for one week and escalate as appropriate. If symptoms recur, adjust the maximum tolerated dose to prevent recurrent symptoms.

Mouth Ulcers: MTX should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity ulcers until there is resolution and then resume at 50% of original dose with gradual dose escalation.

Appendix D

IDF and the NCEP III modified by Cook et al., (2008)

IDF definition (having central obesity plus two or more additional criteria)		NCEP III definition (having at least three MS criteria)	
10 – 15 years WC ≥ 90th centile	≥ 16 years WC ≥94 cm for men and WC ≥ 80 cm for women	5 – 19 years WC ≥ 90th centile	≥ 19 years WC ≥102 cm for men and WC ≥ 88cm for women
TG ≥ 1.7 mmol/L	TG ≥ 1.7 mmol/L	TG ≥ 1.24 mmol/L	TG ≥ 1.69 mmol/L
HDL-C < 1.03 mmol/L	HDL-C < 1.03 mmol/L in males and < 1.29 for females	HDL-C ≤ 1.03 mmol/L	HDL-C ≤ 1.03 mmol/L for men and HDL-C ≤ 1.29 mmol/L for women
SBP ≥ 130 or DBP ≥ 85 mm Hg	SBP ≥ 130 or DBP ≥ 85 mm Hg	BP ≥ 90th centile	SBP ≥ 130 or DBP ≥ 85 mm Hg
FG ≥ 5.6 mmol/L	FG ≥ 5.6 mmol/L	FG ≥ 6.1 mmol/L	FG ≥ 6.1 mmol/L

WC: Waist circumference; TG: Triglycerides; HDL-C: high density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; FG: Fasting glucose

Appendix E

BMADI$_{LS}$ calculation

An example:

Girl with age 14.1 years old performed by DXA. The results were as following

BMD$_{LS}$ (L2-L4) = 0.815 g/cm^2

Width of L2= 3.2 cm

Width of L3= 3.6 cm

Width of L4= 4.0 cm

Solution:

By applying the following equation:

BMAD$_{LS}$= aBMD$_{LS}$ X [4/ (Ω X width)]; (Ω= 3.14)

Width (L2-L4) = (3.2 + 3.6 + 4.0)/ 3

BMAD$_{LS}$= 0.815 X 0.353= 0.288

Then, adjust BMAD$_{LS}$ according to mean (SD) age and gender reference data.

Mean (SD) of bone mineral apparent density lumbar spine (BMAD$_{LS}$) in boys and girls suggested by van der Sluis et al. (2002)

Age (y)	BMAD$_{LS}$ (g/cm³) Mean
Boys	
4–4.9	0.250
5–5.9	0.262
6–6.9	0.269
7–7.9	0.273
8–8.9	0.276
9–9.9	0.278
10–10.9	0.280
11–11.9	0.282
12–12.9	0.285
13–13.9	0.290
14–14.9	0.300
15–15.9	0.315
16–16.9	0.332
17–17.9	0.349
18–18.9	0.360
19–19.9	0.367
20–20.9	0.370
21–21.9	0.372
22–22.9	0.373
Girls	
4–4.9	0.280
5–5.9	0.284
6–6.9	0.288
7–7.9	0.293
8–8.9	0.297
9–9.9	0.302
10–10.9	0.309
11–11.9	0.319
12–12.9	0.335
13–13.9	0.355
14–14.9	0.372
15–15.9	0.383
16–16.9	0.391
17–17.9	0.396
18–18.9	0.401
19–19.9	0.406
20–20.9	0.410
21–21.9	0.415
22–22.9	0.419

Appendix F

SIGN treatment of obesity guidelines

TREATMENT OF OBESITY IN CHILDREN AND YOUNG PEOPLE

Treatment programmes for managing childhood obesity should incorporate behaviour change components, be family based, involving at least one parent/carer and aim to change the whole family's lifestyle. Programmes should target decreasing overall dietary energy intake, increasing levels of physical activity and decreasing time spent in sedentary behaviours (screen time).

In most obese children (BMI ≥ 98th centile) weight maintenance is an acceptable treatment goal.

Weight maintenance and/or weight loss can only be achieved by sustained behavioural changes, eg:

- healthier eating, and decreasing total energy intake
- increasing habitual physical activity (eg brisk walking). In healthy children, 60 minutes of moderate-vigorous physical activity/day is recommended
- reducing time spent in sedentary behaviour (eg watching television and playing computer games) to <2 hours/day on average or the equivalent of 14 hours/ week.

The following groups should be referred to hospital or specialist paediatric services before treatment is considered:

- children who may have serious obesity-related morbidity that requires weight loss (eg benign intracranial hypertension, sleep apnoea, obesity hypoventilation syndrome, orthopaedic problems and psychological morbidity)
- children with a suspected underlying medical (eg endocrine) cause of obesity including all children under 24 months of age who are severely obese (BMI ≥ 99.6th centile).

Orlistat should only be prescribed for severely obese adolescents (those with a BMI ≥ 99.6th centile of the UK 1990 reference chart for age and sex) with comorbidities or those with very severe to extreme obesity (BMI ≥ 3.5 SD above the mean of the UK 1990 reference chart for age and sex) attending a specialist clinic. There should be regular reviews throughout the period of use, including careful monitoring for side effects.

Bariatric surgery can be considered for post pubertal adolescents with very severe to extreme obesity (BMI ≥ 3.5 SD above the mean on 1990 UK charts) and severe comorbidities.

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