AN INVESTIGATION INTO CARDIOMETABOLIC RISK IN CHILDREN
AND ADOLESCENTS

by

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A thesis submitted to the University of Bedfordshire, in partial
fulfilment of the requirements for the degree of Doctor of
Philosophy

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DECLARATION

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of Bedfordshire.

It has not been submitted before for any degree or examination in any other University.

Name of candidate: Daniel Bailey

Signature:

Date:
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ABSTRACT

The principle aim of this work was to provide an insight into the prevalence of the metabolic syndrome (MetS) in children and adolescents and to examine the associations of body composition measures, cardiorespiratory fitness (CRF), and physical activity with cardiometabolic risk. The combined association of adiposity and CRF on cardiometabolic risk in youths is also explored, as is the association of CRF with potentially modifiable variables, such as physical activity. This work has shown that, dependent on the definition employed, MetS may be present in 2.3% to 9.8% of children and adolescents in Bedfordshire, UK. When applying modified Adult Treatment Panel III definitions (Cook et al. 2003; de Ferranti et al. 2004), the condition was significantly more prevalent in overweight compared to non-overweight youths. Backward regression analyses identified that only body mass index (BMI) explained significant amounts of variance in clustered cardiometabolic risk, although being overweight according to internationally proposed cut points for BMI, waist circumference (WC), and waist-to-height ratio conferred participants to increased risk compared to their non-overweight counterparts. Clustered risk was also elevated in children and adolescents with low levels of CRF compared to those with high levels, whereas time spent in moderate-to-vigorous physical activity and vigorous physical activity (VPA) held no association. When stratified into groups according to level of fatness (BMI z-score) and CRF, those with high fatness/low CRF generally exhibited the most unfavourable cardiometabolic risk profiles. Cardiometabolic risk was higher in the high fatness/low CRF group compared to those with low fatness/low CRF and low fatness/high CRF when excluding WC from the score, and those with low fatness/low CRF when including WC in the score. Multiple regression and ANCOVA revealed that increased visceral fatness (indirectly measured using WC) was associated with reduced CRF, while increased time spent in VPA was associated with elevated CRF. These data suggest that BMI may be the best simple measure of obesity to employ when exploring adiposity-related cardiometabolic in children and adolescents. In addition, results from this
investigation indicate that low CRF and overweight/obesity may have deleterious effects on the cardiometabolic health of children and adolescents and that interventions to reduce risk may target decreases in fatness and improvements in CRF and VPA as standard.
# ACKNOWLEDGEMENTS

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1.0 Introduction

Cardiometabolic risk factors are those related to both cardiovascular disease (CVD) and metabolic disorders, such as type 2 diabetes mellitus. Cardiometabolic risk factors such as insulin resistance, obesity, dyslipidaemia, and hypertension are all independent risk factors for CVD and T2DM in adults (Pyorala et al. 1994; Graham et al. 2007). Clustering of these risk factors can often occur and represents a decreased sensitivity of peripheral tissues to the action of insulin (DeFronzo et al. 1991). This clustering has thus been termed the ‘insulin resistance syndrome’ or ‘metabolic syndrome’ and has received much attention in the scientific literature in recent decades (Gami et al. 2007). It has been evidenced that adults with the metabolic syndrome (MetS) are at increased risk of all-cause mortality, CVD, and T2DM (Isomaa et al. 2001; Ford 2005), and that the presence of multiple risk factors may confer excess additive risk beyond the level predicted by the individual components (Golden et al. 2002). There is also evidence that the clustering of these cardiometabolic risk factors can also occur in childhood and adolescence (Chen et al. 1999) and that clustering during these years persists into adulthood (Raitakari et al. 1994; Eisenmann et al. 2005; Camhi et al. 2010).

Although the prevalence of MetS in children and adolescents has frequently been reported (Cook et al. 2003; Ford et al. 2008; Ekelund et al. 2009), inconsistencies in the definitions used to classify the syndrome have made comparisons across studies and geographic areas difficult. The prevalence of MetS in US adolescents, for example, has been reported as 4.5% using the International Diabetes Federation (IDF) definition (Ford et al. 2008), whereas when using a paediatric modification of the Adult Treatment Panel III (ATP III) definition, 9.2% of adolescents were classified as having the syndrome (de Ferranti et al. 2004). The syndrome appears less prevalent in European youths, with 0.2 and 1.4% of 10- and 15-year-olds, respectively, meeting the IDF MetS criteria (Ekelund et al. 2009), while 4.1% of adolescents (16 to 19 years) display
the syndrome when using a modified ATP III definition (Vissers et al. 2007). In addition to the use of different cut points and criterion, prevalence rates may also vary due to differences in age and country of residence. The use of different MetS criteria warrants further investigation, and is hence investigated in this thesis given that there is a need for researchers to agree on a single preferable definition that will allow comparisons between studies. Furthermore, to the author’s knowledge, the prevalence of MetS in UK youths has only been reported in one previous article that examined only obese individuals (Viner et al. 2005).

Obesity plays a central role in MetS, often preceding the hyperinsulinaemic state in childhood and may have a pre-eminent role in the development of CVD and T2DM (Caprio 2002; Steinberger et al. 2003). This evidence is concerning given the rise in childhood overweight and obesity in recent decades (Wang et al. 2006). 31.9% of US children and adolescents are currently overweight or obese (Ogden et al. 2008), while in England the prevalence is 17.9% and 21.8% for boys and girls, respectively (Stamatakis et al. 2010). Although the obesity trend appears to be stabilising in some populations (Ogden et al. 2008; Sjoberg et al. 2008; Lloret et al. 2009; Salanave et al. 2009; Stamatakis et al. 2010), the current childhood obesity crisis will continue to be apparent unless fatness is drastically reduced on a global scale. This is concerning given that fatness in young people is associated with insulin resistance, dyslipidaemia, hypertension, and markers of inflammation (Andersen et al. 2008; Thomas et al. 2008).

Body mass index (BMI) is widely used as a measure to explore the impact of obesity on cardiometabolic risk factors in adults and children (Cook et al. 2003; de Ferranti et al. 2004). However, in children, BMI is strongly related to growth and maturation and hence BMI measures have to be expressed as z scores or percentiles relative to age and sex (Cole et al. 1995). In addition, the same cut off points to define overweight and obesity cannot be used across different ethnic groups (Ashwell et al. 2005);. Furthermore, BMI cannot differentiate fat mass from bone and muscle mass and does not accurately reflect central adiposity.
(Neovius et al. 2008). This is an important observation given that excess central fatness (particularly visceral) may be more closely related to cardiovascular risk than peripherally distributed fat (Zamboni et al. 1994; Daniels et al. 1999; Despres 2006). Measures of waist circumference (WC) are now used in most MetS definitions due to its representation of abdominal and visceral fatness (Cook et al. 2003; de Ferranti et al. 2004; Alberti et al. 2007). However, the measure of waist-to-height ratio (WHTR) has recently been proposed as an effective global indicator for health risks of obesity in both adults and youths (Ashwell et al. 2005; Browning et al. 2010) and may be more appropriate to use than WC given that the same boundary values may be used across genders, ethnicities, and for both children and adults (Ashwell et al. 2005). The associations of these measures to cardiometabolic risk warrants further investigation and is explored in this thesis.

In spite of issues surrounding the use of various MetS definitions, it is still clear that clustering of cardiometabolic risk factors is evident in a proportion of children and adolescents. As such, researchers have sought to identify the correlates of clustered cardiometabolic risk in youths so that effective preventive strategies can be developed. Increased levels of cardiorespiratory fitness (CRF) and physical activity have been consistently associated with lower risk of CVD outcomes in adults (Blair et al. 2001) and it is thought that these associations may also be evident in children. Indeed, higher levels of CRF have been negatively associated with single cardiometabolic risk factors in youths (Benson et al. 2006; Ekelund et al. 2007; Ruiz et al. 2007; Aires et al. 2010) and features of MetS (Brage et al. 2004), although inconsistencies in the evidence exist (Shaibi et al. 2005).

A number of studies have shown that increased physical activity engagement is associated with improved body composition (Abbott et al. 2004; Rennie et al. 2005) and cardiometabolic risk profiles in children and adolescents (Mitchell et al. 2010). Previous government guidelines have suggested that children and
adolescents should engage in 60 minutes of moderate-to-vigorous physical activity (MVPA) every day (Department of Health 2008). Although some data has linked MVPA engagement with individual cardiometabolic risk factors (Martinez-Gomez et al. 2010; Mitchell et al. 2010; Steele et al. 2009), numerous investigations have found no such associations (Janz et al. 2002; Ruiz et al. 2006). Recent UK, US, and Canadian physical activity guidelines have alternatively suggested that in addition to taking part in at least 60 minutes of MVPA every day, three of these days should include vigorous physical activity (VPA) (US Department of Health and Human Services 2008; Canadian Society for Exercise Physiology 2011; Department of Health 2011). Recent studies have suggested that youths engaging in larger amounts of VPA are more likely to benefit from improved body composition (Janz et al. 2002; Abbott et al. 2004; Patrick et al. 2004; Gutin et al. 2005). However, little evidence is yet available concerning the effects of VPA on other cardiometabolic risk factors such as lipid profile, blood glucose levels, and blood pressure, or the clustering of these risk factors. The associations of CRF, MVPA, and VPA with cardiometabolic risk are thus examined in this thesis.

Cardiometabolic risk factors are associated with both fatness and CRF in children and adolescents (Benson et al. 2006; Chen et al. 2006; Ekelund et al. 2007; Andersen et al. 2008). The likelihood of having abnormal levels for total cholesterol (TC), systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and fasting insulin, are significantly higher in overweight compared to non-overweight youths (Freedman et al. 1999). In young people with MetS, CRF is significantly reduced (Torok et al. 2001), while boys and girls with high CRF are more likely to have reduced clustered cardiometabolic risk (Ruiz et al. 2007). Previous research suggests that adiposity may mediate the relationship between CRF and cardiometabolic risk in youths (Boreham et al. 2001; Rizzo et al. 2007). It has also been postulated that CRF may attenuate the negative impact of obesity on cardiometabolic risk in children (DuBose et al. 2007). The potential
combination of various levels of adiposity and CRF on clustered cardiometabolic risk in youths is currently unconfirmed and under researched, and no studies have explored this hypothesis in any European region. The combined association of fatness and CRF on clustered cardiometabolic risk is therefore explored within this thesis.

Mounting evidence suggests that CRF has an important cardioprotective role in young people (Ruiz et al. 2007; Benson et al. 2006; Ekelund et al. 2007). It is thus of importance to researchers and health practitioners to identify modifiable factors that may influence CRF so that effective strategies to reduce cardiometabolic risk may be implemented. CRF has often been associated with various physical activity variables in children and adolescents (Morrow et al. 1994; Ekelund et al. 2007). There is evidence that VPA may be more beneficial for CRF compared with activities of a lower intensity (Gutin et al. 2005). However, this has not yet been confirmed in the 10 to 14 year-old age range or in UK youths. In addition to physical activity, adiposity also appears to influence CRF (Brunet et al. 2007). It has been postulated, though, that obesity may not actually decrease CRF, but instead limit performance in CRF assessment due to an increased effort to move a larger body mass (Rowland 1991; Norman, Drinkard et al. 2005). However, recent evidence has suggested that visceral obesity may be detrimental to CRF via increased expression of bioactive compounds that may directly or indirectly affect muscle metabolism (Miyatake, Takanami et al. 2004). Some literature has indeed shown that increased visceral fat and WC; which is a good indicator of visceral fatness in youths (Janssen, Heymsfield et al. 2002; Brambilla, Bedogni et al. 2006); are associated with reduced exercise capacity (Miyatake, Takanami et al. 2004; Brunet, Chaput et al. 2007), although the evidence is inconsistent (Shaibi et al. 2005). To date, the degree of association between WC and CRF in UK youths is under researched. The association of different physical activity intensities and WC with level of CRF is thus investigated.
1.1 Aims and Objectives

The principle aim of this work was to provide an insight into the prevalence of MetS in UK children and adolescents and to examine the associations of body composition measures, CRF, and physical activity with cardiometabolic risk. The combined influence of adiposity and CRF on cardiometabolic risk in youths is also explored, as is the association of CRF with potentially modifiable variables, such as physical activity.

The primary objectives are outlined as follows:

Study 1: Comparison of metabolic syndrome prevalence in UK children and adolescents using three different paediatric definitions

   a) To investigate the prevalence of individual risk factors and MetS in a small sample of 10 to 14 year-olds
   b) To explore differences in MetS prevalence in children and adolescents across various proposed definitions (IDF and modified ATP III definitions)
   c) To explore variation in MetS prevalence according to varying degrees of adiposity

Study 2: Relation of waist circumference, waist-to-height ratio, and body mass index to clustered cardiometabolic risk and cardiorespiratory fitness in children and adolescents

   a) To calculate clustered cardiometabolic risk with and without CRF included as a risk factor, and explore variation according to BMI, WC, and WHTR.

Study 3: An investigation into the relation of cardiorespiratory fitness and physical activity with cardiometabolic risk in children and adolescents

   a) To investigate the associations of CRF, MVPA, and VPA with cardiometabolic risk factors in children and adolescents
b) To estimate clustered cardiometabolic risk and explore variation according to varying degrees of objectively determined CRF and time spent in MVPA and VPA

Study 4: The combined influence of cardiorespiratory fitness and body mass index on clustered cardiometabolic risk in children and adolescents

   a) To estimate clustered cardiometabolic risk and explore differences according to different combinations of CRF and fatness levels in children and adolescents

Study 5: Relations of waist circumference and physical activity intensity to cardiorespiratory fitness in children and adolescents

   a) To investigate the degree of association between physical activity intensities and waist circumference with level of CRF in 10 to 14 year-old children and adolescents
2.0 Pathogenesis of the Metabolic Syndrome

The metabolic syndrome (MetS) (also referred to as the insulin resistance syndrome) has been defined as a cluster of the most dangerous risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), which include abdominal obesity, insulin resistance, abnormal lipid profile, high blood pressure (BP), impaired fasting blood glucose or diabetes, and microalbuminuria (WHO 1999). MetS is multifactorial in its origin and its pathogenesis is underlined by two tightly intertwined conditions: obesity and insulin resistance (Grundy et al. 2005). Obesity can be defined as an excess level of body fat (Cole et al. 2000), while insulin resistance is characterised by a reduced response of liver, fat, and muscle cells to insulin (Saltiel et al. 2001). Associations between obesity and insulin resistance have been observed in children and adolescents (Sinaiko et al. 2001; Steinberger et al. 2003) and together these conditions can lead to dyslipidaemia, hypertension, impaired fasting blood glucose or diabetes, and microalbuminuria (Bao et al. 1996; Sinaiko et al. 2001; Grundy 2004).

2.0.1 Overweight and obesity

Some researchers have argued that obesity is the most critical factor in the pathogenesis of cardiometabolic abnormalities (Kahn et al. 2006), while others argue that insulin resistance is the key driving force behind cardiometabolic risk (Eckel et al. 2005). The prior argument is supported by literature that suggests obesity precedes the hyperinsulinaemic state in childhood, (Sinaiko et al. 2001; Steinberger et al. 2003). Either way, there is growing evidence that overweight or obese youths are more likely to have raised cardiometabolic risk (Cook et al. 2003; Weiss et al. 2004). This is alarming given the current childhood obesity epidemic that has developed in recent decades (Wang et al. 2006). In US non-Hispanic black and Mexican-American adolescents, the prevalence of overweight increased more than 10 percentage points between 1988-1994 and 1999-2000 (Ogden et al. 2002). In English children (4 to 11 years), the prevalence of
overweight increased from 5.4% to 9.0% in boys (increase of 3.6%, 95% CI: 2.3-5.0%) and from 9.3% to 13.5% in girls (increase of 4.1%, 95% CI: 2.4-5.9%) between the years of 1984 and 1994 (Chinn et al. 2001). According to data published in the 1990’s, rates of obesity increased 2.3- to 3.3-fold over approximately 25 years in US children and adolescents and 2.0- to 2.8-fold over 10 years in English children (Ebbeling et al. 2002). In 2006, it was estimated that the prevalence of overweight and obesity was 27.7%, 23.5%, and 25.5% in US, Eastern Mediterranean, and European children, respectively (Wang et al. 2006). There is now evidence that the overweight and obesity trend has levelled off or decreased in English, US, French, and Swedish children and adolescents in recent years (Ogden et al. 2008; Sjöberg et al. 2008; Lioret et al. 2009; Salanave et al. 2009; Stamatakis et al. 2010). However, a large proportion of youths still remain overweight or obese, and this is concerning given that fatness tracks into adulthood (Clarke et al. 1993). Of note, those children and adolescents with BMI values at the 95th percentile for age and sex (obesity) have a 62% to 98% likelihood of being overweight at 35 years of age (Guo et al. 2002).

There are a number of potential mechanisms by which excess adiposity may negatively affect cardiometabolic health. Adipose tissue modulates metabolism in the body by releasing non-esterified fatty acids, glycerol, hormones (such as leptin and adiponectin), and proinflammatory cytokines (Wellen et al. 2005; Shoelson et al. 2006). With excess adiposity, the production and release of many of these products is increased (Wellen et al. 2005; Shoelson et al. 2006) and has been associated with insulin resistance, dyslipidaemia, and hypertension in both adults (Kahn et al. 2006) and youths (Sinaiko et al. 2001; Lambert et al. 2004).

Secretion of adiponectin is characteristically low in obesity (Hu et al. 1996; Arita et al. 1999) and has been linked to the development of insulin resistance (Hu et al. 1996), hypertension (Iwashima et al. 2004), increased fatty acid concentrations (Yamauchi et al. 2002), coronary artery disease (Ouchi et al. 1999; Hotta et al. 2000), and T2DM (Spranger et al. 2003). As adiponectin is an anabolic
hormone that drives free fatty acids (FFAs) into adipocytes for esterification, the reduced secretion and circulating levels of adiponectin observed in overweight and obese individuals (Weiss et al. 2003) appears to be a mechanism by which the body attempts to prevent excessive expansion of fat mass (Attie et al. 2009). However, in the liver, adiponectin improves insulin sensitivity, decreases the influx of fatty acids, increases fatty acid oxidation, and reduces hepatic glucose output (Yamauchi et al. 2002), while in muscle, this adipokine appears to activate AMP-activated protein kinase (AMPK) that leads to increased glucose use and fatty acid oxidation (Yamauchi et al. 2002). Moreover, adiponectin appears to be protective against vascular damage via suppression of monocyte attachment to endothelial cells (Okamoto et al. 2000). In combination the health-benefiting actions that are lost with reduced adiponectin appear to contribute to insulin resistance (Stefan et al. 2002) in the overweight and obese and low levels of this adipokine indeed independently predict the development of T2DM (Spranger et al. 2003).

Leptin is another adipocyte implicated in glucose homeostasis and is thought to have a role in regulating insulin sensitivity (Ceddia et al. 2002). It is generally accepted that in early obesity adipocytes increase the secretion of leptin to enhance oxidation of surplus lipids in nonadipose tissues (Kennedy et al. 1997; Banerji et al. 1999; Unger 2003). In muscle and beta cells, leptin promotes lipid oxidation and inhibits lipid synthesis, thus promoting insulin sensitivity (Muioio et al. 1997; Shimabukuro et al. 1997). In skeletal muscle, leptin appears to have a similar role to insulin in stimulating glucose uptake. It appears that leptin may regulate intracellular signalling pathways that are mediated by insulin, such as attenuation of insulin-induced tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) that is responsible for transmitting signals from insulin receptors to intracellular pathways (Ceddia et al. 2002). This, though, may interfere with the insulin signalling cascade within cells and hence contribute to the progression of obesity-associated insulin resistance via decreased glucose uptake (Ceddia et al. 2002). Serum leptin concentrations have been strongly
associated with insulin resistance as measured by the homeostasis model assessment (HOMA-IR); an association that may even be independent of body fat mass or BMI (Fischer et al. 2002; Silha et al. 2003). It is suggested that obese individuals may also display unresponsiveness or deficiencies in leptin and thus fail to benefit from the protective effects of this hormone, consequently resulting in accumulation of lipids (Unger 2003). It is also postulated that glucose transport and metabolism are important in regulating leptin secretion from adipocytes, and that the same inhibitors of glucose transport inhibit the release of leptin from these cells (Mueller et al. 1998). Hence, in an insulin resistant state, the inability of insulin to stimulate glucose metabolism may be another mechanism by which leptin deficiencies become apparent (Larsson et al. 1996; Mueller et al. 1998; Levy et al. 2001).

Several cytokines secreted from adipose tissue have been closely associated with obesity and insulin resistance (Pittas et al. 2004). There is increasing evidence that obesity is associated with chronic low-grade inflammation (Das 2001), which may have a key role in the development of insulin resistance (Grimble 2002). Increasing levels of cytokines released by adipocytes, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), are associated with obesity, impaired glucose tolerance, insulin resistance, and T2DM (Pickup et al. 2000; Bastard et al. 2002; Hotamisligil 2003). Although the mechanisms by which these cytokines induce insulin resistance are not well understood, it appears that they may be responsible for phosphorylation of IRS-1, therefore directly inhibiting the insulin signalling cascade (Hotamisligil et al. 1996; Aguirre et al. 2002). It has also been suggested that IL-6 and TNFα induce the expression of cellular proteins that inhibit insulin receptor signal transduction, thereby inducing insulin resistance (Mooney et al. 2001; Rieusset et al. 2004).

2.0.2 Insulin resistance

As stated previously, some investigators have argued that insulin resistance is the critical factor in the pathogenesis of MetS (Eckel et al. 2005). The major
contributor to the development of insulin resistance appears to be excess levels of circulating FFAs. FFAs are derived mainly from adipose tissue triglyceride stores through the action of the cyclic AMP-dependent enzyme hormone sensitive lipase, and also via lipolysis of triglyceride-rich lipoproteins by the action of lipoprotein lipase (Eckel et al. 2005). In an insulin resistant state, the antilipolytic action of insulin is reduced, thus resulting in increased lipolysis of adipose-stored triglycerides. More fatty acids are consequently secreted from adipocytes, therefore inducing further inhibition of the antilipolytic action of insulin and hence creating additional lipolysis (Eckel et al. 2005).

In muscle, it appears that fatty acids may induce insulin resistance via impairment of glucose transport/phosphorylation, thus inhibiting muscle glycogen synthesis (Savage et al. 2007). Reductions in glucose oxidation and glycogen synthesis by 50% to 60% have been observed following lipid infusion (increasing plasma FFAs) in comparison to glycerol (control) infusion and are associated with a 90% decrease in the increment of intramuscular glucose-6-phosphate concentrations, thus implying reduced glucose transport or phosphorylation activity (Dresner et al. 1999). Given that concentrations of intracellular glucose were lower following lipid infusion compared with glycerol infusion, glucose transport appears to be the rate-limiting step. Insulin stimulated phosphoinositol (PI) 3-kinase activity is a vital component of the insulin signalling pathway that activates skeletal muscle glucose transport (Saltiel et al. 2001). It has been suggested that FFAs may block insulin receptor substrate 1 (IRS-1)-associated PI 3-kinase activity, possibly consequent of serine phosphorylation of IRS-1 and hence reduced tyrosine phosphorylation (Dresner et al. 1999; Yu et al. 2002).

The mechanisms by which FFAs cause insulin resistance in the liver are less clear in comparison with those seen in skeletal muscle. Endogenous production of glucose is evidently higher in T2DM and this appears to be a result of increased gluconeogenesis (Magnusson et al. 1992; Boden et al. 2001). In well-controlled
type 2 diabetics and healthy individuals, increasing plasma FFA concentrations via nicotinic acid administration (which does not directly affect gluconeogenesis (Chen et al. 1999)) are mirrored by increased gluconeogenesis, while the opposite is apparent when FFA levels decrease (Chen et al. 1999; Boden et al. 2001). Overall, changes in FFA concentrations appear to have little effect on endogenous glucose production since changes in gluconeogenesis and glycogenolysis are balanced via hepatic autoregulation (Chen et al. 1999). The mechanisms by which FFAs affect gluconeogenesis remain unclear. Increased production of ATP and NADH by increased pyruvate carboxylase activity (an enzyme responsible for gluconeogenesis) (Jitrapakdee et al. 1999) via acetyl-CoA or long-chain fatty acyl-CoA (generated during FFA oxidation (Roden et al. 1996)) has been proposed as a means of FFA-enhanced gluconeogenesis (Chen et al. 1999). However, other researchers have challenged this hypothesis by reporting that gluconeogenesis is driven by amino acid oxidation without requiring ATP generation from other fuels (Jungas et al. 1992).

2.0.3 Impaired fasting glucose and glucose intolerance

However insulin resistance occurs, this state increases the likelihood of cardiometabolic abnormalities and the development of CVD and T2DM (DeFronzo et al. 1991). Impaired fasting glucose and glucose intolerance have both been commonly used to identify T2DM (WHO 1999) and each of these states reflects a deficiency in the ability of insulin to suppress glucose production and mediate glucose uptake and metabolism in skeletal muscle and adipose tissue (Kahn et al. 2006). This hyperglycaemia due to insulin insensitivity presents a stimulus to the pancreatic beta cells, which then secrete large amounts of insulin; particularly after meals; in an attempt to stimulate glucose uptake and suppress gluconeogenesis (Miranda et al. 2005). However, due to a lack of sensitivity to insulin in muscle, adipose tissue, and/or the liver, euglycaemia is not achieved, and thus the feedback loop to the beta cells to secrete more insulin continues (Miranda et al. 2005). Over time, this ‘overproduction’ or
‘overworking’ of the beta cells can lead to a decline in their function and the occurrence of T2DM (Kahn 2001) and/or elevated levels of postprandial and fasting glucose (Kahn et al. 2006).

2.0.4 Dyslipidaemia

Dyslipidaemia in MetS is characterised by increased levels of triglycerides and low-density lipoprotein cholesterol (LDL), and decreased levels of high-density lipoprotein cholesterol (HDL) (Eckel et al. 2005). The role of LDL is to transport fats to cells, including the smooth muscle walls of arteries (McArdle et al. 2007). When oxidised, LDL participates in artery-clogging plaque-forming atherosclerosis via stimulating monocyte-macrophage infiltration and lipoprotein deposition (McArdle et al. 2007). HDL, on the other hand, facilitates reverse transport of surplus cholesterol from peripheral tissues (including arterial walls) for transport to the liver where it is ultimately excreted from the system (McArdle et al. 2007). In the insulin resistant state, serum LDL levels are increased, whereas the concentration of HDL is decreased (Eckel et al. 2005). This is partly as a result of the antilipolytic effects of insulin on adipose tissue being compromised, which leads to increased amounts of FFAs being released and transported to the liver (Miranda et al. 2005).

The increased flux of FFAs augments hepatic triglyceride-rich very low-density LDL (VLDL) synthesis (Miranda et al. 2005). VLDL exchanges triglyceride for cholesteryl ester from LDL and HDL and lipases then act on triglyceride-rich LDL to create small dense LDL particles (Miranda et al. 2005). The triglyceride-enriched HDL is subject to lipolysis, and once hydrolysed, these particles are cleared more rapidly from the circulation (Brinton et al. 1991). This partly contributes to a strong inverse relationship between triglyceride and HDL levels in the body and appears to be one mechanism by which high triglyceride levels predisposes individuals to a greater risk of CVD. However, it has also been suggested that high fasting levels of triglycerides in the blood may indicate an inability to store excess energy in subcutaneous fat (which should act as a
protective metabolic sink) and may represent associated metabolic complications due to visceral fat accumulation and associated insulin resistance (Lemieux et al. 2007).

This atherogenic profile promotes development of fatty streaks under the endothelial lining in the artery and contributes to narrowing of the artery lumen and a thrombus may form that plugs the blood vessel (McArdle et al. 2007). When a smaller coronary vessel becomes blocked a portion of the heart muscle dies which causes myocardial infarction (McArdle et al. 2007). Coronary artery narrowing can also cause brief periods of inadequate myocardial perfusion, which may cause angina pectoris (temporary chest pains) resultant of insufficient oxygen supply (McArdle et al. 2007).

2.0.5 Hypertension

There is substantial evidence showing that hypertension is a major contributor to CVD outcomes and is related to obesity, insulin resistance, and dyslipidaemia (Ferrannini et al. 1987; Ferrannini et al. 1991). In addition to being a predictor of CVD, elevated blood pressure often coexists with, and predicts the development of, T2DM (Frohlich 1999; Sowers et al. 2001). The relation between insulin resistance and hypertension is well established (Ferrannini et al. 1987) and relates to several different mechanisms. In the insulin resistant state, the mediating role of endothelium-derived nitric oxide can become impaired, thus suppressing the vasodilating effect of insulin (Balletshofer et al. 2000; Stuhlinger et al. 2002). Indeed, past studies have reported positive relationships between endothelial nitric oxide production and insulin sensitivity (Petrie et al. 1996). Insulin also appears to play a secondary role in sodium reabsorption in the kidney (Steinberg et al. 1994; Kuroda et al. 1999). In conditions of hyperinsulinaemia, renal sodium reabsorption may be increased via insulin’s augmentation of the sympathetic nervous system or renin-angiotensin-aldosterone system, thus leading to increased extracellular volume (Kuroda et al. 1999). It has also been observed that increased adipocyte mass can result in
increased angiotensinogen production (which generates angiotensin responsible for vasoconstriction) in adipose tissue (Egan et al. 2001). Additionally, increased FFA concentrations may promote oxidative stress in endothelial cells and consequent atherogenic processes; an effect that is augmented by angiotensin (Egan et al. 2001; Harrison et al. 2003).

2.1 Metabolic syndrome in children and adolescents

2.1.1 Metabolic syndrome and health risk

In adults, the presence of each MetS component has been linked to an increased risk of developing CVD and T2DM (Boyko et al. 2000; Isomaa et al. 2001; McNeill et al. 2005). Furthermore, having a clustering of these risk factors predisposes individuals to a greater risk for all-cause mortality, CVD, and T2DM (Ford 2005). In a longitudinal study over eight years in a population of 3323 middle-aged adults, 174 incident cases of CVD, 107 of coronary heart disease (CHD), and 178 of T2DM, occurred (Wilson et al. 2005). The age-adjusted relative risk in men with MetS at baseline was 2.88 (95% CI: 1.99-4.16) for CVD, 2.54 (1.62-3.98) for CHD, and 6.92 (4.47-10.81) for T2DM, and in women was 2.25 (1.31-3.88) for CVD, 1.54 (0.68-3.53) for CHD, and 6.90 (4.34-10.94) for T2DM. These findings are further supported by another longitudinal study in which the relative risk for T2DM in normal weight participants with MetS was 3.97 (95% CI: 1.35-11.6) and 3.01 (1.68-5.41) for CVD, while in obese individuals with the syndrome the relative risk for T2DM was 10.3 (5.44-19.5) and for CVD was 2.13 (1.43-3.18) (Meigs et al. 2006).

It has been evidenced that the clustering of cardiometabolic risk factors confers additive risk beyond the level predicted by individual components (Kannel et al. 1993; Grundy 2006). In a previous study that analysed the associations of excess carotid intimal-medial thickness (IMT) with independent and 57 possible combinations of MetS risk factors (hypertension, hyperinsulinaemia, obesity,
hypertriglyceridaemia, low HDL, and hyperglycaemia), 29 of the groupings were associated with excess IMT (subclinical atherosclerosis) and displayed greater risk than each component in isolation (Golden et al. 2002). Groupings that included hypertension and hypertriglyceridaemia were most strongly associated with IMT. However, on the contrary, multivariate analysis of MetS components (as defined in the Adult Treatment Panel III [ATP III] MetS definition) plus an indicator for MetS as an entity did not detect any excess risk for CHD (McNeill et al. 2005), while ATP III-defined MetS conferred no excess risk for CHD once the individual risk factors had been accounted for in multiplicative risk models (Alexander et al. 2003). In spite of contradictory evidence, it is still clear that individuals with MetS or components of MetS are at an increased risk of cardiovascular outcomes.

It has been suggested that a quarter of the world’s adult population has MetS (Alberti et al. 2007) and the syndrome is becoming seemingly more evident in children and adolescents due to the continued rise in overweight and obesity in this population (Stratton et al. 2007). Given that MetS increases the likelihood of CVD and T2DM in adult years, the presence of the condition in youths is concerning when considering data that demonstrates a tracking of cardiometabolic risk factor clustering from childhood to adulthood (Eisenmann et al. 2005; Camhi et al. 2010). In addition to an increased likelihood of having MetS in adulthood if the syndrome is present during youth (odds ratio, OR = 9.4, 95% CI: 4.0-22.2), there is also an increased likelihood of developing CVD (OR = 11.5, 95% CI: 2.1-63.7) and T2DM (OR = 14.6, CI: 4.8-45.3) 25-30 years later (Morrison et al. 2007; Morrison et al. 2008).

2.1.2 Prevalence of the metabolic syndrome in youths

The prevalence of MetS in children and adolescents has been reported by numerous researchers in recent years using a variety of definitions (Cook et al. 2003; de Ferranti et al. 2004; Viner et al. 2005). A recent review of 36 studies revealed that prevalence estimates from general population and community-
based sampling ranged from 1.2 to 22.6%, with up to 60% of overweight and obese children and adolescents defined as having the syndrome (Tailor et al. 2009). The International Diabetes Federation (IDF) released a consensus definition of MetS in children and adolescents in 2007 (Zimmet et al. 2007) that prompted several subsequent reports on the prevalence of the syndrome in this population. In 10 to 16 year-olds, the IDF classify MetS as having abdominal obesity (waist circumference [WC] ≥ 90\textsuperscript{th} percentile for age and sex) plus any two of the following risk factors: triglycerides ≥ 1.7 mmol.L, HDL ≤ 1.03 mmol.L, systolic blood pressure (BP) ≥ 130 mm Hg and diastolic BP ≥ 85 mm Hg, or fasting glucose ≥ 5.6 mmol.L (or known T2DM). The adult IDF criteria are to be used for persons above 16 years of age, while no definition was made available for individuals below 10 years-old. Using the IDF definition, MetS was present in 0.2, 1.4, and 2.4% of 10-, 15-, and 16-year old European children and adolescents, respectively (Pirkola et al. 2008; Ekelund et al. 2009), while the prevalence in US adolescents was slightly higher (4.5% in 12 to 17 year-olds) (Ford et al. 2008).

In addition to the IDF definition for children and adolescents, numerous modifications of the World Health Organisation (WHO) (WHO 1999) and Adult Treatment Panel III (ATP III) (National Cholesterol Education Program [NCEP] 2001) MetS definitions have been proposed to make them suitable for use in the paediatric population. One of the first reports that proposed paediatric-specific criteria based on the ATP III definition was that of Cook and colleagues (2003) who modified the adult criteria to the closest representative values obtainable from paediatric reference data. Individuals with any three of the following risk factors were classified as having MetS: WC ≥ 90\textsuperscript{th} percentile for age and sex, systolic or diastolic BP ≥ 90\textsuperscript{th} percentile for age, sex, and height, HDL ≤ 1.03 mmol.L, triglycerides ≥ 1.24 mmol.L, and fasting glucose ≥ 6.1 mmol.L. Using these criteria, MetS was identified in 4.2% of US adolescents (12 to 19 years-old) (Cook et al. 2003; Duncan et al. 2004). The ATP III adult criteria have also been adapted by other researchers for use in children and adolescents. Vissers and colleagues (2007), for example, found that 4.1% of Belgian adolescents (16 to 19
years) were classified as having MetS, while de Ferranti et al. (2004) reported a prevalence of 9.2% in US adolescents (12 to 19 years) using their respective adaptations to the ATP III definition, respectively. In addition to differences in criteria used to define MetS, variations in age range, race, degrees of overweight, geographical variation in obesity, and/or epigenetic factors may also explain disparities in reported prevalence rates (Reinehr et al. 2007).

Several investigations have also explored the prevalence of MetS in overweight and obese children and adolescents. Using their modified ATP III definition, Cook and colleagues (2003) observed that 28.7% of overweight US adolescents (BMI ≥ 95th percentile) had MetS. In obese UK adolescents (BMI ≥ 95th percentile), however, 33% were classified as having the syndrome (Viner et al. 2005). The investigators here, though, selected to use a modification of the WHO MetS definition (Alberti et al. 1998), and thus comparison of prevalence between these two studies is impractical. In moderately and severely obese (BMI z-score of 2.0 to 2.5 and 2.5 or more, respectively) US adolescents, the prevalence of MetS has been reported as 38.7% and 49.7%, respectively (Weiss et al. 2004), when using a modification of the ATP III (NCEP 2001) and WHO (Alberti et al. 1998) definitions. Furthermore, for each half-unit increase in BMI, converted to a z-score, there was a significant increase in the risk of MetS (OR = 1.55, 95% CI: 1.16-2.08). Using the same definition for MetS and overweight status, the prevalence in obese Italian adolescents (11.15 ± 3.4 years) was markedly lower, being present in 12.0% and 31.1% of moderately and severely obese participants, respectively (Calcaterra et al. 2008).

2.2 Issues in defining the metabolic syndrome

2.2.1 Criteria and cut-off values

As discussed above, it appears that some of the disparities in prevalence rates reported among children and adolescents are subject to the definition used to
classify MetS. Indeed, several reports have explored differences in the prevalence of MetS according to various criteria (Cook et al. 2003; de Ferranti et al. 2004; Ford et al. 2008). In a study that explored the presence of MetS in overweight and obese children and adolescents across five European countries using various definitions, MetS was present in 16.4%, 20.3%, 31.4%, and 35.7%, according to the IDF (child-specific), ATP III (adult-specific), WHO (adult-specific), and de Ferranti et al. (child-specific) criteria, respectively (Bokor et al. 2008). Only 12.2% of participants had MetS according to all four definitions, hence demonstrating a low degree of overlap between various proposed criteria. The higher prevalence found using de Ferranti et al.’s (de Ferranti et al. 2004) definition can be attributed to the inclusion of the lowest cut-off values for triglycerides and the highest cut-off values for HDL. The high prevalence of hyperinsulinaemia (64.7%) explained why the WHO definition (WHO 1999) classified more children with MetS than the IDF (Zimmet et al. 2007) and ATP III (NCEP 2001) definitions since it is the only definition that includes fasting insulin as a criterion.

A similar study by Reinehr and colleagues (2007) in overweight German children and adolescents that compared the prevalence of MetS using eight different definitions also revealed a greater prevalence of MetS according to de Ferranti et al.’s (2004) definition (39%) in comparison to the IDF (2007) definition (14%) and three other modified ATP III definitions: Cook et al. (2003) 21%, Viner et al. (2005) 18%, and Weiss et al. (2004) 29%. The prevalence according to WHO (Alberti et al. 1998), the European Group for the Study of Insulin Resistance (EGIR) (Balkau et al. 1999), and the ATP III (NCEP 2001) definitions was 6%, 8%, and 13%, respectively. Only 9% of participants had MetS according to all definitions. Reinehr and colleagues (2007) identified that the definition of insulin resistance was a major difference between the criteria. The assessment of fasting insulin levels is limited by large intra- and inter-individual variability (Wallace et al. 2002) and it has been suggested that the measurement of insulin levels without respect to glucose concentrations may offer a poor indication of
insulin resistance (Wallace et al. 2002), although strong correlations have been reported between fasting insulin and the homeostasis model assessment of insulin resistance (HOMA-IR) (Hanley et al. 2002). However, accurate assessment of insulin resistance by means of the hyperinsulinaemic euglycaemic clamp technique (Muniyappa et al. 2008) is invasive and impractical for use in young people. As such, practitioners often prefer to utilise simple tools such as fasting glucose; even though the prevalence of impaired fasting glucose in overweight youths remains low (1% across various the definitions (Cook et al. 2003; de Ferranti et al. 2004; Viner et al. 2005; Zimmet et al. 2007)) and this measure thus seemingly fails to identify an underlying resistance to insulin.

Another important difference between definitions relates to the requirement that an individual must have an elevated waist circumference in addition to at least two other risk factors in order to be classified as having MetS using the IDF criteria (Zimmet et al. 2007). This emphasis on central obesity is based on the premise that visceral adipose tissue is a key driver of insulin resistance, dyslipidaemia, and hypertension (Miranda et al. 2005) and that waist circumference offers a good reflection of fat accumulation in this region (Janssen et al. 2002). That individuals must have an increased waist circumference will inevitably reduce the number of individuals who have MetS in comparison to definitions that permit three or more of any risk factors to be present. However, not all obese individuals are insulin resistant or at increased risk of CVD and T2DM (Abbasi et al. 2002), while risk factor clustering and an associated increase in mortality risk has been shown in men with normal waist circumference (Katzmarzyk et al. 2006). Researchers should therefore seek to reach a consensus as to whether abdominal obesity should be a prerequisite in defining MetS.

Aside from differences in definitions due to practical issues such as the assessment of insulin resistance, disparities in criteria may be attributed to researchers proposing different risk factor cut-off points that are theoretically associated with increased health risk. Many definitions currently exist that
propose different cut-off points for the various MetS components (see Table 2.0 for examples). Indeed, a level above the specified threshold for each risk factor is to imply that there is an associated increase in risk, yet the rationale for specific cut points as opposed to higher or lower values has not been adequately addressed (Kahn et al. 2005). It has been reported though, that in adults, total and CVD mortality is more consistently increased in men when using a waist circumference criterion of ≥ 102 cm (as used in the ATP III MetS definition) in comparison to ≥ 94 cm (IDF definition) (Lakka et al. 2002; Katzmarzyk et al. 2006). On the contrary, other investigators have reported that reducing the threshold for impaired fasting glucose from 6.1 to 5.6 mmol/L (typically used cutpoints in MetS definitions) does not significantly alter hazard ratios for risk of CVD and stroke (McNeill et al. 2005). Increasing levels of other MetS components (BMI, waist-to-hip-ratio [WHR], fasting glucose, 2-hr glucose post OGTT, lipids, and BP), though, have been associated with increased risk of CVD and T2DM (MacMahon et al. 1990; Boyko et al. 2000; Ridker et al. 2005).

However, the above data are relevant only to adults and as yet, to the author’s knowledge, no literature has explored the impact of differing cut points on health risk in youths, nor has any study attempted to optimise the predictive value of any MetS definition by changing risk factor thresholds. It is also important to note that no childhood MetS definition has been validated by assessing their ability to predict health outcomes and they thus have limited utility in the clinical setting with regards to guiding specific therapies for cardiovascular prevention. However, evidence has shown that 6% to 14% of children and adolescents fulfil the criteria for MetS using different adult definitions (Reinehr et al. 2007), of which the cutpoints closely reflect cardiovascular outcomes (Alberti 2006). In addition, dyslipidaemia, hypertension, and impaired glucose metabolism have been associated with atherosclerotic processes in overweight children (Wunsch et al. 2005; Reinehr et al. 2006), while increased clustering of cardiometabolic risk factors has been associated with the severity of these processes (Berenson et al. 1998). Although the integration of
these risk factors in the definition of MetS thus seems meaningful, the concept that risk factor clustering in youth is predictive of health outcomes above the risk associated with individual components requires further exploration.

Table 2.0 Paediatric definitions of the metabolic syndrome

<table>
<thead>
<tr>
<th>IDF</th>
<th>Cook et al (modified ATP)</th>
<th>De Ferranti et al (modified ATP)</th>
<th>Weiss et al (modified ATP and WHO)</th>
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<tbody>
<tr>
<td>WC ≥ 90\textsuperscript{th} percentile</td>
<td>WC ≥ 90\textsuperscript{th} percentile</td>
<td>WC ≥ 75\textsuperscript{th} percentile</td>
<td>BMI ≥ 97\textsuperscript{th} percentile</td>
</tr>
<tr>
<td>HDL &lt; 1.03 mmol/L</td>
<td>HDL &lt; 1.03 mmol/L</td>
<td>HDL &lt; 1.3 mmol/L</td>
<td>HDL &lt; 5\textsuperscript{th} percentile</td>
</tr>
<tr>
<td>TG ≥ 1.7 mmol/L</td>
<td>TG ≥ 1.24 mmol/L</td>
<td>TG ≥ 1.1 mmol/L</td>
<td>TG &gt; 95\textsuperscript{th} percentile</td>
</tr>
<tr>
<td>SBP ≥ 130 / DBP ≥ 85 mm Hg</td>
<td>BP ≥ 90\textsuperscript{th} percentile</td>
<td>BP ≥ 90\textsuperscript{th} percentile</td>
<td>SBP or DBP &gt; 95\textsuperscript{th} percentile</td>
</tr>
<tr>
<td>Glucose ≥ 5.6 mmol/L</td>
<td>Glucose ≥ 6.1 mmol/L</td>
<td>Glucose ≥ 6.1 mmol/L</td>
<td>IGT &gt; 7.8 mmol/L at 2h</td>
</tr>
</tbody>
</table>

IDF, International Diabetes Federation, ATP, Adult Treatment Panel, WHO, World Health Organization, WC, waist circumference, BMI, body mass index, HDL, high-density lipoprotein cholesterol, TG, triglycerides, SBP, systolic blood pressure, DBP, diastolic blood pressure, BP, blood pressure, IGT, impaired glucose tolerance. In the IDF definition, metabolic syndrome is defined as abdominal obesity plus at least two other risk factors. The presence of ≥ three risk factors defines the metabolic syndrome in all other definitions. Table references: IDF (Zimmet et al. 2007); Cook et al. (Cook et al. 2003); (de Ferranti et al. 2004); Weiss et al. (Weiss et al. 2004).
In this sense, as no current paediatric MetS definition has been validated against health outcomes, it is thus difficult to know how accurate and effective MetS is as a screening tool to identify young people who may benefit from preventive or treatment therapies. Two previous studies did show, though, that the likelihood of developing CVD and T2DM in adulthood was significantly increased in those who had MetS during childhood compared with those who did not (according to a paediatric-modified Adult Treatment Panel III [ATP III] definition) (Morrison et al. 2007; Morrison et al. 2008). However, whether the same association would hold true for different MetS definitions, or whether other MetS definitions may be more strongly associated, is unknown, and to the author’s knowledge, there are no other investigations that have explored this hypothesis.

One of the fundamental objectives of MetS is that it can aid clinicians in the identification of individuals who may benefit from preventive or treatment therapies. In that respect, if two children presented blood pressure and triglyceride concentrations that were high enough to satisfy the criteria of the Cook definition (Cook et al. 2003) and merit diagnosis of MetS, but neither had a large enough waist circumference or a high enough fasting glucose to qualify for diagnosis; and the only difference between them was that HDL concentration was 1.00 mmol/L in one child and 1.10 mmol/L in the other; by definition, one child has MetS, while the other does not. Are these individuals fundamentally different and would the treatment options differ between them? Does having increased blood pressure and triglycerides not merit appropriate clinical intervention? There is evidence that the presence of individual risk factors in isolation increases the likelihood of CVD outcomes in adults (Bruno et al. 2004; McNeill et al. 2005) and this may also be the case in children. There may thus be a case for treating individual risk factors. Moreover, in a study that applied the ATP III criteria to the Framingham database, adults who met any two criteria were at no less risk than those meeting three criteria (Wilson et al. 2005), thus refuting the notion that clinical intervention is more appropriate for people with MetS compared to those who may satisfy less than three criteria.
There have also been suggestions that labelling patients with the term “metabolic syndrome” should be avoided as this might create the impression that the syndrome denotes a greater risk than its individual components, or that it is more serious than other CVD risk factors (Kahn et al. 2005). Indeed, hazard modelling of MetS components plus an indicator for MetS did not detect excess CHD associated with the presence of the syndrome in adults (McNeill et al. 2005). Similarly, although hypertension, low HDL, and diabetes were significantly associated with the presence of CHD, there was no indication of excess risk once the individual MetS components had been accounted for in multiplicative risk models (Alexander et al. 2003). Conversely, several combinations of cardiometabolic risk factors associated with MetS conferred excess additive risk of subclinical atherosclerosis beyond the level predicted by the individual components (Golden et al. 2002). Further research is needed, particularly in the young population, to confirm whether diagnosing MetS can provide additional clinical benefits, in terms of identifying patients for treatment, compared with diagnosis of its individual components.

2.2.2 Influence of puberty

Another contributor to the controversy surrounding the use of a MetS definition in children and adolescents is puberty. Puberty is a normal phase of development that occurs when a child’s body transitions into an adult body and becomes physiologically capable of sexual reproduction (Foster et al. 1999). Before discussing the issues regarding puberty and defining MetS, it is appropriate to consider the physiological changes that occur during this maturational transition.

Prior to the onset of puberty, an individual can be defined as a child, whereas during the process of development from a child to an adult (puberty), an individual can be defined as an adolescent. During this development, there are rapid changes in body size, shape, and composition, all of which are sexually dimorphic (Rogol et al. 2000). The degree of physiological maturation is often
assessed according to genital and pubic hair development in boys, and breast and pubic hair development in girls (Marshall et al. 1970; Marshall et al. 1969). Individuals are often categorised into one of five chronological Tanner stages (Marshall et al. 1970; Marshall et al. 1969), and, on average, girls enter and complete each stage earlier than boys. The onset of puberty corresponds to an average biological age of 11 years in girls and 13 years in boys (Tanner et al. 1975). In boys, the end of the last stages of genital and pubic hair development is reached at an average age of 14.9 and 15.2 years, respectively (Marshall et al. 1970), while girls reach the end of the last stages of breast and pubic hair development at an average age of 15.3 and 14.4 years, respectively (Marshall et al. 1969).

Growth spurts are one of the trademarks of puberty whereby an individual’s height increases substantially over a relatively short period of time. In girls, this growth spurt typically occurs during Tanner breast stage three (Kelch et al. 1994), while in boys the growth spurt occurs later during Tanner genital stage four (Marshall et al. 1970; Kelch et al. 1994). On average, girls gain a height of 25 cm during puberty, while boys gain an average height of 28 cm. Because of a longer prepubertal growth period in boys and a greater peak height velocity (9 cm/year in girls at age 12 and 10.3 cm/year at age 14 in boys), male adults become on average 13 cm taller than female adults (Rogol et al. 2000).

Significant weight gain also occurs during puberty and 50% of adult body weight is gained during adolescent years (Rogol et al. 2000). Distinct changes in body composition, including alterations in the relative proportions of water, muscle, fat, and bone, are also observed and result in marked sex differences (Rogol et al. 2000). Gonadal steroid hormones and growth hormone cause increases in bone mineral content and muscle mass and the deposition of fat becomes distinctly different between sexes. Changes in body fat distribution (central vs. peripheral, subcutaneous vs. visceral, and upper vs. lower body) leads to the typical android (males) and gynoid (females) patterns of fat distribution in older
adolescents and adults (Johnston 1992). These differences in fat distribution may have pronounced effects on the metabolic health of an individual given evidence that fat accumulated centrally and viscerally is associated, and possibly causal, of metabolic disorders (Despres 2006). Furthermore, the degree of muscle mass gain during maturation may also be influential on current and future metabolic health. An increased muscle mass would provide a larger surface area for glucose disposal and would also promote a greater level of fat oxidation at rest and during exercise (Poehlman et al. 2000; Brooks et al. 2007).

It was observed that insulin resistance increased and insulin sensitivity decreased during puberty in both diabetic and nondiabetic youngsters and a compensatory increase in insulin secretion is therefore often seen during this insulin resistant phase (Caprio et al. 1989; Cook et al. 1993). Some investigators have proposed that changes in insulin sensitivity during puberty are sex-dependent and are related to changes in body composition (Travers et al. 1995), while others have suggested that insulin hypersecretion may reflect the puberty-associated increase in circulating growth hormones (Caprio et al. 1989). Other evidence suggests that puberty-associated insulin resistance is independent of changes in body and visceral fat and is instead associated with increased total body lipolysis and decreased glucose oxidation (Goran et al. 2001; Hannon et al. 2006). Moreover, reductions in TC and HDL and increases in triglyceride levels have been observed during puberty (Hannon et al. 2006; Moran et al. 2008), while systolic BP has been shown to rise with pubertal stage independent of age (Weir et al. 1988). It has been proposed that these metabolic changes are mediated partly by increased growth hormone secretion (Goran et al. 2001; Hannon et al. 2006), although other factors such as the decreased physical activity levels and change in dietary habits often seen during adolescence may be influential (Kimm et al. 2000; Demory-Luce et al. 2004).

The effects of puberty on MetS prevalence varies widely according to the definition used. A three- to five-fold increase in the prevalence of the syndrome
has been reported in pubertal male and female adolescents compared with prepubertal children in the US (Cook et al. 2003). Using the same modified ATP III definition of MetS (Cook et al. 2003), another study also found a higher prevalence of the syndrome in German pubertal adolescents, although this was evident only in boys and not in girls (Reinehr et al. 2007). However, in Reinehr and colleagues’ study (2007), pubertal stage had no influence on MetS according to various definitions (Alberti et al. 1998; Balkau et al. 1999; 2001; de Ferranti et al. 2004; Weiss et al. 2004; Alberti et al. 2005; Viner et al. 2005), possibly due to differences in criteria and thresholds. Although pubertal insulin resistance appears to be a normal physiologic process and returns to near prepubertal levels by the end of puberty (Moran et al. 1999), this state may contribute to a pathological process in the presence of excess adiposity and/or pancreatic beta cell dysfunction and thus increase the risk of impaired glucose metabolism or T2DM during adolescence (Klein et al. 2004; Ball et al. 2006).

2.3 Anthropometry and cardiometabolic risk in youths

2.3.1 Body Mass Index

Obesity is associated with increased risk of CVD and T2DM in adults (Hevener et al. 2010), while in obese children and adolescents, increased cardiometabolic risk if often seen (Andersen et al. 2008; Thomas et al. 2008). As discussed above, the prevalence of MetS rises concomitantly with increasing weight status (Weiss et al. 2004; Calcaterra et al. 2008) and for each half-unit increase in BMI z-score, there is a significant increase in the risk of MetS (OR = 1.55, 95% CI: 1.16-2.08) in overweight and obese youngsters (Weiss et al. 2004). In addition, longitudinal studies have shown that adiposity and fat distribution appears to track through childhood and adolescence into adulthood (Webber et al. 1995; van Lenthe et al. 1998; Garnett et al. 2007). If found to have good predictive value for cardiometabolic risk factors, simple anthropometric indexes may be useful tools in identifying children and adolescents who are at risk.
BMI offers a simple and clinically practical measure of body composition and is often used to explore the impact of obesity on cardiometabolic risk in both youths and adults (Wilson et al. 2002; Savva et al. 2000). Numerous cardiometabolic risk factors, including systolic BP, HDL, triglycerides, fasting glucose and insulin, and 2-hr glucose post OGTT have been unfavourably correlated with increasing BMI in children and adolescents (Lindsay et al. 2001; Weiss et al. 2004). Thresholds for BMI related to CVD risk have thus been proposed in the field. The 85th and 95th percentiles of reference data have been used most frequently to define weight status (Himes et al. 1994; Reilly et al. 1999) and explore associations with risk in youths (Cook et al. 2003). However, age- and sex-specific thresholds were developed by Cole and colleagues (2000) using an international sample that were tied to the adult overweight (25 kg/m²) and obesity (30 kg/m²) thresholds. Although based on adult obesity-related health risks, overweight children and adolescents as defined by these thresholds are at 1.6 to 9.1 times higher risk of elevated cardiometabolic risk than their normal weight counterparts (Katzmarzyk et al. 2003).

However, individuals with excess central (intra-abdominal), or visceral, adipose tissue may be at an increased risk compared to those with excess fat accumulated in peripheral regions of the body (Despres 2006; Stefan et al. 2008). Indeed, increased deposition of centrally distributed fat is associated with less favourable lipid profiles and BP in children and adolescents (Freedman et al. 1989; Daniels et al. 1999), while visceral adipose tissue, but not subcutaneous abdominal adipose tissue, body fat %, or total body fat mass, explains variance in lipid / lipoprotein risk factors in obese children (Owens et al. 1998). BMI becomes problematic in this respect as it does not accurately reflect central adiposity (Neovius et al. 2008), while it also fails to differentiate fat mass from lean mass and thus may classify more muscular individuals as overweight. This is an important limitation given that lean mass is negatively associated with all-cause mortality (Allison et al. 2002). Furthermore, BMI also fails to detect individuals who are metabolically at risk but of normal weight (Lambert et al. 2000).
In a study of 6,123 Caucasian adults, 29% of participants classified as lean, according to BMI, had a body fat % that fell within the obesity range (Gomez-Ambrosi et al. 2011). The limitations of BMI were further emphasised by evidence that the levels of cardiometabolic risk factors are similarly higher in lean or overweight BMI-classified subjects with body fat percentages within the obesity range than in obese BMI-classified individuals with matched body fat % (Gomez-Ambrosi et al. 2011).

2.3.2 Waist circumference

In light of the issues surrounding the use of BMI as a predictor of cardiometabolic risk and that central adiposity is more closely related to risk compared with peripheral adiposity (Owens et al. 1998), the measure of waist circumference has instead been recommended in the screening process for health risk. Indeed, waist circumference has been shown to be a better predictor of cardiometabolic risk factors than BMI in both adults (Janssen et al. 2004) and youths (Savva et al. 2000). In adults, European men and women with waist circumferences of ≥ 102 cm and ≥ 88 cm, respectively, are considered to be at higher risk of obesity-related disorders than those with smaller measures (WHO 2000). Recent studies have shown that these thresholds are suitable for predicting increased metabolic risk in these populations (Janssen et al. 2002; Ardern et al. 2003). In children and adolescents, however, waist circumference guidelines are limited in their predictive ability for associated health risk.

In Cypriot children and adolescents, a waist circumference above the 75th percentile significantly increased the likelihood of having high BP, high TC, high LDL, and high triglyceride levels (Savva et al. 2000). In Italian children, those with a waist circumference above the 90th percentile were more likely to have a clustering of risk factors (19% of participants) compared to those with values below that level (9.4%) (Maffeis et al. 2001). The 90th percentile is a commonly used threshold in various paediatric definitions of MetS (Cook et al. 2003; Weiss et al. 2004; Zimmet et al. 2007) and has been associated with increased risk
factor clustering (Freedman et al. 1999; Maffeis et al. 2001). However, there have been limited attempts to devise waist circumference thresholds in relation to cardiometabolic risk status or health outcomes, and hence the current recommended thresholds (Cook et al. 2003; de Ferranti et al. 2004; Zimmet et al. 2007) may not be the most appropriate. A previous study, however, did report that a threshold corresponding to the 70th percentile (with a sensitivity of 0.76 and a specificity of 0.81) best predicted the presence or absence of MetS in Spanish children, although age-specific values were not presented (Moreno et al. 2002). Katzmarzyk and colleagues (2004), on the other hand, did present age- and sex-specific waist circumference values for US children and adolescents that corresponded to a greater risk of cardiometabolic risk factor clustering.

2.3.3 Waist-to-height ratio

Although BMI and waist circumference are widely used to assess or define cardiometabolic risk in children and adolescents, there have been proposals that waist-to-height ratio (WHTR) may be a more effective indicator of health risk (Ashwell et al. 2005; Mokha et al. 2010). Currently, BMI and waist circumference have to be expressed relative to age, sex, and ethnicity (WHO 2004; Zimmet et al. 2007) and, as discussed above, the cut-off values proposed to define obesity according to these measures are arbitrarily determined and not linked to adverse health outcomes associated with fatness (Ashwell et al. 2005). WHTR has therefore been proposed as an alternative easily measurable anthropometric index for the detection of central obesity since the same boundary values may be used across genders, ethnicities, and for both children and adults (Ashwell et al. 2005). This measure appears to be an effective global indicator for health risks associated with central obesity in both adults (Bosy-Westphal et al. 2006) and youths (Savva et al. 2000; Nambiar et al. 2010).

In adults, a boundary value at WHTR = 0.5 was originally proposed to indicate where health risk starts to increase in Asian and British populations (Hsieh et al. 1995; Ashwell et al. 1996). This threshold has since been identified in other
populations as the simplest value that corresponds to more precise cutoff values in men and women (Ko et al. 1999; Lin et al. 2002; Sargeant et al. 2002; Bertssias et al. 2003; Ho et al. 2003). In youths, in light of evidence that height and waist circumference increase continually during childhood (McCarthy et al. 2003) and that WHTR does not differ between sexes (Kahn et al. 2005), the same boundary of WHTR = 0.5 has been deemed suitable for use across all age groups (Ashwell et al. 2005; Nambiar et al. 2010). Evidence has shown that in children and adolescents, those with WHTR ≥ 0.48 have significantly higher values for waist circumference, body fat %, triglycerides (boys only), systolic BP (girls only), and lower levels of HDL compared to those with ratios < 0.46 (P < 0.05) (Nambiar et al. 2010). Moreover, 5 to 15 year-old children with WHTR > 0.5 are at significantly greater odds of having MetS compared to those with values < 0.5 (OR = 7.0, 95% CI: 3.63-13.48, p < 0.001) (Maffeis et al. 2008). However, it must be noted that WHTR guidelines for children and adolescents have not been based on prospective evidence related to T2DM, CVD, or mortality outcomes in later life.

It has also been suggested that WHTR may permit identification of obese individuals who are metabolically benign and normal weight individuals who are metabolically at risk (Srinivasan et al. 2009; Mokha et al. 2010). In young adults of normal weight (according to BMI), those with central obesity (WHTR ratio ≥ 0.5) have significantly adverse levels of numerous cardiometabolic risk factors, such as BP, fasting insulin, HOMA-IR, CRP, and lipids, in comparison to their non-centrally obese counterparts (WHTR ratio < 0.5) (Srinivasan et al. 2009). Similarly, in children, normal weight (according to BMI) centrally obese (WHTR ≥ 0.5) individuals were 1.66, 2.01, 1.47, and 2.05 times more likely to have adverse levels of LDL, HDL, triglycerides, and insulin, respectively (Mokha et al. 2010). Overweight and obese children who did not have central obesity (WHTR > 0.5) were 0.57 and 0.27 times less likely to have adverse levels of HDL and HOMA-IR, respectively (p < 0.05).
2.3.4 Comparison of anthropometric indices

Given the associations with cardiometabolic risk (Savva et al. 2000; Mokha et al. 2010) and the seeming benefits of WHTR in comparison to BMI and waist circumference (Ashwell et al. 1996), numerous studies have sought to establish whether WHTR is a more appropriate screening tool for identifying metabolically at-risk individuals in comparison to more traditional measures. In a comparison of BMI, waist circumference, and WHTR in non-obese men and women (BMI < 25 kg/m²), WHTR was more sensitive in evaluating the clustering of cardiometabolic risk factors than BMI or waist circumference alone (Hsieh et al. 2005). Additionally, in Chinese adults, WHTR was considered the best simple anthropometric index (in comparison to BMI, waist circumference, and waist-to-hip ratio [WHR]) in predicting cardiometabolic risk, with WHTR displaying the highest correlation with six of 11 tested risk factors in men, and five in women; followed by waist circumference with 4 in men and 6 in women (Ho et al. 2003). In receiver operating characteristic (ROC) analyses, the area under the curve for WHTR was largest for 13 of 21 risk factors in men, and 10 in women; followed by WHR with 14 in women and only five in men.

Contradictory literature exists though in which WHTR was not superior in its association to adverse health risk compared to other simple anthropometric measures such as BMI and waist circumference. In women, BMI correlated more closely with HDL and HOMA-IR in comparison to waist circumference and WHTR (Bosy-Westphal et al. 2006). However, for all other cardiometabolic risk factors (triglycerides, TC, uric acid, systolic BP, and CRP), waist circumference and WHTR were the best predictors in both sexes, while WHTR was shown to be the main predictor of risk in both sexes combined. In predicting risk factor clustering (≥ 2 risk factors), ROC analysis revealed a similar accuracy between BMI, waist circumference, and WHTR. In other literature, WHTR, WHR, waist circumference, and BMI were all found to be similarly sensitive and specific in the identification of dyslipidaemia; classified as TC ≥ 5.2 mmol/L and/or triglyceride ≥ 2.3 mmol/L,
and/or HDL < 0.9 mmol/L (Haffner 1998); and albuminuria; random spot urinary albumin concentration ≥ 20 mg/L (Schwab et al. 1992); in Hong Kong Chinese adults (Ko et al. 1999). However, WHR and WTHR were better predictors of T2DM; fasting glucose ≥ 7.8 mmol/L or 2-hr glucose ≥ 11.1 mmol/L (WHO 1985); and hypertension; systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg (Grundy et al. 1997).

Studies in children and adolescents have also led to contrasting conclusions as to the predictive ability of WHTR for cardiometabolic risk in comparison to BMI and waist circumference. In Japanese schoolchildren (9 to 13 years), WHTR was the most significant predictor for current TC, triglycerides, LDL, atherogenic index (weighed combination of TC and triglycerides), and a lifestyle related disease prevention score in comparison to BMI, waist circumference, and WHR (Hara et al. 2002). Conversely, in US children and adolescents (5 to 17 years), no difference was observed between WHTR and BMI in explaining an overall index of six risk factors (triacylglycerol, LDL, HDL, fasting insulin, systolic BP, and diastolic BP) (Freedman et al. 2007). However, WHTR was more strongly associated with TC:HDL ratio and LDL levels, while BMI was more strongly associated with measures of BP and fasting insulin. In Greek-Cypriot children (11.4 ± 0.4 years), waist circumference explained the most variance in systolic and diastolic BP, TC, and HDL, while WHTR and BMI explained the most variance in LDL and triglycerides, respectively (Savva et al. 2000). However, having a WHTR > 75th percentile resulted in significantly greater odds of having adverse lipid and lipoprotein levels in comparison to being > 75th percentile for BMI or waist circumference, while BMI > 75th percentile resulted in greater odds of having high BP (Savva et al. 2000).

2.4 Cardiorespiratory fitness, physical activity, and cardiometabolic risk

Increased levels of cardiorespiratory fitness (CRF) and physical activity have been consistently associated with lower risk of CVD outcomes and all-cause mortality in adults (Blair et al. 2001). Previous evidence has shown that cardiorespiratory
fit individuals have significantly reduced BMI, systolic and diastolic BP, and lower levels of fasting glucose, TC, triglycerides, and uric acid, and are thus at decreased risk of CVD and T2DM (Wei et al. 2000). In a review of literature, it was evidenced that high fit individuals had at least a 50% lower mortality rate compared with low fit individuals (Blair et al. 2001). Some literature has reported three- to four-fold higher mortality rates in the least cardiorespiratory fit compared to the most cardiorespiratory fit participants (Blair et al. 1989; Blair et al. 1991), while men who improve their CRF level from unfit to fit over approximately a five year period reduce their risk of mortality by 44% (95% CI: 25-59%) (Blair et al. 1995). In the case of physical activity, most literature shows an inverse dose-response gradient across activity categories for most health outcomes, although the gradient is steeper for CRF (Blair et al. 2001). In a sample of US men, though, 50% who self-reported physical inactivity suffered from diabetes, whereas only 33% of active men had this disease; no significant difference was noted in the prevalence of diabetes between cardiorespiratory fit and unfit individuals (Wei et al. 2000).

2.4.1 Cardiorespiratory fitness and risk in youths

It has been proposed that higher levels of CRF and physical activity may also be associated with reduced risk of CVD outcomes in children and adolescents. Indeed, numerous studies have linked CRF with single cardiometabolic risk factors in youths (Reed et al. 2005; Ruiz et al. 2007; Aires et al. 2010; Steele et al. 2008) and in 10 to 15 year-olds, individuals with high CRF were seen to be 95% less likely to have high insulin resistance compared with their low fit counterparts (OR = 0.05, 95% CI: 0.004-0.492) (Benson et al. 2006). Arterial compliance is an important early predictor of chronic vascular disease risk, and in 9 to 11 year-olds, those in the lower two quartiles of CRF (according to number of 20 m laps completed) were at a decreased likelihood of having large artery compliance, while those in the second lowest quartile were less likely to have small artery compliance, in comparison with those in the highest CRF quartile.
(Reed et al. 2005). Moreover, in 11 to 18 year-olds, CRF is inversely correlated with BMI ($r = -0.2, p < 0.05$), while increasing levels of CRF are associated with a lower risk of being overweight and obese ($OR = 0.968, 95\% CI: 0.939-0.998$ for) (Aires et al. 2010). Numerous features of MetS, including insulin, triglycerides, systolic BP, and HDL have also been significantly negatively (positive in the case of HDL) correlated ($p \leq 0.033$) with CRF in youths (9.6 ± 0.44 years), while no associations were evident with fasting glucose or diastolic BP (Brage et al. 2004). Higher fasting insulin values have been observed in both girls (1%, 15%, and 21%) and boys (23%, 13%, and 20%) in the least fit quartile (quartile 1) compared to the second, third, and fourth quartiles, respectively (Ruiz et al. 2007). However, when adjusting for age, sex, total fat mass, and fat free mass, Shaibi and colleagues (2005) observed that CRF was not significantly correlated with any feature of MetS, which included waist circumference, fasting glucose, 2h glucose, systolic BP, diastolic, BP, HDL, and triglycerides.

2.4.2 Physical activity and risk in youths

A number of studies have shown that higher levels of physical activity are favourably associated with cardiometabolic risk factors in youths from a number of geographic locations and ethnic backgrounds (Owen et al. 2010; Ekelund et al. 2006; Steele et al. 2008). It is generally recommended that children and adolescents engage in 60 minutes of moderate-to-vigorous physical activity (MVPA) each day in order to protect against increased cardiometabolic risk (Department of Health 2011). The percent of time spent in MVPA, as measured by accelerometry over two weekdays and two weekend days, was associated with body fatness (skinfold thickness) in 9 to 10 year-old children ($\beta = -0.002, 95\% CI: -0.004, -0.0001$) (Ekelund et al. 2004). MVPA was also associated with waist circumference, BMI, and fat mass index 10 year-old British children (Steele et al. 2009). Using accelerometry, Mitchell and colleagues (2010) reported a significant correlation between time spent in MVPA (min/d) and HOMA-IR ($r = -0.44, p < 0.01$) in Canadian youths. However, evidence regarding the association
of MVPA with cardiometabolic risk is somewhat inconsistent. Ruiz et al. (2006) reported no significant associations of accelerometry determined MVPA (min/d) with body fatness (skinfold thickness) in European 9 to 10 year-olds, while the same held true when exploring associations of MVPA with dual energy X-ray absorptiometry (DEXA) in 4 to 6 year-olds (Janz et al. 2002). In addition to being unrelated to fasting glucose, fasting insulin, and HOMA-IR, it was observed that time spent in MVPA was not associated with markers of low-grade inflammation (C-reactive protein, interleukin-6, C3, and C4) in 13 to 17 year-old adolescents (Martinez-Gomez et al. 2010). Nonetheless, there is substantial evidence from the European Youth Heart Study that both MPA and VPA are associated with most cardiometabolic risk factors (Ekelund et al. 2007; Ekelund et al. 2004).

Although previous physical activity guidelines recommended that children and adolescents should engage in 60 minutes of MVPA each day to protect against cardiometabolic risk, recent UK, US, and Canadian guidelines have proposed that in addition to 60 minutes of MVPA each day, three days per week should include vigorous physical activity (VPA) (US Department of Health and Human Services 2008; Canadian Society for Exercise Physiology 2011; Department of Health 2011). Whereas MVPA has shown no association with body fatness, minutes spent in VPA was negatively correlated with DEXA determined body fat %, fat mass, and trunk fat mass in both boys and girls (4 to 6 years) (Janz et al. 2002). These findings are similar to those reported by Ruiz et al (2006) in that VPA was significantly associated with skinfold thickness ($\beta = -0.08$, 95% CI: 0.0002-0.0022), while MVPA held no association. Other studies have also found that increasing levels of VPA are negatively associated with body fat % in US and Australian children and adolescents ($\beta = -4.19$, $p < 0.001$ and $r = -0.44$, $p = 0.004$, respectively) and with waist circumference in UK boys ($r = -0.38$, $p < 0.01$) (Abbott et al. 2004; Gutin et al. 2005; Stone et al. 2009). Moreover, at risk of overweight and overweight (BMI $\geq 85^{th}$ percentile for age and sex) boys and girls (11 to 15 years-old) are also reported to engage in significantly less ($p < 0.05$) minutes per day of VPA compared with their non-overweight counterparts (12.4
\( \pm 9.5 \) vs. \( 8.0 \pm 6.3 \) and \( 6.3 \pm 6.3 \) vs. \( 4.2 \pm 4.5 \) min/d, respectively) (Patrick et al. 2004), as have obese \(( \geq 95^{th} \) percentile for age, race, and sex) sixth grade children compared with non-obese children \( (7.1 \pm 1.3 \) vs. \( 13.5 \pm 0.9 \) min/d, \( p = 0.001 \) (Trost et al. 2001).

Some evidence does exist though to suggest that VPA is not associated with body composition. In 6 to 8 year-old children, those who engaged in higher amounts of VPA \(( \geq 6.6\% \) of time per day) did not differ in BMI, waist circumference, and fat mass index compared with those who engaged in low amounts of VPA (Rennie et al. 2005). However, this study differs to those that have reported associations in that physical activity intensity was measured using heart rate. Since heart rate is acutely affected by factors other than physical exercise, such as psychological and environmental stress, caffeine, and some medications (Astrup et al. 1990; Emons et al. 1992), disparate findings may be due to inaccurately defined physical activity levels. In addition, few studies have investigated whether VPA is linked with other features of MetS. Previous studies have observed that blood pressure, endothelial function, and smooth muscle function \((\text{at rest and post-exercise})\) are all unrelated to accelerometry determined VPA in children and adolescents (Gaya et al. 2009; Stone et al. 2009), as are fasting glucose, fasting insulin, HOMA-IR, and inflammatory markers in 13 to 17 year-old adolescents (Martinez-Gomez et al. 2010). However, differences in individual risk markers according to higher and lower amounts of VPA, and indeed CRF, may be too subtle to explore in isolation. Coupled with observations that daily fluctuations in cardiometabolic risk markers occurs (Elveback et al. 1980; Lyons Wall et al. 1994; Froberg et al. 2005), it may be preferable to construct a clustered risk score in an attempt to diminish the error variation that each risk factor includes (Anderssen et al. 2007; Ruiz et al. 2007). Furthermore, cardiometabolic diseases are characterised by a constellation of risk markers, and a clustered risk score may detect an array of cardiometabolic disturbances rather than focussing on one or two particular markers, whilst individuals with
multiple risk factors have a poorer health status than if a single risk factor was present (Gami et al. 2007).

2.4.3 Cardiorespiratory fitness, physical activity and clustered risk

Given the considerations above, several investigations have therefore explored the associations of CRF and physical activity with clustered cardiometabolic risk in children and adolescents. Across decreasing quartiles of CRF, the likelihood of having clustered risk (defined by > 1 SD in the sum of z-scores for systolic BP, triglycerides, TC:HDL ratio, and HOMA-IR) increased significantly in European 9 and 15 year-olds (OR = 1.54, 95% CI: 0.94-2.50; 1.65, 1.02-2.69; 1.89, 1.14-3.13), for quartiles three, two, and one, respectively (Andersen et al. 2008). In the same age group, the odds for having clustered risk when adjusted for country, age, sex, puberty, socioeconomic status, and parent’s history of CVD and T2DM, was 13.0 (95% CI: 8.8-19.1) in the least fit quartile compared to the most fit quartile (Anderssen et al. 2007). Ruiz and colleagues (2007) reported that in addition to the least fit (quartile 1) children having significantly greater odds of having a high clustered risk score compared with those in quartiles two, three, and four, boys with a CRF level > 42.1 mL/kg/min were 3.09 times more likely of having a low clustered risk score (insulin, glucose, HDL, triglycerides, skinfold thickness, and BP [systolic and diastolic]) compared to those with lower values. In girls, a CRF level of > 37.0 mL/kg/min equated to a 2.42 times increased likelihood of having a low risk score compared to those with values below that level.

In the case of physical activity, an index of physical activity (based on the total MET of each activity) was found unrelated to a lipid-metabolic cardiovascular risk index (sum of z-scores for triglycerides, LDL, HDL, and glucose) (Garcia-Artero et al. 2007). However, the recall inaccuracies associated with the use of questionnaires to assess physical activity may have confounded the results (Shephard 2003). Nonetheless, total physical activity as measured by accelerometry was not significantly associated with clustered cardiometabolic risk (sum of z-scores for insulin, glucose, triglycerides, TC:HDL ratio, sum of five
skinfolds, and systolic and diastolic BP) in 9 and 15 year-old boys and 9 year-old girls; although total activity was associated with clustered risk in 15 year-old girls ($\beta = -0.214$, 95% CI: -0.001, -0.000, $p = 0.018$) (Rizzo et al. 2007). In terms of physical activity intensity, clustered cardiometabolic risk has been shown to decrease with increased counts per minute (cpm); OR’s for ascending quintiles of cpm were 3.29 (95% CI: 1.96-5.52), 3.13 (1.87-5.25), 2.52 (1.47-4.26), and 2.03 (1.18-3.5), respectively (Andersen et al. 2006). Such associations have held true even after adjusting for both CRF and skinfold thickness, whereby the likelihood of having clustered risk (> 1 SD of clustered score) was significantly greater in quartiles three (OR = 1.23, 95% CI: 0.79-1.93), two (OR = 2.28, 1.50-3.46), and one (1.81, 1.18-2.76), respectively, compared with the most active (cpm) quartile (quartile 1) (Andersen et al. 2008). Although there is a lack of literature that has explored associations of moderate physical activity (MPA) and VPA with clustered cardiometabolic risk, one investigation observed similar β-coefficients for MPA and VPA (cpm) when adjusting for age group, sex, study location, and waist circumference, in 9 to 10 and 15 to 16 year-old boys and girls from Denmark, Estonia, and Portugal ($\beta = -0.06$, 95% CI: -0.08, -0.03 and $\beta = -0.05$, 95% CI: -0.07, -0.02) (Ekelund et al. 2007).
CHAPTER THREE: METHODOLOGY

3.0 Introduction
The research reported within this thesis was contextualised within a two year school-based intervention study named the Health And Physical activity Promotion in Youth (HAPPY) study, which is described below.

3.1 Health And Physical activity Promotion in Youth (HAPPY) study
3.1.1 Study Objectives
The aim of the HAPPY study was to evaluate the effectiveness of innovative school-based physical activity strategies in improving overall physical activity levels (school-time and leisure time), cardiorespiratory fitness (CRF), physical health, and psychosocial well-being in 10 to 14 year-old school children.

3.1.2 Participants
249 volunteers aged 10 to 14 years were recruited from seven middle and four upper schools in Bedfordshire, UK. Schools in the Bedford Borough and Central Bedfordshire areas were approached and were subsequently recruited based on their willingness to take part in the research study and to maximise representativeness to a wider population. A cross-section of mixed sex, single-sex, state, and independent schools were therefore included. According to the Child Well-Being Index scores (Child and Maternal Health Observatory 2009), which is a national measure of deprivation in children, the Bedford Borough and Central Bedfordshire areas in which the schools in this study were recruited fall within the second and third quintiles (lowest quintile representing the most deprived), respectively. The participants included in this research may therefore be representative of other regions in the UK with similar levels of child deprivation.
Each school was provided with information sheets and consent forms, which also included a Physical Activity Readiness Questionnaire (PAR-Q) (see Appendix 1), to pass on to all pupils’ parents that fell within the age range for the study. To volunteer to take part in the study, consent was obtained from the parent on the child’s behalf prior to any testing procedures. Volunteers were required to return their forms to the appropriate school contact (Head of Physical Education, Head of Year, or Deputy Head) who then passed on the relevant documents to the research team. Individuals were excluded if they were unable to take part in physical activity as indicated on the PAR-Q and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. All other children who returned consent forms were invited to take part in the study.

3.1.3 Study design

The data used for the purposes of the experimental chapters within this thesis was collected from participants at baseline i.e. before receiving any intervention. Each school was allocated two full days for data collection during the first half of each school term allowing all measurements to take place over four weeks (with the exception of seven day accelerometry data collection which extended over a six week period). The data used in this thesis was thus collected in the first half of the autumn term. Measures took place in a room allocated by the school. Children were measured in pairs and the data collection took a maximum of an hour per child. Body fat measures and the finger prick sample for lipid profile and glucose took place first thing in the school morning as participants were required to be fasted for these measures from the night before. Participants were advised to bring breakfast or a snack to school that they could consume immediately after these initial measures.
3.2 Measurements

3.2.1 Ethnicity and socioeconomic status

Ethnicity was recorded as one of the following: a) white, b) mixed, c) Asian or Asian British, d) black or black British, or e) Chinese or other ethnic group (see Appendix 2). For the purposes of the studies presented within this thesis, ethnicity was subsequently coded as white or non-white. A score of socioeconomic status (SES) was calculated from the 2007 Indices of Multiple Deprivation (IMD) from each participant’s postcode (MIMAS 2008; Fairclough et al. 2009). Postcodes were obtained from participants and converted into IMD scores using the GeoConvert application (MIMAS 2008). These scores were categorised into tertiles with the lowest tertile indicating the most deprived.

3.2.2 Weight, Stature, and Waist Circumference

Standing height was measured without shoes to the nearest 0.5 cm using the portable Leicester Height Measure (Seca, Birmingham, UK). During measurements, participants were asked to take a deep breath and look straight ahead with the head upright, whilst ensuring heels remained on the floor and together. Weight was measured to the nearest 0.1 kg with the Tanita BC-418MA® Segmental Body Composition Analyser (Tanita Corp., Tokyo, Japan). Participants were asked to wear light clothing and to remove their shoes prior to measurement. Waist circumference was measured using an adjustable tape (Hoeachstmass, Germany) to the nearest 0.5 cm at the end of gentle expiration at the level of the umbilicus.

3.2.3 Body composition

Body fat % and fat free mass (FFM) were measured to the nearest 0.1 % and 0.1 kg, respectively, via bioelectrical impedance analysis (BIA) using the Tanita BC-418® Segmental Body Composition Analyser (Tanita Corp., Tokyo, Japan). Participants were required to stand barefoot on a base which has two metal plates and hold two hand grip electrodes. BIA assesses body fat by measuring
bioelectrical impedance in the body. This method is based upon the principle that the electrical conductivity of fat free tissue mass is far greater than that of fat tissue (Lukaski et al. 1985). The degree of difficulty with which electricity passes through a substance is known as the electrical resistance, and the percentage of fat and other body constituents can be inferred from measurements of this resistance (Heyward et al. 2004).

The Tanita BC-418® utilises an isolated high frequency current (50 kHz, 500 µA) to estimate body composition. The eight electrodes are positioned so that electric current is supplied from the electrodes on the tips of the toes of both feet and the fingertips of both hands, and voltage is measured on the heel of both feet and the inner side of both hands. The current flows into the upper limbs or lower limbs, depending on the body part(s) to be measured. The BIA estimates bioconductor volume and resistive impedance (corrected for stature), which allows prediction equations from the equipment manufacturer to obtain values such as water, body content of fat and FFM (Tanita BC-418® instruction manual). BIA in children has been shown to provide comparable fat levels ($r = 0.98$) with dual-energy x-ray absorptiometry (DEXA) body composition estimates (Tyrrell et al. 2001).

### 3.2.4 Blood pressure

Sitting blood pressure was measured on the left arm at the brachial artery using an Omron M5-I automated oscillatory device (Omron Matsusaka Co. Ltd., Matsusaka, Japan) after the participant had rested for five minutes. Three blood pressure readings were obtained, with two minute intervals between each measure, and the average for the lowest two readings recorded (Chobanian et al. 2003).

### 3.2.5 Lipid profile and fasting glucose

Blood samples of 40 µl were obtained by finger prick with an autolancet followed by gentle massage to promote the appearance of small drops of blood at the
skin’s surface. The first drop of blood was discarded and then 40 µl of blood was collected into a capillary tube which was immediately transferred into a cassette sample well for measurement of total cholesterol (TC), HDL, TC:HDL ratio, triglycerides, and glucose. Each cassette was placed in the drawer of a Cholestech LDX analyser (Cholestech Corp., Hayward, CA.) to obtain results within approximately six minutes. Prior to and following daily data collection, the analyser was calibrated with standard controls provided by the manufacturer. Previous studies have shown the Cholestech LDX System to be a valid and reliable tool to measure blood lipids (Parikh et al. 2009; Bard 1997). In adults, values determined using the Cholestech LDX analyser for TC, HDL, LDL, and triglycerides presented correlation coefficients of > 0.77 with core laboratory measures (Parikh et al. 2009). The sensitivity of the Cholestech LDX analyser for categorising patients as adherent to the ATP III definition for abnormal lipid profiles was ≥ 76% and this met the accuracy and precision definitions set by the NCEP (Parikh et al. 2009).

3.2.6 Habitual physical activity

RT3® triaxial accelerometers (Stayhealthy, Inc., Monrovia, CA.) were used to measure seven consecutive days of minute-by-minute habitual physical activity and to determine time spent in moderate-to-vigorous physical activity (MVPA) and vigorous physical activity (VPA). The RT3® is a small device worn on the waistband that measures accelerations and decelerations of movement in three dimensions (vertical, anterioposterior, and mediolateral). The device has been validated against oxygen uptake relative to body mass in children in a laboratory setting \( r = 0.87, p < 0.01 \) (Rowlands et al. 2004) and against oxygen uptake in children and adolescents in free-living contexts \( r = 0.87, p < 0.001 \) (Vanhelst et al. 2010). The RT3® is reliable during moderate and vigorous physical activities (intra-instrument coefficient of variation 9.3% and 6.6%, respectively) (Vanhelst et al. 2010) and has previously been used to assess habitual physical activity levels in children (Rowlands 2007; Rowlands et al. 2008). Participants were asked
to wear the accelerometer from the time they woke up until they went to bed. Exceptions included when the participant was bathing, showering or swimming, during sleep, or participation in contact sports that may have resulted in the accelerometer being damaged. Accelerometers were initialised and their data downloaded via a computer interface, which has no external controls that participants could manipulate. Each accelerometer was programmed to record activity counts in one-minute time frames (epochs). Stayhealthy (Stayhealthy Inc, Ca.) computer software was used to derive the accelerometer activity counts.

Data from the vector magnitude calculated from the output of the three axes (vertical vector (x), anterior-posterior vector (y) and medial-lateral vector (z)) was used to define activity intensity according to the values presented in Table 3.0. Time spent in MVPA and VPA was calculated and presented as the average time per day during the monitoring period. Participants were only included for data analysis if they had worn the accelerometer for a minimum of three days (Mattocks et al. 2008) and acquired a minimum daily wear time of nine hours for weekdays (Mattocks et al. 2008) and eight hours for weekend days (Rowlands et al. 2008). Sustained 10 minute periods of zero counts were removed during the recoding process as it was deemed that the accelerometer had not been worn during these time periods (Riddoch et al. 2004).
Table 3.0 Threshold RT3 counts relating to sedentary, light, moderate, and vigorous intensity activity

<table>
<thead>
<tr>
<th>Activity Intensity</th>
<th>Activity counts (counts/min⁻¹)</th>
<th>Metabolic Equivalent (MET value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>&lt; 288</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>Light</td>
<td>288-969</td>
<td>1.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>970-2332</td>
<td>3</td>
</tr>
<tr>
<td>Vigorous</td>
<td>&gt;2332</td>
<td>6</td>
</tr>
</tbody>
</table>

Table adapted from Rowlands et al. (2004).

3.2.7 Cardiorespiratory fitness

Participants completed an age- and sex-specific (see Table 3.1) all-out progressive cycle ergometer test to exhaustion using a previously validated protocol in children and adolescents (Hansen et al. 1989; Riddoch et al. 2005). Participants cycled at 50, 60, or 70 rpm (set according to individual preference) on an electronically braked Monark Ergomedic 824 E cycle ergometer (Monark, Varberg, Sweden). Following the initial work rate for three minutes, the incremental workloads increased every three minutes until participants were no longer able to continue. Participants wore a Polar FS1 heart rate (HR) monitor (Polar Electro, Kempele, Finland). An exhaustive effort was considered to have been achieved if HR was ≥ 185 bpm or the researcher perceived that the child could not continue. If the child’s pedaling rate dropped below 30 rpm, the subject was considered to have stopped the test.

Maximal power output ($watt_{max}$) was then calculated for each participant according to the following formula (Hansen et al. 1989):
[W1] + W2 *T/180

Where,

W1 = workload (in watts) at last fully complete stage,

W2 = workload increment (in watts) at final incomplete stage,

T = time (in seconds) at final incomplete stage.

For calculation of maximal oxygen uptake, CRF was expressed as \( VO_{2\text{max}} \) per kilogram of body mass (mL/kg/min) or FFM (mL/kg FFM/min). For maximal oxygen uptake the following formulae were applied from the European Youth Heart Study (Riddoch et al. 2005):

10-11 year-olds: \( VO_{2\text{max}} = (12.44 \times \text{watt} - 250) \)

13-14 year-olds: \( VO_{2\text{max}} = (11.87 \times \text{watt} - 365) \)

The cycle ergometer was electronically calibrated once every test day and mechanically calibrated after being moved between schools.

Table 3.1 Cardiorespiratory fitness assessment protocol workloads

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Initial work rate (W)</th>
<th>Δ Work rate (W)</th>
<th>Stages (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls and Boys</td>
<td>10-11</td>
<td>&lt;30</td>
<td>20</td>
<td>20</td>
<td>180</td>
</tr>
<tr>
<td>Girls and Boys</td>
<td>10-11</td>
<td>&gt;30</td>
<td>25</td>
<td>25</td>
<td>180</td>
</tr>
<tr>
<td>Girls</td>
<td>13-14</td>
<td>-</td>
<td>40</td>
<td>40</td>
<td>180</td>
</tr>
<tr>
<td>Boys</td>
<td>13-14</td>
<td>-</td>
<td>50</td>
<td>50</td>
<td>180</td>
</tr>
</tbody>
</table>

Table adapted from Riddoch et al. (2005).
3.3 Power Calculations

Power analyses were conducted separately for each study a-priori using GPower version 3.1.0. As the focus of Study 1 (Chapter 4) in this thesis was on the prevalence of the metabolic syndrome (MetS) in children and adolescents (i.e. the percentage of the total sample who had MetS), power calculations were not performed prior to investigation.

For Study 2 (Chapter 5), data from Freedman et al.’s (2007) investigation into the relations between BMI and waist-to-height ratio (WHTR) to cardiovascular disease (CVD) risk factors in children was used to calculate the required sample size. BMI ($R^2 = 0.32$) and WHTR ($R^2 = 0.34$) both explained significant proportions of a clustered CVD risk score and using these data, a required sample size of 41 was required to achieve a power of 95% at the 5% alpha level in regression analysis.

Study 3 (Chapter 6) of this thesis aimed to explore the associations of MVPA, VPA, and CRF with clustered cardiometabolic risk. Previous studies have reported large effect sizes when comparing cardiometabolic risk in higher vs. lower levels of physical activity and CRF in children (Ruiz et al. 2007; Andersen et al. 2006; Anderssen et al. 2007). Thus, to produce a large effect size (Cohen 1988) at a power of 95% at the 5% alpha level, a sample size of 100 was required for comparison of a clustered risk score across MVPA and VPA tertiles with four covariates included in ANCOVA analysis. For comparison of high vs. low CRF, a sample size of 84 was required.

Large effect sizes have also been reported when comparing cardiometabolic risk factors across various combinations of fatness and CRF groups in children (Eisenmann et al. 2005; Eisenmann et al. 2007; DuBose et al. 2007). Therefore, to produce a large effect size (Cohen 1988) at a power of 95% at the 5% alpha level in Study 4 (Chapter 7), a sample size of 112 was required for comparison of a clustered risk score across four fatness and CRF groups when four covariates were included in the ANCOVA analysis.
For Study 5 (Chapter 8), data from Gutin et al’s (2005) investigation into the relations of MPA and VPA to CRF and fatness in adolescents was used to calculate the required sample size. MPA ($R^2 = 0.37$) and VPA ($R^2 = 0.42$) both explained significant proportions of CRF following multiple regression analyses. The required sample size to achieve 95% power at the 5% alpha level was 25 and 21 for MPA and VPA, respectively.
CHAPTER FOUR: STUDY ONE

Comparison of metabolic syndrome prevalence in UK children and adolescents
using three different paediatric definitions

4.0 Introduction

Childhood overweight and obesity has risen greatly in recent decades across the
globe (Chinn et al. 2001; Ogden et al. 2002; Wang et al. 2006). Increased adiposity in childhood and adolescence is associated with a range of health complications and predisposes individuals to early illness and mortality in later
life (Ebbeling et al. 2002). Being overweight or obese during these years can contribute to dyslipidaemia, hypertension, hypertriglyceridaemia, insulin resistance, and impaired glucose metabolism (Lindsay et al. 2001; Weiss et al. 2004). Abdominal obesity in particular may play a vital role in the development of cardiometabolic disorders (Despres et al. 2006). The clustering of cardiometabolic risk factors is termed the metabolic syndrome (MetS); also known as syndrome X, the insulin resistance syndrome, and the deadly quartet (Eckel et al. 2005); and indeed occurs more frequently in overweight and obese youths (Cook et al. 2003; Weiss et al. 2004).

The clustering of cardiometabolic risk factors in younger years warrants attention in light of evidence suggesting that these risk factors can track into adulthood (Eisenmann et al. 2005; Camhi et al. 2010). Moreover, risk factor clustering in childhood confers individuals to an increased likelihood of developing cardiovascular disease (CVD) and type 2 diabetes (T2DM) 25 to 30 years later (Morrison et al. 2007; Morrison et al. 2008). The risk associated with clustering also appears to be predictive of CVD above and beyond that associated with individual components (Golden et al. 2002), although this is controversial (McNeill et al. 2005). Multiple definitions to identify risk factor clustering in adults have been proposed by the World Health Organisation (WHO) (Alberti et al. 1998), the National Cholesterol Education Program’s (NCEP)
Adult Treatment Panel III (ATP III) (NCEP 2001), the European Group for the Study of Insulin Resistance (Balkau et al. 1999), and the International Diabetes Federation (IDF) (Alberti et al. 2005), and each body agreed on the inclusion of impaired glucose metabolism, central obesity, hypertension, and dyslipidaemia as criteria. Numerous researchers have attempted to adapt these adult definitions so they can be applied to paediatric populations (Cook et al. 2003; Weiss et al. 2004; Viner et al. 2005; Jolliffe et al. 2007; Zimmet et al. 2007).

In children and adolescents, the prevalence of MetS remains unclear, highlighted by a recent review in which the frequency of the syndrome ranged from 1.2% to 22.6% across various worldwide general population and community-based samples (Tailor et al. 2009). In addition to variations in age range and region of investigation, geographical variation in obesity and/or epigenetic factors may also explain disparate findings between the reviewed studies (Reinehr et al. 2007). However, dissimilarities in the frequency of MetS in youths, particularly in studies of the same region, can also be attributed to differences in the criteria used to define the syndrome. This is in spite of the IDF consensus definition that was proposed to facilitate international comparisons of MetS in youths, which since its release in 2007, has had a poor uptake (Zimmet et al. 2007). One subsequent study, though, did report that 4.5% of US adolescents have MetS according to the IDF consensus definition (Ford et al. 2008). In comparison, the condition was identified in 4.2% of US adolescents when a modification of the ATP III definition was employed (Cook et al. 2003), whereas an alternative ATP III-modified definition and modified-IDF criteria reported frequencies of 7.6% and 9.6%, respectively (Jolliffe et al. 2007). Further confusion is underlined by de Ferranti and colleagues’ (2004) evidence demonstrating that 9.2% of US adolescents displayed the condition when assessed using their modified ATP III criteria.

In Belgian adolescents, 4.1% were classified as having MetS using an ATP III-modified definition (Vissers et al. 2007). However, it is difficult to compare these
results to those published in the US given the differences in the criteria thresholds used. Nonetheless, there have been several investigations in European youths that have used the IDF definition, therefore permitting comparisons. In Finnish adolescents, 2.4% of participants were classified as having MetS (Pirkola et al. 2008), whereas in 10 and 15 year-old European children and adolescents from Estonia, Denmark, and Portugal, 0.2% and 1.4% had the syndrome, respectively (Ekelund et al. 2009).

There is currently a lack of studies that have explored the prevalence of risk factor clustering in UK youths, although one previous study reported that 28% of obese individuals (body mass index [BMI] > 95th percentile) in this region had MetS according to a modified WHO definition (Viner et al. 2005). In Hungarian children, the prevalence in obese children (BMI ≥ 95th percentile) was lower with only 15% displaying a clustering of three or more cardiometabolic risk factors when defined using a definition proposed by the authors that differed to Viner et al.’s MetS definition in respect to criteria for fasting lipid (total cholesterol, triglycerides, and high-density lipoprotein [HDL]) and insulin levels and oral glucose tolerance test (OGTT) (Csábi et al. 2000). In moderate (BMI z-score 2 to 2.5) and severely (BMI z-score > 2.5) obese US adolescents, the prevalence of MetS was 38.7% and 49.7%, respectively, according to criteria based on the adult ATP III and WHO definitions (Weiss et al. 2004). It is of course difficult to make comparisons between investigations though due to variations in MetS definitions.

In addition to limited UK data regarding the prevalence of MetS in children and adolescents, literature that has investigated variation in MetS prevalence using different proposed definitions, and according to varying degrees of fatness, is scarce. Therefore, the objectives of this investigation were to 1) compare MetS prevalence using different existing definitions in a small sample of children and adolescents, and 2) explore variation in MetS according to varying degrees of adiposity.
4.1 Methodology

Sample

Baseline data from 133 children and adolescents who took part in the Health And Physical activity Promotion (HAPPY) study in Bedfordshire, UK, as well as data collected from additional participants recruited at the schools taking part in the HAPPY study (N = 26), was analysed. Participants were excluded from the HAPPY study if they had any contraindications to taking part in physical exercise and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. An inclusion criterion was age between 10 and 17 years-old. The study was approved by the University of Bedfordshire ethics review board and written informed consent was obtained from participants’ parents before any testing procedures.

Experimental design

Data collection took place in participants’ schools. Participants visited the research team between 8-10 am in a room allocated to the research team. Children were instructed to fast from 9 pm the night before and only consume water until all testing was completed.

Measurements

Anthropometry

Waist circumference (WC), stature, and body mass were measured and calculated as described in methodology section 3.2.2. BMI was calculated using the equation: BMI = body mass (kg) ÷ stature^2 (m^2).

Cardiometabolic risk factors

Sitting blood pressure (BP) was measured following the protocol outlined in methodology section 3.2.4, while blood samples were collected using a finger
prick method to determine TC, HDL, TC:HDL ratio, triglycerides, and blood glucose (see methodology section 3.2.5).

**Metabolic syndrome definitions**

The IDF consensus definition (Zimmet et al. 2007) and two modified ATP III definitions (Cook et al. 2003; de Ferranti et al. 2004) (reported in Table 4.0) were used to assess MetS prevalence.

**Statistical analysis**

All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as mean (SD). Sex differences in descriptive variables were determined by a one-way ANOVA test. Prevalence data are presented as percentages (%). British-specific percentiles for WC were used in these analyses, which were based on reference values for UK children and adolescents (McCarthy et al. 2001). High BP (≥ 90th percentile) definitions were based on values from the National High Blood Pressure Education Program’s report on high BP in children and adolescents (1996); height percentiles based on reference values from WHO height-for-age tables (Ten 2004). In order to assess the impact of adiposity on MetS prevalence, participants were split into non-overweight (NO) and overweight (OW) groups based on Cole et al’s (2000) international cutpoints for BMI. T-tests were performed to compare prevalence differences between weight categories. A p value < 0.05 was considered significant.
Table 4.0 Paediatric definitions of the metabolic syndrome

<table>
<thead>
<tr>
<th>IDF (Zimmet et al. 2007)</th>
<th>Cook et al. (Cook et al. 2003)</th>
<th>De Ferranti et al. (de Ferranti et al. 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile (age- and sex-specific)</td>
<td>WC ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile (age- and sex-specific)</td>
<td>WC ≥ 75&lt;sup&gt;th&lt;/sup&gt; percentile (age- and sex-specific)</td>
</tr>
<tr>
<td>HDL &lt; 1.03 mmol/L</td>
<td>HDL &lt; 1.03 mmol/L</td>
<td>HDL &lt; 1.3 mmol/L</td>
</tr>
<tr>
<td>Triglycerides ≥ 1.7 mmol/L</td>
<td>Triglycerides ≥ 1.24 mmol/L</td>
<td>Triglycerides ≥ 1.1 mmol/L</td>
</tr>
<tr>
<td>Systolic BP ≥ 130 / diastolic ≥ 85 mm Hg</td>
<td>BP ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile (age-, sex-, height-specific)</td>
<td>BP ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile (age-, sex-, height-specific)</td>
</tr>
<tr>
<td>Fasting glucose ≥ 5.6 mmol/L</td>
<td>Fasting glucose ≥ 6.1 mmol/L</td>
<td>Fasting glucose ≥ 6.1 mmol/L</td>
</tr>
</tbody>
</table>

IDF, International Diabetes Federation, WC, waist circumference, HDL, high-density lipoprotein, BP, blood pressure. In the IDF definition, MetS is defined as abdominal obesity (WC ≥ 90<sup>th</sup> percentile) plus at least two other risk factors. Cook and de Ferranti definitions classify MetS as the presence of any three or more risk factors.

4.2 Results

Participants

Table 4.1 shows the descriptive characteristics of the participants. One way ANOVA revealed that weight, WC, diastolic BP, TC:HDL ratio, and triglyceride levels were significantly greater in the overweight compared to the non-overweight participants, while HDL was significantly lower in the overweight group.
Table 4.1 Descriptive characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All (N = 133)</th>
<th>OW (N = 20)</th>
<th>NO (N = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.77 (2.09)</td>
<td>12.40 (1.97)</td>
<td>12.84 (2.11)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.52 (12.72)</td>
<td>155.35 (11.18)</td>
<td>155.55 (13.02)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46.66 (13.88)</td>
<td>61.47 (13.59)*</td>
<td>44.04 (12.24)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>64.94 (9.73)</td>
<td>80.08 (11.13)*</td>
<td>62.26 (6.51)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>107.74 (11.00)</td>
<td>109.43 (12.31)</td>
<td>107.44 (10.78)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>67.45 (6.92)</td>
<td>72.70 (6.91)*</td>
<td>66.53 (6.52)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.96 (0.67)</td>
<td>4.10 (0.59)</td>
<td>3.94 (0.69)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.39 (0.38)</td>
<td>1.19 (0.33)*</td>
<td>1.42 (0.37)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>3.06 (1.04)</td>
<td>3.84 (1.72)*</td>
<td>2.92 (0.81)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.84 (0.51)</td>
<td>1.11 (0.54)*</td>
<td>0.79 (0.50)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.96 (0.48)</td>
<td>5.15 (0.43)</td>
<td>4.93 (0.48)</td>
</tr>
</tbody>
</table>

OW, overweight; NO, non-overweight; BMI, body mass index; BP, blood pressure; TC, total cholesterol; HDL, high-density lipoprotein. Data reported as mean (SD).

* p < 0.01 between overweight and non-overweight groups.

Comparison of metabolic syndrome definitions

Figure 4.0 shows the overall prevalence of MetS and its individual components according to the IDF (Zimmet et al. 2007), Cook (Cook et al. 2003) and de Ferranti (de Ferranti et al. 2004) definitions. The highest prevalence was observed when using the de Ferranti criteria (9.8%), while the IDF criteria identified the least
number of participants as having the condition (2.3%). MetS occurred in 4.5% of children and adolescents according to the Cook criteria. In boys, the prevalence of MetS according to the IDF, Cook, and de Ferranti definitions was 0%, 3.4%, and 5.2%, respectively, while in girls, the prevalence was 4%, 5.3%, and 13.3%, respectively. The prevalence of MetS in children and adolescents according to all, three, two, one, or none of the definitions was calculated. 89% of participants were free from MetS according to any of the three definitions, while 10.5% had had MetS according to one definition, 7% according to two definitions, and 1.5% according to all three definitions.

Of the individual components, abdominal obesity was the most prevalent MetS component in the IDF and Cook definitions (16.5%), while it was the second most prevalent component in de Ferranti’s definition (33.1%) (see Figure 4.0). Low HDL was the most prevalent risk factor according to de Ferranti’s definition (42.1%), while it was the second and third most prevalent risk factor in the IDF and Cook definitions (13.5%), respectively. Impaired fasting glucose was the least prevalent risk factor in the Cook and de Ferranti definitions (2.3%), while fasting hyperglycaemia was apparent in 9.8% of participants according to the IDF criteria. Hypertension was the least prevalent risk factor when employing the IDF criteria, with zero participants displaying both high systolic and high diastolic BP, while it was the second least prevalent component of the Cook and de Ferranti definitions (4.5%).
Figure 4.0 Prevalence of the metabolic syndrome and its individual components according to different proposed definitions in 133 children and adolescents.

**Comparison of prevalence by weight status**

In non-overweight children and adolescents, MetS occurred more frequently according to the de Ferranti definition (5.3%), while it occurred least frequently according to the Cook definition (0.9%), and was present in 1.8% of participants according to the IDF definition (see Figure 4.1). In overweight children, the syndrome was also identified more frequently according to de Ferranti’s definition (45%) in comparison to the Cook (25%) and IDF definitions (5%). MetS prevalence was significantly more frequent in overweight individuals compared with non-overweight according to the Cook and de Ferranti definitions ($p < 0.001$), while there was no significant difference between weight groups when using the IDF definition.
Figure 4.1 Prevalence of the metabolic syndrome in overweight and non-overweight children and adolescents according to different proposed definitions. * $p < 0.001$ between weight categories.

The prevalence of the individual components of MetS in overweight children and adolescents can be seen in Table 4.2. All of the overweight participants had abdominal obesity according to the de Ferranti definition, while it was slightly less prevalent according to the IDF and Cook definitions. Hypertriglyceridaemia was present in half of the overweight population according to de Ferranti’s definition, and was less frequent according to the Cook and IDF definitions. IDF-defined hypertension was not present in any participant, while one in five had elevated blood pressure according to the Cook and de Ferranti definitions. Low HDL was seen in 25% of the population according to the IDF and Cook criteria, while it was markedly more frequent according to de Ferranti’s definition. The prevalence of high fasting glucose was relatively low in this sample according to all three definitions.
Table 4.2 Prevalence of metabolic syndrome components according to different proposed definitions in 20 overweight children and adolescents

<table>
<thead>
<tr>
<th>Component</th>
<th>IDF (Zimmet et al. 2007)</th>
<th>Cook (Cook et al. 2003)</th>
<th>De Ferranti (de Ferranti et al. 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>80</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>10</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Low HDL</td>
<td>25</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Fasting hyperglycaemia</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

IDF, International Diabetes Federation, HDL, high-density lipoprotein.

4.3 Discussion

The results of this study demonstrated that the prevalence of MetS may range from 2.3% to 9.8% in Bedfordshire children and adolescents. Few previous studies have compared MetS prevalence according to different proposed definitions in children and adolescents. These findings demonstrate that the prevalence of the syndrome is highly dependent on the definition used. Only 1.5% of participants fulfilled all definitions of MetS, indicating a low degree of overlap between the different proposed criteria. Comparisons between studies that have used different definitions of MetS are thus not meaningful in youths.

According to the IDF definition, the prevalence of MetS observed in this sample of UK youths (2.3%) is lower than that observed in the US; 4.5% (Ford et al. 2008). However, differences may be explained by a smaller sample size in the current study, while participants were also self-selected, which may have lead to
the more ‘healthier’ children and adolescents volunteering to take part. In comparison to other European populations, the frequency of MetS in this sample is similar to that observed in Finnish 16 year-olds (2.4%) (Pirkola et al. 2008), while the prevalence in 10 and 15 year-old children and adolescents from Estonia, Denmark, and Portugal, according to the IDF criteria, is lower (0.2% and 1.4% in 10 and 15 year-olds, respectively). According to the Cook definition, MetS prevalence in this sample (4.5%) is similar to that reported by Cook et al. (2003) in 12 to 19 year-old US adolescents (4.2%). However, Cook et al. (2003) studied data available from the Third National Health and Nutrition Examination Survey (NHANES) between 1988 and 1999 and it is possible that the syndrome has become more prevalent since this report. The de Ferranti definition identified 9.8% of participants as having MetS, which is similar to the frequency reported by de Ferranti et al. (2004) in 12 to 19 year-old US adolescents (9.2%).

The lowest prevalence of MetS was observed when employing the IDF criteria (2.3%), which is not surprising given that this definition requires an individual to have abdominal obesity plus at least two other risk factors. On the contrary, the Cook and de Ferranti definitions require the presence of any three risk factors in classifying MetS. Other contributing factors to the low prevalence of IDF-defined MetS are that none of the participants had elevated blood pressure (≥ 130 / 85 mm Hg). However, this threshold for elevated blood pressure adheres to the values in the IDF adult definition of MetS (Alberti et al. 2006). Other health organisations propose that increased risk of adverse health may actually occur at a lower threshold in children and adolescents and the diagnosis of high blood pressure should be age-, sex-, and height-specific in this population (Falkner et al. 2004). Hypertriglyceridaemia was also substantially less prevalent according to the IDF definition in comparison to the de Ferranti and Cook definitions, while impaired fasting glucose was more prevalent according to the IDF definition (9.8%). The highest MetS prevalence was identified by the de Ferranti definition, which can be largely attributed to the use of lower thresholds for WC and HDL in
comparison to the IDF and Cook criteria, which resulted in 33.1% of participants being classified as abdominally obese and 42.1% as having low HDL.

The present investigation found that the prevalence of MetS in overweight children and adolescents varies substantially according to the definition used (5% to 45%). Large discrepancies in MetS prevalence according to different proposed definitions has also been observed in German four to 16 year-olds (Reinehr et al. 2007). According to the Cook and de Ferranti definitions, the prevalence reported in the current study is similar to that seen in German youths; 25% and 45% vs. 21% and 39% (Reinehr et al. 2007), respectively. The lowest frequency observed according to a paediatric-specific definition in Reinehr et al’s (2007) study was that proposed by Viner and colleagues (2005), which identified 18% of 1205 overweight youths as having MetS. This frequency is still markedly higher than the lowest frequency observed here using IDF criteria (5%), although comparisons are impractical due to differences between the definitions. In a population of overweight and obese French youths, the frequency of MetS according to the IDF definition for children and adolescents was 8.9% (compared with 14.5% identified according to the authors’ modified ATP III definition) (Druet et al. 2008), and is thus higher than that observed in the current sample of overweight youths. In comparison to the present study, the IDF definition also identified MetS more frequently (17.3%) in a population of 1241 overweight youths from Hungary, France, Italy, Greece, and Poland (Bokor et al. 2008).

The prevalence of MetS was significantly higher in this sample of overweight children and adolescents in comparison to non-overweight individuals according to the Cook and de Ferranti definitions (25% vs. 0.9% and 45% vs. 5.3%, respectively), while MetS prevalence did not differ significantly between weight categories according to the IDF definition (5% vs. 1.8%). Given that only one of the 20 overweight and three of the 113 non-overweight participants had MetS according to the IDF definition, it is likely that reduced statistical power may explain the non-significant difference. Since WC is strongly related to BMI (Savva
et al. 2000), it might be expected that MetS prevalence according to the IDF definition would be higher in those with a high BMI seeing that individuals cannot be defined as having MetS unless they have an elevated WC. If the IDF did not require abdominal obesity when diagnosing MetS, the prevalence of the condition would be higher. Although the current IDF criteria may enable more specific selection of theoretically high-risk youngsters for intervention, it may neglect individuals who are at moderate risk of CVD and T2DM, and hence excludes them from preventive actions that may in fact be more cost-effective than late-stage symptomatic treatment (Druet et al. 2008). Indeed, evidence has shown that a third of men with a normal WC present multiple cardiometabolic risk factors and a high risk of mortality (Katzmarzyk et al. 2006), while a clustering of cardiometabolic risk factors may also occur in 2.1% of youths who have both a normal WC and a normal BMI (Maffeis et al. 2001). It has been proposed that cardiometabolic disorders are primarily associated with visceral fat accumulation (Nguyen-Duy et al. 2003), and although WC explains 64% of the variance in visceral fat mass in obese children (Brambilla et al. 2006), there appears to be discrepancies in visceral fat mass for a given WC value across race/ethnicities (Carroll et al. 2008).

As stated, when defined using the Cook definition, MetS prevalence was significantly higher in the overweight BMI category. Similarly, MetS prevalence was also substantially higher in overweight compared to non-overweight US adolescents according to the Cook definition (28.7% vs. 6.9%, respectively) (Cook et al. 2003). However, comparisons are difficult given that Cook et al. (2003) defined overweight as BMI ≥ 95th percentile, whereas in the current study a high BMI was classified according to Cole et al’s (2000) age- and sex-specific internationally proposed thresholds. In obese Hungarian children (BMI ≥ 95th percentile), a clustering of three or more MetS risk factors occurred more frequently in comparison to their non-obese counterparts (15% vs. 0.4%) (Csábi et al. 2000), although the authors’ proposed definition did not match any of those used in the present study (cut off points for lipids differed and definition
included fasting insulin and OGTT). To allow for future comparisons between overweight and non-overweight children and adolescents, researchers should seek to use uniformly accepted thresholds. The age- and sex-specific overweight and obesity thresholds proposed by Cole et al. (2000) may be preferable since they are based on international data linked to the widely accepted adult cutpoints (25 and 30 kg/m², respectively) and hence are less arbitrary in that researchers need not to decide the reference data and cut off points to be used.

There are certain limitations of the present study. The cohort was relatively small and based in a single region within the UK, hence it is difficult to suggest that these findings may be representative of other child and adolescent populations. However, socioeconomic status of the regions from which participants were recruited was similar to other areas of the UK and the results may therefore be generalised to other areas of the nation. Participants were also recruited on a voluntary basis, and it may be that ‘less healthy’ individuals were more reluctant to volunteer for the study. In addition, the effect of pubertal development was not accounted for as data on pubertal stage was not available. Literature suggests that during puberty a transient increase in insulin resistance, dyslipidaemia, and blood pressure can occur (Hannon et al. 2006; Moran et al. 2008). Although a previous study has documented an influence of puberty on MetS prevalence using Cook et al. (2003) and de Ferranti et al.’s (2004) definitions, other definitions (Alberti et al. 1998; Balkau et al. 1999; NCEP 2001; Weiss et al. 2004; Alberti et al. 2005; Viner et al. 2005) were unaffected (Reinehr et al. 2007). It is also important to note that none of the paediatric MetS definitions used here have been validated in their abilities to predict disease outcomes and hence such a classification system may have limitations in clinical settings.

In conclusion, this study found that the overall prevalence of MetS in a small sample of Bedfordshire children and adolescents was 2.3%, 4.5%, and 9.8% using the IDF, Cook, and de Ferranti definitions, respectively. The prevalence of MetS
in overweight youths is higher compared to those who are non-overweight. However, the frequency of the syndrome in overweight youths differs substantially according to the definition used. An internationally accepted uniform definition for childhood MetS is necessary so comparisons between different studies and populations can be made and so researchers and practitioners can avoid the possibility of different diagnosis of the same individual depending on the criteria used. Longitudinal studies are thus needed to confirm which proposed cut off points best predict adverse health outcomes and whether MetS in childhood and adolescence is predictive of cardiometabolic illness. Studies on larger sample sizes of children and adolescents are also needed in the UK so that researchers can better understand the severity of the MetS problem.
CHAPTER FIVE: STUDY TWO

Relation of waist circumference, waist-to-height ratio, and body mass index to clustered cardiometabolic risk and cardiorespiratory fitness in children and adolescents

5.0 Introduction

Obesity increases the likelihood of cardiovascular disease (CVD) and type 2 diabetes (T2DM) in adults (Hevener et al. 2010) and attributes to approximately 280,000 to 325,000 adult deaths per year in the US (Allison et al. 1999). In children and adolescents, overweight and obesity confers to increased risk of dyslipidaemia, hypertension, impaired glucose metabolism, and decreased cardiorespiratory fitness (CRF) (Chen et al. 2006; Andersen et al. 2008; Thomas et al. 2008). Additionally, longitudinal studies have shown that adiposity and fat distribution may track through childhood and adolescence into adulthood (Webber et al. 1995; van Lenthe et al. 1998; Garnett et al. 2007). Childhood overweight also increases the likelihood of all-cause and cardiovascular mortality in adulthood (Gunnell et al. 1998), even after adjustment for adult body mass index (BMI) (Must et al. 1992).

It has been proposed that cardiometabolic abnormalities are primarily related to visceral fat accumulation (Nguyen-Duy et al. 2003). In adults, visceral fatness as measured by computed tomography (CT) correlates with triglycerides, high density-lipoprotein (HDL), total cholesterol (TC):HDL ratio, fasting insulin, and glucose metabolism (Pouliot et al. 1992; Nguyen-Duy et al. 2003). Visceral adipose tissue as measured by dual X-ray absorptiometry (DEXA) is also associated with reduced insulin sensitivity and glucose metabolism, increased blood pressure (BP), less favourable lipid profile, and increased left ventricular mass in children and adolescents (Daniels et al. 1999; Bacha et al. 2003). Visceral fat accumulation as measured by magnetic resonance imaging (MRI) also correlates negatively with lipid profile and insulin action in youths (Caprio et al.
1995), although in an alternative study, MRI-determined visceral fat was not predictive of current serum lipid levels in children (Leung et al. 1998).

However, CT, DEXA, and MRI techniques are expensive and can require irradiation of participants and therefore have limited application for mass screening and routine daily clinical practice (Savva et al. 2000). Instead, a simple, inexpensive and non-invasive tool for screening cardiometabolic risk factors in children and adolescents is needed. BMI offers a simple and clinically practical measure of body fatness and is currently the most frequently used tool in classifying obesity (Stevens et al. 2008; Barlow 2007). In overweight and obese adults (BMI ≥ 25 and 30 kg/m², respectively), the relative risk of cardiometabolic abnormalities, CVD, T2DM, and mortality is increased compared to those who are non-overweight (Wilson et al. 2002; Hu et al. 2004; Wang et al. 2005). Increasing BMI is also associated with less favourable systolic BP, HDL, triglycerides, fasting glucose, insulin, and 2-h glucose in youths (Lindsay et al. 2001; Weiss et al. 2004). However, no uniformly accepted definition of overweight and obesity that relates BMI to health measures exists in this population. The 85th and 95th percentiles of reference data have frequently been used to define weight status (Himes et al. 1994; Reilly et al. 1999) in children and explore associations with health risk (Cook et al. 2003). In addition, Cole and colleagues (2000) developed international age- and sex-specific thresholds that were tied to the adult overweight (25 kg/m²) and obesity (30 kg/m²) thresholds. Although based on adult obesity-related health risks, children who exceeded Cole et al’s (2000) proposed overweight threshold were at a 1.6 to 9.1 times higher risk of elevated cardiometabolic risk than their normal weight counterparts (Katzmarzyk et al. 2003).

BMI becomes particularly problematic in that it only offers a surrogate measure of body fatness and does not accurately reflect body composition (Neovius et al. 2008). WC, on the contrary, offers a more accurate reflection of visceral adipose tissue in adults (Pouliot et al. 1994; Conway et al. 1997). It is also a good
indicator of MRI-assessed visceral fat mass in children and adolescents (explaining 64.8% of the variance) and is a better predictor than BMI (Janssen et al. 2002; Brambilla et al. 2006). Indeed, increased WC; independent of race, sex, age, weight, and height; is unfavourably related with triacylglycerol, LDL, HDL, and insulin concentrations in youths (Freedman et al. 1999; Flodmark et al. 1994). It is proposed that WC is a better predictor of cardiometabolic risk in young people than BMI (Moreno et al. 2002) and in Greek-Cypriot children (1037 boys and 950 girls; mean age 11.4 ± 0.4 years), WC explained a higher amount of variance in systolic and diastolic BP than BMI (14.2% vs. 1.8% and 9.8% vs. 0.6%, respectively) and was also a significant predictor of current TC, HDL, and LDL levels, whereas BMI was a significant predictor only for current triglyceride levels (Savva et al. 2000). Like BMI, there is no uniformly accepted definition of childhood overweight and obesity that relates WC to health measures. A frequently used cutoff for WC-defined central obesity in children and adolescents is the 90th percentile for age, sex, and ethnicity (Cook et al. 2003; Zimmet et al. 2007) and it has been evidenced that children with a WC above this threshold are more likely to have multiple cardiometabolic risk factors compared to those with values below (Maffeis et al. 2001).

However, like BMI, proposed thresholds to define obesity in youths according to WC are arbitrary and not linked to cardiometabolic health outcomes associated with fatness (Ashwell et al. 2005). Add this to the fact that BMI and WC need to be expressed relative to age, sex, and ethnicity (WHO 2004; Zimmet et al. 2007), authors have proposed that waist-to-height ratio (WHTR) may be a more effective and simple measure of health-related obesity in children and adolescents (Hara et al. 2002; Ashwell et al. 2005). On average, men are taller and have larger waist circumferences than women and thus WHTR values are closer between sexes compared with average WC values. Couple this with the fact that height and WC increase continually as children and adolescents age, it has been proposed that the same boundary value to define abdominal obesity may be used in males and females, old or young, as well as in different ethnic
groups (Ashwell et al. 2005). WHTR is indeed associated with visceral adipose tissue in adults (Hsieh et al. 2005) and is also a better predictor of cardiovascular and all-cause mortality than BMI in longitudinal studies (Cox et al. 1996; Zhang et al. 2007). WHTR is also associated with cardiometabolic risk factors in adults, including TC, HDL, LDL, triglycerides, 2h glucose, systolic BP, and diastolic BP (Patel et al. 1999; Ho et al. 2003), and is also a better predictor of cardiometabolic health outcomes, such as coronary heart disease (CHD), angina, and hypercholesterolaemia, compared with WC and BMI (Ho et al. 2003). In children and adolescents, the use of WHTR as an anthropometric index appears to be clinically, biologically, and statistically acceptable, in that it appropriately adjusts height for WC and effectively screens for abdominal obesity-related cardiometabolic health problems (Nambiar et al. 2009). It has been evidenced in this population that central obesity according to WHTR presents significantly higher systolic BP (girls only), higher triglyceride concentrations (boys only), and lower HDL concentrations (boys and girls) compared to those who are non-centrally obese (Nambiar et al. 2010).

In addition to being a good predictor of cardiometabolic health, WHTR may also offer the advantage of identifying individuals with increased cardiometabolic risk who are not overweight according to BMI (Mokha et al. 2010). A clustering of cardiometabolic risk factors is present in approximately 23.5% of normal weight US adults according to BMI, while 51.3% and 31.7% of overweight and obese adults, respectively, are metabolically healthy (Wildman et al. 2008). Moreover, obese adults (BMI ≥ 30 kg/m²) who are insulin sensitive have similar insulin sensitivity and intima-media thickness compared with their normal weight counterparts (Stefan et al. 2008). In children and adolescents, those who are normal weight BMI but are centrally obese according to WHTR have significantly greater odds of having adverse levels of LDL, HDL, triglycerides, and insulin and have a significantly higher prevalence of the metabolic syndrome compared to non-overweight individuals without central obesity (Mokha et al. 2010). In youths who are overweight or obese according to BMI but without central
obesity, the likelihood of having adverse levels of HDL and insulin resistance was 0.53 (95% CI: 0.30-0.96) and 0.27 (0.08-0.90) less compared to those with central obesity, while the prevalence of the metabolic syndrome was also significantly lower \((p < 0.0001)\). Evidence also suggests that WHTR can be more sensitive than WC in identifying diabetes and abnormal levels for BP, fasting glucose, HbA1c, and cholesterol (Hsieh et al. 1995; Lee et al. 1995; Lin et al. 2002), likely because this index encompasses adjustment to different statures and because of the negative relationship height has with cardiometabolic risk factors (Henriksson et al. 2001).

A WHTR of > 0.5 has been proposed to classify abdominal obesity in adults (Ashwell et al. 2005). This threshold was originally proposed as the point at which health risk starts to increase in Asian and British populations (Hsieh et al. 1995; Ashwell et al. 1996). Since then, receiver-operating characteristic analysis has found that cut-offs close to 0.5 are the most sensitive in correctly identifying those with elevated cardiovascular health risks (Ho et al. 2003) and a WHTR > 0.5 indeed identifies increased risk of hypertension, dyslipidaemia, diabetes mellitus, CHD, angina, and hypercholesterolaemia in numerous populations (Ko et al. 1999; Lin et al. 2002; Sargeant et al. 2002; Bertsias et al. 2003; Ho et al. 2003). This threshold may also be suitable for identifying obesity-related health risks in children and adolescents. Indeed, European children with a WHTR > 0.5 are 7.0 times more likely (95% CI: 3.63-13.48) to have increased cardiometabolic risk compared to those with values below that level (Maffeis et al. 2008) and in Australian youths, those with values ≥ 0.48 have, on average, significantly greater triglyceride concentrations, systolic BP, and reduced HDL concentrations compared to those with values < 0.46 \((p < 0.05)\) (Nambiar et al. 2010). However, evidence linking this threshold to increased cardiometabolic risk in this population is under-researched.

To date, few studies have compared the associations of WHTR, WC, and BMI to cardiometabolic risk in children and adolescents. Furthermore, the limited
evidence that has examined the relation of WHTR, WC, and BMI with cardiometabolic risk has explored only single risk factors. Investigating associations with clustered cardiometabolic risk may be preferable as differences in individual risk markers between participants may be too subtle to investigate in isolation, while daily fluctuations in single risk factors is also evident (Elveback et al. 1980; Lyons Wall et al. 1994). Exploring associations with clustered risk can also help reduce the error variation that each risk factor includes (Anderssen et al. 2007; Ruiz et al. 2007). Moreover, cardiometabolic diseases are characterised by a constellation of risk markers, and examining clustered risk may detect an array of cardiometabolic disturbances rather than focusing on one or two particular markers, while having multiple risk factors confers individuals to a poorer health status compared to if only a single risk factor was present (Gami et al. 2007). Furthermore, CRF is typically omitted in cardiometabolic risk profiling and it seems that no previous studies have compared the ability of the aforementioned obesity indexes in explaining variance in global cardiometabolic risk when a CRF score is included. As CRF is an independent risk factor for CVD, T2DM, and mortality in adults (Wei et al. 2000; Blair et al. 2001) and is associated with cardiometabolic risk factors in children and adolescents (Ekelund et al. 2007; Ruiz et al. 2007; Martinez-Gomez et al. 2010), this variable should arguably be considered when profiling an individual’s cardiometabolic risk status.

The objective of this study was therefore to calculate clustered cardiometabolic risk with and without CRF included as a risk factor, and explore variation according to BMI, WC, and WHTR.

5.1 Methodology

Sample

The 184 participants (aged 10 to 14 years) included were part of the HAPPY (Health And Physical activity Promotion in Youth) study. Participants were
recruited on a voluntary basis in 11 schools across Bedfordshire, UK and their baseline data used for analyses in the present study. Participants were excluded from the HAPPY study if they had any contraindications to taking part in physical exercise and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. The study was approved by the University of Bedfordshire ethics review board. Written informed consent was obtained from participants’ parents before any testing procedures commenced.

Experimental design

Data collection took place in participants’ schools. Measures were taken by the research team between 8-10 am in a room allocated by the school. Children were instructed to fast from 9 pm the night before and only consume water until all testing was completed.

Measurements

Age, ethnicity, and socioeconomic status

Age was recorded as a decimal value for each participant on the day of data collection. Ethnicity was recorded as white or non-white. A score for socioeconomic status (SES) was attributed to each participant using home postcode and the 2007 Indices of Multiple Deprivation (IMD) (MIMAS 2008; Fairclough et al. 2009). Postcodes were converted into IMD scores using the GeoConvert application (MIMAS 2008). These scores were categorised into tertiles with the lowest tertile indicating the most deprived.

Anthropometry and body composition

Stature and waist circumference were recorded to the nearest 0.5 cm as outlined in methodology section 3.2.2. Body mass and fat free mass (FFM) were recorded to the nearest 0.1 kg using the Tanita BC-418® Segmental Body Composition
Analyser (see methodology sections 3.2.2 and 3.2.3). BMI was calculated using the equation: \( \text{BMI} = \text{body mass (kg)} \div \text{stature}^2 \text{ (m}^2) \).

**Cardiometabolic risk factors**

Sitting BP was measured as described in methodology section 3.2.4 and fasting blood samples obtained using a finger prick method for determination of TC, HDL, TC:HDL ratio, triglycerides, and blood glucose (see methodology section 3.2.5).

**Cardiorespiratory fitness**

Participants completed an age- and sex-specific all-out progressive cycle ergometer test to exhaustion using a previously validated protocol in children and adolescents (Riddoch et al. 2005) (see methodology section 3.2.7). CRF (\( \text{VO}_{2\text{max}} \)) was expressed relative to FFM (mL/kg FFM/min) to account for between-individual differences in body size (Ekelund et al. 2004).

**Clustered cardiometabolic risk score**

TC:HDL ratio and triglycerides were non-normally distributed and were log-transformed. A continuous clustered cardiometabolic risk variable was then constructed by standardising (to the mean by sex) and then summing the \( z \)-scores of the following continuously distributed variables: hypertension ([systolic BP + diastolic BP]/2), fasting blood glucose, TC:HDL ratio, and fasting triglycerides. A second clustered risk variable was constructed that included the \( z \)-score of CRF as a criterion variable.

**Statistical analysis**

All analyses were completed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as mean (SD). Sex differences in descriptive variables were determined by a One-way ANOVA test. Associations between variables were analysed by partial Pearson correlations after adjustment for age, sex, ethnicity, and SES. ANCOVA was used to explore differences in clustered
cardiometabolic risk between overweight and non-overweight participants according to each anthropometric index. Covariates entered into the model were age, sex, ethnicity, and SES. None of the covariates were strongly related with each other. SES was significantly correlated with age ($r = -0.25$, $p < 0.001$), but this relationship was weak. In addition, the assumption of homogeneity of regression slopes was met for each ANCOVA model, with no significant interaction effects on clustered cardiometabolic risk score observed between any independent or covariate variable ($p > 0.05$) (Pallant 2007). Levene’s test of equality of variances within the ANCOVA was violated in the model exploring differences in risk score excluding CRF between WC fatness categories ($p < 0.05$). However, the $F$-statistic in ANCOVA is remarkably robust in the case that variances are unequal across groups (Lindman 1974).

Multiple regression analyses were conducted to assess the degree to which WC, WHTR, and BMI explained variation in clustered cardiometabolic risk. WC, BMI, and WHTR were non-normally distributed and were log-transformed prior to correlation and multiple regression analyses.

### 5.2 Results

#### Participants

Table 5.0 shows the descriptive characteristics of the participants. One-way ANOVA revealed that BMI, diastolic BP, TC, and CRF were significantly greater in girls than in boys. No significant differences were noted between sexes for any other variable. 78.8% of the sample was white, while 21.2% were non-white.

#### Relation of indices with cardiometabolic risk factors

As shown in Table 5.1, partial correlation analysis revealed that WC, WHTR, and BMI were all significantly correlated with TC:HDL ratio and triglycerides. WC was also significantly correlated with HDL, while BMI was significantly correlated with
diastolic BP. WC and BMI were significantly correlated with CRF, whereas WHTR was not correlated with CRF. All independent variables were significantly correlated with both clustered cardiometabolic risk scores. When CRF was excluded from the score, BMI and WC were more strongly related with clustered risk than WHTR. When CRF was included in the score, BMI was related more strongly with clustered risk than WC and WHTR, and WC was more strongly related with risk than WHTR.

**Weight status and clustered cardiometabolic risk**

Mean (SE) values for clustered cardiometabolic risk in overweight and non-overweight participants according to WC, WHTR, and BMI cut off points can be seen in Table 5.2. The number of non-overweight and overweight participants for the clustered risk score excluding CRF was 152 and 32 for WC, 167 and 17 for WHTR, and 157 and 27 for BMI, respectively. The number of non-overweight and overweight participants for the clustered risk score including CRF was 114 and 20 for WC, 123 and 11 for WHTR, and 117 and 17 for BMI, respectively. Clustered cardiometabolic risk was significantly higher in overweight compared to non-overweight children and adolescents according to each anthropometric index when CRF was included in the score: $F(1, 128) = 29.93$, $F(1, 128) = 14.40$, $F(1, 128) = 24.43$ (all $p < 0.001$) for WC, WHTR, and BMI, respectively. Risk was also significantly higher in overweight compared to non-overweight participants according to each index when CRF was excluded from the risk score: $F(1, 178) = 20.34$ ($p < 0.001$), $F(1, 178) = 5.56$ ($p < 0.05$), $F(1, 178) = 13.24$ ($p < 0.001$) for WC, WHTR, and BMI, respectively. In the risk score excluding CRF, the magnitude of difference (according to the $p$ value) was lower for BMI compared to WC and lower for WHTR compared to WC and BMI.
Table 5.0 Descriptive characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All (N = 184)</th>
<th>Boys (N = 87)</th>
<th>Girls (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.51 (1.94)</td>
<td>12.62 (1.89)</td>
<td>12.40 (1.98)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.19 (11.98)</td>
<td>155.65 (13.56)</td>
<td>152.89 (10.25)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>44.81 (13.66)</td>
<td>44.26 (13.97)</td>
<td>45.31 (13.43)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.61 (3.74)</td>
<td>17.95 (3.05)*</td>
<td>19.21 (4.19)</td>
</tr>
<tr>
<td>Waist girth (cm)</td>
<td>66.16 (9.78)</td>
<td>65.69 (8.96)</td>
<td>66.58 (10.49)</td>
</tr>
<tr>
<td>WHTR</td>
<td>0.43 (0.06)</td>
<td>0.42 (0.04)</td>
<td>0.44 (0.64)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>107.04 (10.44)</td>
<td>108.59 (11.03)</td>
<td>105.65 (9.73)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66.06 (7.20)</td>
<td>64.71 (7.28)*</td>
<td>67.28 (6.95)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.94 (0.68)</td>
<td>3.79 (0.70)**</td>
<td>4.07 (0.63)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.42 (0.38)</td>
<td>1.43 (0.38)</td>
<td>1.41 (0.37)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>2.97 (0.99)</td>
<td>2.84 (0.98)</td>
<td>3.08 (1.00)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.83 (0.49)</td>
<td>0.75 (0.37)</td>
<td>0.89 (0.58)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.02 (0.50)</td>
<td>5.07 (0.48)</td>
<td>4.98 (0.52)</td>
</tr>
<tr>
<td>CRF³ (mL/kg FFM/ min)</td>
<td>52.43 (8.70)</td>
<td>54.55 (7.98)**</td>
<td>50.50 (8.93)</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; WHTR, waist-to-height ratio; TC, total cholesterol; HDL, high-density lipoprotein; CRF, cardiorespiratory fitness; FFM, fat free mass. Data reported as mean (SD). *In N = 134 (64 male and 70 female) participants. **p < 0.01 between sexes.
Table 5.1 Relationship between anthropometric indices and cardiometabolic risk factors. These are adjusted for age, sex, ethnicity, and SES

<table>
<thead>
<tr>
<th></th>
<th>WC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>WHTR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>BMI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>0.13</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.16</td>
<td>0.13</td>
<td>0.25**</td>
</tr>
<tr>
<td>TC</td>
<td>0.08</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.18&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.13</td>
<td>-0.14</td>
</tr>
<tr>
<td>TC:HDL ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25**</td>
<td>0.23**</td>
<td>0.24***</td>
</tr>
<tr>
<td>Triglycerides&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.31***</td>
<td>0.29***</td>
<td>0.31***</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.12</td>
<td>0.10</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>-0.39***</td>
<td>-0.14</td>
<td>-0.46***</td>
</tr>
<tr>
<td>Clustered risk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.36***</td>
<td>0.23**</td>
<td>0.38***</td>
</tr>
<tr>
<td>Clustered risk&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.27**</td>
<td>0.21*</td>
<td>0.29***</td>
</tr>
</tbody>
</table>

BP, blood pressure, TC, total cholesterol, HDL, high-density lipoprotein. <sup>a</sup>log transformed, <sup>b</sup>clustered risk score excluding cardiorepiratory fitness, <sup>c</sup>clustered risk score including cardiorepiratory fitness. <sup>*</sup>p < 0.05, <sup>**</sup>p < 0.01, <sup>***</sup>p < 0.001.
Table 5.2 Comparison of clustered cardiometabolic risk between overweight and non-overweight children and adolescents according to WC, WHTR, and BMI cut points (controlling for age, sex, ethnicity, and socioeconomic status)

<table>
<thead>
<tr>
<th>Groups according to WC 90\textsuperscript{th} percentile</th>
<th>Groups according to WHTR 0.5</th>
<th>Groups according to BMI international cutpoints (Cole et al. 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>OW</td>
<td>NO</td>
</tr>
<tr>
<td>Clustered risk\textsuperscript{a}</td>
<td>-0.33 (0.17)</td>
<td>1.58 (0.38)***</td>
</tr>
<tr>
<td>Clustered risk\textsuperscript{b}</td>
<td>-0.68 (0.22)</td>
<td>2.58 (0.55)***</td>
</tr>
</tbody>
</table>

WC, waist circumference, WHTR, waist-to-height ratio, BMI, body mass index, OW, overweight, NO, non-overweight. Data reported as mean (SE). \textsuperscript{a}clustered risk score excluding cardiorespiratory fitness, \textsuperscript{b}clustered risk score including cardiorespiratory fitness. * \( p < 0.05 \), ** \( p < 0.01 \), *** \( p < 0.001 \) between overweight and non-overweight groups.

**Anthropometric indices and clustered cardiometabolic risk**

Two different regression analyses were performed; one with clustered cardiometabolic risk without CRF as a criterion variable, and one with clustered cardiometabolic risk including CRF as a criterion variable. The anthropometric indices were entered into the regression equation using the backward method. Although simple correlation analysis revealed that each of the independent variables were significantly correlated with one another (\( p < 0.01 \)), correlation coefficients did not exceed 0.9 (BMI and WC \( r = 0.89 \); BMI and WHTR \( r = 0.33 \); WC and WHTR \( r = 0.21 \)), which is the threshold suggested by Field (2009) that indicates multicollinearity between predictor variables. Moreover, the VIF and
tolerance statistics were within the acceptable range (i.e. VIF < 10, tolerance > 0.2) in the regression model for clustered risk score that included CRF, therefore not indicating multicollinearity (Field 2009). In the regression model for clustered risk score that excluded CRF, VIF statistics were < 10. Tolerance was marginally below 0.2 for BMI (0.19) but this was deemed acceptable as it does not indicate a serious problem (Field 2009). The straight line of points on the normal probability plot of the regression standardised residuals suggested that there were no major deviations from normality in the data (Pallant 2007). In the scatterplot of residuals, most of the scores were concentrated around the zero point, while there were also no obvious outliers, thus suggesting homoscedasticity of the data (Field 2009).

The regression analyses identified BMI as the only obesity index that explained significant amounts of variance in each of the clustered cardiometabolic risk scores. BMI accounted for 16.4% of the variance in clustered cardiometabolic risk without CRF, \( F (1, 182) = 35.8, p < 0.001 \), and 31.0% of the variance in cardiometabolic risk including CRF, \( F (1, 132) = 59.25, p < 0.001 \). In both cases, BMI was positively associated with the clustered cardiometabolic risk scores.

5.3 Discussion

The purpose of this study was to compare the associations between simple anthropometric indexes of obesity with clustered cardiometabolic risk in children and adolescents. This is the first study to report the association of simple measures of obesity with a clustered cardiometabolic risk score that includes CRF in youths. BMI was chosen as it is the most widely used index for the evaluation of obesity in adults (Krauss et al. 1998; Stevens et al. 2008) and young people (Barlow 2007). WC and WHTR correlate well with visceral adipose tissue in adults (Conway et al. 1997) and children (Brambilla et al. 2006) and have been validated in adults as useful predictors for CVD risk factors and CHD (Pouliot et al. 1994; Zhang et al. 2007). WHTR may have additional benefits for health risk screening.
in that the same boundary level may be specified across different ages and ethnicities, and between sexes (Ashwell et al. 2005). Body weight, height, and WC are all simple measures that most health practitioners can precisely measure, while the same does not apply to other measures of adiposity such as skinfold thickness (Savva et al. 2000).

All three anthropometric indexes were positively correlated with TC:HDL ratio and triglycerides. Freedman and colleagues (2007), however, reported no difference in the ability of BMI-for-age and WHTR to identify children aged between 5 and 17 years at risk of CVD risk factors and observed that previous studies demonstrating a stronger prediction of cardiovascular risk using WHTR typically report relatively small differences compared to other anthropometric indices. A study in Japanese schoolchildren found that systolic BP, diastolic BP, triglycerides, LDL, and atherogenic index were all related with BMI, WC, and WHTR (Hara et al. 2002). WHTR, however, was a significant predictor of current triglycerides, LDL, and atherogenic index, whereas BMI only predicted current triglyceride levels, and WC only current LDL levels. The authors concluded that WHTR was therefore the best predictor of current cardiovascular risk factors in this population.

Although all three indexes were negatively associated with HDL, this relationship was only statistically significant for WC. This finding is supported by evidence in adults (Seidell et al. 1992; Pouliot et al. 1994; Dobbelsteyn et al. 2001) and children (Savva et al. 2000) that WC may be a superior index in predicting the presence of central adiposity and dyslipidaemia. However, one study (Bertsias et al. 2003) found that WC was a strong indicator for abnormal lipid profile in female medical students, whereas WHTR was superior in identifying males with dyslipidaemia. In obese youths, WC and WHTR were both significantly correlated with HDL and triglycerides, while BMI was correlated only with triglycerides (Flodmark et al. 1994). In prepubertal children, though, WC did not significantly correlate with TC, HDL, LDL, TC:HDL ratio, or triglycerides (Maffeis et al. 2001),
although associations with BMI and WHTR were not explored. In the present study, all three anthropometric indexes were positively associated with TC:HDL ratio and triglycerides. Freedman et al. (2007) reported that WHTR was a slightly better associate of TC:HDL ratio than BMI-for-age in 5 to 17 year olds, although the difference was small.

Although there were no significant associations between any of the anthropometric indexes and systolic BP, there was a positive relationship between BMI and diastolic BP. There is evidence from previous studies for BMI being more closely associated with BP in children compared to WC and WHTR, but this has typically been for systolic readings (Savva et al. 2000; Kahn et al. 2005; Freedman et al. 2007), with fewer reporting relationships with diastolic pressure (Freedman et al. 2007). In a study of medical students (22 ± 2 years), BMI was the best obesity index for predicting current systolic and diastolic BP in males, with WC also being a significant, but not as powerful, predictor of current systolic BP (Bertsias et al. 2003). It has been noted, though, that those children with increased BMI percentiles are typically taller than those with increased WHTR and this is a likely physiological explanation for the higher BP values observed with higher BMI (Kahn et al. 1986).

WC and BMI were negatively associated with CRF in this sample of children and adolescents, while WHTR held no association. CRF is an independent risk factor for CVD, T2DM, and mortality in adults (Wei et al. 2000; Blair et al. 2001) and is favourably associated with cardiometabolic risk factors in children and adolescents (Ekelund et al. 2007; Ruiz et al. 2007; Martinez-Gomez et al. 2010) and could therefore be considered an important component of cardiometabolic risk profiling. The finding that BMI and WC are associated with CRF in youths is in agreement with previous studies. In 9 to 10 and 15 to 16 year-old European youths, WC was weakly correlated \((r = -0.20)\) with CRF (Ekelund et al. 2007), while in Spanish adolescents, BMI was also weakly correlated \((r = -0.20)\) with CRF (Aires et al. 2010). Stronger relationships between WC and BMI with CRF were
observed in the present study ($r = -0.34$ and $r = -0.32$, respectively). Ekelund and colleagues (2007), however, expressed CRF as watts/kg FFM/min, while Aires and colleagues (2010) recorded CRF as the number of laps taken to complete a 20 m shuttle-run test. These methodological differences may have contributed to the weaker relationships observed in those respective studies due to differences in expression of CRF (Shaibi et al. 2005). In one of the largest cohort studies to date (4,689 Portuguese youths aged 10 to 18 years), BMI was more strongly correlated with CRF ($r = -0.53$) compared to the current findings (Marques-Vidal et al. 2010). In Marques-Vidal and colleagues’ (2010) study, however, CRF was assessed by a 20-m shuttle run and therefore, in contrast to the current investigation, did not use specific criteria to determine whether participants had provided a maximal effort. To the author’s knowledge, no previous studies have explored the relationship between WHTR with CRF in children and/or adolescents. WHTR did not significantly correlate with CRF in this sample of children and adolescents.

Two clustered cardiometabolic risk scores were constructed (one with CRF included as a criterion variable and one with CRF excluded) and their association with each anthropometric index explored. Other studies have reported that compared with BMI, WHTR is more strongly associated with individual CVD risk factors in adults (Hsieh et al. 2005) and children (Savva et al. 2000; Kahn et al. 2005). However, there is a lack of evidence comparing obesity indexes in their associations with a clustered cardiometabolic risk score. One aim of this study was therefore to determine if internationally proposed BMI (Cole et al. 2000), WC (Zimmet et al. 2007), and WHTR (Ashwell et al. 2005) cut off points for child and adolescent overweight could identify those with increased clustered cardiometabolic risk.

It was revealed that clustered risk was significantly higher in overweight compared to non-overweight children and adolescents according to each anthropometric index when CRF was both included and excluded from the risk.
score. Although no other study has compared a clustered cardiometabolic risk score between fatness categories in youths, the metabolic syndrome occurs more frequently in children and adolescents who are overweight (BMI > 95th percentile) or at-risk for overweight (BMI 85th to < 95th percentile) compared to those who are non-overweight (Cook et al. 2003). However, although commonly used (Barlow 2007), the BMI cut off points in Cook et al’s (2003) study are arbitrary and based on nationally representative survey data from the US and thus may not be appropriate for use in other countries (Cole et al. 2000). Cole et al. (2000) therefore developed internationally acceptable age and sex specific cut off points for BMI for overweight and obesity in children using dataset specific centiles linked to adult cut off points. In addition to the current observation that clustered cardiometabolic risk is increased in overweight youths using Cole et al’s (2000) proposed thresholds, another study observed that TC:HDL ratio, fasting glucose, systolic BP, and diastolic BP were all significantly higher, and HDL and CRF significantly lower, in overweight 9 to 18 year-olds according to these same thresholds (Katzmarzyk et al. 2003).

There are a number of potential mechanisms by which excess adiposity may lead to cardiometabolic disorders. In obesity, increased release of cytokines from adipocytes, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), may lead to inhibition of the insulin signalling cascade (Hotamisligil et al. 1996; Aguirre et al. 2002). Tissues within the body may consequently become insulin resistant, and as a consequence, uptake and storage of glucose and insulin’s inhibition of lipolysis is reduced (Eckel et al. 2005; Kahn et al. 2006). Adiponectin is also secreted less in obesity (Hu et al. 1996; Arita et al. 1999), which is problematic given that this hormone is an insulin sensitiser, increases fatty acid oxidation, and reduces hepatic glucose output (Yamauchi et al. 2002). Collectively, these obesity-related disorders can lead to increased plasma glucose and insulin levels, and elevated concentration of free fatty acids (FFAs) in the circulation (Eckel et al. 2005; Miranda et al. 2005; Kahn et al. 2006). Delivery of FFAs to the liver is subsequently increased, which augments hepatic triglyceride-
rich very low-density LDL (VLDL) synthesis (Miranda et al. 2005). VLDL exchanges triglyceride for cholesteryl ester from LDL and HDL and lipases then act on triglyceride-rich LDL to create small dense LDL particles (Miranda et al. 2005). The triglyceride-enriched HDL is subject to lipolysis, and once hydrolysed, these particles are cleared more rapidly from the circulation (Brinton et al. 1991), which thus gives rise to an abnormal lipid profile. FFAs can further induce insulin resistance via interruptions in the insulin signalling pathway (Yu et al. 2002). In conditions of hyperinsulinaemia, renal sodium reabsorption may increase via insulin’s augmentation of the sympathetic nervous system or renin-angiotensin-aldosterone system, thus leading to increased extracellular volume and elevated BP (Kuroda et al. 1999).

Although cardiometabolic risk was increased in children and adolescents with high overall fatness (high BMI), some researchers have suggested that abdominal obesity is especially important in the manifestation of cardiometabolic disorders (Despres et al. 2008). The finding that children and adolescents with abdominal obesity have increased clustered cardiometabolic risk supports this notion. Similarly, another study reported that 19% of Italian prepubertal children with a WC > 90th percentile had two or more cardiometabolic risk factors, compared with only 9% of children with a WC ≤ 90th percentile (Maffeis et al. 2001). Children with a WC > 90th percentile were also less likely to have no risk factors (35% were free from risk factors) compared with children who had a WC ≤ 90th percentile (80% were free from risk factors). Differences in cardiometabolic risk factor levels (LDL, HDL, triacylglycerol, and fasting insulin) have also been observed in children and adolescents who have a WC at the 90th percentile compared with those who have a WC at the 10th percentile (Freedman et al. 1999). The authors suggested that WC may be a good detector of cardiometabolic risk as this measure functions as an index of both fat distribution and generalised obesity.
Nonetheless, just because an individual is overweight or obese it cannot be assumed that they have cardiometabolic abnormalities and are at an increased risk of developing CVD and T2DM (Reaven 2006). It was observed that WHTR, however, may have particular clinical value by identifying young people at particular risk of unfavourable cardiometabolic profiles associated with central obesity; whether in normal weight or overweight/obese categories for overall fatness (Mokha et al. 2010). A WHTR value of 0.5 has been proposed to indicate when health risk starts to increase (Hsieh et al. 1995; Ashwell et al. 2005). Similar to the current study, other evidence shows that the likelihood of having a clustering of cardiometabolic risk factors is greater in children with a WHTR > 0.5 compared with those with a WHTR < 0.5 (Maffeis et al. 2008). Additionally, in Australian children and adolescents, those with a WHTR ≥ 0.48 had higher values for body fat %, triglycerides (boys only), systolic BP (girls only), and lower levels of HDL (boys and girls) compared to those with ratios < 0.46 (Nambiar et al. 2010).

Regression analyses identified BMI as the obesity index that explained significant proportions of variance for each of the clustered cardiometabolic risk scores. BMI accounted for 16.4% of the variance in clustered risk when CRF was not included in the score and 31.0% of the variance when CRF was included. Although few studies have explored the association of WC, WHTR, and BMI for identifying clustered risk, Hara and colleagues (2002) did construct a CVD risk score using a weighed combination of serum lipids, BP, and body weight in Japanese schoolchildren. BMI, WC, and WHTR were all moderately correlated with the logarithm of the risk factor score, but regression analysis revealed that WHTR was the best predictor. It has been proposed that WHTR may be a more sensitive predictor of poor cardiometabolic health in relation to both BMI and WC since it is a relatively constant anthropometric index of abdominal obesity across different ages, sex, or racial groups (Ashwell et al. 2005). It also allows comparisons across studies which may employ different ethnic groups and age categories and encompasses the adjustment to different statures (Ashwell et al.
However, the current findings suggest that WHTR is not as effective as BMI in predicting current clustered risk in children and adolescents.

Potential limitations of indexes for abdominal obesity have been highlighted. For instance, although WC is correlated with the amount of intraabdominal visceral fat, which may be the most detrimental fat depot in adults (Despres 2006) and youths (Caprio et al. 1995), this measure is also associated with subcutaneous abdominal fat and total body fat (Lean et al. 1996; Molarius et al. 1998). Moreover, a study in adults demonstrated that WHTR and BMI were more strongly associated with each other ($r = 0.85-0.91$) than with body fat percentage ($r = 0.69-0.76$), as determined by air-displacement plethysmography (Bosy-Westphal et al. 2006). These associations emphasize the potential problems in using WHTR and BMI as indexes of abdominal and generalised adiposity, respectively. In addition, given that height is a key denominator of BMI and height and may be associated with disease risk (Hebert et al. 1993; Rich-Edwards et al. 1995; Honjo et al. 2011), the interpretation of these obesity indexes is further complicated.

The observation that BMI may be more strongly associated to health risk in children and adolescents is supported by other previous research. A stronger association was observed between BMI in mid-childhood and adverse CVD risk factor clustering eight years later compared with WC (Garnett et al. 2007). It was theorised that this was a result of BMI status tracking from childhood to adolescence; BMI tracked in 78.9% of those who were overweight or obese at baseline, while 69.2% of those with increased WC tracked during the same period. It was also concluded that the addition of WC to BMI added no clinical benefit to identifying children who were more likely to have risk factor clustering in later life. These may be important observations given that BMI is a quick routine measure, whereas measures of waist girth often involve the location of bony landmarks, removal of clothing, and careful placement of the tape measure.
to avoid fat rolls that can be uncomfortable, awkward, or embarrassing for overweight or obese children.

The current study has several potential limitations that should be considered. CRF was normalised by FFM to account for between-individual differences in body size (Ekelund et al. 2004). This may be a potential source of bias since FFM was correlated with WC \( (r = 0.75; \text{ data not shown}) \) and BMI \( (r = 0.76; \text{ data not shown}) \) in this sample of children and adolescents. The observed magnitude of associations between the obesity indexes and clustered risk when CRF is included as a criterion variable may have therefore been slightly overestimated. Statistical adjustment for biological maturity was also not permitted as no measure was available. Although age-related changes in cardiometabolic variables were accounted for, risk markers such as BP and lipid profile are influenced by puberty (Weir et al. 1988; Hannon et al. 2006; Moran et al. 2008). The cross-sectional nature of this study also limits drawing causal inferences, and prospective investigations in this area are needed to draw conclusions regarding the predictive ability of simple measures of obesity for long-term health risk.

In conclusion, the results of the present study indicate that being overweight according to BMI, WC, or WHTR is associated with increased clustered cardiometabolic risk in children and adolescents. WC appears to be more strongly associated to HDL levels in young people, while BMI is more strongly associated to diastolic BP. In terms of overall cardiometabolic risk, this study suggests that BMI may be superior measure for exploring obesity-related clustered risk in comparison to WC and WHTR. Further studies are needed to explore these findings in other age groups and populations, as are data to validate currently proposed child and adolescent obesity cut off points in relation to health outcomes.
CHAPTER SIX: STUDY THREE

An investigation into the relation of cardiorespiratory fitness and physical activity with cardiometabolic risk in children and adolescents

6.0 Introduction

Insulin resistance, obesity, dyslipidaemia, and hypertension are all independent risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2DM) in adults (Graham et al. 2007). The clustering of these risk factors may confer additive disease risk beyond the level predicted by individual components (Golden et al. 2002; Ford 2005). There is evidence that the clustering of cardiometabolic risk factors can occur in childhood and adolescence (Chen et al. 1999) and its incidence may be increasing due to the continued rise in overweight and obesity in this population (Stratton et al. 2007). Evidence shows that clustered risk persists into adulthood with approximately 25% of Finnish youths ‘at risk’ having remained there for a period of six years (Raitakari et al. 1994), while 50% and 42% of Danish males and females, respectively, remained in the upper quintile of a clustered risk factor score over an eight year period (Andersen et al. 1993). There is also evidence that atherosclerotic processes manifest during childhood (McGill et al. 2000) and that the severity of these processes is associated with risk factor clustering (Berenson et al. 1998). Moreover, individuals who have clustered risk during youth are at an increased likelihood of developing T2DM and CVD in their adult years (Morrison et al. 2007; Morrison et al. 2008).

Low levels of cardiorespiratory fitness (CRF) are consistently associated with increased risk of CVD outcomes and all-cause mortality in adults (Blair et al. 2001). Higher levels of CRF also confer adults to decreased adiposity, reduced systolic and diastolic blood pressure (BP), lower fasting glucose, and improved lipid profile (Wei et al. 2000). Similarly, there is increasing evidence that CRF is associated with adiposity, systolic and diastolic BP, lipid profile, fasting glucose, and insulin resistance in children and adolescents (Benson et al. 2006; Ekelund et
al. 2007; Aires et al. 2010). When stratified according to level of CRF, 9 and 15 year-old children in the least fit quartile were 4.97 (95% CI: 3.20-7.73) times more likely to have clustered CVD risk compared with those in the most fit quartile (Andersen et al. 2008). In addition, the prevalence of the metabolic syndrome decreased across low, moderate, and high CRF tertiles in US male (24.3%, 5.0%, and 0.1%, respectively) and female (17.3%, 5.9%, and 0.9%, respectively) 12 to 19 year-olds (Janssen et al. 2007). However, CRF was not correlated with features of the metabolic syndrome in overweight Latino youths, while children with zero, one, two, three, or more risk factors also did not differ in their level of CRF (Shaibi et al. 2005). Nonetheless, longitudinal studies have shown that increases in CRF during childhood leads to improved adiposity and lipid profile in adolescence and adulthood (Janz et al. 2002; Twisk et al. 2002), thus suggesting that childhood CRF may have an important cardioprotective role. This gives cause for concern given recent evidence that CRF levels are declining in children; even in those who are lean (Stratton et al. 2007).

Although CRF appears to have an important influence on cardiometabolic risk, it is not clear whether health criteria values for CRF can be identified. Nonetheless, some worldwide recognised organisations have suggested health related thresholds for CRF. The European Group of Pediatric Work Physiology considered a \( VO_{2\text{max}} \) of \( \geq 35 \) mL/kg/min for adolescent girls and \( \geq 40 \) mL/kg/min for adolescent boys as a “Health Indicator” (Bell et al. 1986), while the Cooper Institute for Aerobics Research suggests a minimum level of 42 mL/kg/min for boys (\( \geq 13 \) years) and 35 mL/kg/min (\( \geq 13 \) years) for girls in order to protect against the development of diseases that result from sedentary living (FITNESSGRAM 2008). However, these proposed thresholds are yet to be validated against health and CVD outcomes. Ruiz and colleagues (2007) have identified that CRF levels similar to these proposed values represent increased cardiometabolic risk in 9 to 10 year-old European children: that is CRF levels of \( > 37.0 \) and \( > 42.1 \) mL/kg/min for girls and boys, respectively. Girls and boys with CRF levels above these values were 3.09 and 2.42 times, respectively, more likely
to have a low metabolic risk score compared to those with CRF levels below these values. It is of interest to know whether the CRF thresholds proposed by Ruiz et al (2007) may also apply to older children and adolescents in terms of identifying those with higher cardiometabolic risk.

In the case of physical activity, literature has shown an inverse dose-response gradient across activity categories for most health outcomes in adults (Blair et al. 2001). Markers of systemic inflammation, including tumor necrosis factor-α, C-reactive protein (CRP), and inteleukin-6 (IL-6), are also favourably associated with increased physical activity engagement in adults (Colbert et al. 2004), while the prevalence of diabetes was 50% in US men who self-reported physical inactivity, whereas only 33% of active men had the condition (Wei et al. 2000). In children, higher physical activity levels have often been associated with improved body composition (Abbott et al. 2004; Rennie et al. 2005; Stone et al. 2009). It was also reported that the amount of time spent in moderate physical activity (MPA) and vigorous physical activity (VPA) is related to the sum of skinfold thicknesses in 9 to 10 year-olds, although this relationship was weak and explained less than 1% of the variance (Ekelund et al. 2004). Nonetheless, obese children (11.4 ± 0.6 years) typically accumulate significantly less minutes of MPA (62.6 ± 4.5 vs. 78.2 ± 3.2 min/day, \( p < 0.01 \)) and VPA (7.1 ± 1.3 vs. 13.5 ± 0.9 min/day, \( p < 0.01 \)) compared to their non-obese counterparts (Trost et al. 2001). Given the evidence that MPA and VPA may protect against adverse health risk in youths, it has been recommended that young people take part in at least 60 minutes of moderate-to-vigorous physical activity (MVPA) every day (Department of health 2011).

One study reported that higher daily minutes of MVPA was indeed associated with decreased insulin resistance in healthy young people (Mitchell et al. 2010), while greater levels of MVPA engagement were also associated with decreased body fatness (Ekelund et al. 2004). However, other investigations have observed no association of MVPA with cardiometabolic risk in children and adolescents.
Martinez-Gomez and colleagues (2010) reported that minutes spent in MVPA was not associated with insulin resistance or concentrations of insulin, glucose, CRP and IL-6 in a representative sample of Spanish adolescents, while body fat %, fat mass, and trunk fat mass were also unrelated to MVPA in young children (4 to 6 years) (Janz et al. 2002). UK, US, and Canadian physical activity guidelines now suggest that in addition to taking part in at least 60 minutes of MVPA each day, three days per week should include VPA (US Department of Health and Human Services 2008; Canadian Society for Exercise Physiology 2011; Department of Health 2011).

Recent studies have suggested that youths engaging in larger amounts of VPA are more likely to benefit from improved body composition (Janz et al. 2002; Abbott et al. 2004; Patrick et al. 2004; Gutin et al. 2005). Lower body fat %, fat mass, and trunk fat mass are all associated with higher daily minutes of VPA in both boys and girls (Janz et al. 2002; Abbott et al. 2004). VPA also explained significant proportions of variance in the sum of skinfold thicknesses, while MPA and MVPA were not associated with adiposity in 9 to 10 year-olds (Ruiz et al. 2006). However, little evidence is yet available concerning other cardiometabolic risk factors such as lipid profile and BP, or indeed the clustering of these risk factors. Some of the limited evidence to date has shown that the amount of time adolescents spend in VPA (min/d) is unrelated to glucose, insulin, insulin resistance, CRP, and IL-6 (Martinez-Gomez et al. 2010), while VPA was also uncorrelated with BP in UK youths and microvascular function in Portuguese youths (Stone et al. 2009). However, in an alternative sample of European children and adolescents, VPA was significantly correlated with systolic and diastolic BP, plasma insulin and glucose, and a clustered metabolic risk score (Ekelund et al. 2007).

To date, relatively little is known about the relationship of CRF, MVPA, and VPA with cardiometabolic risk in children and adolescents. Furthermore, it is of interest to explore if existing proposed thresholds for CRF can identify 10 to 14
year-olds who may have increased cardiometabolic risk. The objectives of this study were therefore to 1) investigate the associations of CRF, MVPA, and VPA with cardiometabolic risk factors in children and adolescents, and 2) estimate clustered cardiometabolic risk and explore variation according to varying degrees of objectively determined CRF and time spent in MVPA and VPA.

6.1 Methodology

Sample

The 100 participants included were part of the HAPPY (Health And Physical activity Promotion in Youth) study. Participants were recruited on a voluntary basis in 11 schools across Bedfordshire, UK and their baseline data used for analyses in the present study. Participants were excluded from the HAPPY study if they had any contraindications to taking part in physical exercise and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. The study was approved by the University of Bedfordshire ethics review board. Written informed consent was obtained from participants’ parents before any testing procedures.

Experimental design

Data collection took place in participants’ schools. Measures were taken by the research team between 8-10 am in a room allocated by the school. Children were instructed to fast from 9 pm the night before and only consume water until all testing was completed.
Measurements

Age, ethnicity, and socioeconomic status

Age was recorded to two decimal places for each participant on the day of data collection. Ethnicity was recorded as white or non-white. A score for socioeconomic status (SES) was attributed to each participant using their home postcode and the 2007 Indices of Multiple Deprivation (IMD) (MIMAS 2008; Fairclough et al. 2009). Postcodes were converted into IMD scores using the GeoConvert application (MIMAS 2008). These scores were categorised into tertiles with the lowest tertile indicating the most deprived.

Anthropometry and body composition

Stature and waist circumference were recorded to the nearest 0.5 cm as outlined in methodology section 3.2.2. Body mass and body fat % were recorded to the nearest 0.1 kg and 0.1%, respectively (see methodology sections 3.2.2 and 3.2.3). BMI was calculated using the equation: BMI = body mass (kg) ÷ stature² (m²).

Cardiometabolic risk factors

Sitting BP was measured as outlined in methodology section 3.2.4. Fasting blood samples were obtained using a finger prick method (see methodology section 3.2.5) for determination of total cholesterol (TC), HDL, TC:HDL ratio, triglycerides, and blood glucose.

Cardiorespiratory fitness

Participants completed an age- and sex-specific all-out progressive cycle ergometer test to exhaustion using a previously validated protocol in children and adolescents (Riddoch et al. 2005) (see methodology section 3.2.7). CRF (VO₂max) was expressed relative to body mass (mL/kg/min).
Physical activity

RT³® triaxial accelerometers (Stayhealthy, Inc., Monrovia, CA.) were used to measure seven consecutive days of minute-by-minute habitual physical activity and to determine time spent in MVPA and VPA (see methodology section 3.2.6). Time spent in MVPA and VPA was calculated and presented as the average minutes per day during the monitoring period.

Clustered cardiometabolic risk score

Waist circumference, TC:HDL ratio, and triglycerides were non-normally distributed and were subsequently log-transformed. A continuous clustered cardiometabolic risk variable was then constructed by standardising (to the mean by sex) and then summing the z-scores of the following continuously distributed variables: waist circumference, hypertension ((systolic BP + diastolic BP)/2), fasting blood glucose, TC:HDL ratio, and fasting triglycerides.

Statistical analysis

All analyses were completed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as mean (SD). A p value < 0.05 was considered significant in all analyses. Sex differences in descriptive variables were determined by a One-way ANOVA test. Associations between variables were analysed by simple correlation coefficients and partial correlations after adjustment for age, sex, ethnicity, and SES. BMI, body fat %, waist circumference, TC:HDL ratio, and triglycerides were non-normally distributed and were log-transformed prior to correlation analyses. ANCOVA was used to investigate differences in clustered risk score between high and low CRF groups according to Ruiz et al’s (2007) proposed thresholds to identify increased metabolic risk in children. CRF levels of > 37 mL/kg/min for girls and > 42.1 mL/kg/min for boys were identified as minimum thresholds to protect against having a high metabolic risk score. ROC analysis showed a significant discriminating accuracy of CRF identifying low/high metabolic risk in girls (area under curve [AUC] = 0.68,
95% CI: 0.62-0.73; \( p < 0.001 \), and in boys (AUC = 0.67, 95% CI: 0.61-0.73; \( p < 0.001 \)) (Ruiz et al. 2007).

ANCOVA was also used to investigate differences in clustered risk between MVPA and VPA tertiles. Covariates entered into the model were age, sex, ethnicity, and SES. None of the covariates were strongly correlated with each other. In addition, the assumption of homogeneity of regression slopes was met, with no significant interaction effects on clustered cardiometabolic risk score observed between any independent or covariate variables (\( p > 0.05 \)) (Pallant 2007). Levene’s test of equality of variances within the ANCOVA was violated (\( p < 0.05 \)). However, the \( F \)-statistic in ANCOVA is remarkably robust in the case that variances are unequal across groups (Lindman 1974).

6.2 Results

Participants

Table 6.0 shows the descriptive characteristics of the participants. One-way ANOVA revealed that body fat % was significantly greater in girls than in boys. CRF and minutes spent in MVPA and VPA were significantly greater in boys than in girls. No significant differences were noted between sexes for any other variable.

CRF, MVPA, VPA and cardiometabolic risk factors

Tables 6.1 and 6.2 show simple and partial Pearson correlations of CRF, MVPA, and VPA with cardiometabolic risk factors. Partial Pearson correlation revealed that after adjusting for age, sex, ethnicity, and SES, CRF was negatively associated with waist circumference and clustered cardiometabolic risk score. MVPA was positively associated with triglycerides in partial correlation analysis, while VPA was negatively associated with diastolic BP. Simple correlation analysis revealed that in addition to waist circumference and clustered cardiometabolic
risk, CRF was also negatively associated with triglycerides, while VPA was negatively associated with body fat % in addition to diastolic BP. Significant correlations between VPA and CRF were revealed following simple and partial correlation analysis, \( r = 0.39, p < 0.001 \), and \( r = 0.34, p < 0.001 \), respectively. Only simple correlation analysis revealed a significant relationship between MVPA and CRF \( r = 0.22, p < 0.05 \).
<table>
<thead>
<tr>
<th></th>
<th>All (N = 100)</th>
<th>Boys (N = 41)</th>
<th>Girls (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.76 (1.33)</td>
<td>11.77 (1.32)</td>
<td>11.76 (1.34)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>150.90 (10.20)</td>
<td>150.41 (10.64)</td>
<td>151.24 (9.95)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.49 (11.41)</td>
<td>39.64 (11.00)</td>
<td>42.77 (11.61)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.94 (3.58)</td>
<td>17.20 (2.93)</td>
<td>18.46 (3.91)</td>
</tr>
<tr>
<td>Body fat %</td>
<td>20.79 (6.60)</td>
<td>16.74 (5.79)**</td>
<td>23.53 (5.66)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>62.26 (8.32)</td>
<td>61.45 (7.06)</td>
<td>62.82 (9.10)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>105.62 (10.69)</td>
<td>106.59 (10.47)</td>
<td>104.94 (10.88)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>65.27 (7.19)</td>
<td>64.50 (7.99)</td>
<td>65.80 (6.60)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.98 (0.72)</td>
<td>3.82 (0.71)</td>
<td>4.09 (0.71)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.48 (0.41)</td>
<td>1.50 (0.45)</td>
<td>1.46 (0.38)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>2.88 (0.97)</td>
<td>2.70 (0.71)</td>
<td>3.00 (1.10)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.85 (0.60)</td>
<td>0.73 (0.33)</td>
<td>0.94 (0.72)</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>5.06 (0.50)</td>
<td>5.07 (0.47)</td>
<td>5.05 (0.52)</td>
</tr>
<tr>
<td>CRF (mL/kg/min)</td>
<td>41.58 (9.38)</td>
<td>45.96 (8.21)**</td>
<td>38.54 (8.98)</td>
</tr>
<tr>
<td>Time in MVPA (min/d)</td>
<td>109.24 (37.31)</td>
<td>119.10 (37.13)*</td>
<td>102.40 (36.18)</td>
</tr>
<tr>
<td>Time in VPA (min/d)</td>
<td>23.33 (16.77)</td>
<td>30.09 (18.12)**</td>
<td>18.64 (14.10)</td>
</tr>
</tbody>
</table>

BMI, body mass index, BP, blood pressure, TC, total cholesterol, HDL, high-density lipoprotein, CRF, cardiorespiratory fitness, MVPA, moderate-to-vigorous physical activity, VPA, vigorous physical activity. Data reported as mean (SD). *p <0.001, **p < 0.001 between sexes.
Table 6.1 Simple and partial Pearson correlations for cardiorespiratory fitness and cardiometabolic risk factors (partial correlations adjusted for age, sex, ethnicity, and SES)

<table>
<thead>
<tr>
<th></th>
<th>Simple CRF correlations</th>
<th>Partial CRF correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mL/kg/min)</td>
<td>(mL/kg/min)</td>
</tr>
<tr>
<td>Waist circumference (cm)^a</td>
<td>-0.43***</td>
<td>-0.46***</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-0.26**</td>
<td>-0.16</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>-0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>TC:HDL ratio^a</td>
<td>-0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>TRI (mmol/L)^a</td>
<td>-0.20*</td>
<td>-0.07</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>-0.09</td>
<td>-0.07</td>
</tr>
<tr>
<td>Clustered risk score</td>
<td>-0.27**</td>
<td>-0.23*</td>
</tr>
</tbody>
</table>

CRF, cardiorespiratory fitness, SBP, systolic blood pressure, DBP, diastolic blood pressure, TC, total cholesterol, HDL, high-density lipoprotein, ^a log transformed, *p < 0.05, **p < 0.01, ***p < 0.001.
Table 6.2 Simple and partial Pearson correlations for MVPA and VPA with cardiometabolic risk factors (partial correlations adjusted for age, sex, ethnicity, and SES)

<table>
<thead>
<tr>
<th></th>
<th>Simple MVPA (min/d)</th>
<th>Partial MVPA (min/d)</th>
<th>Simple VPA (min/d)</th>
<th>Partial VPA (min/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.02</td>
<td>0.05</td>
<td>-0.13</td>
<td>-0.11</td>
</tr>
<tr>
<td>Body fat %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.14</td>
<td>0.00</td>
<td>-0.27**</td>
<td>-0.09</td>
</tr>
<tr>
<td>Waist circumference (cm)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.00</td>
<td>0.07</td>
<td>-0.10</td>
<td>-0.04</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.07</td>
<td>-0.16</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-0.12</td>
<td>-0.06</td>
<td>-0.27*</td>
<td>-0.28*</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>-0.03</td>
<td>-0.12</td>
<td>-0.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.06</td>
<td>0.02</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>TC:HDL ratio&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.08</td>
<td>-0.02</td>
<td>-0.12</td>
<td>-0.09</td>
</tr>
<tr>
<td>TRI (mmol/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.17</td>
<td>0.26*</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>0.06</td>
<td>0.06</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>Clustered risk score</td>
<td>0.06</td>
<td>0.11</td>
<td>-0.05</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

MVPA, moderate-to-vigorous physical activity, VPA, vigorous physical activity, BMI, body mass index, SBP, systolic blood pressure, DPB, diastolic blood pressure, TC, total cholesterol, HDL, high-density lipoprotein, <sup>a</sup>log transformed, *p < 0.05, **p < 0.01, ***p < 0.001.
CRF, VPA and clustered cardiometabolic risk

To explore the effects of CRF, MVPA, and VPA on clustered cardiometabolic risk, participants were divided into fit/unfit groups (Ruiz et al. 2007) and into tertiles for time spent in MVPA and VPA. ANCOVA analysis showed that when controlling for age, sex, ethnicity, and SES, those participants classified as fit had a significantly lower ($F_{[1, 94]} = 9.23, p < 0.01$) clustered risk score than their unfit counterparts (Figure 6.0). No significant differences were found between tertiles for time spent in MVPA ($F_{[2, 93]} = 2.03, p > 0.05$) and VPA ($F_{[2, 93]} = 1.55, p > 0.05$) (Figures 6.1 and 6.2, respectively).

Figure 6.0 Association of cardiorespiratory fitness (unfit/fit) with clustering of cardiometabolic risk factors (cardiometabolic risk score) in children and adolescents. Data shown as mean and SE. Participants in the unfit group had a higher cardiometabolic risk score than in the fit group (* $p < 0.01$).
Figure 6.1 Association of time spent in moderate-to-vigorous physical activity (tertiles) with clustering of cardiometabolic risk factors (cardiometabolic risk score) in children and adolescents. Data shown as mean and SE. Tertile 1 represents least amount of time spent in MVPA.

Figure 6.2 Association of time spent in vigorous physical activity (tertiles) with clustering of cardiometabolic risk factors (cardiometabolic risk score) in children and adolescents. Data shown as mean and SE. Tertile 1 represents least amount of time spent in VPA.
6.3 Discussion

The primary findings of this study were that children and adolescents with higher levels of CRF had reduced clustered cardiometabolic risk scores, whereas higher levels of MVPA and VPA were not associated with lower clustered risk. This is an important finding given the literature that has reported decreases in childhood CRF in recent years (Stratton et al. 2007; Boddy et al. 2010) and that CRF during youth is related to cardiometabolic risk profile in adulthood (Twisk et al. 2002).

CRF was negatively associated with waist circumference, diastolic BP, and triglycerides when adjusting for age, sex, ethnicity, and SES. Other research has also reported that CRF is negatively associated with adiposity, diastolic BP, and triglycerides in youths (Ekelund et al. 2007; Ruiz et al. 2007), while CRF has also frequently been linked with improved insulin sensitivity (Imperatore et al. 2006; Lee et al. 2006; Martinez-Gomez et al. 2010) and decreased inflammation (Martinez-Gomez et al. 2010). Unlike the current findings, however, previous investigations have found significant relationships of CRF with systolic BP, HDL, and fasting glucose in European children and adolescents (Brage et al. 2004; Ekelund et al. 2007). Moreover, CRF was favourably associated with arterial compliance in 9 to 11 year-old children, which may be an important early indicator of chronic vascular disease risk (Reed et al. 2005).

Nevertheless, like the findings within, a lack of association between CRF and fasting glucose levels has often been observed in various child and adolescent cohorts (Brage et al. 2004; Ruiz et al. 2007; Martinez-Gomez et al. 2010), while no features of the metabolic syndrome was associated with CRF in overweight Latino adolescents (Shaibi et al. 2005). The lack of association observed in overweight Latino adolescents may, however, be due to little variation in CRF within the sample, or it may be that CRF has little influence on cardiometabolic health in specific obese populations. Nonetheless, significant relationships were observed with waist circumference, systolic BP, HDL, and triglycerides following simple correlation analysis in Shaibi et al’s (2005) study when oxygen
consumption was expressed relative to body mass and fat free mass. The relationship between CRF and individual cardiometabolic risk factors is evidently controversial and may be due to differences in sample sizes, cohort characteristics, or the expression of CRF across studies.

Time spent in MVPA was not favourably related with any cardiometabolic risk factor in this study, although unexpectedly, a positive correlation was observed with triglycerides. Currently, there is no hypothesis as to why this unexpected correlation was observed. Other published evidence has shown that MVPA is not favourably associated with glucose, insulin, insulin resistance, CRP, IL-6, or measures of adiposity in children and adolescents (Janz et al. 2002; Gutin et al. 2005; Ruiz et al. 2006; Martinez-Gomez et al. 2010). However, in 9 to 10 year-old Europeans, MVPA was significantly associated with the sum of skinfold thicknesses (Ekelund et al. 2004). These inconsistent findings may be due to differences in the assessment of physical activity, such as the use of questionnaires and recall, or the use of inconsistent classifications of physical activity intensity, either due to the utilisation of different proposed thresholds, or the use of different accelerometer models (i.e. RT3 vs. Actigraph). In addition, the quality of investigation should also be considered when making comparisons. For instance, the current study examined only a small sample of children and adolescents, whereas other studies such as the European Youth Heart Study have reported associations between MPA and VPA with most metabolic risk factors in a large number of participants (Ekelund et al. 2007). Indeed, the exploration of a larger and more representative sample may have yielded different results in the present study.

It is possible that increased energy expenditure during and post vigorous exercise in comparison to moderate intensity exercise may contribute to improved cardiometabolic health via reductions in body fat (Rennie et al. 2003). Increases in VPA may also lead to reductions in CVD and T2DM risk via increases in CRF (Rennie et al. 2003). Furthermore, upregulation of signalling pathways that
stimulate glucose uptake, insulin sensitivity, and free fatty acid oxidation have also been observed following vigorous intensity exercise. In adults, AMP-activated protein kinase (AMPK) activity; which stimulates fatty acid oxidation, glucose uptake, and modulates insulin secretion; increases not only from low to moderate intensity exercise, but also from moderate to high intensity exercise, compared to resting conditions (Chen et al. 2003). A 3- to 4-fold activation of α2-AMPK immediately after high intensity exercise (~75% VO2max) was also observed in adults, whereas no activation was observed after lower intensity exercise (~50% VO2max) (Wojtaszewski et al. 2000). However, it is currently unclear whether such responses occur in children and adolescents.

In this study, VPA was negatively associated with body fat % and diastolic BP, although the relationship with body fat % disappeared when controlling for age, sex, ethnicity, and SES. This is an important finding in light of the current childhood obesity epidemic (Wang et al. 2006) and evidence that obesity tracks (Power et al. 1997; Dietz 1998) and confers individuals to increased risk of morbidity and mortality disease in adulthood (Power et al. 1997). VPA has previously been associated with body fat % (Abbott et al. 2004) in addition to other measures of adiposity, such as BMI, sum of skinfold thicknesses, and waist circumference, in other child and adolescent samples (Ekelund et al. 2004; Ekelund et al. 2007). Few studies have explored the association of VPA with other individual cardiometabolic risk factors, although of those to date, a lack of association with inflammatory markers, such as CRP and IL-6, glucose, insulin, and insulin resistance has been reported (Thomas et al. 2008; Martinez-Gomez et al. 2010). Contrary to these reports and the findings presented here, VPA was also correlated; in addition to diastolic BP; with systolic BP, glucose, triacylglycerol, and insulin in 9 to 10 and 15 to 16 year-old European youths (Ekelund et al. 2007).

In addition to differences in sample sizes, participant characteristics, and methodologies, it is possible that differences in individual risk markers between
participants may be too subtle to investigate in isolation. Moreover, the daily fluctuations seen in individual cardiometabolic risk factors (Elveback et al. 1980; Lyons Wall et al. 1994; Froberg et al. 2005) may affect the outcomes of studies exploring their association with physical and lifestyle factors. Investigating associations with clustered cardiometabolic risk may therefore be preferable as a clustered score can compensate for daily fluctuations in individual markers (Anderssen et al. 2007). Furthermore, cardiometabolic diseases are characterised by a constellation of risk markers, and a clustered risk score may detect an array of cardiometabolic disturbances rather than focusing on one or two particular markers, whilst individuals with multiple risk factors have a poorer health status than if only a single risk factor was present (Gami et al. 2007).

The finding that children and adolescents with higher levels of CRF have reduced clustered cardiometabolic risk is in agreement with other recent evidence (Anderssen et al. 2007; Ruiz et al. 2007). Ruiz and colleagues (2007) found that CRF levels > 37.0 mL/kg/min and > 42.1 mL/kg/min identified 9 to 10 year-old girls and boys, respectively, who had low metabolic risk. Similarly, the present study found that 10 to 14 year-old girls and boys with CRF levels above these thresholds had significantly reduced clustered risk scores compared to those who had CRF levels below these levels. In a study by Anderssen and colleagues (2007) in 9 to 15 year olds, the odds of having clustered risk also increased across decreasing quartiles of CRF ($p < 0.001$ for trend), while in Spanish adolescents (13.0 to 18.5 years), boys in the highest tertile for CRF had a significantly reduced lipid-metabolic index (triglycerides, LDL, HDL, and glucose) compared with the middle and lowest CRF tertiles (Garcia-Artero et al. 2007). However, no differences were observed between CRF tertiles in girls. When controlling for maturation, height, SES, parental smoking, and total physical activity, both male and female 9 and 15 year-olds in the highest quintile for CRF had significantly lower clustered risk scores in comparison to those in the lowest quintile (Rizzo et al. 2007). The results presented within suggest that high levels of CRF may be important for cardiometabolic risk protection in later childhood (10 to 14 years).
Furthermore, favourable associations of CRF with clustered risk have been shown to exist in spite of using alternative health markers when constructing clustered risk scores. Ruiz et al. (2007), for example, included insulin, glucose, HDL, and skinfold thickness in their clustered risk score, but excluded waist circumference and TC:HDL ratio; factors which were included in the current study.

CRF is mainly influenced by two components. One of these is the genetic constitution of the person (Bouchard et al. 2001; Rankinen et al. 2002), while the other concerns the set of stimuli that the organism encounters, which includes the physical activities an individual takes part in (Bouchard et al. 2001). It is known that physical exercise results in skeletal muscle cell adaptations in adults (Hawley 2002). Some of these adaptations, such as increased capillary density and limb blood flow (Holten et al. 2004), increased mitochondrial electron transport chain enzyme activity (Hawley 2002), and increased mitochondrial volume and density (Hawley 2002), may be mediating factors in improved cardiometabolic health in adults and children, although further investigations are needed to confirm these hypotheses.

The present study found that time spent in MVPA was not associated with clustered risk. Rizzo and colleagues (2007) observed that total physical activity had a significant association with clustered risk in 15 year-old girls after controlling for confounders, although this effect disappeared when CRF was additionally entered into the regression, suggesting that total physical activity does not have an independent influence on risk. A physical activity index that was calculated based on the total MET of self-reported activities was also unrelated to clustered risk in Spanish adolescents (Garcia-Artero et al. 2007), although these findings may be approached with caution as physical activity was not measured objectively. In the case of VPA, this physical activity subcomponent was also not associated with clustered risk in this sample. Although limited data is available concerning the influence of VPA on clustered risk, one previous study
by Ekelund et al. (2007) reported findings contrary to this that demonstrated a negative correlation between VPA and clustered metabolic risk in 9 to 10 and 15 to 16 year-old youths. However, the current study used RT3® accelerometers to measure physical activity, while most other studies have used Actigraph accelerometers. The cut-points to define VPA may have therefore differed and it is possible that not all recorded VPA was truly vigorous (i.e. lower metabolic equivalents to define VPA) in the present study, which may therefore have masked links with cardiometabolic risk.

The amount of time children and adolescents engaged in MVPA in this study was weakly correlated with CRF and held no relation when controlling for age, sex, ethnicity, and SES, whereas time spent in VPA was weak-moderately correlated with CRF even after controlling for age, sex, ethnicity, and SES. Ekelund and colleagues (2007) also reported that the association of MPA and VPA with CRF in youths is weak, while other studies have also observed only weak associations of physical activity variables (expressed in metabolic equivalents) with CRF (Imperatore et al. 2006; Garcia-Artero et al. 2007). These findings suggest that CRF and physical activity may influence cardiometabolic risk through separate pathways, or that CRF is a marker for specific muscle characteristics that favour cardiometabolic health. An increased proportion of slow-twitch muscle fibres is indeed associated with increased lipid oxidation in adults (Turpeinen et al. 2006), although further research is needed to explore whether these associations exist in youths. Alternatively, CRF may be the critical factor that determines the relationship between physical activity and cardiometabolic health, and as such, it may be preferable to focus physical activity engagement towards improving CRF (Garcia-Artero et al. 2007).

One of the limitations of this study is its cross-sectional design, and hence the direction of causality cannot be determined. Secondly, the effects of maturation on cardiometabolic risk were not controlled for and since transient changes in cardiometabolic risk factors occur during puberty (Hannon et al. 2006; Moran et
al. 2008), their associations with CRF and physical activity may have been confounded. Although the use of accelerometry now appears to be the gold standard measure of physical activity levels, this method of measurement still has limitations. In addition to issues regarding intensity threshold cut-points, accelerometers cannot be used during water-based activities and also fail to accurately reflect energy expenditure associated with cycling, upper body movements, and walking up-hill (Campbell et al. 2002). Also, given the sporadic nature of children’s physical activity (Baquet et al. 2007), the use of one minute measurement time frames (epochs) may lead to under-estimations of time spent in higher intensity activities. Although the use of five second epochs were beyond the scope of the equipment used in the present study, technological advances mean five second epochs are now possible and should be used in similar studies in the future.

In conclusion, the present study found that higher levels of CRF, but not increased time spent in MVPA or VPA, were associated with reduced clustered cardiometabolic risk in children and adolescents. Since the clustering of risk factors persists into adulthood, these data suggest that interventions to reduce the likelihood of developing CVD and T2DM may target improvements in CRF as standard. Further cross-sectional studies with a greater sample size and longitudinal prospective studies are needed to confirm the roles of CRF, MVPA, and VPA in cardiometabolic risk protection.
CHAPTER SEVEN: STUDY FOUR

The combined influence of cardiorespiratory fitness and body mass index on clustered cardiometabolic risk in children and adolescents

7.0 Introduction

Overweight and low levels of cardiorespiratory fitness (CRF) are independent risk factors for cardiovascular disease (CVD) and mortality in adults (Blair et al. 1989; Lee et al. 1999; Melanson et al. 2001). CVD risk factors have often been associated with increased fatness and decreased CRF in young people (Benson et al. 2006; Chen et al. 2006; Ekelund et al. 2007; Andersen et al. 2008). Body mass index (BMI) has been shown to explain 14% and 20% of diastolic and systolic blood pressure, respectively, in children and adolescents (Gaya et al. 2009). The prevalence of the metabolic syndrome is also markedly higher in overweight and obese youths (Viner et al. 2005; Csábi et al. 2000). These data are concerning given that the likelihood of developing CVD and type 2 diabetes (T2DM) in adulthood may be higher if a person has a clustering of cardiometabolic risk factors during their child and adolescent years (Morrison et al. 2007; Morrison et al. 2008).

Evidence suggests that CRF is significantly reduced in young people who have the metabolic syndrome (Torok et al. 2001), while the prevalence of the syndrome increases across decreasing tertiles of CRF in both male (24.3%, 5.0%, and 0.1%, respectively) and female (17.3%, 5.9%, and 0.9%, respectively) adolescents (Janssen et al. 2007). Furthermore, boys and girls with high levels of CRF are 2.42 and 3.09 times more likely, respectively, of having a low clustered cardiometabolic risk score compared to those with low levels of CRF (Ruiz et al. 2007). CRF is also associated with insulin resistance and markers of inflammation, such as C-reactive protein and interleukin-6 (Thomas et al. 2008; Martinez-Gomez et al. 2010) and increases in childhood CRF appear to have a
beneficial effect on cardiometabolic health profile in adulthood (Janz et al. 2002; Twisk et al. 2002).

Due to the interrelation between CRF and fatness, past investigations have explored their independent associations to cardiometabolic risk by statistically controlling for the concomitant effects of the other variable (Hansen et al. 1990; Bergstrom et al. 1997; Boreham et al. 2001). The findings of these studies suggest that adiposity mediates the relationship between CRF and cardiometabolic risk factors in children and adolescents (Boreham et al. 2001; Rizzo et al. 2007). In adults, CRF is a powerful predictor of CVD and all-cause mortality (Blair et al. 1989; Blair et al. 1996; Blair et al. 2001), while CRF also attenuates the relation between BMI and mortality (Barlow et al. 1995). It has therefore been suggested that CRF be considered when examining the relationship between body composition and disease morbidity and mortality (Lee et al. 1999). Indeed, research has consistently evidenced that high levels of CRF reduce the negative health consequences of obesity in adults (Barlow et al. 1995; Lee et al. 1999).

It has been postulated that CRF may also attenuate the negative impact that fatness has on cardiometabolic risk in children (DuBose et al. 2007). The potential interplay between adiposity and CRF in youths is currently unconfirmed and under researched, though. Of the limited studies to date, cross tabulation of Quebec adolescents into distinct fatness and CRF groups revealed that CRF and BMI showed independent associations with individual cardiometabolic risk factors (lipids and blood pressure) (Eisenmann et al. 2005). Low fit males and females also generally had higher blood lipid and glucose levels compared to their high fit counterparts within BMI categories, although none of these differences reached statistical significance. Compared with normal weight and fit Taiwanese youngsters, those who were overweight/obese with low CRF had a significantly greater risk of hypertension in comparison to those who were overweight/obese but had above average levels of CRF (Chen et al. 2006). In a
similar study by Eisenmann and colleagues (2007) in which fatness and CRF groups were cross tabulated according to body fat % and \( \text{VO}_{2\text{max}} \) in Australian 9 to 15 year-olds, blood pressure was significantly reduced in the high fat/low CRF group compared with the high fat/high CRF group. No significant differences, however, were noted for any of the investigated blood lipid measures.

However, differences in specific individual risk markers between participants may be too subtle to investigate in isolation, while some risk factors also appear to fluctuate on a daily basis (Elveback et al. 1980; Lyons Wall et al. 1994). Moreover, cardiometabolic diseases are characterised by a constellation of risk markers, and examining clustered risk may facilitate the detection of an array of cardiometabolic disturbances, while having multiple risk factors confers individuals to a poorer health status compared to if only a single risk factor was present (Gami et al. 2007). It may thus be preferable to examine the combined influence of CRF and adiposity on clustered cardiometabolic risk so that the error variation that each risk factor includes is reduced (Anderssen et al. 2007; Ruiz et al. 2007), whilst also providing a more comprehensive indication of their combined association with overall cardiometabolic risk.

To date, few studies have explored the combined influence that adiposity and CRF may have on cardiometabolic risk factor clustering in children and adolescents. Further data may help provide consistency to the idea that CRF may attenuate the negative health consequences of obesity i.e. the “fat but fit” phenomenon and that the health benefits of being lean are limited only to those individuals who are aerobically fit (Lee et al. 1999; DuBose et al. 2007). In addition, identifying differences in clustered risk between fatness and CRF groups would provide a better understanding of the cardiometabolic risk phenotype in early life. The purpose of this study was therefore to calculate clustered cardiometabolic risk and explore differences according to various combinations of fatness and CRF levels in children and adolescents.
7.1 Methodology

Sample

The 134 participants (aged 10 to 14 years) included were part of the HAPPY (Health And Physical activity Promotion in Youth) study. Participants were recruited on a voluntary basis in 11 schools across Bedfordshire, UK and their baseline data used for analyses in the present study. Participants were excluded from the HAPPY study if they had any contraindications to taking part in physical exercise and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. The study was approved by the University of Bedfordshire ethics review board. Written informed consent was obtained from participants’ parents before any testing procedures.

Experimental design

Data collection took place in participants’ schools. Measures were taken by the research team between 8-10 am in a room allocated by the school. Children were instructed to fast from 9 pm the night before and only consume water until all testing was completed.

Measurements

Age, ethnicity, and socioeconomic status

Age was recorded as a decimal value for each participant on the day of data collection. Ethnicity was recorded as white or non-white. A score for socioeconomic status (SES) was attributed to each participant using home postcode and the 2007 Indices of Multiple Deprivation (IMD) (MIMAS 2008; Fairclough et al. 2009). Postcodes were converted into IMD scores using the GeoConvert application (MIMAS 2008). These scores were categorised into tertiles with the lowest tertile indicating the most deprived.
Anthropometry

Stature and waist circumference were recorded to the nearest 0.5 cm as outlined in methodology section 3.2.2. Body mass and fat free mass (FFM) were recorded to the nearest 0.1 kg (see methodology sections 3.2.2 and 3.2.3, respectively) and BMI was calculated using the equation: BMI = body mass (kg) ÷ stature^2 (m^2).

Cardiometabolic risk factors

Sitting blood pressure (BP) was measured as outlined in methodology section 3.2.4). Fasting blood samples were obtained using a finger prick method (see methodology section 3.2.5) for determination of total cholesterol (TC), HDL, triglycerides, and blood glucose (see methodology section 3.2.5).

Cardiorespiratory fitness

Participants completed an age- and sex-specific all-out progressive cycle ergometer test to exhaustion using a previously validated protocol in children and adolescents (Hansen et al. 1989; Riddoch et al. 2005) (see methodology section 3.2.7). CRF (VO_{2max}) was expressed relative to FFM (mL/kg FFM/min) to account for between-individual differences in body size (Ekelund et al. 2004).

Clustered cardiometabolic risk score

TC:HDL ratio and triglycerides were non-normally distributed and were subsequently log-transformed. A continuous clustered cardiometabolic risk variable was then constructed by standardising (to the mean by sex) and then summing the z-scores of the following continuously distributed variables: hypertension ([systolic BP + diastolic BP]/2), fasting blood glucose, TC:HDL ratio, and fasting triglycerides.

Statistical analysis

All analyses were completed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as mean (SD). A p value < 0.05 was considered
significant in all analyses. Sex differences in descriptive variables were determined by a One-way ANOVA test. Partial Pearson correlations examined the associations between $z$BMI, CRF, and the clustered cardiometabolic risk score when controlling for age, sex, ethnicity, and SES. ANCOVA was performed to explore independent differences between the $z$BMI and CRF groups. Covariates entered into the model were age, sex, ethnicity, and SES. To test the main hypothesis, four $z$BMI/CRF (fatness/CRF) groups were created following median splits for $z$BMI and CRF: 1) low $z$BMI/high CRF, 2) low $z$BMI/low CRF, 3) high $z$BMI/high CRF, and 4) high $z$BMI/low CRF. ANCOVA was performed to explore independent differences between $z$BMI/CRF categories on the clustered risk score. Covariates entered into the model were age, sex, ethnicity, and SES. None of the covariates were strongly correlated with each other. As $z$BMI was used as a predictor variable, and $z$BMI and waist circumference were highly correlated, even after adjustment for age and sex ($r = 0.83$, $p < 0.001$ in this sample), analyses were performed both with and without waist circumference as a criterion variable in the derivation of the clustered risk score (DuBose et al. 2007). All post-hoc comparisons were made using the Bonferroni multiple comparisons test.

7.2 Results

Participants

Table 7.0 shows the descriptive characteristics of the participants. One-way ANOVA revealed that body fat % and TC levels were significantly higher in girls than in boys, while boys had significantly higher levels of CRF. No significant differences were noted between sexes for any other variable.
Table 7.0 Descriptive characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All (N = 134)</th>
<th>Boys (N = 64)</th>
<th>Girls (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.88 (1.34)</td>
<td>12.04 (1.36)</td>
<td>11.73 (1.32)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.56 (10.38)</td>
<td>152.01 (11.33)</td>
<td>151.16 (9.49)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.56 (11.70)</td>
<td>40.98 (11.92)</td>
<td>42.08 (11.55)</td>
</tr>
<tr>
<td>zBMI</td>
<td>-0.32 (1.31)</td>
<td>-0.41 (1.23)</td>
<td>-0.25 (1.39)</td>
</tr>
<tr>
<td>Body fat %</td>
<td>20.13 (6.35)</td>
<td>16.86 (5.41)**</td>
<td>23.13 (5.66)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>64.81 (9.04)</td>
<td>64.63 (8.57)</td>
<td>64.98 (9.50)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>105.57 (9.83)</td>
<td>106.10 (9.58)</td>
<td>105.09 (10.10)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>64.95 (7.02)</td>
<td>63.88 (7.49)</td>
<td>65.93 (6.47)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>2.91 (1.05)</td>
<td>2.83 (1.05)</td>
<td>2.99 (1.05)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.83 (0.53)</td>
<td>0.78 (0.41)</td>
<td>0.88 (0.61)</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>5.05 (0.49)</td>
<td>5.05 (0.49)</td>
<td>5.05 (0.50)</td>
</tr>
<tr>
<td>CRF (mL/kg FFM/min)</td>
<td>52.50 (8.72)</td>
<td>54.55 (7.98)**</td>
<td>50.62 (9.00)</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; CRF, cardiorespiratory fitness; FFM, fat free mass. Data reported as mean (SD). *p < 0.05, **p < 0.001 between sexes.

**Cardiometabolic risk according to zBMI and CRF**

Partial correlation analyses controlling for age, sex, ethnicity, and SES revealed that the relationship between zBMI and the clustered cardiometabolic risk score was stronger when waist circumference was included as a risk factor in the score ($r = 0.61, p < 0.001$) compared to when it was excluded ($r = 0.41, p < 0.001$).
There was a trend for CRF being correlated with clustered cardiometabolic risk when waist circumference was included in the score ($r = -0.17, p = 0.059$), while no such trend was observed when waist circumference was excluded from the score ($r = -0.05, p > 0.05$).

To explore the associations of zBMI and CRF with clustered risk, participants were divided into high and low groups by a median split prior to ANCOVA analysis. The assumption of homogeneity of regression slopes was met in both ANCOVA models (i.e. clustered risk score including waist circumference and clustered risk score excluding waist circumference), with no significant interaction effects on clustered cardiometabolic risk score observed between any independent or covariate variables ($p > 0.05$). Levene’s test of equality of variances was violated in both models ($p < 0.05$). However, the $F$-statistic in ANCOVA is remarkably robust in the case that variances are heteroscedastic (Lindman 1974), particularly in the case of equal group sizes (Hamilton 1977). ANCOVA showed significant differences in clustered risk between high and low zBMI groups when waist circumference was both included ($F [1, 126] = 22.86, p < 0.001$) and excluded ($F [1, 126] = 7.47, p < 0.01$) from the score (see Table 7.1). No significant differences were observed between high and low CRF groups when waist circumference was included ($F [1, 126] = 0.86, p > 0.05$) or excluded from the risk score ($F [1, 126] = 0.08, p > 0.05$) (see Table 7.2).

### Table 7.1 Clustered risk score across zBMI groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>zBMI Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low ($N = 67$)</td>
</tr>
<tr>
<td>Score with WC</td>
<td>-1.43 (0.33)**</td>
</tr>
<tr>
<td>Score without WC</td>
<td>-0.84 (0.30)*</td>
</tr>
</tbody>
</table>

zBMI, body mass index z-score, WC, waist circumference. Data reported as mean (SE). * $p < 0.05$, ** $p < 0.001$ between low and high groups.
### Table 7.2 Clustered risk score across cardiorespiratory fitness groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRF Category</th>
<th>Low (N = 67)</th>
<th>High (N = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score with WC</td>
<td>-0.08 (0.34)</td>
<td>-0.54 (0.34)</td>
<td></td>
</tr>
<tr>
<td>Score without WC</td>
<td>-0.19 (0.31)</td>
<td>-0.32 (0.31)</td>
<td></td>
</tr>
</tbody>
</table>

CRF, cardiorespiratory fitness, WC, waist circumference. Data reported as mean (SE).

### Cardiometabolic risk across zBMI-CRF groups

To explore the combined effects of zBMI and CRF on clustered cardiometabolic risk, participants were grouped into four different zBMI/CRF groups prior to ANCOVA analysis. The assumption of homogeneity of regression slopes was met, with no significant interaction effects on clustered cardiometabolic risk score observed between any independent or covariate variables ($p > 0.05$). Levene’s test of equality of variances was violated ($p < 0.05$). However, the $F$-statistic in ANCOVA is remarkably robust in the case that variances are heteroscedastic (Lindman 1974).

ANCOVA analysis revealed that, when controlling for age, sex, ethnicity, and SES, there were significant differences between fatness/CRF groups for both clustered risk scores (waist circumference included: $F [3, 126] = 10.93, p < 0.001$; waist circumference excluded: $F [3, 126] = 3.77, p < 0.05$). Children and adolescents in the high fatness/low CRF group displayed the highest value in both clustered risk scores. When waist circumference was included in the clustered risk score (Figure 7.0), individuals in the high fatness/low CRF group had significantly increased clustered risk compared to those in the low fatness/high CRF and low fatness/low CRF groups. No significant differences were observed between any other groups. When waist circumference was excluded from the score (Figure 7.1), the high fatness/low CRF group had
significantly increased risk compared to the low fatness/low CRF group. No significant differences were observed between any other groups.

Figure 7.0 Differences in clustered risk across body mass index z-score and cardiorespiratory fitness (CRF) groups with waist circumference included in the score. Data shown as mean and SE. $p < 0.001$ for trend, * in high fatness/low CRF vs. low fatness/low CRF; low fatness/high CRF.
**Figure 7.1** Differences in clustered risk across body mass index z-score and cardiorespiratory fitness (CRF) groups with waist circumference excluded from the score. Data shown as mean and SE. $p < 0.05$ for trend, * $p < 0.05$ in high fatness/low CRF vs. low fatness/low CRF.

### 7.3 Discussion

Although some studies have considered exposure of both fatness and CRF in relation to cardiometabolic risk (Freedman et al. 1999; Benson et al. 2006; Ruiz et al. 2007; Gaya et al. 2009; Rizzo et al. 2007; Andersen et al. 2008), their combined influence has received limited attention (Eisenmann et al. 2007). The main finding of this study was a general increase in clustered cardiometabolic risk across fatness/CRF groups, suggesting that the combination of low levels of CRF and high levels of fatness are associated with increased risk in children and adolescents. In general, children and adolescents in the high fatness/low CRF group had the poorest cardiometabolic risk profile. This is in agreement with previous research (Eisenmann et al. 2005; DuBose et al. 2007; Eisenmann et al.
and thus suggests that the combination of these risks poses a substantial hazard to health.

However, unlike one past study that observed lowest risk in low fatness/high CRF (Eisenmann et al. 2005), this was not the case here. The observation that clustered cardiometabolic risk did not differ between the low fatness categories suggests that leaner children with higher levels of CRF do not benefit from healthier risk profiles compared to those with lower levels of CRF. This contradicts previous evidence that has reported significantly reduced clustered risk in low fatness/high CRF groups compared with low fatness/low CRF groups (Eisenmann et al. 2007; Eisenmann et al. 2007). However, Eisenmann and colleagues (2007) reported that being lean appeared to have a stronger cardioprotective effect than higher levels of CRF in US 8 to 18 year-olds and the current findings support this suggestion given that low fatness was associated with improved risk profile regardless of CRF level.

It has been proposed that higher levels of CRF may protect against the negative health consequences of obesity (Barlow et al. 1995; Lee et al. 1999). Although previous research has shown an attenuation of cardiometabolic risk in youths with high fatness (DuBose et al. 2007), comparison of fatness/CRF groups in the current study suggested that this was not the case in this sample of children and adolescents. However, given that participants were categorised into high and low fatness groups by a median split, it is possible that an attenuating effect of CRF may be seen when youths are split into fatness groups according to international cut points for overweight and/or obesity.

The mechanism(s) by which CRF may attenuate cardiometabolic risk among fat individuals has not yet been investigated. It has been suggested that the “fat but fit” phenotype may be partly attributable to ‘adverse’ genetic polymorphisms for fatness genes and ‘beneficial’ polymorphisms for CRF (Eisenmann et al. 2007). Several genes have so far been identified for obesity (Rankinen et al. 2006) and CRF (Wolfarth et al. 2005). Alternatively, it has been hypothesised that the
oxidative capacity of skeletal muscle and mitochondrial function may contribute to the attenuating role of CRF (Eisenmann et al. 2007). In adults, mitochondrial dysfunction is associated with a wide range of diseases (Lesnefsky et al. 2001; Mootha et al. 2003). In rodents that have been bred for low and high aerobic capacity, those with low CRF have reduced proteins required for mitochondrial biogenesis and function, suggesting that reduced aerobic metabolism plays a causal role in the development of differences between low and high fit rats (Wisloff et al. 2005). Another possibility is that high fat/high fit participants are more physically active (Eisenmann et al. 2007), which may have an independent effect on cardiometabolic health (Ekelund et al. 2007). However, insufficient physical activity data was available to run such an analysis in the current study and this hypothesis has yet to be explored in other investigations.

This study demonstrated that clustered cardiometabolic risk was significantly higher in the high zBMI group compared with the low zBMI group and this association was observed both with and without the inclusion of waist circumference in the risk score. This is in agreement with previous research that shows children with a high BMI (> 75th percentile) have significantly higher systolic and diastolic blood pressure, TC, LDL, and triglycerides, and lower HDL levels compared to individuals with low BMI (≤ 75th percentile) (Savva et al. 2000). In addition, children who exceeded Cole et al’s (2000) proposed overweight threshold for age- and sex-specific BMI were 1.6 to 9.1 times more likely of having elevated cardiometabolic risk compared with their normal weight counterparts (Katzmarzyk et al. 2003). Adipose tissue modulates metabolism in the body by releasing non-esterified fatty acids, glycerol, hormones (such as leptin and adiponectin), and proinflammatory cytokines (Wellen et al. 2005; Shoelson et al. 2006). In individuals with excess adiposity, the production and release of many of these products is increased (Wellen et al. 2005; Shoelson et al. 2006) and is associated with insulin resistance, dyslipidaemia, and hypertension in both adults (Kahn et al. 2006) and youths (Sinaiko et al. 2001; Lambert et al. 2004).
Another finding of this study was that clustered cardiometabolic risk did not differ between youths with high and low CRF. In a similar investigation, the odds of having clustered risk significantly increased across decreasing quartiles of CRF when adjusting for age, sex, puberty, SES, and parental history of CVD and T2DM (Anderssen et al. 2007). However, Shaibi and colleagues (2005) found that CRF was not correlated with any individual risk factor, while CRF levels also did not differ between children with zero, one, two, three, or more metabolic syndrome risk factors when adjusting for age, sex, FFM, and total fat mass. Previous research has also reported greater clustered risk in both boys and girls in the lowest quartile of CRF compared with the second, third, and fourth quartiles, respectively (Ruiz et al. 2007). However, CRF was normalised for body mass in Ruiz et al’s (2007) study as opposed to FFM in the current study, which may have contributed to the disparate findings. Additionally, Ruiz et al. (2007) studied a much larger sample (N = 873) and the reduced number of participants in the present study may have explained the non-significant association. Importantly, it is also possible that the lack of association between clustered risk and CRF was due to the level of CRF being determined via a median split. Had level of CRF been classified according to proposed health-related thresholds, there may have been a greater degree of discrimination concerning clustered risk between high and low fit participants.

However, research in adults has shown that for a given BMI, individuals with high levels of CRF have lower waist circumference and abdominal skinfold thickness compared with their low CRF counterparts, independent of sex (Ross et al. 2003). Similarly, for a given BMI, men with high CRF also have reduced total abdominal, visceral, and abdominal subcutaneous fat levels compared with their low CRF counterparts (Wong et al. 2004). Although evidence in this area is lacking in youths, overweight and obese children with high CRF have significantly lower abdominal adiposity compared with those who have low CRF (Nassis et al. 2005), which suggests that CRF may have a positive effect on body fat distribution in young people. Waist circumference was indeed significantly lower in the high
CRF group in the present study: 67.68 cm (SE 0.99) vs. 61.96 (0.99) ($p < 0.001$; data not show) in low and high CRF groups, respectively. CRF-mediated effects on fat distribution may be an indirect pathway by which CRF affects cardiometabolic health in this population.

One of the limitations of this study was the use of a median split to categorise individuals into low and high groups for zBMI and CRF. Had participants been categorised based on quintiles or proposed clinical thresholds, there would have been insufficient power for statistical analyses given the small number of overweight youths in this sample and the small number of overweight youths with high CRF. The use of clinical cut points for overweight and CRF in future studies would be preferable and would likely allow for more discriminating power to detect group-level differences. In addition, adjustment for biological maturity was not permitted as no measure was available. Although age-related changes in cardiometabolic variables was accounted for, risk markers such as blood pressure and lipid profile are influenced by puberty (Weir et al. 1988; Hannon et al. 2006; Moran et al. 2008), therefore presenting a significant confounding variable that was not accounted for. Lastly, the cross-sectional nature of this study limits drawing causal inferences, and therefore prospective investigations in this area are needed.

In conclusion, this study provides evidence that fatness is an important factor that may affect clustered cardiometabolic risk in children and adolescents and interventions to reduce cardiometabolic risk should target those with a high BMI. Youths with both high fatness and low CRF possess the most unfavourable cardiometabolic profiles. Although CRF did not statistically attenuate cardiometabolic risk in the high or low fatness groups, this should be explored with individuals being split into fatness groups according to internationally proposed overweight/obesity cut points. The data provided here are useful to health practitioners when determining treatment options and further research is needed to establish the cardioprotective role of CRF in overweight and obese
children and adolescents. In addition, longitudinal investigations of the fat-fit phenotype during childhood and adolescence and into adulthood are required to explore the risk of developing CVD and T2DM outcomes.
CHAPTER EIGHT: STUDY FIVE

Relations of waist circumference and physical activity intensity to cardiorespiratory fitness in children and adolescents

8.0 Introduction

Research clearly indicates that low levels of cardiorespiratory fitness (CRF) increase the likelihood of cardiovascular disease (CVD), type 2 diabetes, and mortality in adults (Wei et al. 2000; Blair et al. 2001). Fit adults also have more favourable cardiometabolic risk profiles (reduced adiposity, blood pressure, fasting glucose, total cholesterol (TC), and triglycerides) compared with their unfit counterparts (Wei et al. 2000). In children and adolescents, unfavourable cardiometabolic risk profiles have also been associated with low levels of CRF (Ekelund et al. 2007; Ruiz et al. 2007). It has been reported that youths with high CRF are 95% less likely to have high insulin resistance compared with those who have low CRF (Benson et al. 2006) and the likelihood of having small and large arterial compliance (an important early indicator of chronic vascular disease risk) is significantly reduced in children with lower levels of CRF (Reed et al. 2005). Moreover, higher CRF levels during adolescence are related to healthier CVD risk profiles in adulthood (Twisk et al. 2002).

Given the seemingly important role of CRF in cardiometabolic risk protection in young people, it is important for researchers and health practitioners to explore factors that may influence CRF so that effective strategies to reduce cardiometabolic risk can be implemented. CRF has been associated with various physical activity variables in children and adolescents (Morrow et al. 1994; Ekelund et al. 2007). In a European sample of 9 to 10 and 15 to 16 year-olds, CRF was significantly positively correlated with percentage of time spent in light physical activity (LPA), moderate physical activity (MPA), and vigorous physical activity (VPA) (Ekelund et al. 2007). In 11 to 18 year-old Portuguese youths, CRF was weak-moderately correlated with VPA, very vigorous physical activity
(VVPA), and moderate-to-vigorous physical activity (MVPA), although no correlation was observed with LPA or MPA (Aires et al. 2010). In the limited studies that have explored the degree to which physical activity predicts current CRF, total physical activity, MPA, MVPA, and VPA all explained significant proportions of CRF in 9 to 10 year-old Swedish and Estonian children (Ruiz et al. 2006). In US 9 to 10 year-olds, only VPA explained significant amounts of variance in CRF (Gutin et al. 2005). In addition to cross-sectional studies, there is also evidence that higher intensity (i.e. VPA) exercise training is associated with improved CRF in comparison to lower intensities (i.e. MPA) (Gutin et al. 2002). Although there is increasing evidence that higher intensity activity may be more beneficial for improvements in CRF, data is still lacking and this has been little explored in 10 to 14 year-olds.

Evidence suggests that excess adiposity may have a detrimental effect on CRF (Miyatake et al. 2004; Brunet et al. 2007), which is concerning given the current childhood obesity epidemic (Wang et al. 2006). In children and adolescents, CRF has often been negatively associated with various measures of adiposity. Simple correlation analysis revealed that CRF was weak-moderately associated with BMI in 11 to 18 year-old youths (Aires et al. 2010), while when adjusted for age, sex, and pubertal status, CRF was moderately inversely correlated with the sum of skinfold thicknesses and waist circumference (WC) in Spanish adolescents (Martinez-Gomez et al. 2010). Correlation analysis also showed that CRF was moderately associated with body fat percentage in 16 year-old US adolescents, (Gutin et al. 2005). When grouped according to body mass index (BMI) (i.e. normal weight, overweight, obese), higher BMI was associated with lower CRF (significant differences between all groups) in Taiwanese children (mean age 9.2 years) (Pongprapai et al. 1994).

It has been postulated, though, that obesity may not directly decrease CRF, but instead limit performance during CRF assessment due to an increased effort to move a larger body mass (Rowland 1991; Norman et al. 2005). However, recent
evidence has suggested that visceral obesity may be detrimental to CRF via increased expression of bioactive compounds that may directly or indirectly affect muscle metabolism (Miyatake et al. 2004). Some literature has indeed shown that increased visceral fat and WC; which is a good indicator of visceral fatness in adults and youths (Janssen et al. 2002; Brambilla et al. 2006); are associated with reduced exercise capacity (Miyatake et al. 2004; Brunet et al. 2007). In adults, individuals with high levels of CRF have lower WC and abdominal skinfold thickness compared with their low CRF counterparts, independent of sex (Ross et al. 2003). Similarly, for a given BMI, men with high CRF also have reduced total abdominal, visceral, and abdominal subcutaneous fat levels compared with their low CRF counterparts (Wong et al. 2004). These data suggest that, in adults, abdominal adiposity may have a detrimental effect on CRF beyond that observed with total or peripheral body fatness. In youths, WC is often weakly to moderately correlated with CRF (Ekelund et al. 2007; Hussey et al. 2007), although the evidence is inconsistent (Shaibi et al. 2005).

To date, there are a limited number of studies that have explored the amount of variance in CRF explained by visceral fatness (measured directly or indirectly by WC), while the extent to which CRF differs according to varying degrees of visceral fatness (measured directly or indirectly by WC) in youths is under-researched. The purpose of this study was therefore to investigate the degree of association between physical activity intensities and waist circumference with level of CRF in 10 to 14 year-old children and adolescents.

8.1 Methodology

Sample

The 136 participants (aged 10 to 14 years) included were part of the HAPPY (Health And Physical activity Promotion in Youth) study. Participants were recruited on a voluntary basis in 11 schools across Bedfordshire, UK and their
baseline data used for analyses in the present study. Participants were excluded from the HAPPY study if they had any contraindications to taking part in physical exercise and were excluded from providing a blood sample if they had a known blood-borne disease that might be hazardous to the health of the researchers. The study was approved by the University of Bedfordshire ethics review board. Written informed consent was obtained from participants’ parents before any testing procedures.

**Experimental design**

Data collection took place in participants’ schools. Measures were taken by the research team during the school day in a room allocated by the school.

**Measurements**

**Age and ethnicity**

Age was recorded as a decimal value for each participant on the day of data collection. Ethnicity was recorded as white or non-white.

**Anthropometry**

Stature and WC were recorded to the nearest 0.5 cm as outlined in see methodology section 3.2.2. Fat free mass (FFM) was recorded to the nearest 0.1 kg using the Tanita BC-418® Segmental Body Composition Analyser (see methodology section 3.2.3).

**Cardiorespiratory fitness**

Participants completed an age- and sex-specific all-out progressive cycle ergometer test to exhaustion using a previously validated protocol in children and adolescents (Riddoch et al. 2005) (see methodology section 3.2.7). A weight-supported assessment of CRF was selected so individuals with higher levels of fatness were not at a disadvantage by having to exert more effort by movement
of a heavier load (Rowland 1991). CRF (VO$_{2\text{max}}$) was expressed relative to FFM (mL/kg FFM/min) to account for between-individual differences in body size (Ekelund et al. 2004).

**Physical activity**

RT3® triaxial accelerometers (Stayhealthy, Inc., Monrovia, CA.) were used to measure seven consecutive days of minute-by-minute habitual physical activity and to determine time spent in MPA and VPA (see methodology section 3.2.6). Time spent in MPA and VPA was calculated and presented as the average time per day during the monitoring period.

**Statistical analysis**

All analyses were completed using SPSS version 17.0 (SPSS Inc., Chicago, IL.). Descriptive data are presented as mean (SD). A $p$ value < 0.05 was considered significant in analyses. Sex differences in descriptive variables were determined by a One-way ANOVA test. Standard multiple regression analysis was conducted to assess the degree to which CRF was explained by WC, MPA, and VPA. WC was non-normally distributed and was normalised by log-transformation prior to multiple regression analysis. MPA and VPA were also non-normally distributed and were normalised by square root-transformation prior to regression analysis. A series of models were tested to examine the amount of variance in CRF explained by WC and physical activity variables: model 1 examined the association of WC; model 2 the association of MPA; model 3 the association of VPA. All analyses were adjusted for age, sex, and ethnicity.

ANCOVA was used to explore differences in CRF between tertiles for WC and time spent in VPA (lowest tertile representing participants with the lowest WC scores and those who were the least active, respectively). Covariates entered into the model (age, sex, and ethnicity) were not significantly correlated with each other ($p > 0.05$). In addition, the assumption of homogeneity of regression slopes was met, with no significant interaction effect observed between any
independent or covariate variables ($p > 0.05$). Levene’s test of equality of variances within the ANCOVA was violated ($p < 0.05$). However, the $F$-statistic in ANCOVA is remarkably robust in the case that variances are unequal across groups (Lindman 1974), particularly in the case of equal group sizes (Hamilton 1977). Post-hoc comparisons were made by the Bonferroni multiple comparisons test.

8.2 Results

Table 8.0 shows the descriptive characteristics of the participants. One-way ANOVA revealed that CRF and time spent in VPA were significantly greater in boys than in girls. No significant differences were noted between sexes for any other variable.

Regressions analysis was performed to assess the degree to which WC, MPA, and VPA explained variations in CRF. The VIF and tolerance statistics were within the acceptable range (i.e. VIF < 10, tolerance > 0.2) (Field 2009), suggesting that multicollinearity was not an issue in this analysis. The straight line of points on the normal probability plot of the regression standardised residuals suggested that there were no major deviations from normality in the data (Pallant 2007). In the scatterplot of residuals, most of the scores were concentrated around the zero point, while there were also no obvious outliers, thus suggesting homoscedasticity of the data (Field 2009). The statistics of the regression models are shown in Table 8.1. Each model included age, sex, and ethnicity as covariates. VPA (model 2) and WC (model 3) explained significant amounts of variance in CRF: 20.9% and 24.3% of the variance, respectively. MPA (model 1) did not explain significant amounts of variance.
Table 8.0 Descriptive characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All (N = 136)</th>
<th>Boys (N = 53)</th>
<th>Girls (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.68 (1.33)</td>
<td>11.80 (1.39)</td>
<td>11.60 (1.30)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>150.19 (10.43)</td>
<td>150.42 (12.02)</td>
<td>150.04 (9.35)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.07 (11.92)</td>
<td>40.36 (12.23)</td>
<td>41.53 (11.77)</td>
</tr>
<tr>
<td>Waist girth (cm)</td>
<td>62.07 (9.14)</td>
<td>61.51 (8.72)</td>
<td>62.43 (9.43)</td>
</tr>
<tr>
<td>Time in MPA (min/d)</td>
<td>83.51 (29.28)</td>
<td>87.91 (28.28)</td>
<td>80.70 (29.73)</td>
</tr>
<tr>
<td>Time in VPA (min/d)</td>
<td>21.55 (16.27)</td>
<td>27.34 (16.40)*</td>
<td>17.84 (15.17)</td>
</tr>
<tr>
<td>CRF (mL/kg FFM/min)</td>
<td>51.60 (9.53)</td>
<td>54.88 (8.36)*</td>
<td>49.51 (9.68)</td>
</tr>
</tbody>
</table>

MPA, moderate physical activity, VPA, vigorous physical activity, CRF, cardiorespiratory fitness, FFM, fat free mass. Data reported as mean (SD). *p < 0.001 between sexes.

As WC and VPA explained significant proportions of CRF, the effects of varying degrees of WC and time spent in VPA on CRF were explored using ANCOVA. The analysis showed that when controlling for age, sex, and ethnicity, there was a significant association (F [2, 124] = 8.80, p < 0.001) between WC group and CRF (Figure 8.0). More specifically, children and adolescents with a WC < 57 cm had significantly higher CRF than those with a WC > 64 cm (p < 0.001). CRF was also significantly higher in those with a WC of 57-64 cm compared with those with a WC > 64 cm (p < 0.05). A significant association (F [2, 124] = 4.17, p < 0.05) was also shown between VPA group and CRF (Figure 8.1). Youths who engaged in > 25 min/d of VPA had significantly higher CRF than those who engaged in < 12 min/d (p = < 0.05).
Table 8.1 Unstandardised ($B$) and standardised ($\beta$) regression coefficients, SEs, and model $R^2$ examining the association of cardiorespiratory fitness with MPA, VPA, and WC after adjustment for age, sex, and ethnicity from multiple regression.

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictor variable</th>
<th>$B$</th>
<th>SE $B$</th>
<th>$\beta$</th>
<th>$p$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MPA$^a$</td>
<td>0.78</td>
<td>0.50</td>
<td>0.13</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>VPA$^a$</td>
<td>1.72</td>
<td>0.47</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>WC$^b$</td>
<td>-57.11</td>
<td>12.81</td>
<td>-0.50</td>
<td>&lt;0.001</td>
<td>0.24</td>
</tr>
</tbody>
</table>

MPA, moderate physical activity, VPA, vigorous physical activity, WC, waist circumference. $^a$square root-transformed, $^b$log-transformed.

Figure 8.0 Association of waist circumference tertile with cardiorespiratory fitness in children and adolescents. Data shown as mean and SE. $p < 0.001$ for trend. *significantly different from those with a waist of 57-64 cm and > 64 cm, $p < 0.001$. ^significantly different from those with a waist of > 64 cm, $p < 0.05$. 133
8.3 Discussion

The main findings of this study were that WC (as an indirect measure of visceral fat) and time spent in VPA, but not time spent in MPA, explained significant amounts of variance in CRF. Moreover, CRF decreased across increasing WC categories, while CRF was highest in children and adolescents that engaged in > 25 min/d of VPA. These findings suggest that increased accumulation of visceral fat may confer young people to reduced CRF, while VPA intensities appear more beneficial than MPA intensities for CRF.

In this sample of children and adolescents, WC explained 24.3% of the variance in CRF after adjustment for age, sex, and ethnicity. It seems that only one other previous study in 7 to 10 year-old Irish children (Hussey et al. 2007) has explored the amount of variance in CRF explained by WC in young people. That study also
found that WC explained significant proportions of CRF, thus suggesting that the negative association between WC and CRF holds true throughout a range of childhood years. However, Hussey et al. (2007) used a weight dependent protocol to assess CRF (shuttle-run test), and given that WC and body mass are related ($r = 0.80$ after adjusting for age and sex in the current sample; data not shown), the decreased performance of those with higher WC (and hence higher body mass) may have explained their reduced CRF. Other studies have also reported associations between WC and CRF in a range of differently aged young people from several geographical locations (Brunet et al. 2007; Ekelund et al. 2007; Ortega et al. 2007). However, in one study, CRF was assessed via a shuttle-run test and expressed as laps completed (Brunet et al. 2007). Performance in this test is influenced by body weight and given the association between body mass and WC, this may have contributed to the reduced CRF observed in youths with higher WC. WC was unrelated with CRF in overweight Latino children after adjustment for age, sex, total fat mass, and FFM (Shaibi et al. 2005). This contradictory finding may be due to methodological differences, such as CRF ($\text{VO}_{2\text{max}}$) being directly measured and expressed in absolute terms (L/min); expressing in absolute terms is a crude expression of CRF and does not account for between-individual differences in body size (Ekelund et al. 2004). Alternatively, the use of a weight-bearing treadmill test to assess CRF may have masked the true association between WC and CRF.

In this study, children and adolescents with a WC > 64 cm had significantly lower CRF than those with a WC < 57 cm. In addition, those with a WC of 57-64 cm also had significantly lower CRF than those with a WC < 57 cm. These findings advocate that visceral adiposity may have a deleterious effect on CRF in young people. Similarly, in Spanish adolescents (13 to 18.5 years), moderate to high levels of CRF (assessed by the same cycle ergometer protocol used in the current study) were associated with lower WC in both boys and girls, even after adjusting for age, pubertal maturation status, height, socioeconomic status, leisure time physical activity, and active commuting to school (Ortega et al. 2007).
Furthermore, a significant relationship between WC and CRF was observed after adjusting for BMI in overweight and obese adolescents. In the present study, a negative association between WC and CRF was also present in 10 to 14 year-olds after adjusting for BMI, age, sex, and ethnicity \((r = -0.18, p < 0.05;\) data not shown). Although few data exist that report such associations in children and/or adolescents, similar observations have been seen in adults. For instance, in Canadian men and women, for a given BMI, those in a high CRF group had significantly lower WC compared with those in a low CRF group (Ross et al. 2003), while similar observations were seen for WC, total abdominal adipose tissue, visceral adipose tissue, and subcutaneous abdominal adipose tissue in US men (Wong et al. 2004).

The current observations support the notion that visceral adiposity is deleterious to CRF. However, to date, the mechanisms by which this form of obesity impacts CRF are not yet clearly understood. Visceral adipose tissue appears to be an important site for expression and release of interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) (Frayn 2000; Park et al. 2005; Fontana et al. 2007). IL-6 has shown to be an independent predictor for reduced exercise capacity in well functioning elderly individuals (Yende et al. 2006). Skeletal muscle also appears to express TNFα receptors (Tartaglia et al. 1992) and there is mounting evidence that TNFα may directly inhibit skeletal muscle contractile function (Li et al. 2001), which would limit an individual’s ability to perform exercise. TNFα also appears to be a mediator of muscle atrophy (Li et al. 2001), which would also contribute to decreased CRF. Further research is needed to better understand the mechanisms by which these compounds, and potentially others, may affect CRF.

Time spent in VPA explained 20.9% of the variance in CRF in this sample of children and adolescents after adjusting for age, sex, and ethnicity. Time spent in MPA, on the other hand, did not explain significant amounts of variance in CRF. In US adolescents (16 years-old), time spent in VPA also explained significant amounts of variance in CRF, while time spent in MPA and MVPA did not (Gutin et
al. 2005). Alternatively, in a sample of 9 to 10 year-old Estonian and Swedish children; in addition to VPA; total physical activity, MPA, and MVPA did explain significant amounts of variance in CRF when adjusting for sex, age, and study location (Ruiz et al. 2006). Although CRF was assessed by the same cycle ergometer protocol in Ruiz et al’s (2006) study as used in the current investigation, disparate findings concerning the role of MPA may be due to CRF being expressed relative to body mass. Alternatively, the use of different accelerometer devices to measure physical activity levels may be influential and the classification of activity intensity may have differed between studies. Furthermore, the current study employed a much smaller sample and this may also contribute to conflicting findings. Other investigations have reported conflicting findings regarding the association between physical activity intensity and CRF. In support of the present findings, CRF was correlated with time spent in VPA in 11 to 18 year-old Portuguese youths, while time spent in LPA and MPA were not correlated with CRF (Aires et al. 2010). In a sample of 9 to 10 and 15 to 16 year-old youths from Denmark, Estonia, and Portugal, the percentage of time spent in all activity intensities (LPA, MPA, and VPA) were significantly correlated with CRF (Ekelund et al. 2007). As mentioned previously, differences in accelerometry methodologies may be partly accountable for conflicting observations, whilst differences in protocols and expression of CRF may also contribute to disparate findings.

However, in each of the aforementioned studies, VPA emerged as a significant associate of CRF in various child and adolescent populations. In the current study, participants were split into groups according to the amount of time they spent in VPA. It was revealed that those who engaged in more than 25 min/d of VPA had significantly higher levels of CRF than those who engaged in less than 12 min/d of VPA. Similarly, in 9 to 10 year-old children, those in the highest group for time spent in VPA (> 40 min/d) also had increased CRF compared with those in the bottom two VPA engagement groups; < 10 min/d and 10-18 min/d, respectively (Ruiz et al. 2006). Furthermore, those who accumulated 26-40 min/d
of VPA also had higher CRF compared with those who accumulated 10-18 min/d. Taken together, there is mounting evidence that increased VPA engagement is associated with improved CRF in young people. This suggests that the most effective form of intervention to increase CRF may consist of increasing participation in VPA.

One of the adaptations to physical activity is an ability to perform more intensive work due to an increased functional cardiorespiratory capacity (Massicotte et al. 1974). In the long-term, it is suggested that improvements in CRF are largely attributable to increased stroke volume, while in the short-term, a better distribution of the cardiac output and hence a more complete extraction of oxygenated blood in the working muscles appears to be accountable (Massicotte et al. 1974). In anaerobic conditions associated with high intensity exercise, the impulse drive (increase in heart rate due to a reflex response) from the working muscles becomes particularly intense (Massicotte et al. 1974). This type of training improves the oxygen transport system likely via increases in stroke volume (Ehsani et al. 1982) and consequently, anaerobic conditions are not as easily produced in trained muscles compared with untrained muscles (Massicotte et al. 1974). Indeed, studies have shown that VPA appears to provide a stimulus for cardiac adaptations that contribute to increased stroke volume (improved left ventricular performance) and peripheral adaptations that improve oxygen distribution and utilisation in the working muscles (Clausen 1976; Ehsani et al. 1982).

Of the limited intervention studies to date, controlled physical training has been either effective or ineffective in improving CRF in normal weight (Massicotte et al. 1974; Savage et al. 1986; Tolfrey et al. 1998; Tolfrey et al. 2004) and obese youths (Owens et al. 1999; LeMura et al. 2002). In those that have compared different intensities of exercise training, higher intensity interventions appear more beneficial than lower intensity interventions in terms of CRF outcomes. In normal weight children, those training at a heart rate of 170-180 bpm
significantly increased their VO$_{2\text{max}}$ (46.7 ± 7.5 to 51.8 ± 6.0 mL/kg/min), whereas CRF did not change in those training at lower intensities (150-160 and 130-140 bpm) or those in a control group over a six week training programme (Massicotte et al. 1974). Similarly, children who participated in 10 weeks of exercise training at high intensity (75% VO$_{2\text{max}}$) significantly increased their CRF (55.9 ± 1.12 to 58.5 ± 2.10 mL/kg/min), whereas no improvement was observed in children training at a moderate intensity (40% VO$_{2\text{max}}$) (Savage et al. 1986). However, these studies by Massicotte et al. (1974) and Savage et al. (1986) failed to match energy expenditure across training groups and it is likely that the higher intensity groups expended more calories during training compared with the lower intensity groups. This could have initiated increased fat loss which may have mediated increases in VO$_{2\text{max}}$. However, more recently, an investigation in obese adolescents revealed that eight months of high intensity exercise training (75-80% VO$_{2\text{peak}}$) in combination with lifestyle education increased CRF significantly more compared with lifestyle education alone, whereas moderate intensity exercise training (55-60% VO$_{2\text{peak}}$) plus lifestyle education showed no significant increases compared with lifestyle education alone (Gutin et al. 2002). Energy expenditure was matched in the high and moderate intensity exercise groups in Gutin et al’s (2002) study and hence changes in CRF were not mediated by the degree of fat loss according to calorie expenditure during exercise sessions. Given the important cardioprotective role of CRF (Wei et al. 2000; Rizzo et al. 2007), these observations suggest that health professionals may look to prescribe higher intensity physical activities for improvements in CRF and cardiometabolic health.

Collectively, these data suggest that in order to increase CRF, children and adolescents should take part in higher intensity physical activities. However, MPA may be recommended for unfit children and adolescents in the first instance until higher intensities can gradually be attained. This is because physical activities classified by time-motion analysis as moderate, such as brisk walking, may in fact be quite strenuous for some unfit youths (Gutin et al. 2002).
In addition, VPA is less tolerated than MPA (Barbeau et al. 1999), while activities that are especially tiring may lead individuals to do less physical activity on the following day (Kriemler et al. 1999), thus being counterproductive in the long run. However, the latter does appear to be somewhat dependant on the type of exercise performed (Owens et al. 1999). In addition, VPA may be associated with increased risk of injury, and in adults, injury was the most commonly reported reason for relapses in this type of exercise (Sallis et al. 1990) and this should be considered when prescribing exercise treatments.

One limitation of the present study is that accelerometers cannot be used during water-based activities and they fail to accurately reflect energy expenditure associated with cycling, upper body movements, and walking up-hill (Campbell et al. 2002). There is also controversy regarding the appropriate cut points for physical activity intensity classifications, which makes comparisons across studies difficult (Stone et al. 2009). Another difficulty is that studies often utilise different monitoring times and minimum wear time criteria, which may affect the outcomes of investigations. Also, given the sporadic nature of children’s physical activity (Baquet et al. 2007), the use of one minute measurement time frames (epochs) may give an inaccurate representation of time spent in higher intensity activities (Rowlands et al. 2006). Although the use of five second epochs were beyond the scope of the equipment used here, technological advances mean five second epochs are now possible and should be used in similar studies in the future. Another potential limitation is a possible sample bias. In a previous study, those youths who did not achieve VO\textsubscript{2max} weighed more than those who did and thus may bias the sample in favour of lighter participants. However, there is no way of knowing whether the results would have differed if all of the participants in the present study had achieved a maximal effort in their CRF assessment. Another important limitation is that visceral fat was not directly measured using magnetic resonance imaging or computed tomography. Although WC is a good predictor of visceral fat mass, up to 35% of the variance in visceral fat is unaccounted for by WC in 7 to 16 year-olds (Brambilla et al. 2006).
In conclusion, the results of this study support the notion that visceral obesity (indirectly assessed) may be negatively associated with CRF in children and adolescents. In addition, the present findings suggest that VPA may have a greater impact on CRF than MPA in young people. Longitudinal studies are needed to confirm whether causal links exist between visceral obesity and physical activity intensity with CRF in youths. However, it does seem feasible to encourage youths to maintain a lifestyle that involves regular engagement in VPA and management of obesity, which might involve strict balance of energy intake and expenditure, for example. However, investigations are required to identify suitable strategies in which these objectives can be achieved.
CHAPTER NINE: SUMMARY OF FINDINGS AND GENERAL DISCUSSION

9.0 Integration and summary of research findings

The metabolic syndrome (MetS) is a clustering of the most dangerous risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), which includes abdominal obesity, insulin resistance, abnormal lipid profile, high blood pressure (BP), impaired fasting blood glucose or diabetes, and microalbuminuria (WHO 1999). The clustering of these risk factors is observed in children as well as adults and occurs more often in overweight and obesity (Csábi et al. 2000; Cook et al. 2003), although its true prevalence is difficult to establish due to the existence of various proposed definitions of MetS (Cook et al. 2003; Zimmet et al. 2007; de Ferranti et al. 2004; WHO 1999). The most commonly used tool to assess overweight- and obesity-related risk is body mass index (BMI). However, as cardiometabolic risk is primarily related to visceral adipose tissue, it has been proposed that other simple and inexpensive anthropometric tools, such as waist circumference and waist-to-height ratio (WHTR), may be more appropriate as they offer a more accurate assessment of fatness in this anatomical location (Pouliot et al. 1994; Wu et al. 2009). There is increasing evidence that cardiorespiratory fitness (CRF) has an important cardioprotective role in children and adolescents (Ruiz et al. 2007) and may even protect from the deleterious effects of obesity (DuBose et al. 2007). Being physically active may also reduce cardiometabolic risk in young people (Ekelund et al. 2007; Mitchell et al. 2010) and UK government recommendations state that children and young people should engage in 60 minutes of moderate-to-vigorous physical activity (MVPA) every day (Department of Health 2011). It has been postulated that vigorous physical activity (VPA) may be particularly important for cardiometabolic risk protection and hence the most recent physical activity guidelines state that children and young people should take part in vigorous intensity activities at least three days per week (Department of Health 2011). In addition to direct health benefits, participation in moderate and vigorous intensity physical
activities may indirectly improve cardiometabolic health risk via increases in CRF (Ruiz et al. 2006), while, on the contrary, accumulation of visceral fat appears to have a detrimental effect on CRF (Miyatake et al. 2004). The present research was conducted to investigate whether (1) a sample of children and adolescents in Bedfordshire, UK suffer from MetS, and if its prevalence increases with obesity and differs according to MetS definition used (2) there is a superior simple anthropometric index for assessment of adiposity-associated cardiometabolic risk in children and adolescents (3) cardiometabolic risk varies according to level of CRF and time spent in MVPA and VPA (4) fatness and CRF have combined influences on cardiometabolic risk in children and adolescents (5) specific physical activity intensities and waist circumference (as a marker of visceral fat) explain significant proportions of CRF in children and adolescents.

9.0.1 Cardiometabolic risk in children and adolescents

Study 1 demonstrated that MetS can be detected early in the lifespan and may be present in 2.3% to 9.8% of 10 to 14 year-old children and adolescents in Bedfordshire, UK. This clustering of risk factors for CVD and T2DM may be associated with excess adiposity (Csábi et al. 2000). There is currently debate as to whether individuals are especially at increased cardiometabolic risk if excess adipose tissue is accumulated centrally or viscerally (Owens et al. 1998). Another possibility is that poor cardiometabolic health is a consequence of inadequate participation in physical activities (Mitchell et al. 2010). It is currently unclear whether this is the case (Martinez-Gomez et al. 2010; Mitchell et al. 2010), or, if physical activity is important for young people’s cardiometabolic health, which types of physical activities may be particularly beneficial (Ekelund et al. 2007; Gaya et al. 2009; Stone et al. 2009). As well as physical activity engagement, CRF may also be important for cardiometabolic health in children and adolescents (Ruiz et al. 2007), or it may be that there is an interaction effect of physical activity and CRF on cardiometabolic health. It was therefore appropriate to study
the influence of overweight and obesity, specific physical activity intensities, and CRF on cardiometabolic risk in children and adolescents.

**9.0.2 Obesity and cardiometabolic risk**

Study 1 showed that MetS prevalence was significantly increased in overweight compared with non-overweight children and adolescents according to two of three paediatric MetS definitions investigated: prevalent in 0.9% vs. 25% of non-overweight and overweight youths, respectively, according to Cook et al’s (2003) definition and 5.3% vs. 45%, respectively, according to de Ferranti et al’s (2004) definition. The prevalence of individual risk factors (abdominal obesity, hypertension, dyslipidaemia, impaired fasting glucose) was also substantially higher in the overweight participants. There are a number of mechanisms by which excess adiposity may negatively influence cardiometabolic health. This includes increased production and release of non-esterified fatty acids, glycerol, leptin, proinflammatory cytokines, and decreased expression of adiponectin (Wellen et al. 2005; Shoelson et al. 2006). In addition to a direct influence on cardiometabolic health, previous research has shown that visceral obesity has a detrimental effect on CRF (Miyatake et al. 2004) possibly due to increased circulation of bioactive compounds such as tumor necrosis factor-α (TNFα) and interleukin-6 (IL-6) that appear to affect muscle metabolism (Li et al. 2001; Miyatake et al. 2004; Yende et al. 2006). There is growing evidence that CRF has a strong impact on cardiometabolic health in children and adolescents (Ruiz et al. 2007; Andersen et al. 2008) and given suggestions that visceral obesity may be especially deleterious to health (Despres 2006), it was appropriate to investigate whether a marker of this form of obesity has a deleterious effect on CRF in young people. Study 5 showed that waist circumference; which gives an accurate reflection of visceral fatness in adults and youths (Janssen et al. 2002; Brambilla et al. 2006); explains 24.3% of the variance in CRF and that children and adolescents with a waist circumference > 64 cm had significantly lower levels of CRF compared with those with a waist circumference of 57-64 cm. Those with
waist circumferences of 57-64 cm also had significantly lower levels of CRF compared with those who had a waist circumference < 57 cm.

The most commonly used measure of obesity is BMI (Barlow 2007; Krauss et al. 1998; Stevens et al. 2008). It has been suggested that this measure of overall obesity; as was used to define overweight and non-overweight in Study 1; may be limited in the assessment of adiposity-related health risk (Ashwell et al. 2005). Instead, measures of abdominal obesity may be more appropriate when assessing individuals for risk of progression to CVD and T2DM (Savva et al. 2000; Ashwell et al. 2005). It was therefore appropriate to study whether measures of abdominal obesity that could be routinely used in consultations and on large-scale studies could explain variations in cardiometabolic risk in children and adolescents more accurately than BMI. Study 2 found that BMI explained a significant proportion of variance in a clustered cardiometabolic risk score in children and adolescents, whereas waist circumference and WHTR (measures of abdominal obesity) did not explain significant proportions of variance in cardiometabolic risk. Study 4 also revealed that youths with a high BMI z-score (median split) had significantly increased clustered cardiometabolic risk compared to those with a low BMI z-score; an association that held true when a measure of waist circumference was either included or excluded from the risk score. Nonetheless, Study 2 did show that; as was the case for BMI (Cole et al. 2000); clustered cardiometabolic risk score was significantly higher in children and adolescents classed as abdominally overweight according to internationally recommended cut points for waist circumference (Zimmet et al. 2007) and WHTR (Ashwell et al. 2005). Waist circumference was also significantly correlated with HDL, whereas WHTR and BMI were not. Each of these anthropometric indices may therefore be useful for health risk assessment in this population, although measuring BMI appears to be most preferable according to this data.
9.0.3 Physical activity and cardiometabolic risk

Study 3 showed that when adjusting for age, sex, ethnicity, and socioeconomic status, the amount of time children and adolescents spend in MVPA was not associated with clustered cardiometabolic risk. MVPA was also not favourably related with any individual cardiometabolic risk factor. Previous UK government recommendations suggested that children and young people should take part in at least 60 minutes of MVPA every day (Department of Health 2004). Even in the devise of these guidelines it was recognised that the role of physical activity in protecting against risk factors for CVD and T2DM was unclear. A recent study showed that increasing MVPA engagement was associated with decreased insulin resistance in youths (Mitchell et al. 2010) and this may be an important finding as a resistance to insulin is associated with, and may be causal to, the presence of other cardiometabolic risk factors (Eckel et al. 2005). However, other studies have shown no association between MVPA and insulin resistance, fasting insulin and glucose, CRP, and IL-6 in Spanish adolescents (Martinez-Gomez et al. 2010), and no association with body fat %, fat mass, and trunk fat mass in young children (4 to 6 years) (Janz et al. 2002).

In response to more recent evidence (Department of Health 2008; Kesaniemi et al. 2010), the latest UK government guidelines recommend that in addition to 60 minutes of daily MVPA, children and young people should engage in vigorous physical activities on at least three days per week to experience substantial health benefits (Department of Health 2011). Study 3 demonstrated that the amount of time spent in VPA was not associated with clustered cardiometabolic risk in 10 to 14 year-old youths. VPA was, however, negatively correlated with body fat % and diastolic blood pressure. There is conflicting evidence regarding the association of VPA with clustered cardiometabolic risk (Ekelund et al. 2007) and individual risk factors (Thomas et al. 2008; Martinez-Gomez et al. 2010) in youths. There is a growing body of literature, though, that shows a positive
association of VPA with body composition in this population (Abbott et al. 2004; Ekelund et al. 2004; Ekelund et al. 2007).

Whether physical activity has a direct effect on cardiometabolic risk in children and adolescents is not clear. However, there is stronger and more convincing evidence that youths who engage in more physical activity benefit from higher levels of CRF (Morrow et al. 1994; Ruiz et al. 2006). This may be important as increased CRF has been associated with improved cardiometabolic health in this population (Anderssen et al. 2007; Ruiz et al. 2007). Past studies have reported weak-moderate correlations between physical activity intensities (moderate physical activity [MPA] and VPA) and CRF in European and US children. Studies have also reported that MPA may not influence CRF in 9 to 18 year-old Portuguese and US youths. Whether time spent in MPA and VPA explain variation in the CRF of young people is currently underreported. Study 5 demonstrated that the amount of time children and adolescents spent in MPA did not influence CRF. On the contrary, increased engagement in VPA positively influenced CRF and young people who engage in > 25 min per day of VPA may particularly benefit from increased CRF.

9.0.4 Cardiorespiratory fitness and cardiometabolic risk

Study 3 investigated the impact of CRF on cardiometabolic risk in children and adolescents. Compared to those with high levels of CRF, children and adolescents with low CRF had significantly increased clustered cardiometabolic risk. CRF was also correlated with BMI, body fat %, waist circumference, diastolic blood pressure, and triglycerides. CRF may mediate cardiometabolic health via increased capillary and limb blood flow (Holten et al. 2004), increased mitochondrial electron transport chain enzyme activity (Hawley 2002), and increased mitochondrial volume and density (Hawley 2002). It has been suggested that CRF may even attenuate the deleterious health consequences of obesity and it was therefore appropriate to investigate this theory in children and adolescents. Study 4 demonstrated, though, that having high levels of CRF
were not statistically associated with reduced clustered cardiometabolic risk in youths with high levels of fatness. However, those youths with a combination of high fatness and low CRF did appear to exhibit the most unfavourable cardiometabolic risk profiles, which would suggest that the combination of these risks poses a substantial hazard to health.

9.0.5 Representativeness of findings

Although the findings of this thesis may be important for researchers and health practitioners alike in terms of understanding cardiometabolic risk in children and adolescents, there are limitations in terms of generalising the results. The cohort was relatively small and heterogenous and so may not be representative of a larger population. In addition, the prevalence of overweight and obesity in the current sample was 14.5% in boys and 17.0% in girls, which is lower than that reported in 5 to 10 year-olds (19.8% and 21.8% in boys and girls, respectively) between the years of 1997 and 2007 in the UK (Stamatakis et al. 2010) and that reported in 10 to 11 year-olds in Bedfordshire in 2010 (30.7% were overweight or obese) (NHS National Statistics 2011). The conclusions made within this thesis regarding the prevalence of MetS in overweight youths and the associations of adiposity with cardiometabolic risk and CRF may therefore not be representative of a larger population. Furthermore, all participants were recruited from a single region within the UK (Bedfordshire) and hence the findings presented within may not be representative of the general child and adolescent population. However, socioeconomic status of the areas from which participants were recruited was similar to other areas of the UK (Child and Maternal Health Observatory 2009) and it may therefore be possible to generalise some of the findings to youths in other areas of the nation.

9.0.6 Conclusion

It has been established that a clustering of risk factors for CVD and T2DM (MetS) exists in general representative samples and in overweight and/or obese children and adolescents in a number of geographical regions across the globe. Data
presented here shows that MetS also exists in a small sample of children and adolescents in Bedfordshire, UK. However, the prevalence of MetS remains difficult for researchers to establish as there is currently no validated paediatric definition of MetS. Dependant on the definition employed, MetS may be present in 2.3% to 9.8% of UK children and adolescents, and 5% to 45% of those who are overweight. Given the apparently important role of adiposity, it seemed significant to investigate the most suitable anthropometric index of obesity that could be employed to explore adiposity-related cardiometabolic risk in youths. BMI explained significant amounts of variance in clustered cardiometabolic risk in this sample of children and adolescents, suggesting that a measure of overall obesity may be most suitable. In terms of treatment options, it was revealed that time spent in MVPA and VPA was not associated with clustered risk. Instead, CRF was associated with clustered risk and interventions to reduce the progression to CVD and T2DM may therefore target increases in CRF as standard. Given the seemingly important role of CRF, it was imperative to explore what factors may influence a child or adolescent’s level of CRF. The amount of time participants spent in MPA was not associated with CRF, while time spent in VPA and waist circumference (as an indirect measure of visceral fatness) both explained significant amounts of variance in CRF. Strategies to improve cardiometabolic health in children and adolescents may therefore focus on promoting engagement in VPA and reducing waist girth. Much work is still required in the domain of cardiometabolic risk and the role of obesity, physical activity, and CRF in children and adolescents. It is therefore hoped that the work contained in this thesis makes a vital contribution to this area of interest and helps generate future research ideas.
CHAPTER TEN: REFERENCES


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Re: Health and Physical Activity Promotion in Youth (HAPPY) Study

Your child’s school has agreed to take part in a school-based physical activity promotion research programme which aims to evaluate the impact of 3 school-based strategies designed to increase physical activity levels, fitness, body composition and psychosocial well-being in 10-11 and 13-14 years old. This study is taking place in 8-10 schools across the Bedford Borough but only one intervention will be undertaken per school.

The study will be conducted at the school and within the school timetable over a 2 year period. The strategy will be implemented in blocks of 4 weeks (varies from ½ - 1 ½ hours a week) every second half term in the first year, whilst the second year is the follow-up phase which will take place as part of the school curriculum. The strategies range from acting as a control (children are only involved in data collection), health education during PSHE lessons, health psychology during PHSE lessons and games play during breaks (e.g. lunch time).

Although the intervention outlined above is being built into the school curriculum, the data collection aspect of this study is optional which is why we are asking for your consent. The data collection aspect of this study is vital to demonstrate if any of the above interventions are successful at increasing physical activity amongst children. The data collection (measurement) part of the programme for all interventions will take place during the first half of each school term and at the end of the school year. This will take place within the school and will require a maximum of 45 minutes of your child’s time per data collection session.
What happens in the data collection?

On the night prior to the data collection day, we will ask you to remind your child to fast over night (10-12 hours). Therefore they must not consume any food or drink for 10 hours prior to the school start time (they will be allowed to sip water). Please send your child to school with a snack which they can eat something immediately after they have seen the researchers for the initial data collection.

When the children arrive at the school, they will immediately see the researchers (who will be in a room on the school grounds) to have their initial data collection which includes a measure of their muscle and fat levels (by standing on a scale with two metal plates) and a measure of their blood glucose and cholesterol levels (by taking a finger prick blood sample from your child’s finger or earlobe). This is a very simple and easy procedure and requires the drops of blood collected to be put into a machine to measure cholesterol and glucose. Once these measurements are completed your child will be able to eat their snack and continue their lessons. They will then visit the research team again later during the day to complete the remaining measurements.

For the remaining data collection (about 45 minutes) your child will have his/her height and sitting height measured. Waist circumference, blood pressure and heart rate will also be measured. Your child will also be required to undertake some exercise on a stationary bike. It is expected that towards the end of the session your child will find it hard work but they will be advised they can stop at any point should they wish to. The exercise session will last between 8-12 minutes. There are risks associated with exercise such as light headedness and fainting but every effort will be made to minimise these risks occurring. Your child will also be asked to complete some questionnaires relating to physical activity levels, nutrition and self esteem. Outside the testing room, we will also ask your child to keep a 7-day physical activity diary and they may be given a little box to wear on their waist for 7-days. This is an accelerometer which monitors physical activity levels. This is very expensive and must be removed when swimming or washing. Please make sure your child looks after this.

There is a risk that we might find some abnormal results from your child such as high blood pressure, high blood cholesterol or glucose readings. If so, we will inform you and as a precaution will suggest your child visits their GP.

If you are happy for your child to take part in the data collection part of this study, please could you complete the informed consent. You do have the option of omitting your child from the blood sampling procedure, if you feel this would not be appropriate for your child. However we stress that this is a very simple and quick procedure and would give you an interesting insight into your child’s health (glucose and cholesterol levels). Alternatively, if you know that taking blood from your child might be hazardous to the health of the technician due to aids or HIV, please do not allow your child to be part of the blood sampling procedure. It is also your responsibility to provide information regarding your child’s health status or previous experiences of unusual feelings with exercise. Children will be excluded in the presence of chronic medical conditions such as heart disease, asthma (not controllable with medication) or any other condition that may put the child at risk when performing exercise sessions. Children will
also be excluded if they do not have the ability to successfully complete the exercise sessions highlighted above for any other reason.

Participation in the data collection is entirely voluntary and the results will be confidential (only the researchers, you and your child will see the individual results). Before giving your full consent to the study we ask that you to speak to your child about the research study, to check if they understand what the research involves and to make sure they are not just consenting to please us or their teachers. Please remind your child that the study is voluntary and that he or she can leave the study even after it has begun by telling their own teacher, PE staff or research investigator that they no longer wish to take part. However, we will also ask the children regularly during the study if they are happy to continue participating.

It is hoped that the work from this study will be published in a scientific journal but no data about your child will appear. Your child’s data will be kept confidential at all times.

If you have any questions regarding participation of your child in the data collection for this research project, or the aims of the research, please contact (insert name) on (insert number) or by email on (insert email) or (insert name) on (insert email)

Thank you very much for your support
Informed Consent

HAPPY (Health and Physical Activity Promotion in Youth)

Parental/Guardian Informed Consent Form

Please complete all the details below. All information obtained will be treated as confidential. Completed forms must be returned to (insert name) or the PE office, before any testing commences. Please return as soon as possible.

Please read the following statements carefully. Please sign only when you have agreed with the statements.

I have been asked to allow my child to participate in the data collection aspect of a research project which is evaluating the impact of 3 innovative school-based strategies designed to increase physical activity levels, fitness, body composition and psychosocial well-being in 10-11 and 13-14 years old. I give my free consent by signing this form, should my child wish to take part.

I understand that my child will be involved in the following:

• The research will be carried out as described in the parent covering letter, a copy of which I have retained.

• If I decide not to allow my child to participate, or decide to withdraw his/her participation, my decision will be accepted.

• My consent to allow my child to participate is voluntary and I may withdraw my child from the study at any time. I do not have to give a reason for the withdrawal of consent.

• I understand that I am responsible for providing information regarding my child’s health status or previous experiences of unusual feelings with physical effort.
• My child has no injury or illness that will affect his/her ability to successfully complete the tests.

• By signing this form I give my free consent to allow my child to participate in the research project, should my child wish to take part.

• I have read and understood the information above, and my questions have been answered to my satisfaction.

**Parental/Guardian Informed Consent Form**

Name of Child: .................................................................

Date of Birth

Permanent Address:
............................................................................................................................

Parent/Guardian Contact Telephone
No:......................................................................................................................

Signature of parent/guardian........................................... Date.................................

Signature of tester ..............................................................................................

PLEASE NOTE: If you have signed this document but think it is not in your child’s or researchers best interest to take part in the blood sample procedure, please sign and tick the box here.

☐ Signature of parent/guardian ................................ Date.................................

Along with this form, please also return the following completed forms:

1. Physical activity readiness questionnaire – this checks that your child is well enough to complete the exercise test.
2. Physical activity questionnaire – this is to give us an idea of how active your child is. Please complete this with your child and be as honest as possible.

**Adapted Physical Activity Readiness Questionnaire for Children**

This questionnaire offers a safe, preliminary health-screening for your child prior to their participation in exercise.

- Has your child’s doctor ever said that they have a heart condition?
  
  Yes  ☐  No  ☐

- Does your child have chest pain brought on by exercise?
  
  Yes  ☐  No  ☐

- In the past month, has your child experienced chest pain when they were NOT doing exercise?
  
  Yes  ☐  No  ☐

- Does your child lose consciousness or lose balance as a result of dizziness?
  
  Yes  ☐  No  ☐

- Does your child have a bone or joint problem that could be aggravated by exercise?
  
  Yes  ☐  No  ☐

- Does your child’s doctor currently prescribe medication for blood pressure or a heart condition (e.g., diuretics or water pills)?
  
  Yes  ☐  No  ☐

- Do you know of any other reason why your child should not participate in exercise?
  
  Yes  ☐  No  ☐
If ‘yes’, please give the reason on the next page;

..................................................................................................................................................
..................................................................................................................................................
..................................................................................................................................................


Parent / Guardian (Please PRINT NAME).................................................................

Signed......................................................... Date......................

Child’s name (Please PRINT).................................................................................
APPENDIX 2: HAPPY STUDY RACE AND ETHNICITY FORM

Race and ethnicity

Choose ONE section from A to E and then tick the appropriate box to indicate your ethnic background.

A. White

☐ British
☐ Irish
☐ Italian
☐ Any other white background,

B. Mixed

☐ White and Black Caribbean
☐ White and Black African
☐ White and Asian
☐ Any other mixed background

C. Asian or Asian British

☐ Indian
☐ Pakistani
☐ Bangladeshi
☐ Any other Asian background

D. Black or Black British

☐ Caribbean
☐ African
☐ Any other Black background

E. Chinese or other ethnic group

☐ Chinese
☐ Any other