Cardiovascular Disease Risk in Children: 'Pre-Clinical' Markers and the Impact of Body Composition, Physical Activity and Cardiorespiratory Fitness.

Jayne Henaghan

A thesis submitted in partial fulfilment of the requirements of Liverpool John Moores University for the degree Doctor of Philosophy following work undertaken at the Research Institute for Sport and Exercise Sciences.

October 2008

Abstract

Cardiovascular disease is one of the largest killers in the UK representing 30% of all global deaths. The underlying processes of the disease are thought to begin in childhood. Whilst traditional risk factors of CV disease (e.g. hypertension, hyperlipidemia, obesity, smoking, stress and sedentary lifestyles) are becoming increasingly prevalent within the younger generation there remains the need for the establishment of earlier or "pre-clinical" markers of future CV disease risk or current atherosclerotic load such as left ventricular (LV) mass, diastolic function and carotid intima-media thickness (cIMT). Further, assessing the association of these markers to other risk factors and then determining the impact physical activity (PA) interventions is warranted.

Initially we assessed the impact of body composition, PA and cardiorespiratory (CR) fitness upon left ventricular LV mass, carotid-intima media thickness (cIMT) and LV diastolic function in 218 9-11 year old primary schoolchildren. Pubertal status was assessed through a maturity offset calculation. LV mass, cIMT, and LV diastolic function were assessed via ultrasound. Body mass index was assessed via anthropometry whilst fat mass [FM] and lean mass [LM] were determined via dual X-ray absorptiometry. Average 3-day PA was recorded via a uni-axial accelerometer and CR (VO_{2peak}) was determined from a graded treadmill test. Relationships were analysed using bivariate correlations and forced entry multiple regression. All children were classified as being below their peak height velocity. Together LM, FM, sex and moderate to vigorous (MV)PA accounted for 59% of the variance in LV mass with LM being the most important predictor ($P<0.005$). Sex, LM, FM and VO_{2peak} explained only 19% variance in cIMT and just 9% of the variance in LV diastolic function was accounted for by LM, FM blood pressure and sex. Data for MVPA had no significant relationship to any cardiovascular (CV) variables although was negatively correlated with FM. The strong association between LV mass and body composition likely represents normal growth. The limited shared variance between predictor variables and cIMT and LV diastolic function suggests that those pre-peak height velocity children in the current cohort who were overweight, inactive and unfit were not yet at an increased CV disease risk. Thus there is a window of opportunity for intervention programmes to be implemented that reduce CV disease risk before adolescence and adulthood.

Following this, an exploratory trial was conducted to introduce the use of PA interventions in pre-pubertal children. Sixty-one 10-11 year old Liverpool primary school children volunteered and were randomly assigned by school to a STEX programme (2 x 60 min sessions per week at a heart rate of ~145 beats.min^{-1}), a PASS programme (weekly physical activity tasks and pedometer challenges) and a control (CON; no intervention). Pre-clinical CV measures and body composition were measured before and after the 9–week intervention period. The primary outcome variable was cIMT, with LV mass, LV diastolic function, and body composition defined as secondary outcomes. Delta (Δ) scores were analysed by ANCOVA, with baseline scores as the covariate. For the primary outcome, the probability that the population effect of the intervention is at least as great as the pre-specified minimum clinically importance difference (MCID) was estimated, to evaluate clinical relevance. All participants met 75% compliance criteria for STEX and PASS. The effect of the STEX intervention (compared with CON) was a mean benefit of –0.018 mm for

average maximum cIMT (90% CI, -0.039 to 0.002 mm), and -0.016 mm for average mean cIMT (90 % CI, –0.040 to 0.008 mm). The probability (% chances) that the true population effect of the STEX intervention would be clinically beneficial was 79% for average maximum and 71% for average mean cIMT. The PASS intervention did not result in clinically important effects, and no other substantial changes were observed for the secondary outcome variables. The relatively high probability of clinically beneficial effects of the STEX intervention suggests that a larger, "definitive" randomised trial with longer follow-up is warranted to define the effectiveness of the intervention more precisely.

As a consequence the longer PA intervention study observed 152 children aged 9 to 10 years over 12 months. All of the echocardiographic, body composition, CR fitness and PA variables mentioned were assessed as previously discussed. Children were randomly assigned by school to an intervention group. Control (no intervention), PASS (as before accept delivered during school hours to enhance compliance), high intensity physical activity (the same as STEX but renamed due to the addition of another structured exercise group) or fundamental movement skill ([FMS] 2 x 60 min sessions per week of skill based activities). These interventions took place over a year period with participants being assessed at baseline, approximately mid-way through and post-test (52weeks). Initial factorial ANOVA analysis comparing all 3 intervention groups and a control group before, during and after the 12 month intervention period, found limited statistically significant evidence for a positive impact of PA interventions compared to controls in pre-pubertal children. However, after adjusting for confounding variables in an ANCOVA analysis some, sporadic benefits of PA interventions on CV variables were uncovered. An increase in LV mass over 12 months, after adjustment, was lower in the HIPA group compared to CON group (11.5 g; 90% CI, 2.0 to 21.0 g). This change was also lower in the FMS group compared to CON group (13.8 g; 90% CI, 4.6 to 23.1 g). The ANCOVA adjusted change scores for both mean and max cIMT were less in the intervention groups compared to CON group but only in the PASS group were these differences significant ($P<0.05$). PASS increased its mean cIMT (-0.014mm less than control (90% CI, -0.002 to -0.030). Somewhat surprisingly the intervention programmes had no positive effect on CR fitness (indeed this decreased), PA measures and/or body composition over and above changes observed due to growth.

This thesis has provided a unique insight into the 'pre-clinical' CV disease risk factors in pre-pubertal children and the impact of differing PA activity interventions with this group. Interestingly the research has shown that within this population overweight/obese, inactive low CR fit individuals are generally not at a higher CV disease risk than their aged matched 'healthier' counterparts. When PA interventions are introduced in the short term positive changes in cIMT were seen however this is not reciprocated in longer PA interventions possibly due to a larger maturation effect over 12 months. Interestingly year long provide some attenuation of growth-related changes in CV disease risk factors but these changes are generally small and sporadic. It is suggested that further research over a longer period of time with more 'at risk' populations is needed. The PA interventions adopted achieved high attendance and compliance records and thus may be transferable out of the research process. It is interesting to also speculate that future research may not need to administer high impact activity, as previously thought, as some positive data was obtained in more general lifestyle interventions involving more knowledge transfer.

Acknowledgements

I would like to give my greatest thanks to my Director of Studies, Professor Keith George. Without him I would not be where I am today. He has always believed in me and never once given up. His support, guidance and patience have helped me through this thesis (and life!) for which I will be eternally grateful.

I would also like to thank Professor Gareth Stratton, the daddy of A-CLASS, who without, A-CLASS just would not have existed. Professor Alan Batterham (the king of stats!) for his unbelievable patience and knowledge that has guided me through my tricky stats dilemmas.

A huge thanks to all involved in the A-ACLASS, particularly Macca, Lozamund and Graves. We have worked together for many years and have been there for each other through the good the bad and the ugly. So many laughs and tears have been shared. Best of all lifelong friendships have been established, thanks guys!!

Not forgetting that none of this could have been possible without the financial backing and support of the neighbourhood renewal fund and the SportsLinx team. Also all the children and schools that have supported and taken part in the A-CLASS project.

Thanks to many of the staff at JMU. Professor Tim cable, who helped to start my Sports Science journey when I was just 17 years of age and has provided me with many wise words along the way. George Savage, Nicky Davies and Louise Coyne who are the back bone of JMU and have always offered a helping hand.

Finally I would also like to give a big thank you to my family who have supported me through all of my choices and helped me along the way. To my soul mate Brett, who has always been there and always believed in me. Thank you for never giving up! I love you all deeply.

This thesis has resulted in the following publications and conference communications:

1. Henaghan, J., McWhannell, N., Foweather, L., Cable, N.T., Batterham, A.M., Stratton, G., and George, K.P. (2008). The effect of structured exercise classes and a lifestyle intervention on cardiovascular risk factors in primary school children: an exploratory trial (The A-CLASS Project). *Pediatric Exercise Science,* **20**, 169-180.

2. PWP International Conference (Estonia, 2007). The effect of structured exercise classes and a lifestyle intervention on cardiovascular risk factors in primary school children (The A-CLASS Project). J. Henaghan, N. McWhannell, L. Foweather, T. Cable, A. M. Batterham, G. Stratton and K.P. George (2007)

3. Sports Leisure and Ergonomics Conference (2007). The association of "pre-clinical" cardiovascular disease risk factors with body composition and cardiorespiratory fitness in primary school children (The A-CLASS project). J. Henaghan, N. McWhannell, L. Foweather, T. Cable, A. M. Batterham, G. Stratton and K.P. George (2007)

4. British Association of Sports and Exercise Science (BASES) Conference (2006). Predictors of left ventricular mass in children aged 10-11 years. J. Henaghan, T. Cable, A. M. Batterham, G. Stratton and K.P. George (2006).

Table of Contents

List of Figures

List of Tables

Chapter 1

General Introduction

1.1 Background

The closed-loop human cardiovascular (CV) system moves blood containing nutrients, gases and metabolic waste products to and from cells to maintain homeostasis within the body. The CV system is comprised of the heart, blood and blood vessels. Any disease that impacts on the CV system can be termed a CV disease. Because of the importance of the CV system these diseases are the most prevalent 'killers' in the UK accounting for over 216,000 deaths in 2004 (Office of National Statistics, 2005). In 2005 an estimated 17.5 million people worldwide died from CV disease, representing 30% of all global deaths (WHO, 2007). Treatment, and more importantly prevention, of CV diseases are of great concern and constitute "the" major public health problem to face the "Western" world. To prevent such diseases, a clear understanding of its development, risk factors and early detection is needed. In a majority of cases the atherosclerotic process underpins CV disease. This is a progressive process thought to begin in childhood, despite its clinical symptoms emerging in later life (Edmundson *et al.*, 1994; McGill *et al.*, 2000).

Risk factors for CV disease include a range of lifestyle/environmental issues that are amenable to intervention such as high blood pressure (hypertension), hyperlipidemia (high blood cholesterol), smoking, obesity, physical inactivity and low cardiovascular fitness (Mertens *et al.*, 1998; Mitchell *et al.*, 2002; Andersen *et al.*, 2006; Hill *et al.*, 2007). Hypertension and hyperlipidemia are rarely reported in paediatric populations and smoking prevalence is low (Department of Health, 2002). Obesity, physical inactivity and low cardiovascular fitness are apparent in children and thus may be more important risk factors to assess and then alter.

Obesity or excess body weight is now viewed as an independent risk factor for CV disease (Poirier and Eckel, 2002). Current trends demonstrate a rapid increase in the prevalence of obesity (Eckel *et al.*, 2004; World Health Organisation, 2000). More ominously the recent progression in rates of obesity in children substantially increases the future risk of chronic "lifestyle" diseases that may develop earlier, persist longer and place a tremendous burden on future health care provision (Harrell *et al.*, 2003; Invitti *et al.*, 2006).

Physical activity is any movement created by the body resulting in an energy expenditure exceeding that at rest. High levels of physical activity are thought to have a protective effect for CV disease (Farrell *et al.*, 1998). Decreased physical activity levels have been associated with increased CV risk in both adults (Aadahl *et al*, 2007) and children (Dollman *et al.*, 2005). Whilst this is worrying considering the rapid reduction in physical activity levels reported within the UK (Sproston and Primatesta, 2003; Nelson, *et* al., 2006), encouragingly recent research has extended the role of physical activity in the amelioration of risk factors for CV disease from adult to children (Invitti *et al.*, 2006; Harrell *et al.*, 2003; McGill *et al.*, 2000).

Physical fitness is the ability to perform physical activities. Within this thesis one particular component of health-related physical fitness will be investigated. This is Cardiorespiratory (CR) fitness which represents the overall functional capacity of the CV, respiratory and skeletal muscle system and this also reflects the subjects' ability to carry out prolonged strenuous exercise. Low levels of CR fitness have been found to be a strong and independent risk factor for CV disease

and all cause mortality in adults (Wei *et al.*, 1999; Sui *et al.*; 2007). More recently these associations have been found in paediatric populations (Rizzo *et al.*, 2007; Ruiz *et al.*, 2007). Hurtig-Wennlof and colleagues (2007) also suggested CR fitness has stronger associations with CV risk factor profile than physical (in)activity. Furthermore there is reason to believe there are interactions between CR fitness and obesity in the development of CV disease as it has been proposed increases in body fat are having a negative effect on relative CR fitness scores (Rowland, 2007). Recent data has shown a global decrease in paediatric CR fitness (Tomkinson and Olds, 2007).

Part of any prevention plan or intervention to tackle CV disease is based on risk assessment. Detection of CV disease is vital in all groups, especially older adults. This concept also applies to children, even though traditional risk factors and clinical signs and symptoms of CV disease may be absent. With this in mind the establishment of early or "pre-clinical" markers is warranted to ascertain successful prevention strategies for CV diseases. Advances in non-invasive techniques such as ultrasound have allowed this to become possible giving clinicians and researchers an early understanding into the onset of the disease process via a number of parameters [e.g. left ventricular (LV) mass, diastolic function, and carotid intima-media thickness (IMT) (Daniels *et al.*, 1999; Sorof *et al.*, 2003; Freedman *et al.*, 2004; Meyer *et al.*, 2006; Sharpe *et al.*, 2006)]. Strong links have been reported between childhood "pre-clinical" CV markers (risk factors) and future risk of CV disease in adulthood (Chen *et al.*, 2005).

Despite some encouraging studies using "pre-clinical" markers of CV disease risk in adolescent children (Mitchell *et al.*, 2002; Schiel *et al.*, 2007; Sharpe *et al.*, 2006; Sorof *et al.*, 2003; Sorof *et al.*, 2004) there have been few studies in prepubescent children to document the impact of normal population variance in body composition, physical activity levels and CR fitness upon a combination of "pre-clinical" markers of CV disease. This would provide an estimation of "real" population-risk and also help direct any intervention programme(s) to reduce CV disease risk and positively impact upon known risk factors. This specific issue drove the rationale for the initial cross-sectional study in this thesis where the prevalence of "pre-clinical" markers was assessed in a normal, and apparently healthy, population of primary school children in Liverpool, in whom body weight and body mass index vary significantly and whose percentage distribution of overweight and obese children reflect national/international trends. Further variance in physical activity and CR fitness would likely be considerable.

In addition to assessing baseline risk in children the use of preventative physical activity interventions within this population are limited and have not always assessed "pre-clinical" markers of CV disease. Further, those studies available in the literature have tended to involve traditional structured exercise prescription alone (Bacon *et al.*, 2004; Nottin *et al.*, 2004; Pela *et al.*, 2004; Woo *et al.*, 2004) and less attention has been paid to the integration of physical activity into daily life through less structured/sports-specific exercise programmes that are more pragmatic for population trials (Floriani and Kennedy, 2007). Various theories and models to understand and change lifestyle behaviour have been proposed (Baranowski, *et al.*, 2003) and some recent interventions, based on behaviour

change theories, have been studied in an attempt to decrease sedentary behaviour in children (Salmon *et al.*, 2005). To the authors knowledge the comparison of structured exercise interventions with lifestyle programmes upon 'pre-clinical' CV risk factors in children has never been attempted. These issues drove the rationale for the second and third studies in this thesis. Further, and clearly differentiating studies 2 and 3 is the issue of exercise dose and its effect on "pre-clinical" CV disease markers as well as body composition, physical activity and CR fitness. Many training studies in children have been quite limited in duration and thus "volume" or "dose" of exercise is quite small (Humphries *et al.*, 2002; Woo *et al.*, 2004; Van Sluijs *et al.*, 2007). Therefore, in this study we completed both a short (9 weeks) and long-term (52 weeks) intervention, in two separate cohorts of pre-pubescent children.

1.2 Aims and hypotheses

The specific aims to this thesis are;

(1) to document "pre-clinical" markers for CV disease risk/development in primary school children and to assess the relationship of these "pre-clinical" markers with body composition, physical activity and CR fitness.

(2) to assess the impact of short-term (9 weeks) physical activity interventions (traditional and lifestyle) on "pre-clinical" markers for CV disease, body composition and CR fitness..

(3) to assess the impact of long-term (52 weeks) physical activity interventions (traditional and lifestyle) on "pre-clinical" markers for CV disease, body composition, physical activity levels and CR fitness

The stated null hypotheses are;

Ho_1: Body composition, physical activity levels and CR fitness will not be significantly associated with "pre-clinical" CV disease markers in a "normal" population of prepubescent children.

Ho_2: The implementation of a short-term physical activity intervention will not alter "pre-clinical" markers of CV disease risk/development as well as body composition and CR fitness in prepubescent children.

Ho_3: The implementation of a long-term physical activity intervention will not alter "pre-clinical" markers of CV disease risk/development as well as body composition, physical activity levels and CR fitness in prepubescent children.

Chapter 2

The Cardiovascular System

2.1 Introduction

The aim of this chapter is to provide the reader with a basic knowledge of cardiovascular structure and function as it will apply to the general background of this thesis and also to the specific measurement protocols/variables assessed. In doing so this will replace the often used but non-contextualised "abbreviation list".

The CV system is comprised of the heart, blood and blood vessels. For the blood to be propelled through the blood vessels a driving force must be applied. Cardiac contraction provides this force and the heart circulates the blood through an estimated 100,000 km of blood vessels pumping more than 14,000 L of blood a day (Tortora and Grabowski, 2000). To fully comprehend cardiac function we must first look at its structure particularly that of the left ventricle as this produces the force/pressure to drive blood through the systemic circulatory loop. This supplies all tissues (except alveoli) including skeletal muscle.

2.2 Cardiac structure

The heart is the size of a clenched fist and is positioned near the midline of the thoracic cavity behind the sternum, resting on the diaphragm. About two-thirds of the hearts mass lies left of the body's midline. The apex of the heart is positioned inferior and to the left of the sternum whilst the base is superior and to the right behind the sternum.

The heart is a four chambered organ comprising of two upper (atria) and two lower (ventricles) (Figure 2.1). The septal wall (septum) separates the two

ventricles and atria. It can be considered as two halves (left and right) that work as two synchronised pumps with both atria contracting synchronously followed by both ventricles. The right side pumps blood in to the pulmonary circulatory system (low pressure ~ 25 mmHg) whilst the left pumps to the systemic system (high pressure ~ 125 mmHg). Despite working against different pressures (afterload) both ventricles provide the same stroke volume and thus cardiac output.

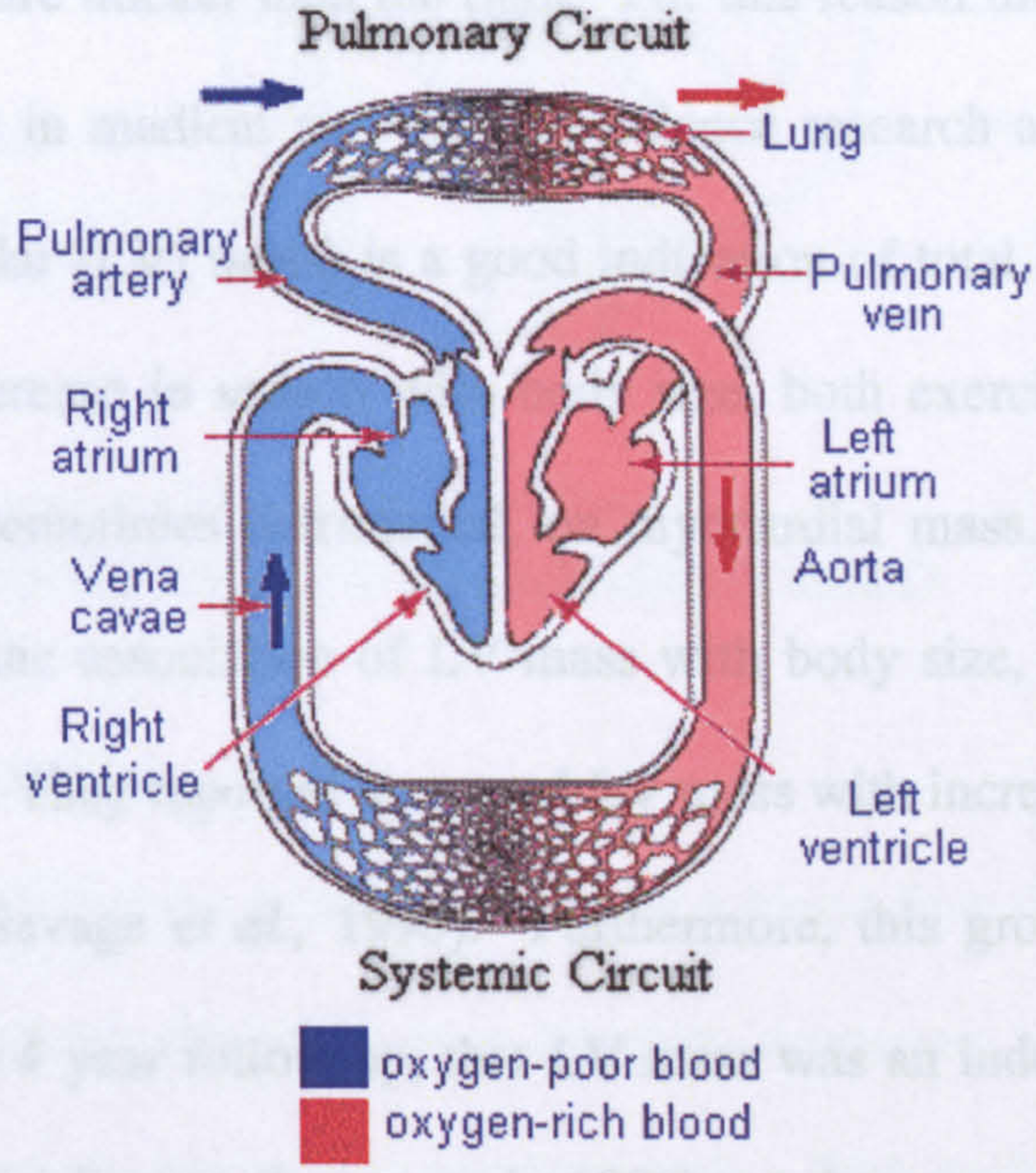

Figure 2.1 Flow of blood through the heart and circulatory systems.
(http://webschoolsolutions.com/patts/systems/pul-circ.gif)

The atria and ventricles are separated by unidirectional atrioventricular valves that open and close passively according to pressure gradient. The right atria and ventricle are separated by the tricuspid valve, the left by the mitral valve (Figure 2.2). The walls of the ventricles are thicker than that of the atria because they provide the force (via contraction) to pump the blood out of the heart to the respective circulatory systems and therefore work against a bigger pressure gradient. Both ventricles receive blood at low pressures (c. 0 mmHg) but have to

increase this pressure to overcome arterial pressure (resistance). This is achieved through a highly orchestrated process of cellular depolarisation and then contraction.

2.2.1 Left ventricular structure

The left ventricle works against a greater resistance than the right ventricle producing 5-7 times the work to generate the same stroke volume. Hence the left ventricular walls are thicker than the right. For this reason the left ventricle is of particular interest in medical and exercise science research as the magnitude of this (left ventricular [LV] mass) is a good indication of total heart mass. Whilst LV mass will increase in unison with body size, both exercise and disease can exert an affect, sometimes detrimental, on myocardial mass. The Framingham Study looked at the association of LV mass with body size, blood pressure and physical activity. They reported increased LV mass with increasing body size and blood pressure (Savage *et al.*, 1990). Furthermore, this group established in a report based over 4 year follow up, that LV mass was an independent risk factor for coronary artery disease (Levy *et al.*, 1989). A key reason for assessing LV mass is the clinical link in adults between LV hypertrophy and increased CV risk (Savage *et al.*, 1990). Whilst cut-off criteria for LV mass in the determination of LV hypertrophy are apparent in adults no clear data are apparent in children.

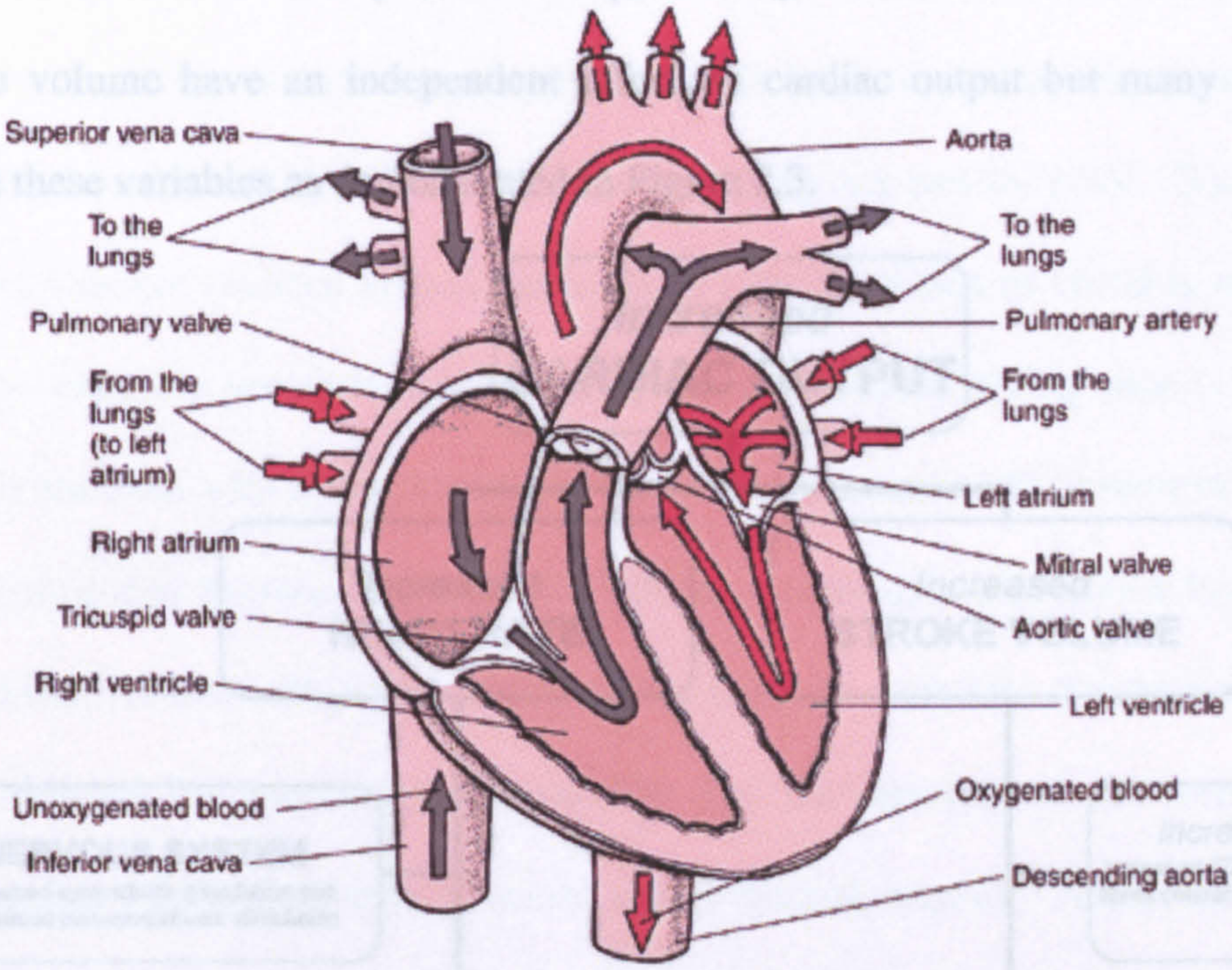

Figure 2.2 Structures and blood flow of the heart.
(http://www.shoppingtrolley.net/images/anatomy/heart.gif)

2.3 Cardiac function

The primary function of the heart is to provide a blood flow (pulsatile in arteries and arterioles) through the body at a pressure necessary to sustain adequate perfusion to the organs, tissues and capillary beds. With each beat of the heart a volume of blood is ejected (end-diastolic volume – end-systolic volume [EDV – ESV]), this is termed stroke volume. Although stroke volume provides an index of global left ventricular systolic function it is governed by preload, afterload and contractility. Often in an attempt to get an index of intrinsic contractile function ejection fraction (stroke volume/EDV) and fractional shortening (degree of ventricular short axis change in contraction) are reported but again these are not entirely load-independent. If stroke volume is multiplied by the frequency of cardiac cycles per minute (heart rate) then the cardiac output is calculated. Cardiac output is a key variable representative of ventricular function as it reflects

total flow into both the systemic and pulmonary circuits. Both heart rate and stroke volume have an independent effect on cardiac output but many factors affect these variables as demonstrated in Figure 2.3.

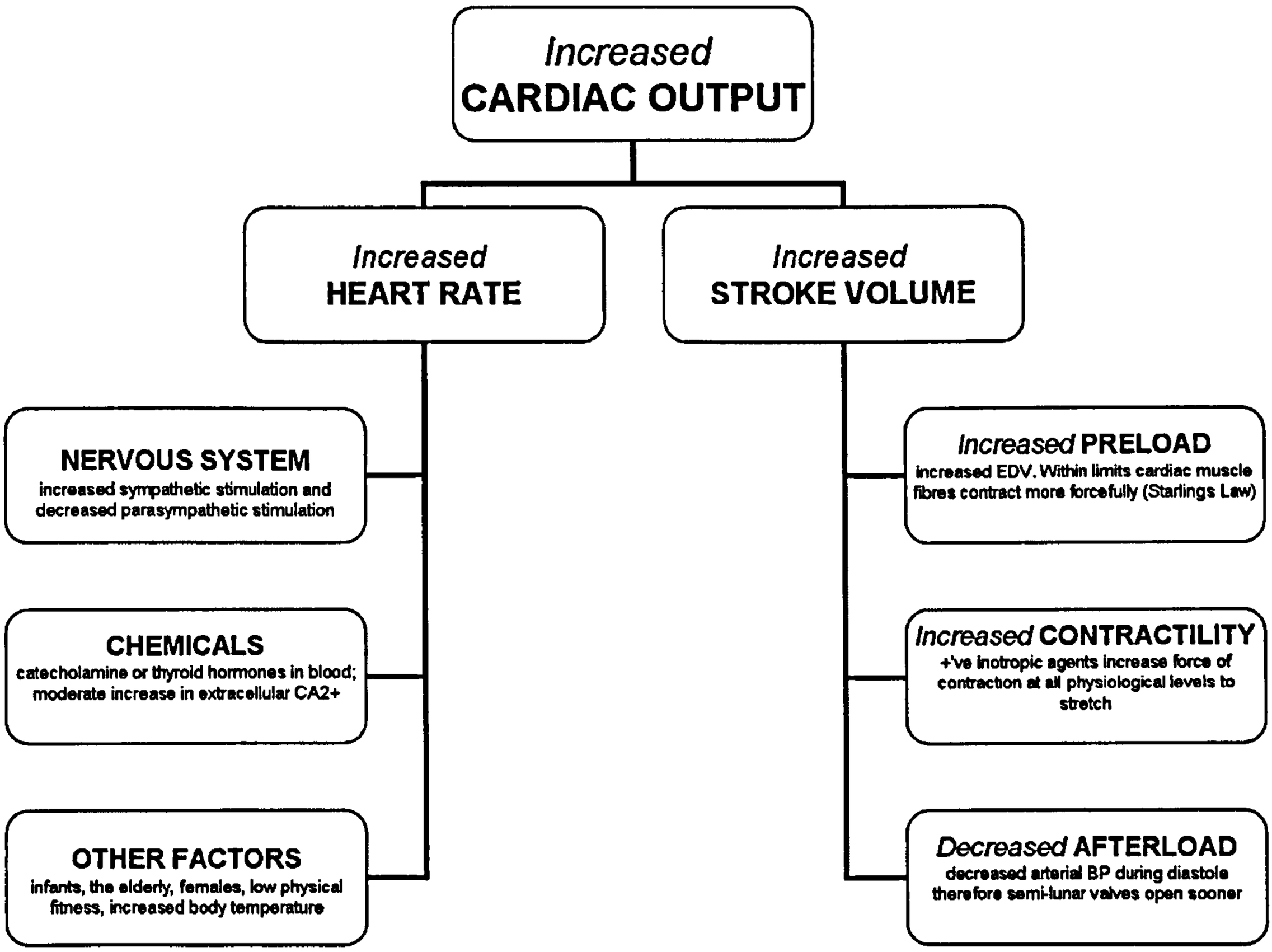

Figure 2.3 The influence of heart rate and stroke volume on cardiac output. (Adapted from Tortora and Grabowski, 2000)

Heart rate is regulated by a combination of local environment (temperature), neural input, hormonal milieu and intrinsic properties. Individual differences in heart rate occur with age, gender and fitness likely via alterations in these control parameters. Heart rate can additionally have a direct affect on stroke volume. Stroke volume is primarily regulated by three factors already mentioned; preload, contractility and afterload. Preload is the degree of stretch in the ventricle before it contracts and is therefore the volume of blood in the ventricle before contraction

(also EDV). The greater the preload the greater the force of contraction (Starlings Law). However, as heart rate increases (such as in exercise) the duration of diastole shortens and less filling can occur resulting in a smaller EDV. Equally, if venous pressure (venous return) increases, a greater volume of blood is returned to the ventricles therefore compensating for the reduced filling time. This is usually the case with dynamic exercise until approximately 160 beats•min^{-1} when filling time may become limiting for LV filling, resulting in a limitation to preload and stroke volume will plateau and possibly begin to decrease. Stroke volume is also affected by myocardial contractility i.e. the strength of the ventricular contraction which also reflects neural and hormonal control. Neural control is maintained by the autonomic nervous system (ANS), in the medulla oblongata, which acts on the heart via the sympathetic (increase heart rate, contractility) and parasympathetic (decrease heart rate and contractility) nervous system. Increased nerve impulses from the cerebral cortex, limbic system, hypothalamus, proprioceptors, chemoreceptors and baroreceptors stimulate the sympathetic nervous system which acts on the SA and AV nodes and myocardium to increase contraction. Parasympathetic nerve fibres also innervate the SA and AV nodes and myocardium and perform a "decelerator" function. Hormones also play a part in this acceleration and deceleration of heart rate and contractility. Adrenaline and noradrenaline (released from the adrenal medulla) increase both heart rate and contractility. The pressure that the ventricles have to generate before it surpases arterial pressure, and the semi lunar valves can open, is representative of afterload. If afterload increases, independently of any change in preload or contractility, stroke volume will decrease as more blood will remain in the ventricle after systole (ESV).

The cardiac cycle represents all the facets of cardiac function interlinked with the electrical stimulus (depolarisation) for cardiac myocyte contraction. The cardiac cycle is split into systolic (contraction) and diastolic (relaxation) periods. Systole begins with the closure of the AV valves and includes an isovolumic contraction period as well as the ejection phase from the ventricles. Diastole begins with the closure of the aortic or pulmonary artery valves and includes isovolumic relaxation, early diastolic filling (passive), diastasis, and late or atrial diastolic filling (active due to atrial systole). As such the cardiac cycle is complex integration of electrical, biochemical and structural changes throughout a cardiac cycle. Changes in pressures, flow volume and electrical activity are shown in Figure 2.4. Electrical activity (action potential) in the cardiac myocytes is the stimulus for contraction and relaxation and this excitation normally originates in the sinoatrial (SA) node. This initially propagates through both atria providing the stimulus for simultaneous contraction. The action potential will then reach the atrioventricular (AV) node which then directs the wave of depolarisation through the bundle of His as this is the only electrical connection between the atria and ventricles. From here the action potential enters both the right and left bundle branches moving towards the apex of the heart and finally into the Purkinje fibres. These conduct the electrical activity from the apex of both the left and right ventricles then very rapidly upwards towards the remainder ventricular myocardium. This propagation is very rapid and provides the stimulus for a synchronous ventricular contraction and thus blood flow out of the heart.

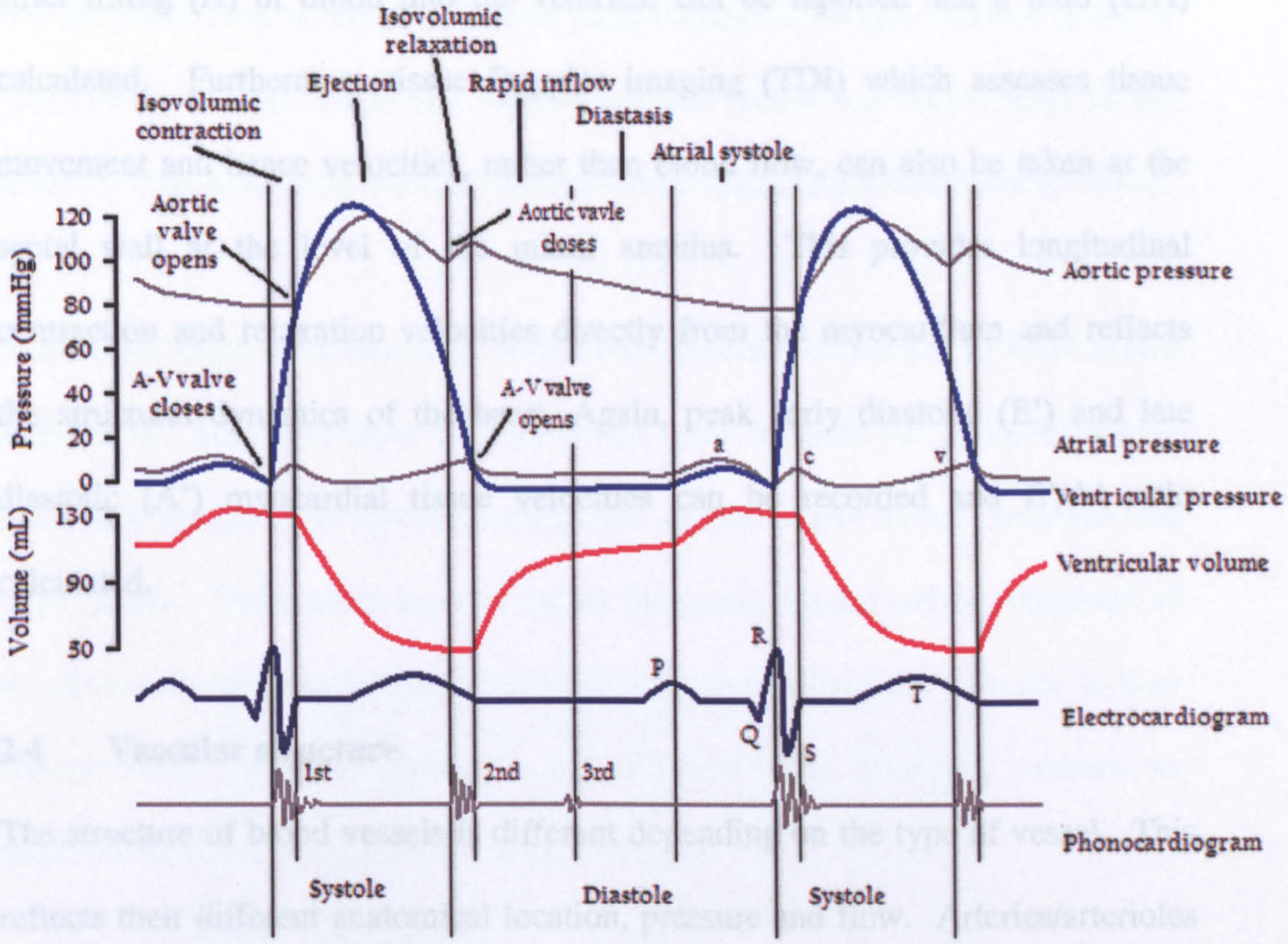

Figure 2.4 Pressure, volume and electrical changes during the cardiac cycle. (http://upload.wikimedia.org/wikipedia/commons/5/5b/Cardiac_Cycle_Left_Ventricle.PNG)

The electrical depolarisation and repolarisation of all cardiac myocytes can be detected on the surface of the body and recorded through an electrocardiogram (ECG). A typical ECG recording is presented in Figure 2.4. The P wave represents atrial depolarisation. The QRS complex represents ventricular depolarisation. The final T wave represents ventricular repolarisation.

Left ventricular systolic and diastolic function can be monitored through a number of echocardiograph techniques. In the assessment of diastolic function, specifically pertinent to this thesis, Doppler flow echocardiography measures peak blood flow velocities at the middle of the mitral valve. This assesses diastolic (or transmitral) blood flow velocities from the atria to the ventricle and reflects the fluid dynamics of the heart. From this peak velocity early (passive) filling (E) and

atrial filling (A) of blood into the ventricle can be reported and a ratio (E/A) calculated. Furthermore tissue Doppler imaging (TDI) which assesses tissue movement and hence velocities, rather than blood flow, can also be taken at the septal wall at the level of the mitral annulus. This provides longitudinal contraction and relaxation velocities directly from the myocardium and reflects the structural dynamics of the heart. Again, peak early diastolic (E') and late diastolic (A') myocardial tissue velocities can be recorded and E'/A' ratio calculated.

2.4 Vascular structure

The structure of blood vessels is different depending on the type of vessel. This reflects their different anatomical location, pressure and flow. Arteries/arterioles are responsible for the distribution of blood from the heart and work under high pressure. Arteries have a pressure storing component called elastin. This enables the arteries to resume their shape after stretching due to the volume of blood ejected or flowing through in a pulsatile fashion. Arterioles also have a resistance function that reflects the activity of the smooth muscle in the vessel wall. Smooth muscle enables the arteries, and particularly arterioles, to not only maintain their shape but also aid in contraction (vasoconstriction) and relaxation (vasodilation) in the regulation of blood flow and pressure. The role of capillary beds is to exchange gases, electrolytes, water and nutrients through its endothelial cells (or gap junctions) into the interstitial space and hence onto specific cells. Capillaries are small in comparison to other vessels however they have a very large surface area. The collecting vessels in both circulatory systems are the veins and venules which have a large volume capacity however work under low pressure as they

carry the blood back to the heart. Their large volume or storage function is due to a low elastin content. Veins and venules are thin walled and major veins below the level of the heart have unidirectional valves to prevent the back flow of blood.

Arteries and veins have the same vessel wall structure consisting of three layers (Figure 2.5). The outer layer of arteries and veins is called the tunica adventitia which is a strong outer covering composed of connective tissue, collagen and elastic fibres. The middle layer is called the tunica media and is composed of smooth muscle and elastic fibres. This is thicker in arteries than veins due to their different roles. The inner layer is the tunica intima which in arteries contains the elastic membrane and smooth endothelial lining.

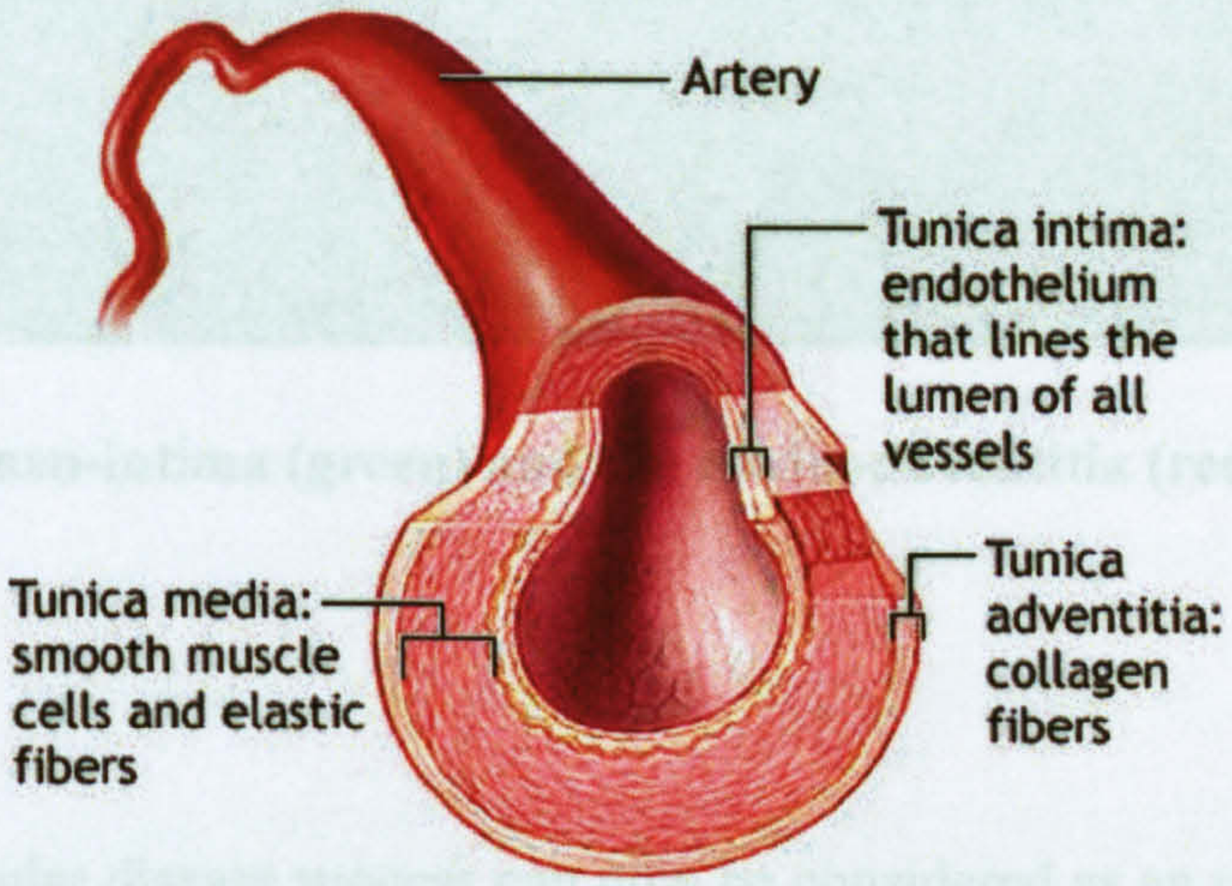

Figure 2.5. Blood vessel structure
(http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/19194.jpg)

The disease process known as atherosclerosis is a result of plaque formation on the inner lining of arteries and reduces blood flow through the vessel. The progression of lesions on the vascular walls can be monitored through measurements of the carotid intima-media thickness (IMT). Carotid IMT has been

found to be thickest at the carotid bulb and increases linearly with age, but most rapidly at the bulb (Stein *et al.*, 2004). It can be assessed non-invasively and is highly reproducible and inexpensive test that is an independent predictor of coronary artery disease (de Groot *et al.*, 2004). This process begins in childhood as age-dependent physiological thickening has been found to appear on the arterial walls of children aged 5-14 years (Ishizu et al., 2004). The initial start of this plaque formation begins within the inner layers of the intima media complex (the distance between the lumen-intima and the media-adventitia) (see Figure 2.6).

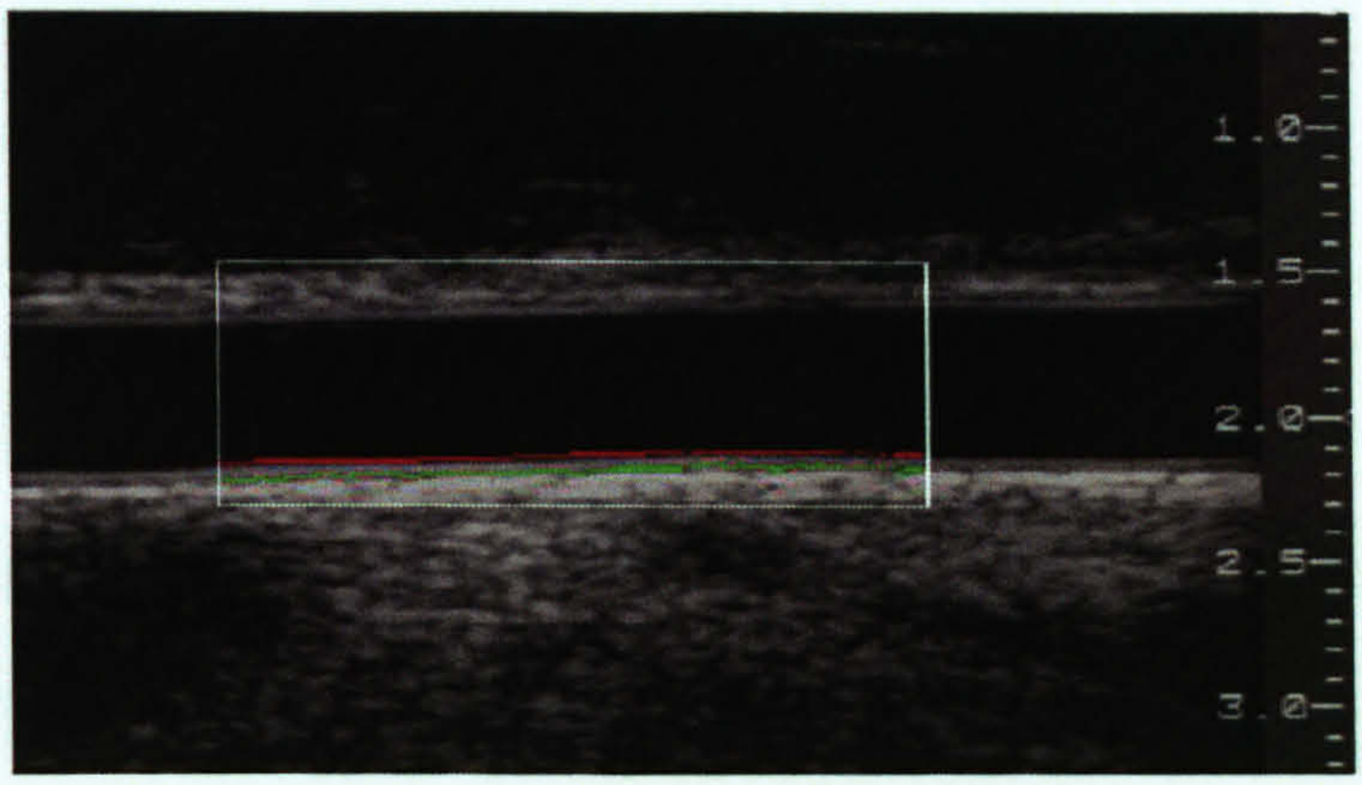

Figure 2.6 Lumen-intima (green) and the media-adventitia (red).

2.5 Summary

The cardiovascular disease process can now be considered as an understanding of cardiac structure, function and vascular structure has been made clear. A focus on previous research will allow an establishment for current interventions in the CV disease prevention.

Chapter 3

Literature Review

3.1 Cardiovascular disease

Cardiovascular (CV) disease refers to any disease that affects the heart and/or blood vessels. Such diseases constitute the most significant "killer" in the UK, accounting for over 216,000 deaths in 2004 (Office of National Statistics, 2005). In 2005 an estimated 17.5 million people worldwide died from CV disease, representing 30% of all global deaths (WHO, 2007). Treatment, and more importantly prevention, of CV diseases are of great concern and constitute "the" major public health problem to face the "Western" world.

3.2 Cardiovascular disease and its origins in childhood

Cardiovascular diseases are deemed to be an adulthood malady and although it appears to manifest clinically in later life the atherosclerotic process, that underpins many CV diseases, begins in childhood (McGill *et al.*, 2000). An autopsy based study found pre-clinical changes in the vascular walls of children as young as 6 years (Edmundson *et al.*, 1994). Traditional risk factors associated with the atherosclerotic process and thus CV diseases are hypertension, hyperlipidemia, obesity, smoking, stress and sedentary lifestyles. Although these risks of CV disease are becoming increasingly prevalent within the younger generation (Steinberger *et al.*, 2001; Gutin *et al.*, 1994), the need for the establishment of earlier or "pre-clinical" markers of future CV disease risk or current atherosclerotic load is warranted. Early risk detection provides the opportunity for pre-emptive strategies to prevent disease progression rather than respond to disease presence.

Advances in non-invasive techniques such as the use of ultrasound have been extremely beneficial in assessment of "pre-clinical" changes in CV structure and/or function. Measurements of left ventricular (LV) mass, diastolic function and carotid intima-media thickness (IMT) have been employed individually in previous studies of both adults and children (Daniels *et al.*, 1999; Sorof *et al.*, 2003; Freedman *et al.*, 2004; Meyer *et al.*, 2006; Sharpe *et al.*, 2006). As a consequence there is some support to the belief that ultrasound tools and specific variables can be employed to detect significantly altered CV disease risk in children, particularly adolescents. These potentially allow an earlier assessment of future CV disease risk as well as prompting rapid and targeted interventions to prevent, delay or offset CV disease. This has an important economic impact as well as significantly altering individual morbidity and mortality whilst increasing quality of life.

Research has reported a strong link between childhood CV risk factors and future risk of clinical CV disease in adulthood. Chen *et al.* (2005) examined 1474 participants aged 4-17 years and then reassessed them at 19-41 years. They found lower IMT, BMI, insulin resistance, systolic blood pressure and total-to-HDL cholesterol ratio in childhood to result in lower CV risk in adulthood. This emphasises the importance that childhood health plays in future cardiac risk.

Evaluation of CV disease progression in children is even more pertinent today because of the significant lifestyle changes in modern society. Specifically, decreasing levels of physical activity in children (Dollman *et al.*, 2005) and increasing levels of obesity (Lobstein *et al.*, 2003) and diabetes (World Health Organisation., 2007) all point to an earlier CV disease development.

In particular, obesity and low cardiorespiratory fitness are strongly associated with CV risk (Sharpe *et al.*, 2006; Rizzo *et al.*, 2007). The combination of excessive body fat and low physical activity levels puts increased demands upon the CV system and can lead to the early development of CV disease and risk factors for CV disease. With the concern related to changing physical activity (PA) as well as the increased prevalence of childhood obesity, it becomes important to assess early "pre-clinical" markers of CV disease in normal, heterogeneous populations of children. Further the necessity to look in younger, pre-pubescent children is also apparent in an attempt to define risk as early as possible and to provide more time for intervention strategies.

3.3 Physical activity (PA) and cardiorespiratory (CR) fitness in children; current trends and technical measurement issues

With the increasing prevalence of sedentary activities and obesity in children (Dollman *et al.*, 2005; Lobstein *et al.*, 2003) there is a considerable interest in the assessment of childhood PA levels and cardiorespiratory (CR) fitness. Whilst some may actually use the terms PA and CR fitness interchangeably these are clearly different phenomena and could have independent effects upon CV health.

PA and inactivity represent opposite ends of a continuum of energy expenditure and thus have opposing health risks/benefits for the CV system. All activities have a degree of energy expenditure required (over and above resting metabolic rate) but some activities obviously require more effort and thus energy than others. Some activities such as TV viewing, computer work/games (screen time)

and reading all have similar energy expenditure to that observed during periods of quiet rest and can be termed sedentary behaviours. Other activities such as participation in recreational or competitive sports such as football, netball (etc.) represents higher levels of PA. It should be noted that it is possible for a person to have both high levels of PA as well as partaking in sedentary behaviour(s) and therefore total daily energy expenditure should be assessed in all subjects/groups to be investigated (Katzmarzyk *et al*, 2007) as well as PA intensity patterns.

Due to the spontaneous, sporadic and unplanned types of activities performed by children (Trost, 2001) the development of a valid measurement of PA, as well as intensities of PA, that captures the full complexity of activity in children has been troublesome. Self reporting PA through questionnaires, diaries and interviews has been popular due to ease of attaining large sample numbers, ease of use, the ability to detail different types of PA behaviour and the low cost (Treuth, 2002; Sirad and Pate, 2001; Harro and Riddoch, 2000). Yet, there are many problems associated with these methods such as the need for the participant to recall their activities, which provides increased subjectivity, difficulties in implementation with children such as boredom and recall accuracy (Kohl *et al.*, 2000; Baranowski, 1988). Heart rate monitors have been used with children (Epstein *et al.*, 2001) as these are easy to use and are more objective than self report data (Sirad and Pate, 2001). Heart rate can be affected by other variables such as emotion and thus may not simply reflect PA. Heart rate monitors can also be obtrusive especially with young children (Janz, 2002). The gold standard for measuring energy expenditure (EE) is doubly labelled water (Schoeller and van Santen, 1982) and this provides the total EE of a free-living individual for a

period of 4 to 20 days. However this method requires the individual to ingest a non-radioactive isotope and its outputs recorded. This method is also very expensive and trained technicians are needed. The invasive nature of this method means it is generally unsuitable and unethical for children.

One potential method of assessment of PA in children that holds some promise is accelerometry. These devices work on the basis that acceleration is directly proportional to the muscular forces and is therefore related to EE. Accelerometers have the benefit that they are unobtrusive, non-invasive, have a large memory capacity that can store PA patterns, amounts and intensities of an individual for many days. Accelerometers do not rely on participant recall, however, not all activity is recorded (i.e. load or gradient). Further they are unsuitable for contact or wet sports and they are relatively expensive compared to paper and pen methods. Nevertheless researchers have reported accelerometers to be both feasible and provide accurate measurement in children (Riddoch *et al.*, 2004). Problems associated with determination of activity 'cut points' (definitions of what constitutes MVPA) as well as the establishment of the number of days of monitoring, lengths of epochs and participant compliance when using accelerometry means comparison between research is often difficult (Trost *et al.*, 2005; Ward *et al.*, 2005).

It is widely reported in cross-sectional research that PA levels decrease with increasing age in children (Armstrong *et al.*, 2000; Riddoch *et al.*, 2004; Stratton *et al.*, 2007) and that girls are less active than their male counterparts (Riddoch *et al.*, 2004). Additionally longitudinal studies have reported a rapid reduction in

physical activity levels within UK schoolchildren (Sproston and Primatesta, 2003; Nelson, *et* al., 2006).

In children the recently recommended PA guidelines, to maintain and/or promote CV health, are 60 minutes of moderate to vigorous physical activity (MVPA) daily (Biddle *et al.*,1998; Strong *et al.*, 2005). Biddle and colleagues (1998) rationalised the need to increase daily PA recommendation from 30 (Pate *et al.*, 1995) to 60 minutes a day as childhood overweight and obesity was increasing despite evidence that previous PA criterion were being met (Armstrong and Welsman, 1997). Moderate activity was defined (Biddle *et al.*, 1998) as any activity which leaves the participant feeling warm and slightly out of breath (e.g. a brisk walk), vigorous was deemed to be activity that made the participant feel out of breath and sweaty (e.g. jogging). However, this definition of MVPA is contentious as different methods of defining PA intensity can be used. In terms of exercise prescription PA is often expressed relative to a person's capacity to perform an activity at a percentage of their CR fitness (ACSM, 2000). Similarly percentage of maximal heart rate can be used (ACSM, 2000). PA intensity can also be expressed in absolute terms to the activity (e.g. walking for 20 minutes at 4 $km.h^{-1}$) or using metabolic equivalents (MET's) in accordance to VO_2 data (USDHHS, 2006). One MET is lying down at rest and has been found to be equivalent to 3.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (ACSM, 2000). Three MET's which is associated with moderate activity is therefore 3 times this and equal to 10.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ which is thought to be around 4 $km.h^{-1}$ (Pate *et al.*, 1995). As people age their physiology and metabolism change such that their maximal oxygen uptake will alter and thus a 4 $km.h^{-1}$ walk may vary considerably in terms of relative intensity.

When describing PA intensity patterns the use of the terms 'light', 'moderate' and 'vigorous' can therefore but controversial. For example Pate and colleagues (1995) described brisk walking as moderate PA but healthy people 2000 reported this as'light to moderate' intensity (USDHHS, 2006). This is particularly problematic in children and adolescents as they go through growth and pubertal development at different and unpredictable time points. This provides a significant difficulty/limitation to work in this area.

Recent research by Andersen and colleagues (2006) has now suggested that 90 minutes a day of MVPA is needed for health improvements in children. They believed the extra 30 minutes is necessary because children who performed activity for over 90 minutes had less of a cardiovascular risk compared to less active cohorts. They suggested MVPA is required in the form of above 2000 counts per minute (CPM), derived from accelerometry, which corresponds to a walking speed of about $4km.h^{-1}$. This study has been criticised not only for its cross sectional nature but also some feel that the 2000 CPM cut point is too low and this, therefore, results in an over estimation of PA frequency, intensity and time. Problems persist in the definition and accurate measurement of activity intensity. As suggested by Ward and colleagues (2005) the development of accurate and valid activity count thresholds (or cut points) for exercise guidelines is essential for future researchers to be able to use comparable moderate to vigorous intensities thresholds. Nevertheless Andersen's study provides us with up to date empirical information which should be recognised when using accelerometers to assess PA and its associations with childhood CV health.

Cardiorespiratory (CR) fitness is one component of physical fitness and represents the overall capacity of the CV, respiratory and skeletal muscle systems (ACSM, 2000). The accepted criterion measure for CR fitness is maximal oxygen uptake ($\dot{V}O_{2max}$) which defines the limits of the CV system and exercising muscles in their ability to deliver and utilise oxygen. $\dot{V}O_{2max}$ is the product of cardiac output (L/min) and arterial-venous oxygen difference (mL O_2/L) and can be defined as the highest rate at which an individual can consume oxygen during exercise, at which point an increase in exercise intensity does not result in a further rise in $\dot{V}O_2$ (ACSM, 2000). Spirometry is used to measure $\dot{V}O_{2max}$ and one of the criteria for adults is that their $\dot{V}O_2$ begins to plateau with an increase in work but other aspects of the test results can be viewed as useful criteria in the absence of a clear plateau. Specifically, the individual should show signs of severe fatigue and an inability to continue exercising. Further attaining a HR close (± 10 beats.min^{-1}) to their age predicted maximum HR or achieving a maximal respiratory exchange ratio (RER) of above 1.10 is considered (ACSM, 2000). These latter criteria are important as in children the 'plateau' in $\dot{V}O_2$, is not always reached (Armstrong *et al.*, 1996). If a child is showing clear signs of fatigue, has reached a heart rate above 95% of their maximum and has a RER above 1.0 then $\dot{V}O_2$ can be accepted as equal to maximum (Armstrong and Welsman, 1994). The term $\dot{V}O_{2peak}$ is often used as a substitute for $\dot{V}O_{2max}$ in children because of such test outcomes.

The assessment of CR fitness requires the individual to perform a dynamic activity in which large muscle groups are being used such as running or cycling. The direct approach to determine maximal oxygen uptake is to measure expired air composition and respiratory volume during maximal exertion. Estimation assessments such as multistage fitness test, which aim to predict CR fitness without gas analysis, appear to be effective in large cohorts. However whilst the direct approach is more expensive and time consuming, this is the desired method of assessment for many researchers due to its accuracy. Within paediatric research CR fitness tests have been performed using both cycle ergometers (Denker *et al.*, 2007; Andersen *et al.*, 2008) and treadmills (Eiberg *et al.*, 2005; Gutin *et al.*, 2005; Obert *et al.*, 2007). Whilst the cycle ergometer provides a more portable, cheaper and less noisy approach compared with the treadmill it can be difficult for children to maintain a fixed pedal speed. Additionally a major disadvantage of using a cycle with children is that a large proportion of the total power output is developed by the quadriceps muscle and therefore test termination may in fact be due to peripheral rather than central fatigue. For this reason the treadmill appears to be the most appropriate method for assessing $\dot{V}O_{2peak}$ in children (Armstrong and Welsman, 2000) as well as providing a greater degree of ecological validity.

Whilst many studies have described CR fitness in children, the complexities of growth-related changes in body size, muscle function, and the heart has led to some concern and inconsistency in the reporting of $\dot{V}O_{2max}$ data in children (Armstrong and Welsman, 2007). Thus assessment of secular trends in paediatric CR fitness is rare. In an attempt to clarify Tomkinson and Olds (2007) conducted

an extensive literature review to quantify the global change in paediatric aerobic fitness test performance. Their findings suggested that in both boys and girls aged 6-19 years aerobic performances have declined precipitously over the last three decades. It was suggested that this was due to increased fatness and decreases in habitual PA (Olds *et al.*, 2007). The impact that a combination of all these factors (decreased PA, decreased CR fitness and increase fatness) has on child health is of great concern.

3.3.1 The impact of PA and CR fitness on cardiovascular disease risk

Both PA and CR fitness have been found to play an important role in CV health. In adults it is readily recognised that low PA is associated with poor CV health (Powell *et al.*, 1987; Berlin and Colditz, 1990; Aadahl *et al*, 2007) and many CV co-morbidities such as hypertension, hyperlipidemia and obesity (Mertens *et al.*, 1998; Paffenbarger *et al.*, 1983). Conversely, high levels of PA are thought to have a protective effect for CV disease (Farrell *et al*, 1998). In children there is less empirical evidence compared to adults to support such an association between PA and CV health although some relationships have been observed.

Some studies have found that children with higher PA levels had lower blood pressures, more desirable lipid profiles and were less likely to be obese (Armstrong and Simons-Morton, 1994; Boreham *et al.*, 1997; Moore *et al.*, 2003; Maziekas *et al.*, 2003; Dollman *et al.*, 2005; Andersen *et al*, 2003; Leary *et al.*, 2008). The European Youth Heart Study (EYHS) observed that PA, CR fitness, skinfold thicknesses and waist circumference all had an independent association with a cluster of CV risk factors (blood pressure and lipids; Andersen *et al.*,

2008). In this study the children with the highest CV risk were those found in the lowest percentiles of moderate PA (less than 38 minutes per day). When using the age-matched waist circumference cut-off values proposed by the Bogalusa Heart Study (Katzmarzyk *et al.*, 2004), Ortega *et al* (2007) observed that children with low levels of total PA, and particularly low levels of vigorous PA, were more likely to be overweight and have a "high-risk" waist circumference than their more active counterparts. Increased TV watching was also associated with a "higher-risk" waist circumference but this was attenuated when total PA or VPA was put into the statistical model.

In adults an inverse relationship between CR fitness and CV disease and its risk factors such as hypertension, hyperlipidemia and obesity has been reported (McMurray *et al,* 1998; Wilmore *et al,* 2001; Talbot *et al,* 2002; Ross and Katzmarzyk, 2003; Lee *et al.*, 2005). Low CR fitness has been found to be a strong independent predictor of CV disease, all cause mortality and CV disease risk factors in adults (Wei *et al,* 1999). In children an association between CR fitness and CV health is less well established, compared to adults, but some recent studies have provided new and illuminating data. In 9-10 year old boys and girls, the EYHS reported that higher CR fitness resulted in a more favourable CV risk profile (blood pressure and blood lipids; Hurtig-Wennlof *et al.*, 2007). Anderssen and colleagues (2007) studied 2845 randomly selected school children from Estonia, Denmark and Portugal (EYHS) aged 9-15. Children performed a maximal CR fitness assessment on a cycle ergometer and cholesterol, triglycerides, insulin resistance, sum of 4 skinfolds and systolic blood pressure were all recorded. They found low CR fitness (following division into quartiles)

to be strongly associated with a cluster of CV disease risk factors in children independent of country, age and sex. Other studies have reported weaker relationships between CV disease risk factors, fitness and fatness in 6-7 year old children (Hansen *et al,* 2005) and some have reported no statistically significant associations (Kwee and Wilmore 1990; Gutin *et al,* 1997; Stensel *et al,* 2001). The inter-study variability in outcomes maybe related to a range of factors including the variety of subjects' age groups, socio-economic status and ethnicities observed.

Whilst there are guidelines, albeit controversial, for the required level of PA that children should be undertaking (Biddle *et al.*,1998; Strong *et al.*, 2005) there is little information available on what constitutes the minimum or appropriate level of CR fitness in children of different ages. Put another way there are few criteria for measurements such as $\dot{V}O_{2max}$ that clearly differentiate between low and high risk of CV disease or its risk factors. One study has attempted to address this issue. Ruiz and colleagues (2007) suggested a hypothetical $\dot{V}O_{2peak}$ cut off point for increased CV risk in 9-10 year old children from Estonia and Denmark (n=1140). Girls with a $\dot{V}O_{2peak}$ above 37.0 $ml.kg.^{-1}.min^{-1}$ were 3.09 times more likely to have a lower metabolic risk than lower CR fitness counterparts. Whilst boys with a $\dot{V}O_{2peak}$ above 42.1 $ml.kg.^{-1}.min^{-1}$ where 2.42 times more likely to have a lower risk. The cross-sectional nature of this study brings obvious limitations in that cause and effect cannot be assumed between variance in $\dot{V}O_{2peak}$ and risk factors. Longitudinal studies that manipulate $\dot{V}O_{2peak}$ and assess

the change in other CV risk factors are clearly required. Whilst this study is noteworthy further research is needed in this area to support clinically relevant CR fitness criteria for elevated disease risk as well as providing criteria for differing age groups.

3.3.2 Are PA and CR fitness assessing the same thing?

Whilst CR fitness is said to have a large genetic component (MacArthur and North, 2005) the impact of lifestyle and environment, through changes in PA, also has a modulating influence on CR fitness. In 9-11 year old children studied as a part of the EYHS all intensities of PA were found to be positively associated with CR fitness. Other data from the same study suggested that lower body fat percentage was significantly associated with higher levels of VPA but not with moderate or total PA. In the same study CR fitness was also a predictor of body fat. The authors concluded that higher PA intensities such as VPA, may have a positive effect on obesity whilst moderate PA and total daily PA may have a greater influence on CR fitness rather than body composition (Ruiz *et al,* 2006). Further work suggested that CR fitness was more strongly correlated with other CV risk factors than total PA (Rizzo *et al.*, 2007) but body fat appeared to have an important mediating role in this relationship (Rizzo *et al.*, 2007). This study reported stronger associations in 15 year olds than 9 year olds and therefore age may have a potential effect upon the inter-relationships between CV disease risk factors. The authors concluded that further studies are needed for a more conclusive statement on the independent effect of PA on younger children's CV risk factor profile and thus provides some of the rationale for the studies in this thesis.

3.3.3 Intervention studies

Research has shown that adult health and PA are associated with childhood PA and health (Blair, 1989). With the increasing prevalence of obesity in today's children the importance of maintaining both childhood PA levels and CR fitness is clear. This has led to a number of intervention studies in children whose aim was to alter PA and CR fitness and determine any effect on CV disease risk factors (Carrel *et al.*, 2005; Gutin *et al.*, 2008). One intervention study conducted by Gutin and colleagues (2008) on children aged 8 found that an after school programme consisting of a 5 day week educational and aerobic classes focusing on MVPA resulted in a beneficial effect of CR fitness and body composition, although there were significant seasonal effects in that during summer months (i.e. no intervention) CR fitness and body composition was similar to the control participants. Similarly, a 9-month school-based fitness programme for fifty overweight children was developed aiming to improve body composition, CR fitness and insulin sensitivity in children aged 11-12 (Carrel *et al.*, 2005). Compared to controls the treatment group demonstrated a significantly greater loss of body fat, greater increase in CR fitness and a greater improvement in fasting insulin levels. With this in mind incorporating such interventions into children's lifestyles particularly that of overweight and obese could have beneficial effects on their CV health. Again there is a clear need to add to the available literature in this area with a specific emphasis on younger children.

3.4 Obesity and its origins in childhood; current trends and technical measurement issues

The accumulation of excessive body fat, over some specifically defined limit, is referred to as obesity (Eckel *et al.*, 2004). Although the aetiology of obesity remains uncertain, it is fundamentally a result of chronic energy imbalance whereby energy consumption exceeds energy expenditure. Obesity is associated with adverse health conditions and is widely recognised as an independent risk factor for CV disease (Poirier and Eckel, 2002) and with current obesity trends in adults rising to epidemic proportions (Eckel *et al.*, 2004; Lobstein *et al.*, 2004; World Health Organisation, 2000) the implications for short and long-term healthcare are enormous. More ominously the increase in the prevalence of obesity in children is threatening an increase in associated chronic diseases such as diabetes in younger generations (Harrell *et al.*, 2003; Invitti *et al.*, 2006). Strong associations have been reported between childhood obesity and adult health (Clarke and Lauer., 1993; Serdula *et al.*, 1993). Data for BMI reported at 9 years has been found to be significantly correlated with BMI at age 50 (Wright *et al.*, 2001), also this study did suggest that being thin in childhood did not necessarily offer protection against adult fatness and therefore other risk factors need also be considered.

Obesity is not only associated with numerous co-morbidities like diabetes, certain cancers, hypertension and hyperlipidemia but it also affects heart structure and function. Adipose tissue has reduced blood flow in comparison with skeletal (lean) tissue and therefore requires a larger vascular bed (Lesser and Deutsch, 1967) to provide enough oxygen and nutrients over the enlarged mass. This, in

part, results in an increment in total blood volume and cardiac output in order to meet the demands of the increased metabolism due to the excess body weight (Alpert, 2001), this is despite fat deposits being "classically" referred to as inert or non-metabolic. Thus at any given activity level, the cardiac workload is greater in obese subjects, which ultimately has implications on both cardiac structure and function (e.g. alterations in blood pressures, diastolic filling parameters).

Assessment of body composition allows the distinction of fat and fat-free mass or lean mass. Fat mass includes all body fat essential and non-essential both visceral and subcutaneous. Confusion can often be made when it comes to fat free mass and lean mass. Fat free mass is the remainder of mass after all fat is removed including fat free muscle mass, fat free body and fat free adipose tissue whereas lean body mass is mineral free fat mass which includes muscle connective tissue and skin (Howes and Martin, 2001). These can be estimated using different methods such as accurate techniques including hydrostatic (underwater) weighing and dual energy x-ray absorptiometry (DEXA). Inexpensive mass screening methods which can be used in the field to estimate body composition include body mass, body mass index (BMI), various body girths and skinfold measures. These have both been found to correlate highly with DEXA in 11-17 year old children (Steinberger *et al,* 2005). Of specific interest is BMI whose use, particularly in children, has been criticised. It is seen as an inappropriate measure of obesity with children because it not only does not decipher between fat mass and FFM or lean body mass but also children have no fixed height as they are growing so changes over time may solely be a result of natural growth rather than adiposity gain or loss (Green and Cable, 2006). For these reasons where possible

laboratory based measures should be used at least in conjunction with simple measures such as BMI.

Hydrostatic weighing is often used as the criterion method to validate new body composition assessments. This works on the principle that body density is the ratio of body mass to body volume and hydrostatic weighing determines this volume, with a correction for pulmonary residual volume, and mass can also be assessed. Archimedes' principle which states when a body is immersed in water, it is buoyed by a counterforce equal to the weight of the water displaced. Thus when density of the water is correct for, the loss of weight in the water is equal to total body volume (ACSM, 2000). However this method is problematic particularly with children in that it assumes the composition of fat and FFM is constant for all individuals in which adults have been used for these calculations. Also practically young children struggle to perform this assessment due to the submersion of the whole body into the water.

A more popular, recently, and practical measure of body composition in children is DEXA. Whilst this is very expensive it appears to be practically superior with children as regional fat mass, lean body mass, and bone mineral density can all be assessed from one 3 minute scan (see general methods for further detail). However this again involves the need for specialist laboratory equipment and highly experienced personnel to conduct this analysis.

3.4.1 Impact of obesity on cardiovascular disease risk

Evidence of elevated/altered pre-clinical CV disease markers has been found in overweight and obese children. Enlarged LV masses (hypertrophy) appear to be closely related to greater central adiposity (Daniels *et al.*, 1999) as well as other variables associated with somatic growth such as body weight, fat free mass and height (Janz *et al.*, 2000). Reduced diastolic function has been found to be apparent in the more obese adults (Di Bello *et al.*, 2006) and children under 16 years of age (12-14 years) (Sharpe *et al.*, 2006). Some controversy exists over the strength of the relationship between obesity and carotid IMT in children (Tounian *et al.*, 2001; Sass *et al.*, 1998; Meyer *et al.*, 2006; Zhu *et al.*, 2005; Iannuzzi *et al.*, 2004; Woo *et al.*, 2004) although it is thought carotid IMT increases with increasing adiposity.

Few studies have documented the impact of variation in body composition, PA and CR fitness upon a combination of non-invasive pre-clinical CV disease "markers" in a representative sample of pre-pubescent children. This, specific rationale underpins study 1 of the thesis whereby pre-clinical CV risk markers were assessed in a heterogeneous population of Liverpool schoolchildren.

3.4.2 Interventions to decrease CV disease risk and obesity in children.

Physical activity (PA) interventions in adults have improved lipid profile, reduced blood pressure, decreased excess body weight (Mertens *et al.*, 1998) and have had a general protective effect for CV disease co-morbidities (Farrell *et al.*, 1998). Similarly in children this traditional CV risk factor profile has been found to improve through the implementation of exercise interventions (Andersen *et al.*,

2006). However, the implementation of effective strategies for the prevention and treatment of obesity remains uncertain and controversial. In children obesity is considered to be a result of decreasing physical activity levels and not increasing food consumption (Prentice and Jebb, 1995). Therefore studies should prioritise PA interventions to increase metabolic activity. However, uncertainty arises as to the type of exercise intervention that should be implemented.

Taylor *et al.* (2005) implemented a twice weekly, eight-week exercise and education programme in overweight 10-year-old children. These sessions consisted of aerobic and strengthening work coupled with informative talks on nutritional information, risk factors for obesity and motivation. They reported a significant improvement in BMI, waist and hip girth, blood pressure, resting heart rate (HR) and recovery HR after exercise training. Although no control group was used this short intervention appeared to be beneficial to the children. McMurray and colleagues (2002) conducted a similar 8-week study with 1140 youths aged 11 to 14. They were randomly assigned to one of 4 groups; exercise only, education only, exercise and education combined or a control group. The exercise group received an additional 30 minutes of aerobic exercise 3 days a week for 8 weeks during their regular PE class. The education session consisted of information on nutrition, smoking and exercise presented in 2 class periods a week over the 8 weeks. The combined group received both exercise and education whilst the control group received neither. Whilst the BMI's did not change significantly between the groups, less of an increase was seen in the sum of skinfolds in the exercise intervention groups than the education only or control. The control group were also reported to have significantly increased blood

pressures compared to other interventions. This evidence suggests that even without weight loss exercise may have an important role in modulating obesity and CV disease risk. Further it would appear from these studies that a "short" intervention might be of benefit to obese children although longer interventions have been recommended (Humphries *et al.*, 2002; Woo *et al.*, 2004). In reality longer interventions are often difficult to complete due to problems with adherence and large drop out rates are often reported (Jones *et al.*, 2005). Before progressing to a difficult and intensive longer-term intervention it is imperative to assess the logistical constraints and issues of a short exercise intervention as well as reporting the impact of such exercise upon pre-clinical CV disease markers. This partially provides the rationale for the second study in this thesis.

Interventions that adopt a lifestyle approach (i.e. focus on behavioural modification rather than structure exercise sessions) have also been considered in the previous literature. Merchant *et al.*, (2007) highlighted that the determinants of obesity in children maybe more complex than originally thought. They found that children in low socio-economic areas had poorer diets, led more sedentary lifestyles and the neighbourhood was perceived as being "less walkable". They concluded that interventions should address environmental factors as well as simply prescribing exercise to a standardised formula. Most lifestyle approaches have, thus, included applied education regarding behaviour modification, nutrition and physical training strategies and problem solving/coping skills as well as issues of travel and the environment. These have been found to be beneficial in terms of weight loss (Savoye *et al.*, 2007) in particular when used in combination with physical activity (Mitchell *et al.*, 2002). Further lifestyle interventions have

concentrated on weight loss maintenance in children and found when maintenance workshops are delivered focusing on either behavioural (e.g. change in PA activity levels) or social (e.g. associate with more active individuals) skills, then weight loss is maintained (Wilfley *et al.*, 2007). Furthermore Carrel *et al.*, (2007) administered life-style focused fitness gym orientated sessions compared to the control group that had standard gym sessions for 9 months. Compared to controls the treatment group demonstrated a significantly greater loss in body fat, greater increase in CR fitness and greater improvement in fasting insulin levels. Therefore supporting the need for a lifestyle focus. Thus the final component of the second study will be to assess different PA interventions in school children and their effect on pre-clinical markers of CV disease.

3.5 Early detection of cardiovascular risk in children; "Pre-clinical" markers

3.5.1 Left ventricular mass: PA, CR fitness and obesity interventions

Left ventricular (LV) mass is an estimate of the actual mass of the muscle surrounding the ventricle and may be related to overall cardiac size. It can be determined accurately through the use of non-invasive echocardiography (Figure 3.1) and it is said to be independently associated with CV disease (Levy *et al.*, 1990).

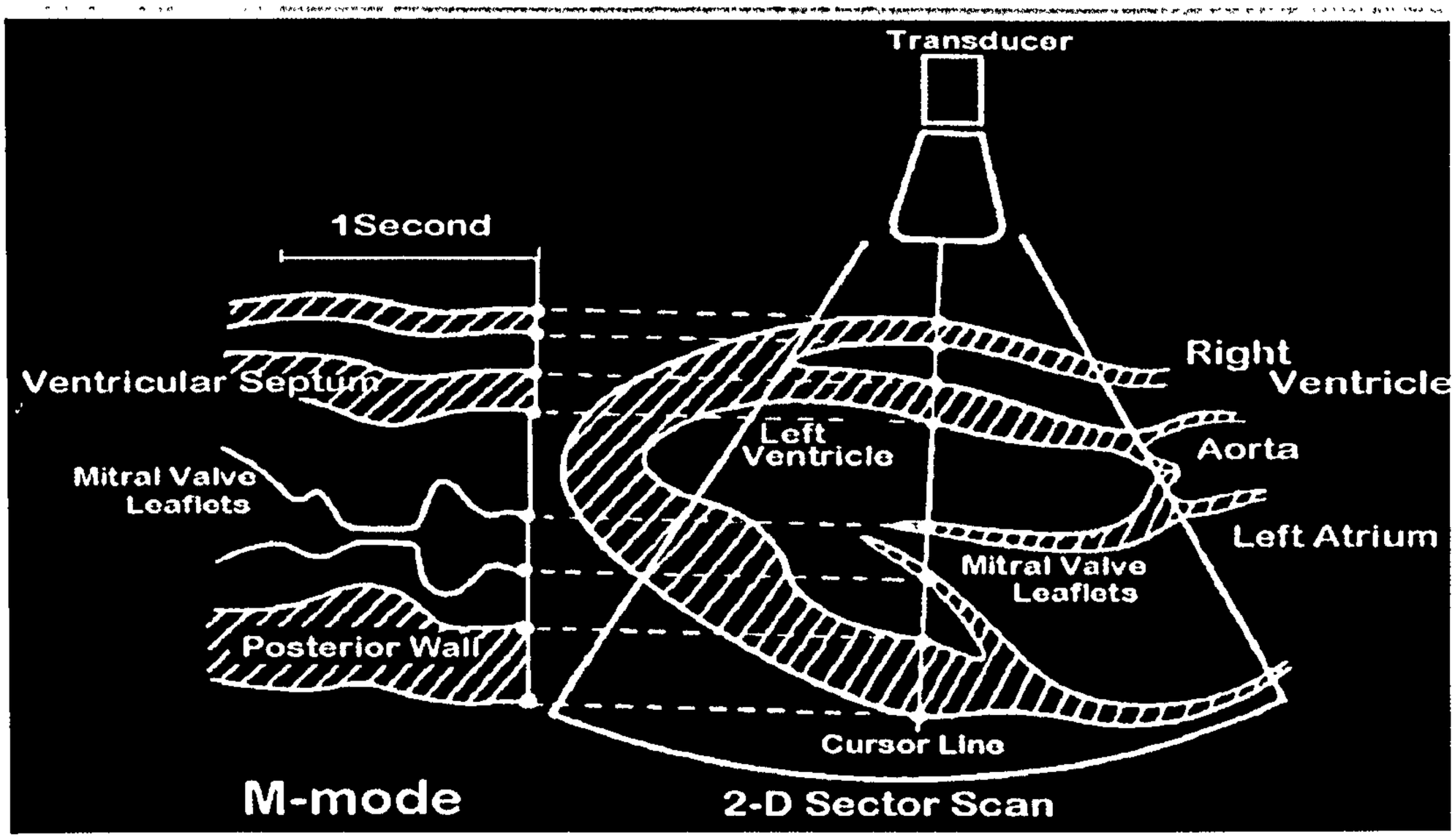

Figure 3.1 Image of the left ventricle as assessed through ultrasound.

Increased LV mass when indexed for height$^{2.7}$ has been found to be associated with increased risk of mortality in adults with or without CV disease (Liao *et al.*, 1997) due to its impact on tissue perfusion, electrical conduction and a potential to reduce cardiac function. LV mass has substantial prognostic importance in the development of heart disease. However, in some cases changes can be non-pathological as a consequence of age and physiological adaptations such as in response to exercise training (Fagard, 1997).

In healthy children and adolescences (10 to 16 years of age) excessive LV mass has been found in those with higher blood pressures and BMI's (Hanevold *et al.*, 2004; Sorof *et al.*, 2004; Sorof, 2001). In obese children (7-9 years) with high BP, LV mass has been found to be larger compared to normal weight individuals (Maggio *et al.*, 2008). Nevertheless this was reported in a small sample and increasing LV mass was positively associated with both FFM and fat mass which indicates the increases may be due to growth rather than adiposity. This was

supported by findings from Eisenmann *et al.*, (2007) who reported that whilst BMI was found to be a correlate of LV structure in 9 to 18 year old healthy subjects these associations became stronger with age. Daniels and colleagues (1995) conducted a study which aimed to separate the effects of lean body mass, fat mass and blood pressure on LV mass in normal children and adolescents. They reported that all three had a statistically significant independent association with LV mass whereas fat mass and BP appeared to have only a small impact. This suggests they are likely to be of only minor clinical importance in determining LV mass. This research also reported sexual maturation to have no significant association with LV mass independent of body size. They also suggested that fat distribution may be a more important CV risk factor than % fat in children and adolescents as greater deposition of central fat resulted in less favourable plasma lipid and lipoprotein concentration, blood pressure and LV mass.

Abnormal LV enlargement (hypertrophy) has been found to reduce through increasing PA levels and could possibly be mediated via a reduction in blood pressure (Bacon *et al.*, 2004). However, few studies have supported this as generally exercise interventions have found no changes in LV mass in children (Humphries *et al.*, 2002; George *et al.*, 2005) although this could reflect the short intervention periods employed.

3.5.2 Diastolic function: PA, CR fitness and obesity interventions

Diastolic function is an overall term used to describe the ability of the heart to maintain diastolic pressures during left ventricular filling and thus attain an

optimal LV end-diastolic volume (Feigenbaum *et al.*, 2005). If diastolic dysfunction occurs due to some disease process (e.g. myocardial infarction) and it is neglected heart failure could result (Feigenbaum *et al.*, 2005). Doppler left ventricular (or mitral) inflow velocities are commonly used to report and represent diastolic function as this reflects the fluid dynamics of the heart. Problems arise with this technique when atrial pressures increase to compensate for any changes in LV pressure decline during diastole resulting in a 'pseudo-normal' phenomenon (Khouri *et al.*, 2004) where early (E) and atrial (A) filling velocity ratios (E/A) remain normal in the presence of disease. Tissue Doppler imaging (TDI) of the mitral annulus allows further clarification of diastolic dysfunction through assessment of structural dynamics (myocardial velocities as opposed to flow velocities) during the cardiac cycle resulting in early (E') and atrial (A') tissue velocities. In pathological conditions, such as LV hypertrophy, the E/A ratio of the mitral valve may be higher than the E'/A' ratio of the mitral annulus and thus the E'/A' ratio is likely to be more important prognostically (Khouri *et al.*, 2004) and unmasks pseudo-normal filling patterns. Research with adults has supported the use of TDI in providing incremental predictive power for cardiac mortality and significant value to other more standard measures (Wang *et al.*, 2003).

Improvements in diastolic function have been seen in trained adults (Pela *et al.*, 2004) and children compared to sedentary counterparts (Nottin *et al.*, 2004). Nottin and colleagues (2004) observed 12 boy cyclists and 11 untrained age-matched (11-13 years) controls as well as trained and untrained adults. They found the trained boys, similar to the trained adults, had improved diastolic

function assessed by TDI as a result of increased LV relaxation properties. Sharpe *et al.,* (2006) assessed 28, <16 years of age, obese children and compared them with age and gender matched controls in Australia. Diastolic function assessed using both TDI and Doppler was significantly reduced in obese subjects compared to age and gender matched lean counterparts (E/A ratio [obese – 1.99± 0.08; lean – 2.13± 0.13] E'/A' ratio [obese - 2.05±0.09; lean – 2.49±0.17]). They concluded that obese children have impaired diastolic function and that further research is warranted in different population groups as well as the impact of structured exercise interventions. However it should be noted that this is a small study population.

Cross-sectional comparisons have been supplemented with a few training studies. Obert *et al.,* (2007) assessed the effects of a 2 month high intensity training protocol had on diastolic function in children aged 9 to 11 years. Twenty five children were controls whilst 25 took part in the intervention which consisted of running drills at 100 - 130% of the childs maximum aerobic capacity, for 25 to 30 minutes, 3 times a week for 2 months. Whilst VO_{2peak} was found to increase by 6.5% after training, both TDI and Doppler measures failed to improve with this training in these children. Despite the very high intensity activity used this was a small sample volume over a short intervention period.

To the authors knowledge very few studies have investigated the impact of PA interventions on diastolic function in obese children unlike normal weight children (George *et al.,* 2005; Obert *et al.,* 2007). Humphries and colleagues (2002) looked at obese 7–11 year olds and randomised them into either control or

exercise groups. The exercise intervention involved 40 minutes of aerobic activity with an average attendance of 80% on 4 days of the week for a 4-month period. They found although there were positive improvements in body composition no changes in diastolic function were found. However, it should be noted that the use of TDI was not employed and only Doppler measures of cardiac output were taken as a representation of function. A more in depth measure of analysis is therefore needed throughout this thesis.

3.5.3 Carotid intima-media thickness; PA, CR fitness and obesity interventions

Coronary atherosclerosis, although vitally important in CV diseases, is difficult to directly assess and therefore the progression of lesions on the vascular walls are difficult to monitor. An alternate approach has been developed to assess, non-invasively, an estimate of coronary artery atherosclerotic load by assessing the thickness of the arterial wall in the carotid arteries. The intima-media (IMT) complex is the distance between the lumen-intima and the media-adventitia (see Figure 3.2) and it can be monitored through ultrasound measurements in the carotid arteries. Carotid IMT has been found to be a valid measuring tool for assessing coronary atherosclerotic load and thus CV risk (de Groot *et al.*, 2004).

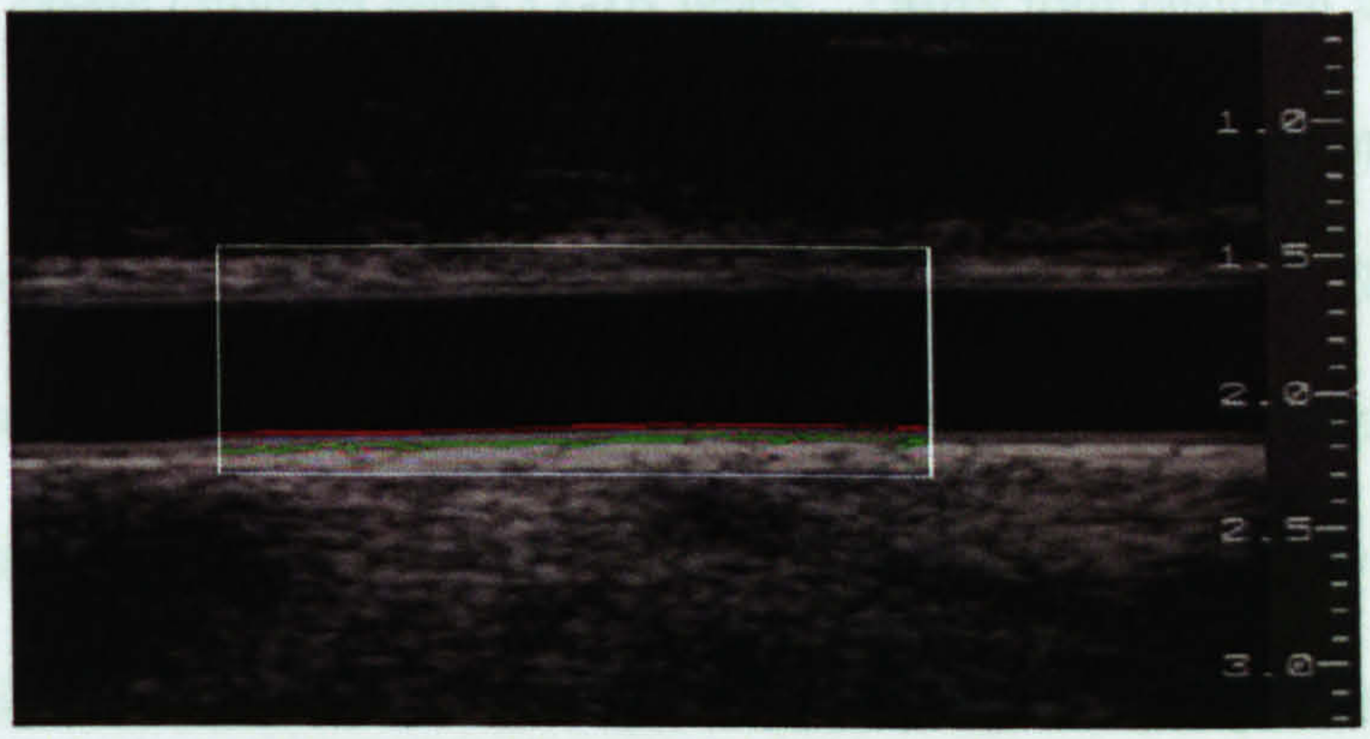

Figure 3.2 Lumen-intima (green) and the media-adventitia (red).

Carotid IMT has been found to be thickest at the carotid bulb and increases linearly with age, but most rapidly at the bulb (Stein *et al.*, 2004). Development of atherosclerosis begins in childhood as age-dependent physiological thickening has been found to appear on the arterial walls of children aged 5-14 years (Ishizu *et al.*, 2004). Additionally the cIMT of children is thought to be a good predictor of adult cIMT as it increases linearly with age (de Groot *et al.*, 2004; Stein et al 2004).

Significantly reduced carotid IMT has been reported as a result of exercise interventions in overweight children (Woo *et al.*, 2004). They observed 82 overweight children aged 9-12 years. Random allocation to dietary modification only or diet plus supervised exercise was given and after 1 year the combined diet and exercise group had significantly less carotid wall thickening than the diet alone group. There was, however, no control group to compare these groups therefore this could have been a normal result of growth for these children. A control group is important to show what a 'normal' population carotid IMT would have shown over this time period. This database suggests that exercise can modulate IMT and thus reduce CV disease risk. Similarly Meyer *et al.* (2006) observed 67 obese children aged 11-16 years. Thirty four children were assigned to control group and the remaining 33 completed an exercise training protocol of 3 times a week for 60-90 minutes a session in aerobic activities. They found at baseline obese children had a higher IMT than leaner subjects (0.47±0.06 compared to 0.37±0.05) and the exercise intervention improved IMT (by 0.04±0.08) in obese individuals compared to obese controls (0.02±0.06). What

remains unclear is the nature of the PA stimulus or length (volume) of intervention required to facilitate clinically significant changes in IMT compared to control subjects. Thus an intervention that recommends a desired PA intensity and time to implement these positive effects is therefore warranted for future prescription in children.

3.6 Summary

From the literature discussed it is clear further research is needed in the assessment of pre-clinical markers of CV disease in pre-pubescent children. Initially this will simply be to assess the impact of a wide heterogeneity in body size (and composition), cardiorespiratory fitness and PA on pre-clinical markers of CV disease. Once this has been established the impact of these predictor variables can be made apparent on pre-clinical CV disease risk. Secondly, the impact of different PA and lifestyle interventions upon pre-clinical markers of CV disease will be assessed, initially, with a short intervention to assess feasibility.

Study 1. A cross-sectional study to assess the relationship between a range of non-invasive, pre-clinical CV disease markers and parameters of body composition and physical fitness in a heterogeneous sample of primary school children.

Study 2. An exploratory 9-week trial to investigate the effects of structured exercise classes and a lifestyle intervention on pre-clinical CV disease risk markers in primary school children

Study 3. A 52-week intervention study investigating the effects of high intensity exercise classes, fundamental movement based exercise classes and a lifestyle intervention on pre-clinical CV risk markers, CR fitness and PA in primary school children.

Chapter 4

General Methods

This chapter discusses the common methods used throughout this thesis and any additional information, specific to a study, will be explained in the relevant chapter. All measures were carried out by fully trained individuals.

4.1 Preliminary information

Ethical approval for all studies was provided by the Exercise and Sports Science Department at Liverpool John Moores University. Schools within Merseyside were recruited via direct contact. Schools were selected based on school size (large i.e. >400 pupils if a primary school and >250 if only a junior school), availability of school sports facilities (accessible 2 nights per week), current after-school club provision (limited), and socioeconomic status of the area (deprived according to the index of multiple deprivation [Office of Deputy Prime Minister, 2004] a score >40). After fully informed agreement from Head Teachers children were informed about the project and asked to return signed parental consent and medical forms. Exclusion criteria included current use of prescription medication, any personal history of asthma/respiratory problems, heart or vascular complaints as well as an early family history of sudden death. Children also signed consent forms following an explanation of all procedures and were informed they could refrain from taking part in any of the procedures at any time.

4.2 Anthropometry, heart rate and blood pressure.

Standard anthropometrics including body mass (Seca Limited, Birmingham UK), stature (Leicester height measure, Birmingham UK) and body mass index (weight [kg]/height [m]^2) were recorded. Triplicate skinfold measurements where taken and then averaged from a number of sites along the right side of their body

including the tricep, bicep, subscapular, iliac, supraspinarly, abdominal, thigh and medial calf. Additionally triplicate girth measures were taken around the arm (relaxed and tense), waist, gluteals and calf at their largest circumference. Humerus and femur bone breaths were also recorded. All of these measurements were performed by a researcher fully qualified in ISAK (International Society for the Advancement of Kinanthropometry).

4.2.1. DEXA

Body composition was assessed using dual-energy x-ray absorptiometry (DEXA) (Lunar Hologic QDR, USA) in which the whole body was scanned. Participants were scanned in the supine position and wore lightweight clothing and no shoes. All scans were carried out by the same qualified researcher and were analysed after each assessment using Hologic QDR software for Windows version 11.2 (©1986-2001 Hologic Inc.). Key variables assessed were absolute (kg) fat mass (FM) and lean tissue mass (LM) and relative (%) percent body fat (%BF) data from the total body scan. Distribution of body fat mass and lean mass was also achieved through segmental analysis. All scans were completed in accordance with standard operating procedures.

4.2.2. Maturity

Maturation was assessed via a validated maturity offset calculation in which sitting height and stretched stature were used in these calculations to derive peak height velocity. The calculation used is;

Maturity offset = -9.236 + (0.0002708 * leg length and sitting height interaction) + (-0.001663 * age and leg length interaction) + (0.007216 * age and sitting height interaction) + (0.02292 * weight by height ratio)

(Calculation from Sherar *et al.*, 2005)

4.2.3 Heart rate and blood pressure

After 5 min of lying in the supine position, resting brachial artery systolic and diastolic blood pressures and heart rate (Bosch and Sohn, Germany) were assessed three times with the lowest score noted.

4.3 Echocardiography

Echocardiography uses ultrasound techniques to image 2D slices of the heart which provides real time structural images of the myocardium. Additionally it can provide an accurate assessment of velocity of blood and cardiac tissue through Doppler ultrasound allowing for functional assessment. A single trained ultrasound technician performed all ultrasound measurements. Two-dimensional/B-mode, M-mode, Doppler and tissue Doppler imaging (TDI) echocardiographic scans were performed using a portable ultrasound system (Mylab30CV system, ESAOTE, Italy). All system settings including gain, filter, PRF, sector size and depth were adjusted to optimise the image quality.

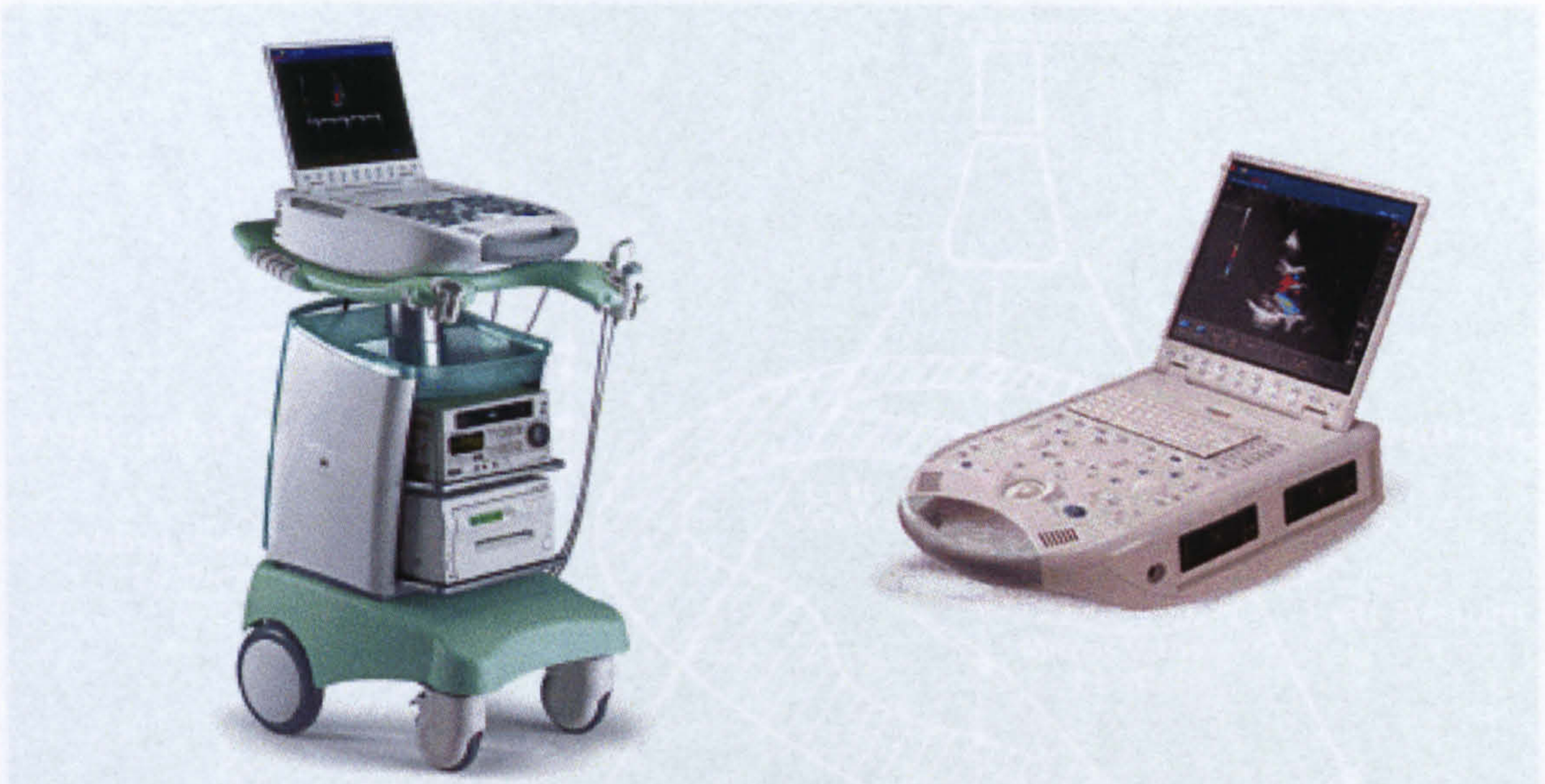

Figure 4.1 Echocardiograph used for scans. Images taken from;
http://www.medicalsearch.com.au/products/images/p21421_5.gif
http://www.us-tip.com/devgifs/mylab30cv.gif

4.3.1. Assessment and measurement procedures

Cardiac measurements;

With the participant in the left lateral decubitas position and following 10 minute of quiet rest, left ventricular structures and LV mass were assessed using parasternal long axis (see figure 4.2) images and M-mode scans at the level of the mitral valve with a 2.5 MHz phased array transducer. End-diastolic and end-systolic wall thickness and cavity dimensions were measured according to the American Society of Echocardiography (Lang *et al.*, 2006; Schiller *et al.*, 1989). Left ventricular mass was calculated according to a validated, regression-corrected formula (Devereux *et al.*, 1986).

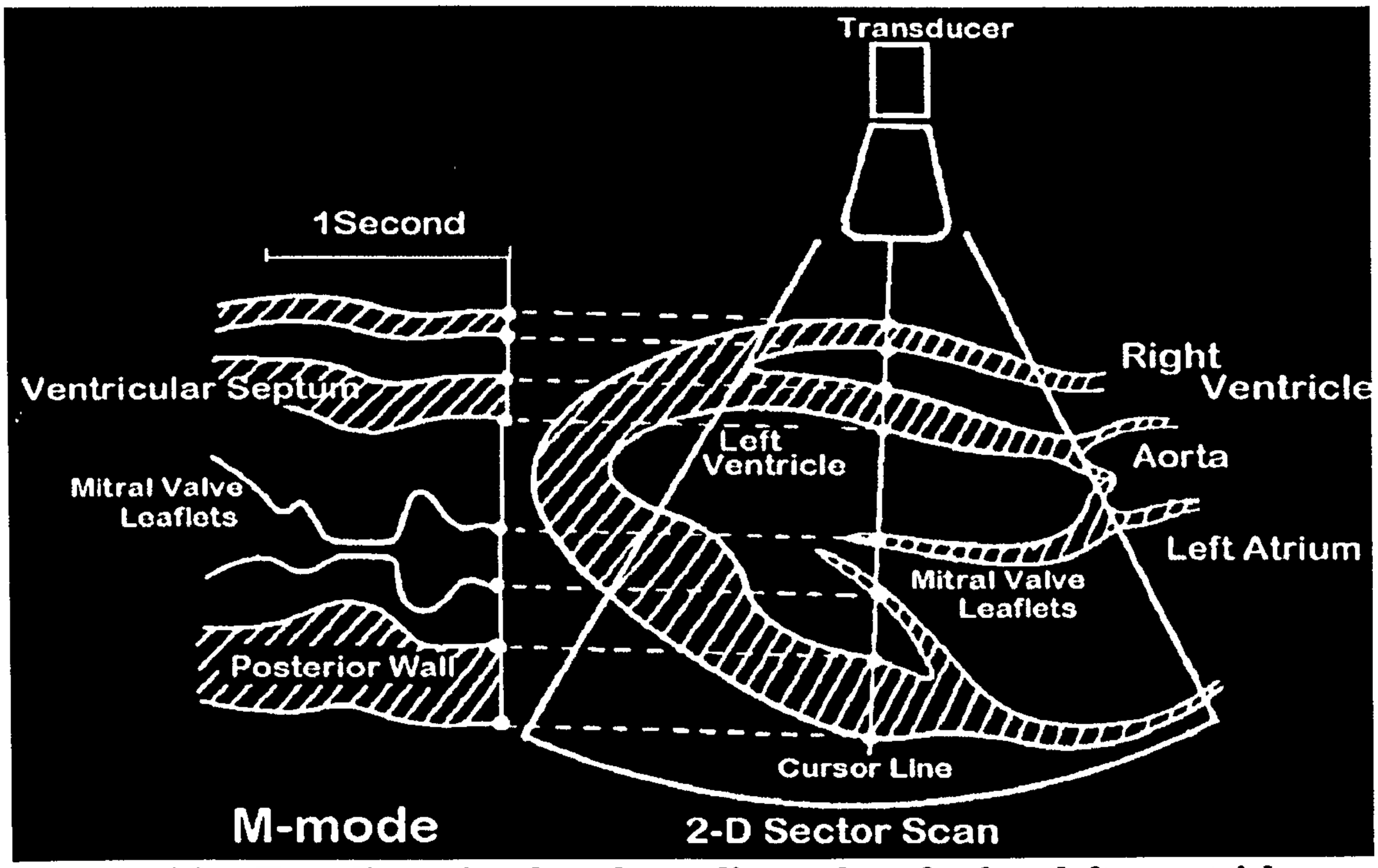

Figure 4.2. Two-dimensional echocardiograph of the left ventricle (parasternal view) with an M-mode trace at the level of the mitral valve.

LV mass was divided by height$^{2.7}$ (De Simone *et al.*, 2005 [included children]) to provide a size independent index of LV mass.

From the apical four-chamber view Doppler recordings were taken of mitral inflow by placing a 2 mm sample volume at the tips of the mitral leaflets and parallel with flow. Peak early (E) and late/atrial (A) flow velocities were obtained and E/A ratio reported. In the same view pulsed tissue Doppler (TDI) velocities were obtained from the septum at the mitral annulus using a 2 mm sample volume. Peak early diastolic (E') and late diastolic (A') myocardial tissue velocities were recorded and E'/A' ratio was derived.

Carotid intima-media thickness (IMT)

In the supine position participants were asked to position their head away from the side of interest and their neck slightly extended. Ten millimetre segments of the far wall of the common carotid artery (CCA) 1-2 cm proximal to the carotid bulb

were imaged with a 10-15 MHz linear transducer on both the left and right sides of the neck. Four images were taken bilaterally and analysed off-line (IMT.LAB version 1.1, Pie Medical Equipment, Netherlands). This software provided average mean and maximum values for carotid IMT via tracking the interfaces of the lumen-intima and media adventitia.

4.3.2. Error in assessment and measurement

As with any measurement tool there can be error in both the assessment and measurement procedure in echocardiography. It is important to not only recognise these but also limit their possible effect on variables. These will be discussed.

Transducer selection; High frequency transducers produce better resolution but lack in penetration. In cardiac anatomy most of the relevant structures lie within 2-16cm from the transducer. Therefore a transducer frequency of 2.5 - 4 MHz was chosen to allow for good resolution to such depths. Previous studies which have looked at cardiac structure and function in children have used a similar transducer (George *et al.*, 2005). For assessment of cIMT a 10-15 MHz linear array transducer was used as less penetration was needed.

Display size; the display size was adjusted accordingly for each individual so that the structures of interest filled a large proportion of the screen. Width of the 2D sector was also adjusted to allow greater resolution without loss of structure visibility.

Doppler Alignment; accurate assessment of Doppler and TDI velocity are taken when blood flow is parallel to the acoustic beam axis. Every effort was made to attain this through transducer movement.

Formulas; Whilst some structures are measured directly from the echocardiograph image other data such as LV mass and ejection fraction, are calculated from formally validated mathematical calculations (Devereux *et al.*, 1986). However, all of these calculations are based on some assumptions or approximations hence small errors may occur.

Operator variability; The largest potential source of variation is that of the sonographers skill and experience. The ability to not only generate the clearest and most appropriate image but also to be able to interpret those images in not an easy task. In this case to reduce the chance of error the same sonographer was used throughout the data collection and analysis process. For a cohort of n = 30 scans were taken three times and analysed separately without knowledge of previous scores. From this repeated measures ANOVA and ICC for systematic and random error were calculated. These were as follows; LVM f = 1.895 ($p=0.159$) ICC = 0.862 ($p<0.005$); E/A f = 0.710 ($p=0.496$) ICC = 0.731 ($p<0.005$); TDI f = 0.016 ($p=0.984$) ICC = 0.794 ($p<0.005$); and cIMT f = 2.323 ($p=0.107$) ICC = 0.555 ($p<0.005$).

Chapter 5

Study 1 - The association of "pre-clinical" cardiovascular disease risk factors with body composition, physical activity and cardiorespiratory fitness in primary school children (The A-CLASS project).

5.1 Introduction

Cardiovascular (CV) diseases are the most frequent "killer" within the UK, accounting for over 216,000 deaths in 2004 (Office of National Statistics, 2005). Although CV disease is deemed an adulthood malady the atherosclerotic process begins in childhood (McGill *et al.*, 2000) and is provoked by a range of risk factors that include obesity, physical inactivity and low cardiorespiratory fitness (Sharpe *et al.*, 2006; Rizzo *et al.*, 2007).

Obesity or excess body weight, are widely recognised as an independent risk factor for CV disease (Poirier and Eckel, 2002). Current trends demonstrate a rapid increase in the prevalence of obesity (Eckel *et al.*, 2004; World Health Organisation, 2000). More ominously the recent progression in rates of obesity in children substantially increases the future risk of chronic "lifestyle" diseases that may develop earlier, persist longer and place a tremendous burden on health care provision (Harrell *et al.*, 2003; Invitti *et al.*, 2006). Furthermore this increase in body fat is having a negative effect on physical activity and relative cardiorespiratory fitness (Rowland, 2007) with recent data demonstrating a global decrease in paediatric physical activity and cardiorespiratory fitness (Tomkinson and Olds, 2007; Sproston and Primatesta, 2003; Nelson, *et* al., 2006).

Traditional risk factors or markers that are associated with the coronary atherosclerosis such as hypertension and hyperlipidemia normally manifest themselves in adulthood, although there is some recent evidence that they are becoming more prevalent even within the younger generation (Steinberger *et al.*, 2001; Gutin *et al.*, 1994). The existence of early or "pre-clinical" markers of

future CV disease risk or current "atherosclerotic load" in children, especially those who are obese, physically inactive or have low cardiorespiratory fitness, is of increasing interest. Earlier assessment of future CV disease risk could instigate prompt interventions aimed at reducing individual morbidity, increasing quality of life and reducing the lifelong personal and economic impact of CV disease.

Recent advances in non-invasive techniques such as ultrasonography have been extremely useful in the assessment of "pre-clinical" changes in CV structure and/or function such as left ventricular [LV] mass, diastolic function, and carotid intima-media thickness [IMT]; Daniels *et al.*, 1999; Sorof *et al.*, 2003; Freedman *et al.*, 2004; Meyer *et al.*, 2006; Sharpe *et al.*, 2006).

Indeed increased IMT, LV mass and a reduction in LV diastolic function have been reported in overweight and obese children of different ages (Sharpe *et al.*, 2006; Zhu *et al.*, 2005; Iannuzzi *et al.*, 2004; Janz *et al.*, 2000; Daniels *et al.*, 1999). However to date there have been few studies in prepubescent children to document the impact of overweight/obesity, physical inactivity and/or low cardiorespiratory fitness upon a combination of pre-clinical markers of CV disease. Our primary hypothesis is that "pre-clinical" markers of CV disease are associated with variance in body composition, physical activity and cardiorespiratory fitness in normal, healthy primary schoolchildren.

5.2 Methods

5.2.1 Participants

After local ethical approval, nine schools within Merseyside agreed to participate in the study. Full agreement from Head Teachers was obtained and all year 5 and 6 children (age 9-11 years) were informed about the project and asked to return signed parental consent and medical forms. Exclusion criteria included current use of prescription medication, any personal history of asthma/respiratory problems, heart or vascular complaints as well as an early family history of sudden death. Two hundred and eighteen children (129 female and 89 male) with an age range of 9 – 11 (mean ± SD age 10.1 ± 0.7 years) met inclusion criteria, provided written and parental consent and went on to complete the study. Children's maturity was assessed using a validated maturity offset calculation (Sherar *et al.*, 2005). This is a non-intrusive method for estimating a child's biological maturity by assessing their rate of somatic growth using stretched stature and sitting height. All children were found to be pre-peak height velocity.

5.2.2 Design

This was a cross-sectional cohort study in which participants were required to attend Liverpool John Moores University on one occasion. All measurements, except assessment of physical activity, were made at this visit after full details had been provided of all assessments. Physical activity assessments were made over 7 days and included visits to school by research staff to apply, check and collect accelerometers.

5.2.3 Protocols

Cardiovascular and body composition measures were taken as discussed in ***General Methods***

Physical Activity

A sub-sample of children (150) were assessed using a uni-axial accelerometer; MTI Actigraph (MTI Health Services, Florida) for their PA. Accelerometers were fitted to the right hip of each child during school time and set at a 5 second epoch. Children were asked to wear the accelerometer (whilst awake) for 7 consecutive days. For this study the "wear-time" inclusion criteria were a minimum of any 3 days for minimum of 9 hours a day. Assessment of total moderate to vigorous PA (MVPA) was provided by total time spent in PA above a velocity of 4 $km.hr^{-1}$ (Treuth *et al.*, 2004). For each child this was individually calibrated from their CR fitness treadmill data.

Cardiorespiratory Fitness

After appropriate familiarisation cardiorespiratory fitness (VO_{2peak}) was assessed with a discontinuous graded treadmill protocol (adapted from Armstrong, 2002) using a motorised treadmill. The treadmill was set at a 1% increment and the initial pace was freely chosen as a comfortable walking speed. At 3-minute intervals participants were given a 30 s rest period in which the speed was increased by 2 $km{\cdot}hour^{-1}$. This continued until volitional exhaustion. The Oxycon Pro (Jaeger, Hoechberg, Germany) was used to record respiratory data breath by breath (VE, VO_2, VCO_2, RER) after standard calibration prior to each test. A heart rate monitor (Polar Electro, Kempele, Finland) was fitted to the child's chest

before the test started. Criteria for attaining VO_{2peak} were a heart rate above 200 beats·min^{-1} and/or RER above 1.05.

5.2.4 Statistical analysis

Descriptive data included the generation of mean ± SD and range for all variables assessed. Initially descriptive analysis recorded the frequency of children who were classified as obese, overweight or normal/underweight according to Chinn and Rona (2004). Classification of PA was performed by recording the frequency of children who did (or did not) meet the 60 min-day criteria (Biddle *et al.*, 1998), those who recorded 60-90 min PA per day and those who performed > 90 min PA per day. Cardiorespiratory scores were categorised according the gender specific criteria of Ruiz *et al.*, (2004) who suggested a VO_{2peak} of above 37.0 ml.kg.$^{-1}$.min^{-1} for girls and above 42.1 ml.kg.$^{-1}$.min^{-1} for boys representing those with a low risk of CV disease. Both BMI and waist circumference were removed statistical analysis due to co-linearity issues with fat mass and lean mass. The inter-relationships between FM, LM, PA and cardiorespiratory fitness were assessed via bivariate linear correlation. Initial analysis of the relationships between pre-clinical markers of CV disease (LV mass, LV mass index, E/A, E'/A', max cIMT, mean cIMT) and body composition (FM, LM), physical activity (average time per day spent in MVPA over 4 km.hr^{-1}), cardiorespiratory fitness (VO_{2peak}) and blood pressures were performed via bivariate linear correlation tests. Subsequently forced entry multiple regression analysis was used to establish relationships between combinations of significantly associated variables. All analyses were carried out on SPSS statistical package 14.0 (SPSS Inc., Chicago, USA).

5.3 Results

Anthropometric and cardiovascular data is presented in Table 5.1. Of the 218 participants a DEXA scan was not performed on three children as requested by their parents. Eighteen children did not partake in the treadmill assessment of VO_{2peak} or there were problems with data collection. Three of the LV and five of the cIMT scans could not be analysed due to the poor quality of images. Of the 150 participants who were asked to wear the accelerometers 145 (girls = 87, boys = 58) children met the "wear-time" criteria of any 3 days.

Table 5.1. Anthropometric and physical activity data

	N	Mean	SD	Range
Age	218	10.1	0.7	9.1 - 11.5
LV mass (g)	215	114	30	46 - 227
LV mass indexed ($g \cdot m^{-2.70}$)	215	46.2	9.9	21.6 – 82.0
E:A ($cm \cdot s^{-1}$)	218	2.06	0.44	1.32 – 3.51
E'/A' ($cm \cdot s^{-1}$)	218	2.52	0.62	1.14 – 4.73
cIMT mean (mm)	212	0.440	0.057	0.269 – 0.563
cIMT max (mm)	212	0.455	0.057	0.279 – 0.576
Stature (m)	218	1.41	0.08	1.20 – 1.65
Mass (kg)	218	38.4	9.0	21.9 – 78.8
BMI (kg/m^2)	218	19.1	3.2	12.7 – 31.9
Waist Circumference (cm)	149	62.9	7.3	49.2 – 89.5
Fat mass (g)	215	10930	4936	3370 – 31997
Lean body mass (g)	215	26801	4989	16616 – 45264
% Fat mass	215	27.1	6.6	13.1 – 44.7
PA average time per day in MVPA (min) (above $4km.hr^{-1}$)	145	81.3	27.7	26.2 – 153.6
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	200	47.5	9.9	18.1 – 71.8
Heart Rate ($beats \cdot min^{-1}$)	218	72	10	49 - 106
Systolic BP (mmHg)	218	111	11	81 – 145
Diastolic BP (mmHg)	218	66	5	52 - 85

In the entire cohort 27 children (12.4%: girls=9, boys=18) were classified as obese, 65 (29.8%; girls=36, boys=29] were overweight and 126 (57.8%; girls=85, boys=41) were normal or underweight according to Chinn and Rona (2004) cut-off points. For PA data; 43 (30%; 26 girls and 17 boys) averaged less then 60 min per day, 51 (35%; 37 girls and 14 boys) performed between 60 and 90 min per day and 51 (35%; 24 girls and 27 boys) had a mean daily PA over 90 min. For cardiorespiratory fitness; 161 children (80.5%; 98 girls and 63 boys) exceeded the criteria proposed for VO_{2peak} (Ruiz *et al.*, 2007). Table 5.2 contains the inter-relationship results of the bivariate correlations between FM, LM, PA and cardiorespiratory fitness. With increasing FM, cardiorespiratory fitness decreased ($p<0.005$) as did time spent in MVPA ($p=0.028$). Cardiorespiratory fitness also showed a negative correlation with BP ($p<0.05$). No other correlations were found with PA.

Table 5.3 contains the results of the bivariate correlations between predictor and CV outcome variables. Both LV mass and LV mass index were significantly correlated with all predictor variables of body composition and cardiorespiratory fitness ($p<0.005$, Table 2). Regression analysis demonstrated that LM, FM, sex and MVPA accounted for 59% of variance in LV mass (~21g). LM appeared to have the greatest influence ($t = 6.556$, $p< 0.005$) explaining 49% of the variance. For LV mass index these variables explained only 28% of the variance with FM appearing to be most influential ($t = 2.484$, $p = 0.014$, *21% of the variance*).

Table 5.2. Correlation analysis of the inter-relationship between BMI, PA and cardiorespiratory fitness.

		Fat mass (g)	Lean mass (g)	% Fat mass	VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	Systolic BP (mmHg)	Diastolic BP (mmHg)	MVPA (min/day)
Fat mass (g)	*r*		0.649	0.878	-0.407	0.336	0.237	-0.185
	p		*0.000**	*0.000**	*0.000**	*0.000**	*0.000**	*0.028**
Lean mass (g)	*r*			0.265	-0.313	0.502	0.309	-0.029
	p			*0.000**	*0.000**	*0.000**	*0.000**	*0.735*
% Fat mass	*r*				-0.359	0.117	0.118	-0.227
	p				*0.000**	*0.088*	*0.083*	*0.007**
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	*r*					-0.206	-0.154	0.040
	p					*0.003**	*0.029**	*0.642*
Systolic BP (mmHg)	*r*						0.584	-0.008
	p						*0.000**	*0.923*
Diastolic BP (mmHg)	*r*							-0.072
	p							*0.390*

Table 5.3. The association between pre-clinical CV disease risk factors and anthropometric, cardiorespiratory fitness, physical activity and blood pressure data

Outcome variables		Fat mass (g)	Lean mass (g)	% Fat mass	VO_{2peak} (ml·kg^{-1}·min^{-1})	Systolic BP (mmHg)	Diastolic BP (mmHg)	MVPA (min/day)
LV mass (g)								
	r	0.576	0.736	0.318	-0.218	0.407	0.273	0.069
	p	*0.000**	*0.000**	*0.000**	*0.002**	*0.000**	*0.000**	*0.408*
LV mass indexed (g/m²)								
	r	0.384	0.333	0.289	-0.051	0.195	0.132	0.118
	p	*0.000**	*0.000**	*0.000**	*0.480*	*0.004**	*0.054*	*0.159*
E:A (cm/s)								
	r	-0.036	0.079	-0.105	0.024	-0.087	-0.147	0.092
	p	*0.601*	*0.251*	*0.123*	*0.732*	*0.200*	*0.030**	*0.273*
E'/A' (cm/s)								
	r	-0.137	-0.010	-0.159	0.013	-0.133	-0.245	0.031
	p	*0.045**	*0.890*	*0.020**	*0.851*	*0.050**	*0.000**	*0.715*
cIMT mean (mm)								
	r	-0.153	-0.205	-0.116	0.389	-0.121	-0.015	0.031
	p	*0.270*	*0.003**	*0.095*	*0.000**	*0.078*	*0.828*	*0.716*
cIMT max (mm)								
	r	-0.148	-0.191	-0.118	0.379	-0.116	-0.008	0.036
	p	*0.032**	*0.006**	*0.089*	*0.000**	*0.092*	*0.907*	*0.677*

E/A was significantly and negatively correlated with diastolic BP. E'/A' was significantly and negatively correlated with FM, % FM, systolic and diastolic blood pressure. All correlations were low (<0.25) and thus in the regression analysis; sex, systolic blood pressure, LM, FM and MVPA explained only 7% of the variance in E:A with SBP (*t = -2.723, p = 0.007, 23% of the variance*) being the only significant predictor. Similarly for E'/A' only a small percentage (9%) of the variance was explained by sex, systolic blood pressure, diastolic blood pressure, LM and FM. Only diastolic blood pressure (*t = -3.027, p = 0.003, 21% variance*), FM (*t = -2.366, p = 0.019, 16%*) and LM (*t = 2.195, p = 0.029, 15%*) were significant predictors.

Mean cIMT was significantly and negatively correlated with LM but positively correlated with cardiorespiratory fitness. Max cIMT was associated in a similar fashion with these predictor variables and further correlated negatively with FM. Again correlation coefficients were generally low. Regression analysis reported VO_{2peak}, sex, LM and FM to account for 19% of the variance in mean cIMT, with VO_2 (*t = 4.466, p = 0.00, 31%*), LM (*t = -2.695, p = 0.008, 19%*), sex (*t = 2.201, p = 0.029, 15%*) and FM (*t = 1.974, p = 0.050, 14%*) being significant predictors. Similarly these variables explained 16% of the variance in max cIMT with VO_{2peak} a significant predictor (*t = 4.422, p = 0.000, 31%*) and LM (*t = -2.336, p = 0.021, 17%*). Of interest, measures of PA were not significantly associated with any of the cardiovascular outcome variables (Table 5.3).

5.4 Discussion

In a large cohort of pre-pubescent primary schoolchildren, heterogeneous for body composition, PA and cardiorespiratory fitness, LV mass was significantly related to body composition and cardiorespiratory fitness variables. These variables explained >50% of the variance in LV mass. Indices of left ventricular diastolic function and cIMT were associated to only a small degree with parameters of body composition and cardiorespiratory fitness. No "pre-clinical" CV variable was related to measures of PA.

The association between LV mass and parameters of body composition and cardiorespiratory fitness have been reported before (de Simone *et al.*, 1995; Daniels *et al.*, 1999). Many studies of children, adults and athletes have demonstrated a strong relationship between LM and LV mass (Batterham *et al.*, 1999). Interestingly, it appears that both FM and LM are linearly and positively related to LV mass. This is likely due to the fact that as body mass increases there is a tendency for an increase in both FM and LM (Batterham and George, 1997). The impact of lean body mass maybe more important because it is the larger component of body composition in normal children and this agrees with past research (e.g. Batterham *et al.*, 1999). This suggests that the increase in LV mass associated with increasing FM in children may be simply a consequence of an increase in total body size. Interestingly when LV mass was indexed for body size (height$^{2.7}$) the influence of LM was not as strong as FM and MVPA. This suggests that adiposity could also have a small but significant impact on LV mass independent of body size in this cohort and as MVPA correlated with FM this could also have an indirect effect although this correlation was small. This therefore requires further substantiation. Cardiorespiratory fitness was

significantly related (r= -0.218) to LV mass. This may suggest a shared variance between VO_{2peak} and body size in prepubescent schoolchildren. This is supported by evidence that aerobic training studies do not result in an increase in LV mass in schoolchildren (e.g. George *et al.*, 2005).

Interestingly, and counter-intuitively, measures of cIMT and LV diastolic function were negatively related to indices of body composition but positively related to cardiorespiratory fitness. These relationships were, however, collectively small and likely of limited clinical significance. To support this, multiple regression analysis could predict only a very small percent of the shared variance between CV variables and the predictor variables. The effective interpretation of this data is that schoolchildren in this cohort who were obese/overweight, inactive and /or had low cardiorespiratory fitness were not at an obvious increased CV disease risk when employing these specific "pre-clinical" markers. This finding disagrees with Sharpe and colleagues (2006) who reported significantly reduced diastolic function in obese children compared to age matched normal weight children. It should be recognised however, that this smaller sample of children were older and likely peri- or post-pubertal. The current findings and comparison to other studies represents an important and potentially "positive" outcome. Specifically, despite poor cardiorespiratory fitness and excess adiposity in some 9-11 year old schoolchildren in the current cohort collectively there was no evidence of advanced or early risk of CV disease that is normally seen in adults (Diaz *et al.*, 2006) and occasionally other studies in children (Sharpe *et al.*, 2006; Rizzo *et al.*, 2007). This provides an interesting "window of opportunity" whereby CV health intervention programmes (that aim to reduce adiposity and/or increase cardiorespiratory fitness by changing

PA) could be implemented before a significant increase in CV disease risk that is often seen in adolescents or adults with obesity or low fitness (Borodulin *et al,* 2005; Hu *et al.,* 2004).

The amount of time spent in MVPA appeared to have little effect on cardiovascular variables unlike previously reported (Andersen *et al,* 2003; Leary *et al.,* 2008). This, however, may partially be explained by the nature of the PA assessment as well as the fact that different CV variables were assessed in the current study (no lipid data was collected). On a positive note most children (70%) did appear to be meeting the recommended daily requirements of 60 minutes per day in MVPA (Biddle *et al.,* 1998). No significant differences were reported between boys and girls, which is in contrast to previous research (Riddoch *et al.,* 2004). This may be a result of the younger age of the children in this study. The lack of inter-relationship between PA and cardiorespiratory fitness may be a product of the PA assessment. However as previously reported (Rizzo *et al.,* 2007; Hurtig-Wennlof *et al,* 2007) this study supports the idea that cardiorespiratory fitness may have more of an influence on CV health than PA as cardiorespiratory fitness was negatively correlated with FM and blood pressure. Nevertheless MVPA was negatively associated with FM albeit not strongly.

Some limitations of the current study are note-worthy to prompt on-going research. The current study reflects a cross-sectional design and thus cannot assess cause and effect relationships between changes or differences in body composition, cardiorespiratory fitness, physical activity and pre-clinical markers of CV disease risk. Longitudinal intervention programmes best resolve this issue and warrant

further investigation. Furthermore, research should be undertaken in other geographical locations with different nationalities in order to better understand diversity in different populations.

5.5 Conclusion

The data in the current study suggests that in a cohort of pre-pubescent primary schoolchildren in Liverpool, heterogeneous for body composition, PA and cardiorespiratory fitness there are few negative consequences for "pre-clinical" markers of CV disease. Thus there remains a "window of opportunity" to intervene by increasing PA and thus altering adiposity and cardiorespiratory fitness leading to a reduction in CV disease risk as these children progress into adolescence and adulthood.

Chapter 6

Study 2 - The effect of structured exercise classes and a lifestyle intervention on cardiovascular risk factors in primary school children: An exploratory trial (The A-CLASS project).

6.1 Introduction

A substantial body of scientific work promotes the importance of an active lifestyle in the prevention of CV diseases (Farrell *et al.*, 1998; Mertens *et al.*, 1998). This literature has recently extended to the role of physical activity in the amelioration of risk factors for CV disease in children (Invitti *et al.*, 2006; Harrell *et al.*, 2003; McGill *et al.*, 2000). Such interest has been prompted, partially, due to reports of increasing levels of childhood obesity and physical inactivity (Nelson, *et* al., 2006; Lobstein and Frulet, 2003; Sproston and Primatesta, 2003).

Signs and symptoms of clinical CV disease are rarely evident in children. However, early (pre-clinical) non-invasive indicators of CV disease such as an elevation of carotid intima media thickness (IMT), an increased left ventricular (LV) mass and/or a decrease in diastolic function have been utilised in recent research with children (Daniels *et al.*, 1999; Sorof *et al.*, 2003; Freedman *et al.*, 2004; Meyer *et al.*, 2006; Sharpe *et al.*, 2006; Sharpe *et al.*, 2006). Of further relevance to such risk factors is the fact that increased physical activity can have a positive impact upon carotid IMT (Woo *et al.*, 2004), abnormal LV mass (Bacon *et al.*, 2004) and diastolic function (Nottin *et al.*, 2004; Pela *et al.*, 2004). Due to the rarity of clinical vascular events in the young, carotid IMT may be especially relevant as a primary outcome variable for epidemiological and treatment studies in young population samples (Lorennz *et al.*, 2007).

Physical activity interventions to reduce CV disease risk in children have tended to involve traditional structured exercise prescription (Bacon *et al.*, 2004; Nottin *et al.*, 2004; Pela *et al.*, 2004; Woo *et al.*, 2004) and less attention has been paid to the

integration of physical activity into daily life through less structured/sports-specific exercise programmes (Floriani and Kennedy, 2007). Various theories and models to understand and change lifestyle behaviour have been proposed (Baranowski, *et al.*, 2003) and some recent interventions, based on behaviour change theories, have been studied in an attempt to decrease sedentary behaviour in children (Salmon *et al.*, 2005). The comparison of structured exercise interventions with lifestyle programmes upon CV risk factors in children has rarely been attempted.

The purpose of this study was, therefore, to assess the impact of a traditional exercise prescription and a lifestyle intervention programme upon early prognostic risk factors for CV disease in primary school children. Both groups were compared to a control group who received no formal physical activity intervention. The current study was defined as an *exploratory* randomized trial (Phase II), in accordance with the phased approach to the development and evaluation of interventions to improve health proposed by Campbell *et al.* (2000).

6.2 Methods

6.2.1 Participants

After local ethical approval, schools within Merseyside were recruited via direct contact. Eight schools were selected based on school size (large), availability of school sports facilities (accessible), current after-school club provision (limited), and socioeconomic status of the area (deprived). Three schools volunteered to participate. After fully informed agreement from Head Teachers all year 6 children (age 10-11 years (n=180) were informed about the project and asked to return signed parental consent and medical forms. Exclusion criteria included current use of prescription

medication, any personal history of asthma/respiratory problems, heart or vascular complaints as well as a family history of early sudden death. Sixty-one children (36 female and 25 male) 10 – 11 (11.0±0.3) years of age met these criteria, provided written and parental consent and went on to complete the study.

6.2.2 Design

Schools were randomly assigned to one of three groups, to mitigate potential contamination effects across arms of the trial. The three groups were a structured high intensity exercise programme (STEX), a lifestyle intervention group within a physical activity signposting scheme (PASS); or a control (CON) group. All laboratory data was collected at baseline and after 9 weeks (post intervention).

Physical activity signposting scheme (PASS)

Social cognitive theory (Bandura, 1986) and ecological theory (Sallis and Owen, 1999) were the basis for the PASS intervention. Nine weekly missions/tasks were sent by post to each child. Missions were derived using an intervention mapping approach to try to link the theories specifically to each task with the aim to increase habitual physical activity and decrease sedentary behaviour (e.g. to promote active transport and reduce TV viewing). In accordance with the social cognitive theory children were informed of the benefits of being active including the enhancement of confidence and skill level. Different environmental contexts were used including the home and local neighbourhood. In line with the ecological theory this aimed to help them understand their surroundings and how to become active within it, both on their own as well as with family and friends. Pedometers were used as a physical activity promotion tool in conjunction with the missions. Examples of some of the tasks

included a "switch off TV challenge" after 2 hours of viewing a day, increasing activity by monitoring active transport e.g. get off the bus a stop earlier, and take part in a new activity at least once a week with your family. Ninety-two percent of the children returned the mission in week one and all met the criteria of 75% return rate for the duration of the study.

Structured high intensity exercise programme (STEX)

Children attended twice-weekly hour long after school exercise sessions for 9 weeks. These consisted of multi activities such as circuits, dance and games. The aim of the session was to perform whole body muscular activity which was non-sports specific and to maintain heart rate above 70% of maximum heart rate (~145 beats.min^{-1}). This was verified by intermittent heart rate monitoring (Polar Electro, Kempele, Finland). All children met the criteria for attendance of at least 75% of STEX sessions.

Control (CON)

The CON group was asked to maintain their normal activity levels. They received the same pre-study information packs as the other two groups however no further physical activity information was given.

Ultrasound measurements and other outcome measures

As discussed in **general methods.**

6.2.3 Statistical analysis

Values were presented as mean ± SD. The carotid IMT was defined *a priori* as the primary outcome variable, with the other measured variables classed as secondary

outcomes. Analysis of covariance was conducted to evaluate the effectiveness of the 9-week interventions. The independent variable was the type of intervention (STEX, PASS and CON), with the dependent variable as the change score (post minus baseline). The baseline score served as the covariate to control for chance imbalances across groups at baseline (Vickers and Altman, 2001). Exploratory analyses indicated no substantial interactions with gender; therefore, boys and girls were merged into a single group for the primary analysis. An estimation approach was considered superior to a null hypothesis-testing framework (Curran-Everett *et al.*, 1998), presenting the mean effects of each intervention (versus control) on the primary outcome, together with 90% confidence intervals as suggested by Sterne and Smith (2001). In line with the recommendations of Perneger (1998), Bonferroni corrections of confidence intervals were not applied.

Adjusted mean intervention effects were evaluated for their clinical significance by pre-specifying the minimum clinically importance difference (MCID) (Batterham and Hopkins, 2006). In the absence of a robust clinical anchor, the MCID is defined conventionally using a distribution-based method as a Cohen's *d* (difference in the change scores between groups) of 0.2 between subject standard deviations (Cohen, 1988). The SD of the pooled baseline scores was used for this purpose, as the post-test SD may be inflated by individual differences in responses to the intervention. The MCID was interpreted as 'benefit' or 'harm' according to the direction of the effect on the intervention for a given variable. As a Phase II exploratory trial, the current study is not powered to precisely define changes as small as the MCID. However, the effects observed will provide important information to inform sample size estimations in any subsequent Phase III trial (Campbell *et al.*, 2000).

Using the mean intervention effect, together with its uncertainty, the probability (percent chances) that the true population effect was as least as large as the MCID was calculated (Batterham and Hopkins, 2006; Froehlich, 1999; Shakespeare *et al.*, 2001). Briefly, this process requires the calculation of a *t* statistic for the intervention effect. The conventional t statistic involves a test against the null hypothesis of zero effect (*t* = (mean difference between groups-zero)/ standard error of the difference). To calculate the probability of clinical benefit, the zero in this formula is replaced by the pre-specified value for the MCID: *t* = (mean difference between groups-MCID)/ standard error of the difference. With the correct degrees of freedom for the comparison, the area under the *t* distribution curve to the left of the |t| value returns the probability that the true population effect of the intervention is at least as large as the MCID. All analyses were carried out on SPSS statistical package 14.0 (SPSS Inc., Chicago, USA).

6.3 Results

Data for age, body size and composition is presented in Table 6.1. Between-group differences in variables at baseline were not substantial although there was a trend for a greater BMI, waist circumference, fat mass and percent body fat in the control group. After the 9-week intervention there were no clinically substantial differences in Δ scores between groups for all body size variables.

Data from cardiovascular primary and secondary outcomes are presented in Table 6.2. There were no clinically substantial intervention effects for any secondary variable. Figure 6.1 and 6.2 demonstrate the mean Δ scores (adjusted for baseline imbalance) for average mean and average maximum cIMT, respectively. The minimum clinically

important difference (MCID), defined as 0.2 between-subject standard deviations, was 0.008 mm for both average mean cIMT and average maximum cIMT. The effect of the STEX intervention (compared with CON) was a mean benefit of –0.018 mm for average maximum cIMT (90% CI, -0.039 to 0.002 mm), and -0.016 mm for average mean cIMT (90 % CI, –0.040 to 0.008 mm). The probability (% chances) that the effect of the STEX intervention was at least the MCID was 79% for average maximum and 71% for average mean carotid IMT (Figure 6.3). The PASS intervention did not result in clinically important effects.

Table 6.1. Anthropometrics data in all groups pre and post-intervention

		CON (n=30)		PASS (n=15)		STEX (n=16)	
		Mean value	(SD)	Mean value	(SD)	Mean value	(SD)
Age (yr)							
	Baseline	11.0	(0.3)	11.0	(0.3)	11.1	(0.3)
	Post test	11.2	(0.3)	11.2	(0.4)	11.3	(0.3)
	Δ	0.2	(0.3)	0.2	(0.3)	0.2	(0.3)
Body mass (kg)							
	Baseline	40.7	(7.6)	40.7	(8.9)	41.4	(10.7)
	Post test	44.8	(9.4)	42.4	(9.6)	42.9	(11.1)
	Δ	4.1	(7.4)	1.7	(8.4)	1.5	(10.6)
Stature (m)							
	Baseline	1.48	(0.09)	1.44	(0.07)	1.48	(0.07)
	Post test	1.49	(0.09)	1.46	(0.07)	1.50	(0.07)
	Δ	0.01	(0.09)	0.02	(0.07)	0.02	(0.07)
BMI (kg/m^2)							
	Baseline	19.8	(3.1)	19.3	(3.0)	18.7	(3.3)
	Post test	20.0	(3.1)	19.7	(3.3)	18.8	(3.3)
	Δ	0.2	(0.5)	0.4	(0.5)	0.1	(0.3)
Waist circumference (cm)							
	Baseline	69.6	(9.6)	68.0	(10.0)	65.6	(10.9)
	Post test	70.9	(10.8)	68.5	(9.5)	64.9	(10.9)
	Δ	1.3	(4.7)	0.5	(2.7)	-0.7	(-2.7)
Fat mass (g)							
	Baseline	12018	(5240)	10618	(4547)	11452	(6324)
	Post test	12667	(5431)	11394	(4831)	11819	(6687)
	Δ	649	(966)	776	(904)	368	(563)
Lean mass (g)							
	Baseline	30383	(5047)	29234	(5168)	29060	(4886)
	Post test	31265	(5136)	30226	(5628)	30307	(4995)
	Δ	882	(845)	992	(826)	1246	(796)
% Fat mass (%)							
	Baseline	26.7	(7.4)	25.1	(5.8)	26.2	(7.3)
	Post test	27.1	(7.1)	25.7	(5.9)	26.0	(7.6)
	Δ	0.4	(7.3)	0.6	(5.8)	-0.2	(7.6)

Table 6.2. Cardiovascular data in all groups pre and post-intervention

	Control group (n=30)		PASS (n=15)		Exercise (n=16)	
	Mean value	**(SD)**	**Mean value**	**(SD)**	**Mean value**	**(SD)**
Systolic BP (mmHg)						
Baseline	118	(12)	118	(13)	118	(7)
Post test	113	(12)	111	(9)	110	(10)
Δ	-5	(12)	-7	(12)	-8	(10)
Diastolic BP (mmHg)						
Baseline	67	(7)	68	(8)	68	(4)
Post test	62	(5)	61	(7)	62	(5)
Δ	-5	(6)	-7	(8)	-6	(6)
Resting heart rate (bpm)						
Baseline	73	(10)	75	(9)	74	(11)
Post test	70	(9)	73	(10)	71	(8)
Δ	-3	(9)	-2	(9)	-3	(9)
LV mass (g)						
Baseline	126	(26)	130	(34)	113	(24)
Post test	134	(30)	137	(41)	123	(39)
Δ	8	(21)	7	(23)	10	(23)
LV mass indexed (g/m²)						
Baseline	42.1	(10.5)	47.6	(9.6)	39.8	(6.8)
Post test	45.0	(7.0)	48.8	(12.4)	40.2	(7.9)
Δ	2.8	(10.7)	1.2	(8.1)	2.4	(7.9)
E/A ratio (m/s)						
Baseline	2.12	(0.52)	1.98	(0.45)	2.04	(0.47)
Post test	2.05	(0.50)	1.87	(0.41)	2.01	(0.55)
Δ	-0.07	(0.42)	-0.11	(0.31)	-0.03	(0.51)
E'/A' ratio (cm/s)						
Baseline	2.65	(0.70)	2.24	(0.57)	2.58	(0.67)
Post test	2.85	(0.60)	2.36	(0.50)	2.62	(0.67)
Δ	0.20	(0.64)	0.12	(0.53)	0.04	(0.51)
Average mean cIMT (mm)						
Baseline	0.389	(0.043)	0.409	(0.032)	0.423	(0.039)
Post test	0.400	(0.045)	0.405	(0.067)	0.402	(0.029)
Δ	0.011	(0.039)	-0.004	(0.061)	-0.021	(0.047)
Average max cIMT (mm)						
Baseline	0.405	(0.041)	0.425	(0.031)	0.440	(0.040)
Post test	0.419	(0.046)	0.437	(0.053)	0.423	(0.026)
Δ	0.015	(0.035)	0.011	(0.045)	-0.017	(0.043)

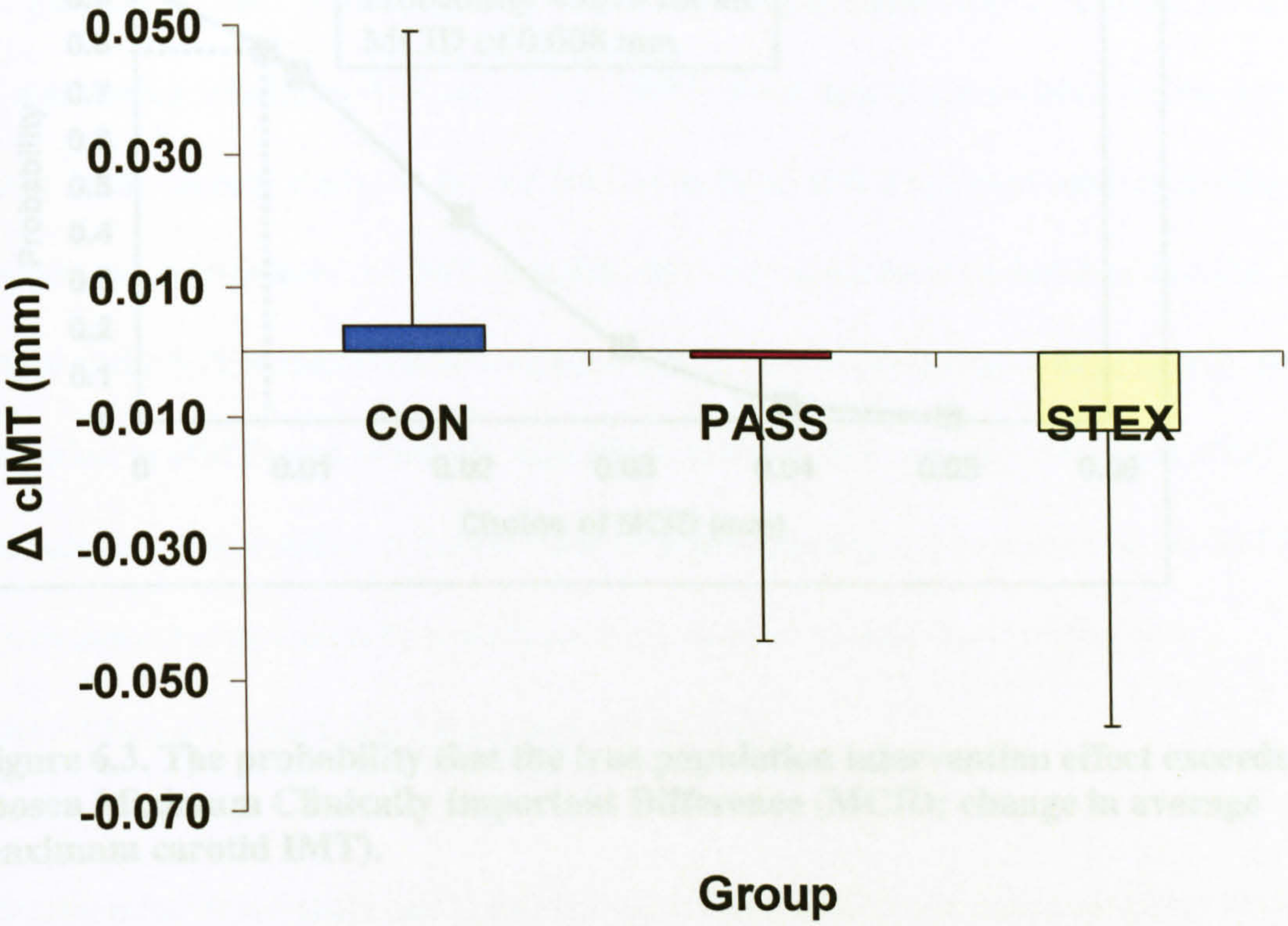

Figure 6.1. Δ scores for adjusted average mean carotid IMT over the 9-week intervention period in all groups.

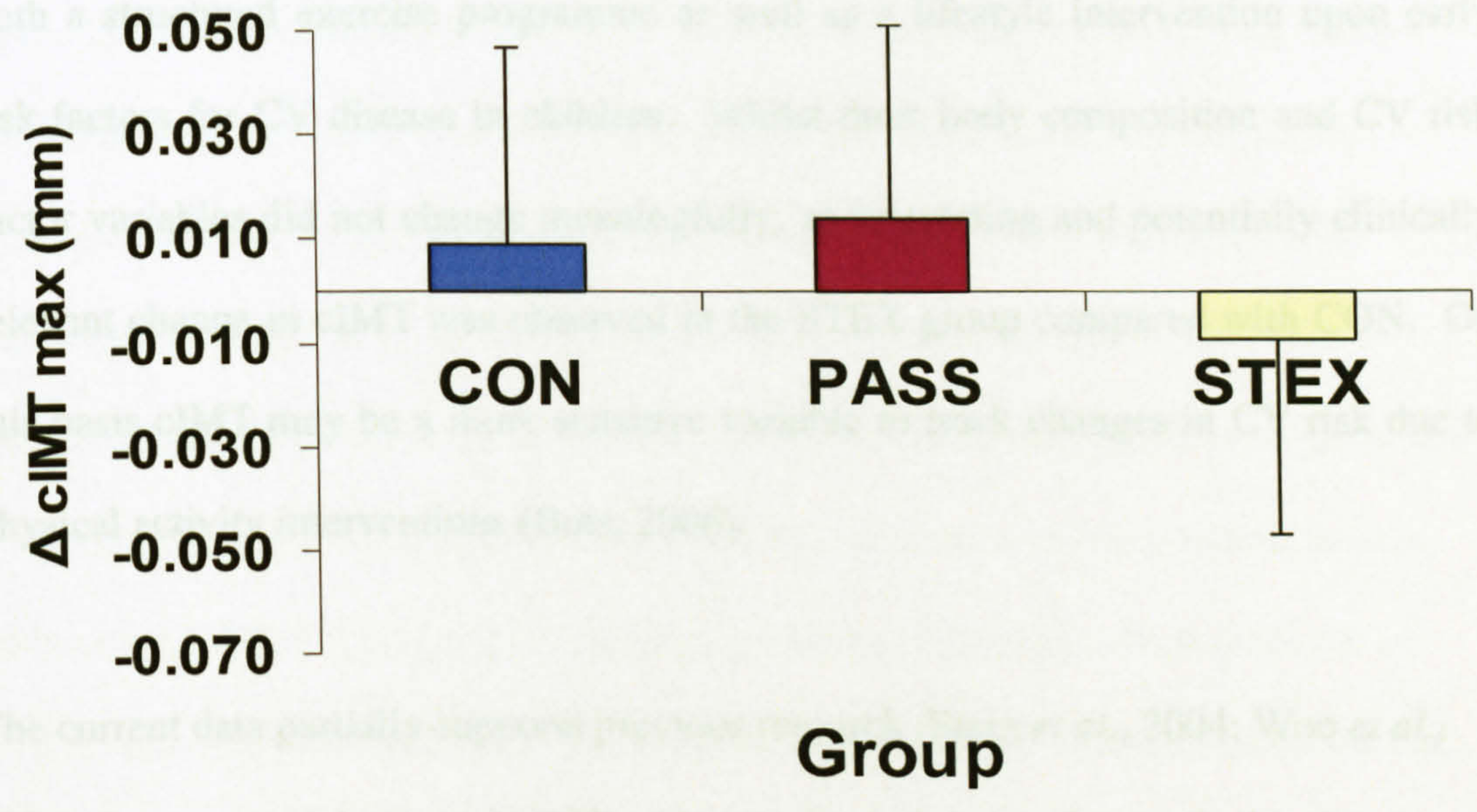

Figure 6.2. Δ scores for adjusted average maximum carotid IMT over the 9-week intervention period in all groups.

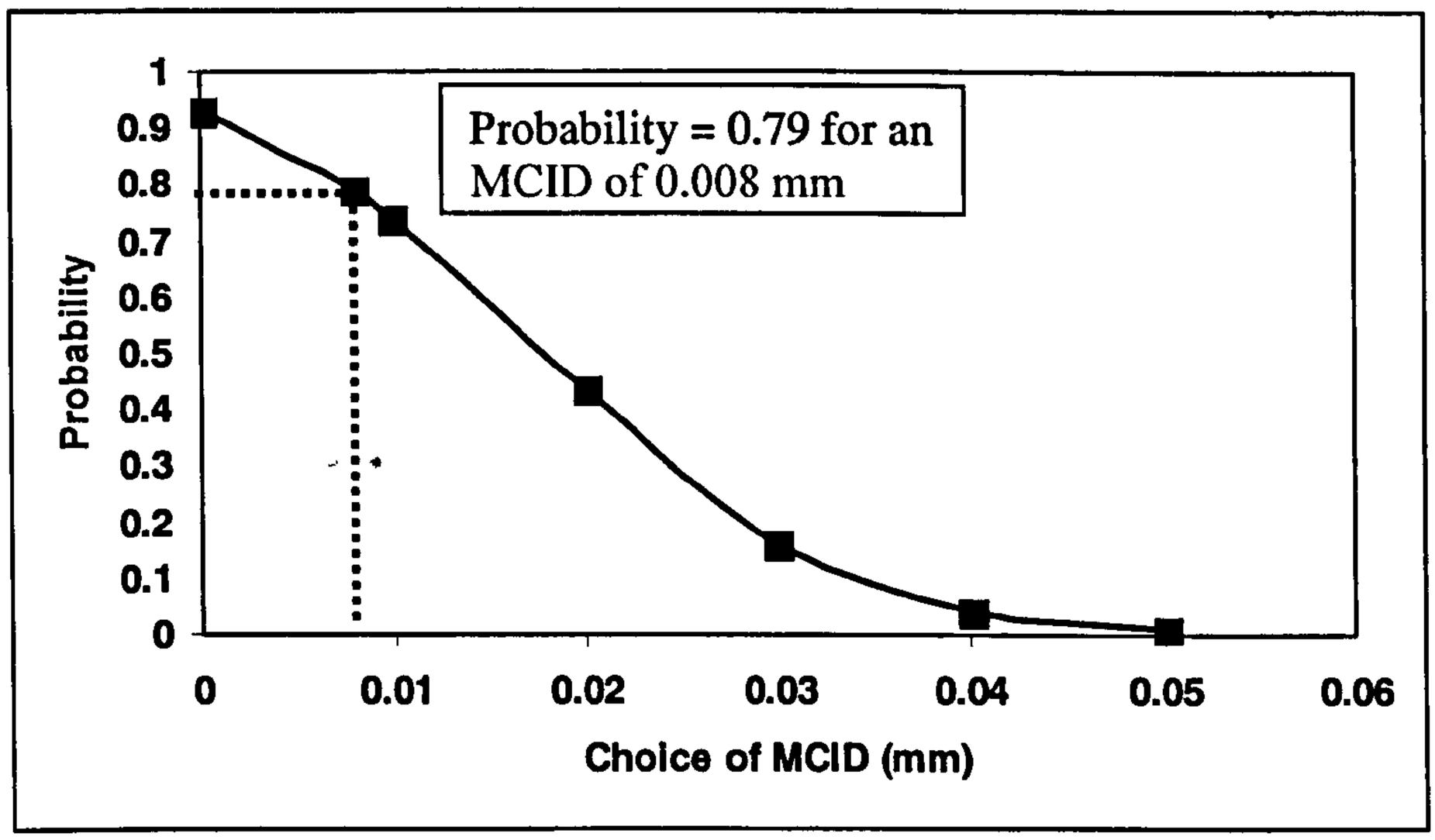

Figure 6.3. The probability that the true population intervention effect exceeds a chosen Minimum Clinically Important Difference (MCID; change in average maximum carotid IMT).

6.4 Discussion.

To the authors' knowledge this is the first exploratory trial to assess the impact of both a structured exercise programme as well as a lifestyle intervention upon early risk factors for CV disease in children. Whilst most body composition and CV risk factor variables did not change meaningfully, an interesting and potentially clinically relevant change in cIMT was observed in the STEX group compared with CON. On this basis cIMT may be a more sensitive variable to track changes in CV risk due to physical activity interventions (Bots, 2006).

The current data partially supports previous research (Stein *et al.*, 2004; Woo *et al.*, 2004) that reported decreased cIMT with exercise training and extends this data to suggest that even short-term interventions may produce favourable responses in cIMT. Research with adults has proposed that an increase in cIMT of just 0.034mm a

year is an independent risk factor for CV disease (Hodis, *et al.*, 1998). Similarly, a 1 SD increase in cIMT was associated with a ~2-fold increased risk of ischemic stroke or myocardial infarction (O'Leary *et al.*, 1999). Such data is unavailable for the age range in the current study, so the MCID was defined as 0.2 between-subject standard deviations - a reduction in cIMT of 0.008 mm. The calculated probability that the effect of the STEX intervention exceeded this threshold (defining clinical benefit for reduction in cIMT) was relatively high (0.71 to 0.79). For average maximum cIMT, the calculated probability reflected odds of approximately 4:1 in favour of the STEX intervention being clinically beneficial, with odds of greater than 2:1 that the intervention was beneficial for average mean cIMT.

Clearly, other researchers and clinicians may disagree with the value specified in the current study for the MCID. For those desiring a different threshold to define the MCID, an example of a clinical significance curve (as recommended by Shakespeare *et al.*, 2001) is presented in Figure 6.3. In the current study, pre-specifying a larger MCID of half a standard deviation (0.02 mm) for average maximum cIMT, for example, results in a probability of clinical benefit of 0.44 (indicating that the intervention would be about as likely to be clinically worthwhile as not). Half a standard deviation, however, represents a moderate effect size, and it is believed that even small changes of carotid IMT may be clinically relevant at a population level (Woo *et al.*, 2004). Certainly, the findings provide sufficiently robust evidence of STEX benefit to warrant further investigation in a definitive randomized controlled trial. The PASS group did not produce such positive results for average mean and maximum cIMT. This is likely to be a result of a reduced intensity, duration and thus volume of physical activity in PASS compared to STEX.

Changes in other CV risk variables were not substantially different between groups. This likely reflects the short nature of the intervention and/or the relative health of the heterogeneous primary school population. A longer intervention may be warranted to assess the impact of STEX and PASS on LV mass and diastolic function possibly in more "at risk" children. The lack of change in diastolic functional variables is somewhat at odds with past research (Nottin *et al.*, 2004; Pela *et al.*, 2004) but is likely due to the fact these data were derived from cross-sectional comparisons of trained and untrained children, which represents a greater exercise stimulus accumulated over many years. Moreover, it is almost axiomatic that cross-sectional effects are larger than those observed in experimental designs.

As with CV risk factors there were no substantial between group differences in Δ scores for body size and composition variables. However, of some interest was a small decrease in waist circumference and percentage fat mass in the STEX group compared to a small increase in the CON and PASS groups. Such group differences would be interesting to explore further in a more prolonged intervention.

Of potential interest to future research was the relative success of the implementation of both the PASS and STEX interventions in primary school children. As an exploratory trial it was positive to observe participants attain a 75% criterion for attendance or completion of signposting tasks. Additionally, a post study review of attendance/return, logistics of delivery, logistics of testing and assessment were all positive. Positive feedback was also given from questionnaires completed by subjects and parents. It is, though, pertinent to note some lessons for future studies. In the PASS scheme response rates varied task to task and generally declined over the 9-

week period. It is recommended that attention needs to be paid to nature of the tasks including an attempt to enhance the intensity of the programme similar to that of the STEX group. Implementation of positive reinforcement such as a reward scheme could be introduced as well as structured support from the child's school and family is also important to help maintain adherence. Additionally, data related to habitual physical activity levels would be useful and provide extra insight into the effectiveness of the specific interventions. Physical activity data collection was attempted in this exploratory trial but logistical and technical problems prevented these data being included in the analyses.

On the basis of the current findings and the lessons learned from this exploratory study we propose the implementation of a reward scheme to reinforce positive behaviour change, in addition to a longer intervention period with a larger sample size in a definitive (Phase III) randomised controlled trial (Campbell et al., 2000). A larger trial would enable the potential clinical benefit of the intervention to be estimated more precisely. The targeting of children with higher risk of cardiovascular disease would also be valuable (e.g. overweight and obese). Additionally, in future research the impact that the STEX and PASS interventions have on habitual physical activity and associated energy expenditure should be considered.

6.5 Conclusion

This exploratory trial of a STEX and PASS intervention in primary school children showed the interventions to be feasible, while the STEX intervention produced small but potentially clinically beneficial changes in the cIMT primary outcome variable. The focus of the current study on quantifying the probability for the potential benefit

of the intervention encourages researchers and clinicians to justify their choice of the smallest clinically worthwhile effect, and enhances clinical decision-making (Shakespeare *et al.*, 2001). Future research might provide greater insight into changes in cIMT after exercise interventions in children but may wish to target longer training periods and more at risk cohorts.

Chapter 7

Study 3 - The effects of a year-long programme of high intensity exercise classes, fundamental movement based exercise classes and a lifestyle intervention on 'pre-clinical' cardiovascular risk factors, cardiorespiratory fitness and physical activity in primary school children (The A-CLASS Project).

7.1 Introduction

The early establishment of 'pre-clinical' markers of future CV disease risk such as increased left ventricular (LV) mass, decreased diastolic function and increased carotid intima-media thickness (cIMT) has been reported in both children and adults (Daniels *et al.*, 1999; Sorof *et al.*, 2003; Freedman *et al.*, 2004; Meyer *et al.*, 2006; Sharpe *et al.*, 2006). Although not unanimous in children (see cross-sectional data), the appearance of some of these risk-factors has been associated with decreases in PA levels (Dollman *et al.*, 2005; Nelson *et al.*, 2006), CR fitness (Tomkinson and Olds, 2007) and an increase in obesity (Lobstein *et al.*, 2003). This is thought to underpin an increased future risk of CV disease (Chen *et al.*, 2005; Dollman *et al.* 2005). Indeed, a strong link between childhood CV risk factors and future risk of clinical CV disease in adulthood has been shown (Chen *et al.*, 2005) therefore the implementation of effective interventions in children is of paramount importance in an attempt to offset and/or reduce this CV disease burden.

Whilst some PA inventions in children have been found to improve CR fitness and body composition (Carrel *et al.*, 2005; Gutin *et al.*, 2008) data related to the impact on 'pre-clinical' CV risk factors have been limited and inconsistent (Humphries *et al.*, 2002; Bacon *et al.*, 2004; Woo *et al.*, 2004; George *et al.*, 2005; Henaghan *et al.*, 2008). Whilst some improvements have been reported in cardiac and/or vascular structure in children (Bacon *et al.*, 2004; Woo *et al.*, 2004) not all have supported these and positive functional changes have yet to be found (Humphries *et al.*, 2002; George *et al.*, 2005; Henaghan *et al.*, 2008). This could be related to the PA intensity and duration (and thus volume) of the interventions as the more prolonged higher intense studies appear to show the most positive changes. Data from our own short

exploratory trial (Henaghan *et al.*, 2008) supports the adoption of longer intervention periods.

Most PA interventions that aim to improve overall CV health in children have focused on traditional structured sports-specific exercise prescription in which children adhere to the coaches instructions for a designated time period (Bacon *et al.*, 2004; Nottin *et al.*, 2004; Pela *et al.*, 2004; Woo *et al.*, 2004; George *et al.*, 2005). Less attention has been paid to alternate models such as the integration of PA into daily life through less structured/sports-specific exercise programmes (Floriani and Kennedy, 2007). Differing psychological theories and models (e.g. social learning theory, ecological theory etc.) to understand and change lifestyle behaviour have been proposed (Baranowski, *et al.*, 2003). Some recent interventions, based on behaviour change theories, have been studied in an attempt to decrease sedentary behaviour in children (Salmon *et al.*, 2005). This study was found to be successful in reducing time spent watching television through both behavioural modification and the learning of fundamental movement skills. The comparison of a structured exercise intervention with lifestyle programmes and their effects upon CV risk factors in children has rarely been attempted. Those that have, report some positive preliminary data including a modest reduction in cIMT but suggest a longer intervention period with an increased sample size (Henaghan *et al.*, 2008).

In addition to the importance of increasing PA in children, their fundamental skill base (e.g. running, hoping, jumping, catching, throwing etc.) should also be considered as this is thought to provide the foundation for participation in sporting activities (Haywood and Getchell, 2005). Failure to be competent in such skills may

provide a barrier for participation in future PA (van Beurden *et al.*, 2003) which may have an impact of CV disease risk. Improvements in fundamental movement skills (FMS) have been reported to be positively correlated with both CR fitness and body composition (Okely *et al.*, 2001; Okely *et al.*, 2004). Interventions to develop such skills have been found to be successful with children in that their basic skill level was found to improve (van Beurden *et al.*, 2003; Foweather *et al.*, 2008) however no research has been reported to assess the effect of FMS interventions on CV health in 'pre-pubescent' children.

The purpose of the current study was, therefore, to assess the impact of high intense exercise training (HIPA), FMS based classes and a lifestyle intervention programme (PASS), compared to a control (CON) group, on early prognostic risk factors for CV disease in primary school children. In addition the impact these intervention groups have on body composition, PA levels and CR fitness was also assessed.

7.2 Methods

7.2.1 *Participants*

Following local ethics approval 112 schools were approached to take part in the project. Sixteen schools consented and were found to be eligible in that they had; 1) a large number of pupils in the school, 2) an accessible school sports facility, 3) limited after school clubs and 4) were classified as being in a "deprived" neighbourhood according to the index of deprivation scores (Office of the Deputy Prime Minister, 2004). From this 8 schools were randomly selected and further randomised into 2 schools per condition: (i) control, (ii) HIPA (high intensity physical activity), (iii) FMS (fundamental movement skill) and (iv) PASS (physical activity signposting

scheme). After receiving informed agreement from Head Teachers all year 5 children (aged 9 -10 years) were alerted to the nature of the project and invited to return signed parental consent and medical forms. The children themselves also provided assent at the beginning of the study. Exclusion criteria included current use of prescription medication, any personal history of asthma/respiratory problems, heart or vascular complaints as well as an early family history of sudden death. One hundred and fifty-two children (90 female and 62 male) with a mean ± SD age of 9.7 ± 0.3 years met these criteria and provided written personal and parental consent at the beginning of the study. Subject numbers in each group at the outset of the project were as follows: CON, *n*=34 [19*f* and 15*m*], HIPA, *n*=36 [24*f* and12*m*], FMS, *n*=37 [20*f* and 17*m*] and PASS, *n*=45 [27*f* and 18*m*]. Between baseline and mid-test (9 months: October to July) 2 children left school from PASS and 1 child left the project from HIPA. At final testing (12 months: October/November) 4 children left school, 1 from control, 2 from PASS and 1 from HIPA.

7.2.2 *Design*

All laboratory data was collected at baseline, mid-test (9 months) and post-test (12 months). Interventions took place over the 12 month period during school term time. No interventions were given during school holidays; Christmas break, February half term, Easter half-term, May week break and 6 weeks during the summer at the end of the school year. The four intervention groups are detailed below.

Control (CON)

The CON group were asked to maintain their normal activity levels. They received the same pre-study information packs as the other two groups however no further information or intervention was provided.

Fundamental movement skill (FMS)

Children attended twice weekly hour long after school skill based coaching sessions during the 12 month period. The sessions consisted of skill based activities such as throwing, catching, skipping, striking, running, hopping, leaping, dodging and kicking. The aim of these sessions was to help teach children the basic skills needed to participate in daily sporting activities. At the end of each session all skills learnt were used in a game situation such as cricket and volleyball. A-CLASS coaches delivered and monitored these sessions and progression of these skills was implemented through successive session plans.

High intensity physical activity (HIPA)

This was previously called structure exercise (STEX) in the exploratory trial however it was felt with the introduction of another structure exercise intervention (FMS) the need to clarify its intensity was needed. Children attended twice weekly hour long after school exercise sessions during the 12 month school period. These consisted of multi-activities such as circuits, dance and games. The aim of this session was to perform whole body muscular activity which was non-sports specific and to maintain heart rate above 70% of maximum heart rate (~145 beats.min^{-1}). This was verified by intermittent heart rate monitoring (Polar Electro, Kempele, Finland). A-CLASS

coaches delivered and monitored these sessions and increased the intensity over time accordingly to allow for the children to progress.

Physical activity signposting scheme (PASS).

Similar to the scheme used in the exploratory trial the social cognitive theory (SCT) (Bandura, 1986) and ecological theory (Sallis and Owen, 1999) were the basis for the PASS intervention. The SCT suggests that when the positives of behaviour outweigh the negatives then a person is motivated to try this behaviour. The ecological approach considers the determinants from multiple environments, in that they can restrict the range of behaviour by promoting and sometimes demanding certain actions and by discouraging or prohibiting other behaviours. Rather than contacting children through the post as in study two, one of the A-CLASS members was allocated 30 min of school time each week to deliver these sessions in PASS schools to help improve compliance. Children were given weekly missions/tasks that aimed to increase their activity levels and awareness of their surroundings. Each week children were encouraged to discuss what they enjoyed or found problematic and any other issues they may have with their tasks. Missions were derived using an intervention mapping approach to try to link the theories specifically to each task with the aim to increase habitual physical activity and decrease sedentary behaviour (e.g. to promote active transport and reduce TV viewing). In accordance with the social cognitive theory children were informed of the benefits of being active including the enhancement of confidence and skill level. Different environmental contexts were used including the home and local neighbourhood. In line with the ecological theory this aimed to help them understand their surroundings and how to become active within it, both on their own as well as with family and friends. Pedometers were used

as a physical activity promotion tool in conjunction with the missions. Examples of some of the tasks included a "switch off TV challenge" after 2 hours of viewing a day, increasing activity by monitoring active transport e.g. get off the bus a stop earlier, and take part in a new activity at least once a week with your family.

Rewards

To assist with the children's compliance rewards were used with all groups. Control groups were given incentives to attend labs and wear activity monitors. Children in the HIPA, FMS and PASS groups were also given rewards for wearing activity monitors but also for attending a certain number of sessions (e.g. 20 sessions and the children were given an A-CLASS t-shirt). Rewards included caps, water bottles, frisbees, beach balls and yo-yo's and were received throughout the 12-month training intervention.

7.2.3 *Protocols*

Ultrasound measurements

As discussed in **general methods**

Other outcome measures

As discussed in **general methods** and includes height, weight, lean body mass, fat mass, percentage fat mass, blood pressure, resting heart rate and maturity.

Physical activity monitoring

Children were assessed using a uni-axial accelerometer; MTI Actigraph (MTI Health Services, Florida) for their PA levels. Accelerometers were worn on the right hip

during 7 consecutive days of a normal school week. Accelerometers were set at 5 second epoch in order to assess the sporadic spontaneous nature of the children's activity. Due to problems with compliance with these monitors data was only used on those children who wore the monitor for at least 3 days in the week for a minimum of 9 hours each day. PA was assessed in this way at baseline, mid and post tests. Individual accelerometer count thresholds were derived from a calibration during an initial treadmill walking/ running test, accounting for individual differences in the intensity-counts relationship. Subsequently, free-living activities eliciting an accelerometer count beyond the cut-point derived in the treadmill test at 4 $km.hr^{-1}$ was defined as moderate to vigorous physical activity (MVPA), above 6 $km.hr^{-1}$ was vigorous activity (VPA), and above 8 $km.hr^{-1}$ was very vigorous activity (VVPA).

Cardiorespiratory (CR) fitness

After appropriate familiarisation physical fitness ($\dot{V}O_{2peak}$) was assessed with a discontinuous treadmill protocol (adapted from Armstrong, 2002) using a motorised treadmill. The treadmill was set at a 1% increment and the initial pace was freely chosen as a comfortable walking speed. At 3-min intervals participants were given a 30 s rest period in which the speed was increased by 2 $km.hr^{-1}$. This continued until volitional exhaustion. The Oxycon Pro (Jaeger, Hoechberg, Germany) was used to record respiratory data breath by breath ($\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER) after standard calibration prior to each test. A heart rate monitor (Polar Electro, Kempele, Finland) was fitted to the child's chest before the test started. Criteria for attaining $\dot{V}O_{2peak}$ were a heart rate above 200 $beats{\cdot}min^{-1}$ and/or RER above 1.05.

7.2.4 *Statistical analysis*

Values are presented as mean ± SD. Preliminary inspection of all variables was undertaken using 4 x 3 two-way ANOVAs which assessed the main effects of Group [4: CON, PASS, HIPA and FMS] and Time [3: baseline, 9 month, 12 month] as well as the interaction of Group and Time upon measures of CR fitness, PA, body composition and CV variables. For the primary analysis, those CV variables where a substantial change with time, group or an interaction was observed in the ANOVA statistics, between group ANCOVAs where performed. *A priori* we chose the 12 month score minus the baseline score for relevant CV variables and compared the responses of each intervention group to the CON group. In this analysis sex was assigned as a fixed effect and baseline CV data was input as a covariate (to adjust for any baseline imbalance between groups. Further covariates used where any of the CR fitness, PA and body composition/maturation data that changed over time or were different between groups and for this purpose the covariate change score (12 months minus baseline) was used. This was done in an attempt to unravel mechanistic underpinnings of change in the CV variables, by accounting for simultaneous change in related factors. Specifically in this study we observed time-related changes in peak height velocity and body composition variables (e.g. FM and LBM). Because most of the body composition variables were collinear, changes in FM and peak height velocity were selected in an attempt to separate the effects of growth etc. upon CV variables from any potential effect of the training.

An estimation approach was considered superior to a null hypothesis-testing framework (Curran-Everett *et al.*, 1998), presenting the mean effects of each intervention (versus control) on the primary outcome, together with 90% confidence intervals as suggested by Sterne and Smith (2001). In line with the recommendations

of Perneger (1998), Bonferroni corrections of confidence intervals were not applied. All analyses were carried out on SPSS statistical package 14.0 (SPSS Inc., Chicago, USA).

7.3 Results

Of the 152 children, data was collected at all 3 time points for the CV and predictor variables in 123 children. Those that did not complete stages are shown in figure 7.1. Of this 123, PA data was collected for 104 children and CR fitness data was collected on 104. A total of 92 children had all data sets at all time points (control n= 20, PASS n=26, HIPA n=23 and FMS n= 23). In the HIPA group 68% (15g & 6b) achieved 70% of attendance to sessions and in the FMS group 72% (11g & 12b) also achieved 70% of attendance to sessions. In the PASS group 100% of children attended the sessions as this was given during the normal school day.

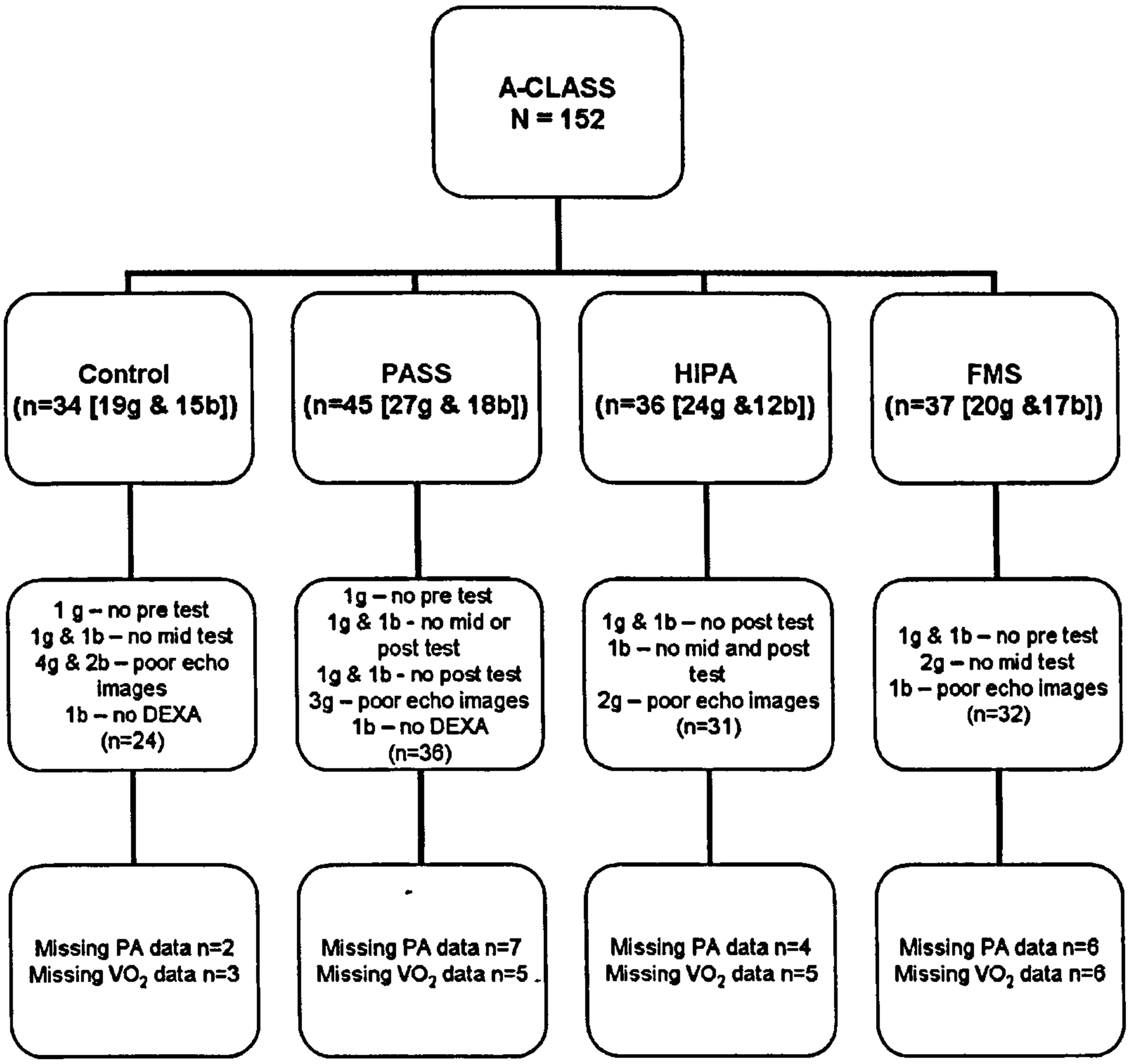

Figure 7.1. Participant numbers in their groups (g=girls and b=boys).

Data for age, body composition, PA and CR fitness over the 12-month training programme are presented in table 7.1.

Table 7.1. Anthropometric, PA and CR fitness data in all groups pre, mid and post intervention.

	Control (n=24)		PASS (n=36)		HIPA (n=31)		FMS (n=32)	
	Mean Value	(SD)	Mean Value	(SD)	Mean Value	(SD)	Mean Value	(SD)
Age (yr)								
Baseline	9.7	(0.3)	9.6	(0.3)	9.7	(0.3)	9.6	(0.3)
Mid-test	10.3	(0.3)	10.3	(0.3)	10.4	(0.3)	10.3	(0.3)
Δ baseline - mid	0.6	(0.4)	0.7	(0.6)	0.7	(0.6)	0.7	(0.2)
Post test	10.7	(0.3)	10.7	(0.3)	10.7	(0.3)	10.7	(0.3)
Δ baseline - post	1.0	(0.1)	1.1	(0.1)	1.1	(0.1)	1.0	(0.1)
Peak height velocity								
Baseline	-3.26	(0.48)	-3.29	(0.44)	-3.18	(0.39)	-3.47	(0.42)
Mid-test	-2.89	(0.57)	-2.72	(0.46)	-2.63	(0.39)	-2.97	(0.43)
Δ baseline - mid	0.37	(0.18)	0.57	(0.09)	0.55	(0.12)	0.50	(0.16)
Post test	-2.66	(0.54)	-2.39	(0.48)	-2.35	(0.42)	-2.67	(0.45)
Δ baseline - post	0.60	(0.14)	0.90	(0.13)	0.83	(0.14)	0.80	(0.17)
Body Mass (Kg)								
Baseline	35.4	(8.5)	39.2	(8.4)	39.6	(7.7)	32.4	(7.6)
Mid-test	37.6	(8.9)	42.4	(9.3)	43.0	(8.2)	35.4	(8.5)
Δ baseline - mid	2.2	(1.3)	3.3	(1.9)	3.2	(1.5)	3.0	(2.6)
Post test	39.8	(9.9)	45.0	(10.0)	45.3	(8.5)	37.6	(8.8)
Δ baseline - post	4.4	(2.0)	5.9	(2.4)	5.7	(2.3)	5.1	(3.1)
Stature (m)								
Baseline	1.38	(0.08)	1.38	(0.06)	1.40	(0.05)	1.37	(0.07)
Mid-test	1.42	(0.09)	1.43	(0.07)	1.45	(0.05)	1.40	(0.08)
Δ baseline - mid	0.04	(0.01)	0.05	(0.02)	0.05	(0.01)	0.03	(0.02)
Post test	1.43	(0.09)	1.45	(0.07)	1.46	(0.05)	1.43	(0.08)
Δ baseline - post	0.05	(0.01)	0.07	(0.02)	0.07	(0.02)	0.06	(0.02)
BMI (kg/m^2)								
Baseline	18.4	(2.9)	20.3	(3.1)	20.2	(3.0)	17.1	(2.8)
Mid-test	18.6	(2.9)	20.6	(3.3)	20.4	(3.1)	17.8	(2.8)
Δ baseline - mid	0.2	(0.7)	0.3	(0.9)	0.2	(0.7)	0.7	(1.1)
Post test	19.2	(3.1)	21.2	(3.6)	21.1	(3.2)	18.1	(2.8)
Δ baseline - post	0.8	(0.8)	0.9	(1.1)	0.9	(1.0)	1.0	(1.3)
Waist circumference (cm)								
Baseline	60.9	(7.0)	65.1	(6.9)	65.4	(7.3)	59.3	(6.8)
Mid-test	61.2	(6.8)	67.9	(7.4)	67.0	(7.6)	60.3	(9.7)
Δ baseline - mid	0.3	(1.9)	2.8	(3.5)	1.6	(1.9)	1.0	(6.1)
Post test	63.1	(7.4)	68.5	(8.2)	68.3	(7.7)	62.2	(7.2)
Δ baseline - post	2.2	(2.1)	3.4	(3.7)	2.9	(2.3)	2.9	(2.3)
Fat mass (g)								
Baseline	9991	(4220)	12346	(4747)	11871	(5275)	8382	(4133)
Mid-test	10302	(4023)	13094	(5310)	12597	(5682)	8872	(4587)
Δ baseline - mid	331	(968)	749	(1399)	725	(1015)	490	(1044)
Post test	11337	(4675)	14124	(5661)	13513	(5964)	9519	(4805)
Δ baseline - post	1346	(1358)	1779	(1647)	1641	(1573)	1135	(1261)
Lean mass (g)								
Baseline	24651	(5011)	26356	(4016)	26981	(3354)	23851	(4365)
Mid-test	26450	(5448)	28589	(4648)	29404	(3606)	25593	(4640)
Δ baseline - mid	1799	(916)	2233	(1052)	2424	(1060)	1742	(1573)
Post test	27624	(5961)	29994	(4835)	30896	(3779)	6976	(4618)
Δ baseline - post	2973	(1302)	3638	(1408)	3915	(1644)	3125	(1634)
% fat mass (%)								
Baseline	27.3	(5.2)	30.3	(5.1)	28.6	(7.4)	24.2	(7.0)
Mid-test	26.6	(5.0)	29.7	(5.7)	28.0	(7.8)	23.8	(7.1)
Δ baseline - mid	-0.7	(1.7)	-0.6	(2.3)	-0.6	(1.5)	-0.4	(1.7)
Post test	27.6	(5.4)	30.3	(5.5)	28.5	(8.1)	24.1	(7.0)
Δ baseline - post	0.3	(2.4)	0.3	(2.4)	-0.1	(2.4)	-0.1	(2.1)
PA > 4km/hr (mins) (MVPA) *								
Baseline	77.67	(28.71)	82.57	(28.82)	88.44	(29.34)	83.47	(22.24)
Mid-test	86.93	(38.89)	87.69	(35.47)	90.43	(32.75)	94.07	(28.94)
Δ baseline - mid	9.25	(28.45)	5.12	(31.89)	1.99	(29.14)	10.60	(25.99)
Post test	66.92	(28.46)	67.04	(27.24)	65.78	(20.56)	63.76	(18.79)
Δ baseline - post	-10.75	(19.09)	-15.53	(27.30)	-22.65	(31.66)	-19.71	(25.31)
VO_2 peak ($ml.kg^{-1}.min^{-1}$) **								
Baseline	47.5	(6.8)	45.4	(6.5)	44.2	(7.6)	51.4	(7.5)
Mid-test	45.7	(6.0)	43.1	(4.8)	42.9	(5.3)	47.0	(7.2)
Δ baseline - mid	-1.7	(3.7)	-2.3	(4.9)	-1.3	(4.4)	-4.4	(3.8)
Post test	45.8	(5.7)	43.7	(6.1)	45.2	(6.4)	49.6	(7.4)
Δ baseline - post	-1.6	(4.5)	-1.7	(3.6)	1.0	(4.8)	-1.8	(2.9)

The initial two-way ANOVA of CR fitness data (n=104) resulted in a significant main effect for time with a decrease over the training period (Figure 7.2). No significant

group main effect or time by group interaction was noted. For PA data (n=104) there were no significant main effects or interactions, although a trend for an increase and then decrease in PA over the 12 months is visually apparent (figure 7.3).

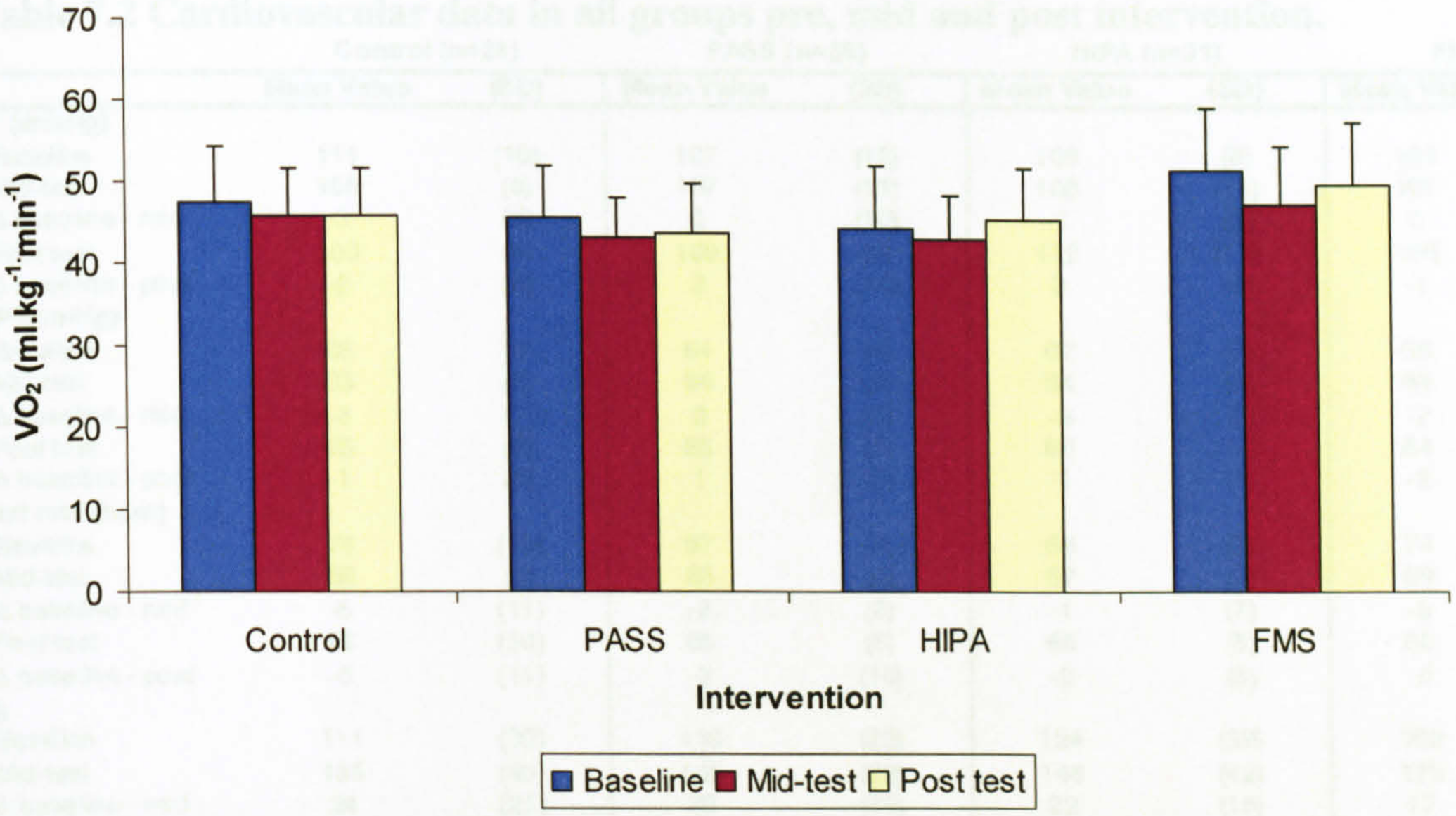

Figure 7.2 Changes in VO_{2peak} for all groups over the 1 year intervention.

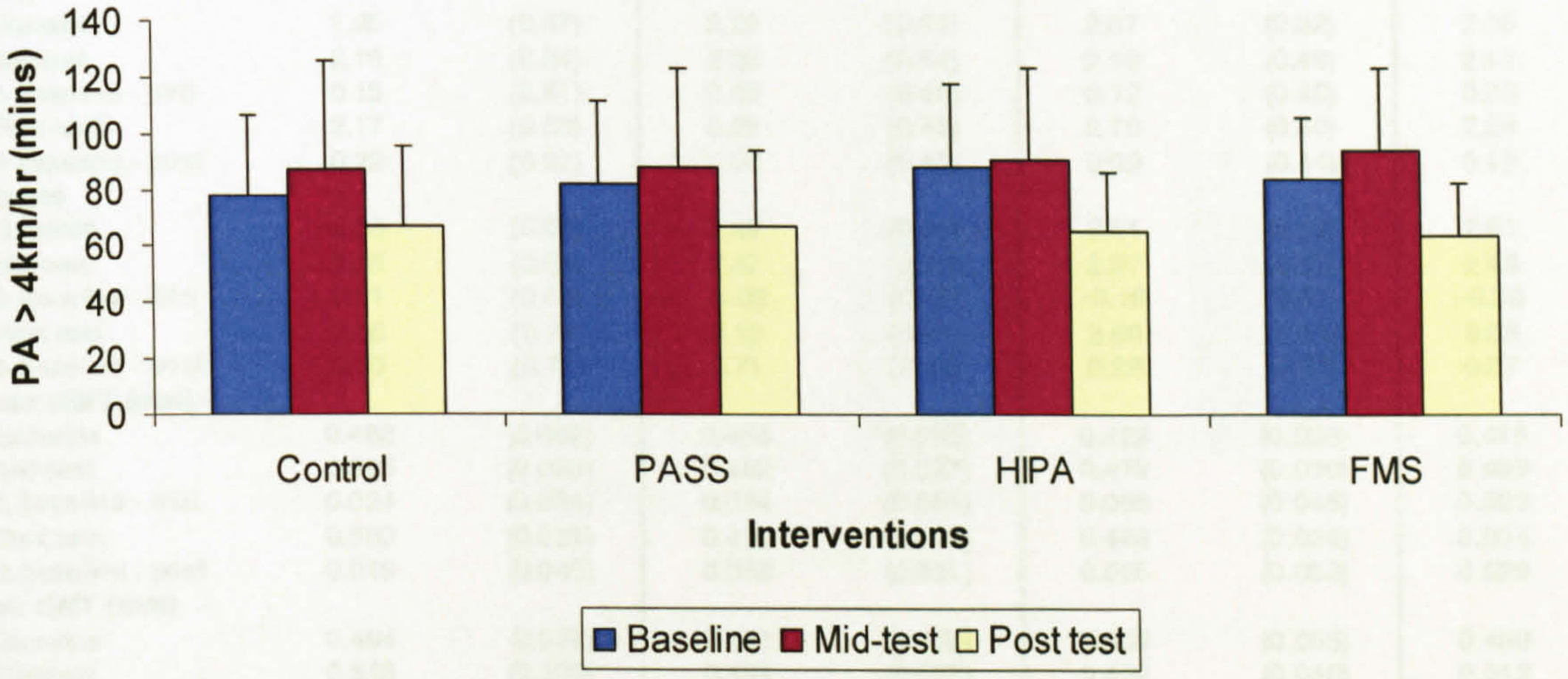

Figure 7.3 Changes in PA for all groups over the 1 year intervention

Fat mass and LM both significantly increased over time however no significant group main effect or time by group interactions were reported. Similarly over the year all

children significantly reduced their time to peak height velocity although again this was not significantly different between the groups and did not display a significant time by group interaction.

Table 7.2 Cardiovascular data in all groups pre, mid and post intervention.

	Control (n=24)		PASS (n=36)		HIPA (n=31)		FMS (n=32)	
	Mean Value	(SD)	Mean Value	(SD)	Mean Value	(SD)	Mean Value	(SD)
Systolic BP (mmHg)								
Baseline	111	(10)	107	(12)	109	(8)	107	(10)
Mid-test	108	(8)	107	(11)	108	(11)	107	(9)
Δ baseline - mid	-3	(8)	0	(10)	-1	(9)	0	(7)
Post test	109	(8)	109	(9)	112	(11)	106	(9)
Δ baseline - post	-2	(8)	2	(10)	3	(8)	-1	(6)
Diastolic BP (mmHg)								
Baseline	66	(6)	64	(4)	67	(5)	66	(5)
Mid-test	63	(5)	64	(5)	64	(6)	64	(4)
Δ baseline - mid	-3	(7)	0	(6)	-3	(5)	-2	(6)
Post test	65	(3)	65	(5)	66	(7)	64	(3)
Δ baseline - post	-1	(6)	1	(5)	-1	(7)	-2	(4)
Resting heart rate (bpm)								
Baseline	74	(15)	67	(8)	68	(9)	74	(9)
Mid-test	69	(8)	65	(9)	67	(9)	69	(9)
Δ baseline - mid	-5	(11)	-2	(8)	-1	(7)	-5	(8)
Post test	69	(10)	65	(8)	66	(8)	68	(8)
Δ baseline - post	-5	(11)	-3	(10)	-2	(8)	-6	(8)
LV mass (g)								
Baseline	111	(30)	119	(23)	124	(39)	109	(34)
Mid-test	135	(43)	149	(29)	146	(42)	126	(37)
Δ baseline - mid	24	(21)	30	(19)	22	(15)	17	(14)
Post test	142	(45)	155	(31)	155	(44)	136	(37)
Δ baseline - post	31	(22)	36	(18)	31	(21)	27	(15)
LV mass indexed (g/m^2)								
Baseline	45.7	(9.0)	49.5	(9.4)	49.5	(12.6)	46.3	(12.1)
Mid-test	52.4	(13.8)	56.5	(9.4)	53.5	(12.9)	50.2	(11.7)
Δ baseline - mid	6.7	(7.7)	7.0	(7.1)	4.0	(5.9)	3.9	(5.9)
Post test	52.8	(12.6)	56.5	(10.5)	54.6	(12.0)	51.6	(12.1)
Δ baseline - post	7.1	(6.8)	7.0	(6.8)	5.1	(6.6)	5.3	(6.2)
E/A ratio (m/s)								
Baseline	1.95	(0.47)	2.20	(0.51)	2.07	(0.32)	2.06	(0.32)
Mid-test	2.10	(0.34)	2.26	(0.54)	2.19	(0.48)	2.11	(0.38)
Δ baseline - mid	0.15	(0.51)	0.06	(0.45)	0.12	(0.40)	0.05	(0.45)
Post test	2.17	(0.53)	2.22	(0.45)	2.16	(0.40)	2.24	(0.37)
Δ baseline - post	0.22	(0.37)	0.02	(0.47)	0.09	(0.41)	0.18	(0.45)
E'/A' ratio (cm/s)								
Baseline	2.56	(0.64)	2.49	(0.62)	2.51	(0.67)	2.51	(0.54)
Mid-test	2.55	(0.58)	2.47	(0.53)	2.37	(0.45)	2.43	(0.44)
Δ baseline - mid	0.01	(0.66)	-0.02	(0.48)	-0.16	(0.67)	-0.08	(0.51)
Post test	3.06	(0.70)	3.19	(0.71)	2.80	(0.61)	3.08	(0.58)
Δ baseline - post	0.50	(0.74)	0.71	(0.60)	0.29	(0.67)	0.57	(0.80)
Average mean cIMT (mm)								
Baseline	0.482	(0.062)	0.456	(0.056)	0.423	(0.053)	0.475	(0.038)
Mid-test	0.506	(0.028)	0.482	(0.027)	0.479	(0.039)	0.499	(0.026)
Δ baseline - mid	0.024	(0.034)	0.024	(0.056)	0.056	(0.045)	0.023	(0.041)
Post test	0.500	(0.031)	0.492	(0.026)	0.488	(0.034)	0.504	(0.032)
Δ baseline - post	0.019	(0.045)	0.036	(0.051)	0.065	(0.063)	0.029	(0.031)
Average max cIMT (mm)								
Baseline	0.494	(0.037)	0.471	(0.057)	0.439	(0.055)	0.489	(0.039)
Mid-test	0.518	(0.029)	0.494	(0.027)	0.492	(0.040)	0.512	(0.027)
Δ baseline - mid	0.024	(0.035)	0.023	(0.055)	0.053	(0.047)	0.023	(0.042)
Post test	0.514	(0.032)	0.504	(0.026)	0.501	(0.035)	0.516	(0.035)
Δ baseline - post	0.019	(0.047)	0.033	(0.052)	0.062	(0.065)	0.027	(0.032)

Initial two-way ANOVA analysis of the CV variables (n=123) demonstrated significant main effects for time in LVM (figure 7.4), E'/A' (figure 7.5), mean cIMT

(figure 7.6), max cIMT and diastolic BP (figure 7.7) over the 12 month period ($p<0.005$). LV mass is shown to significantly increase over time both between baseline and mid test and post test. This occurred in all groups.

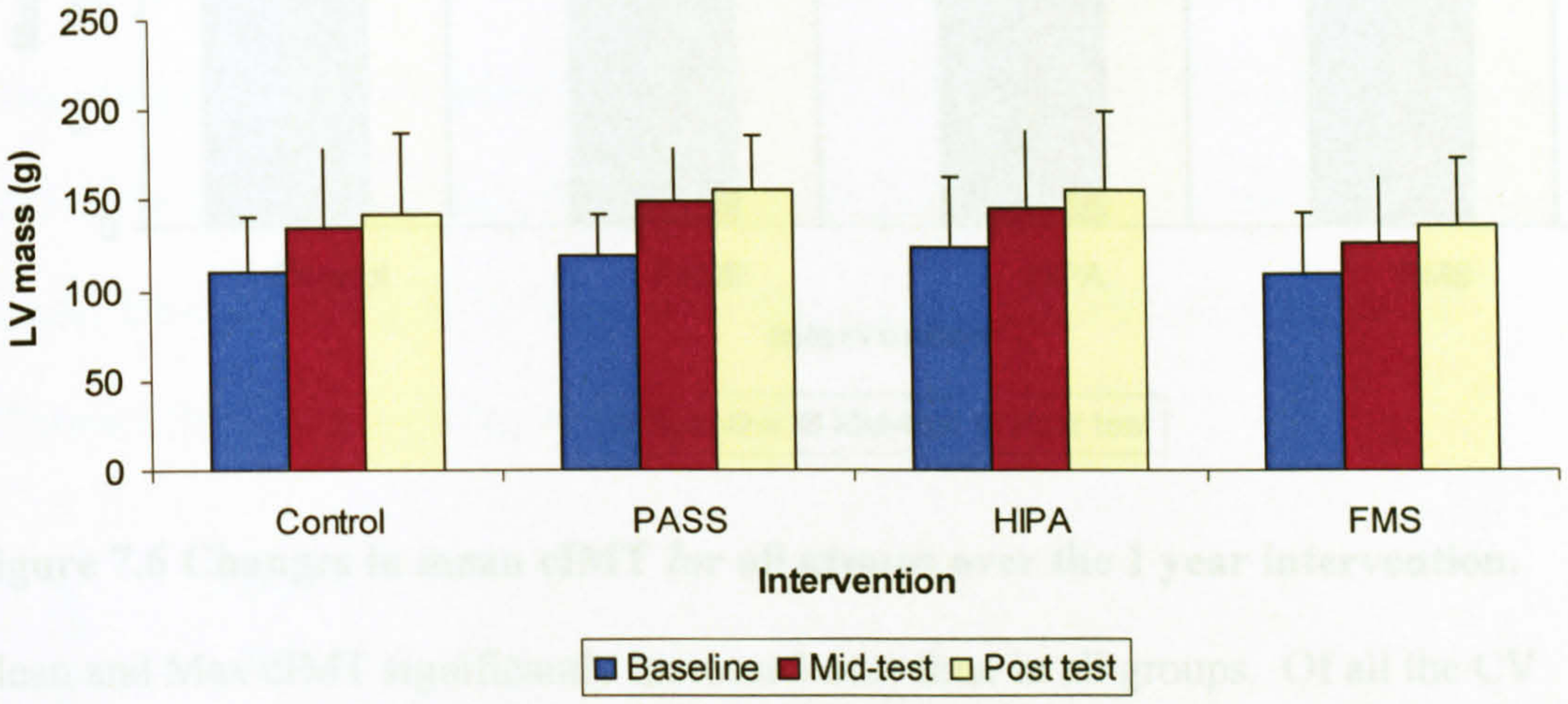

Figure 7.4 Changes in LV mass changes in all groups over the 1 year intervention.

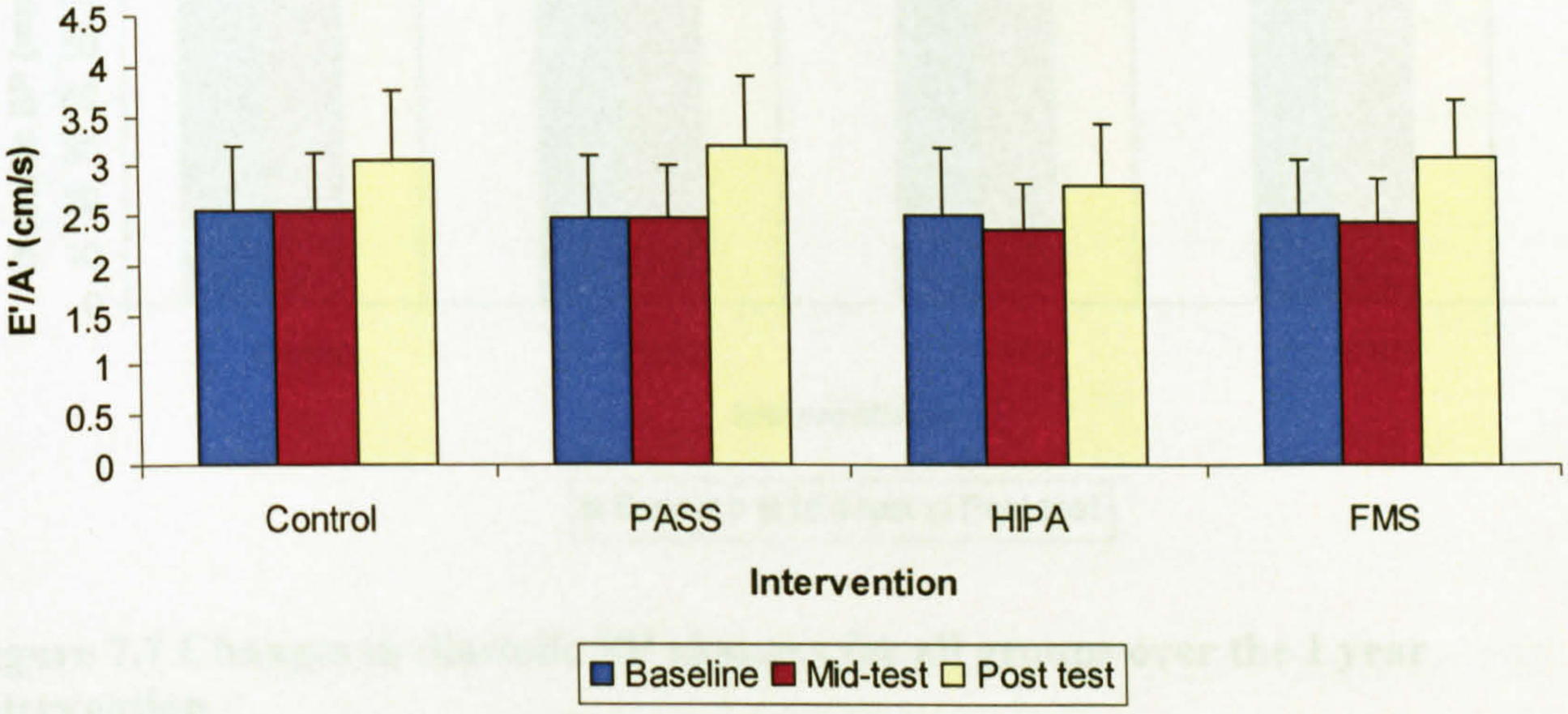

Figure 7.5 Changes in E'/A' for all groups over the 1 year intervention.

Diastolic function (E'/A') did not change significantly between baseline and mid-testing however from baseline to post-test this did improve significantly in all groups.

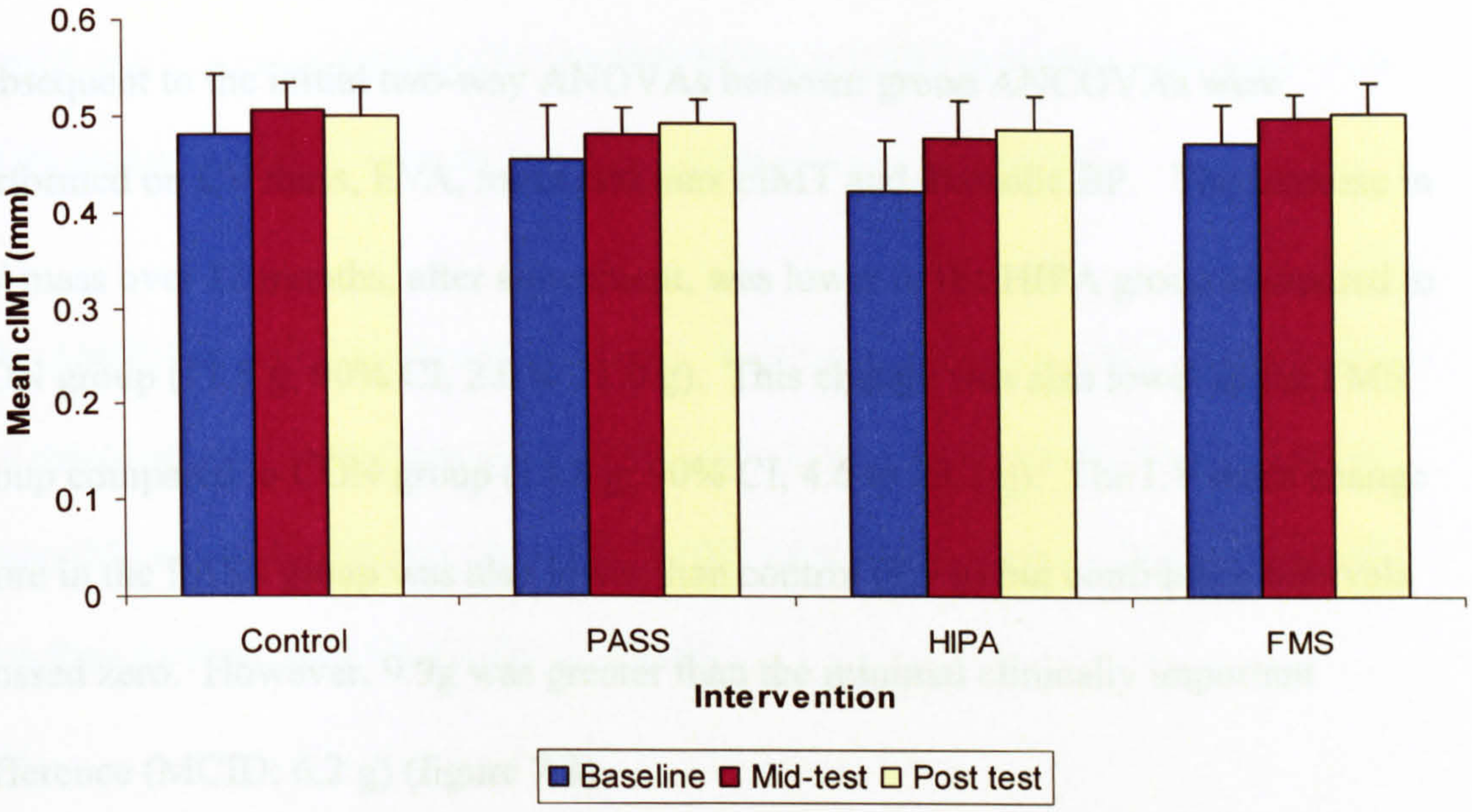

Figure 7.6 Changes in mean cIMT for all groups over the 1 year intervention.

Mean and Max cIMT significantly increased over time in all groups. Of all the CV variables only mean and max cIMT presented a significant time by group interaction with changes in both HIPA and PASS increasing more than the CON group ($P<0.05$).

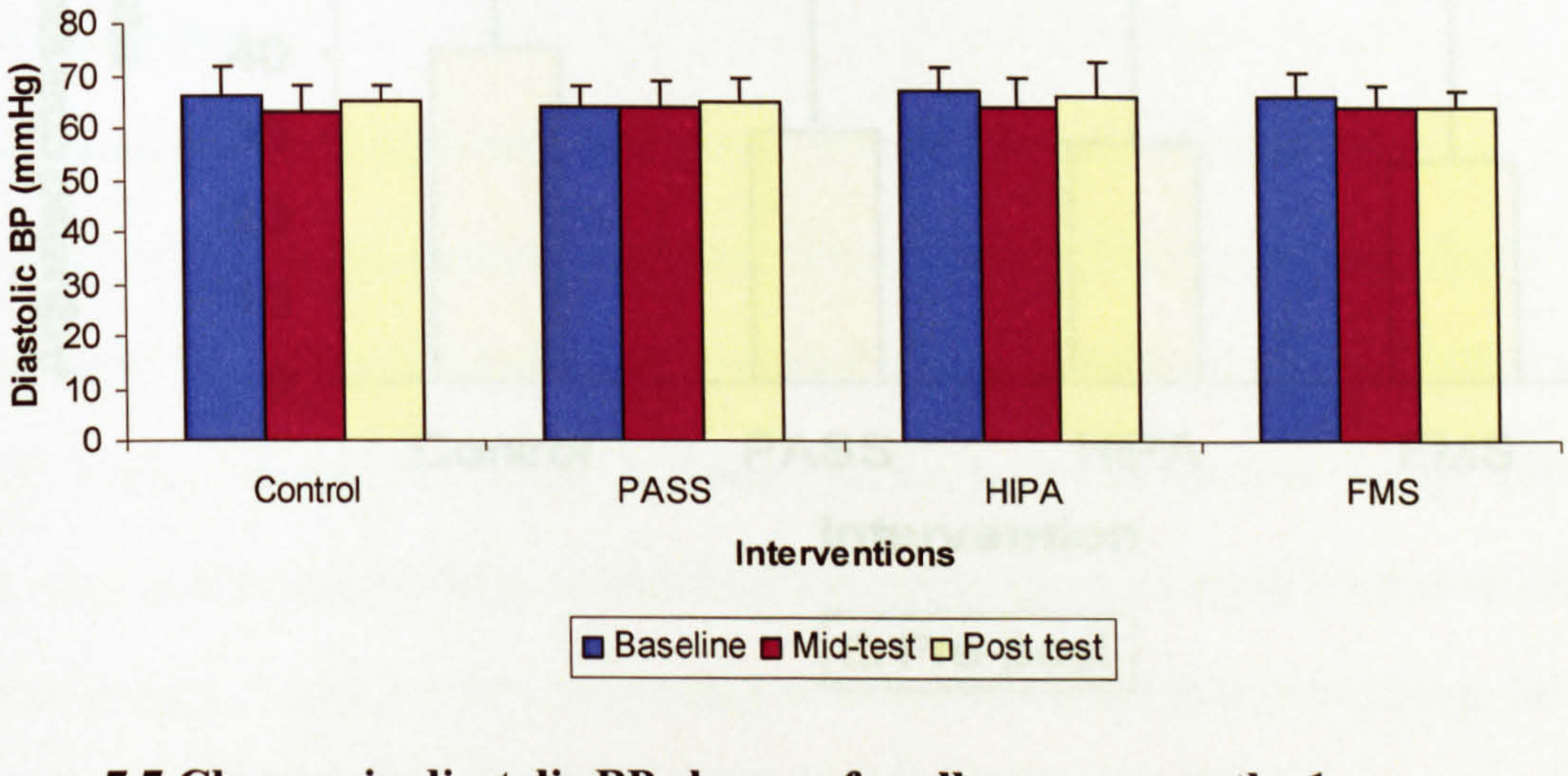

Figure 7.7 Changes in diastolic BP changes for all groups over the 1 year intervention.

Diastolic BP was found to significantly decrease over time. This was more apparent between baseline and post-analysis. There were no significant differences between the intervention groups and control.

Subsequent to the initial two-way ANOVAs between group ANCOVAs were performed on LV mass, E'/A, mean and max cIMT and diastolic BP. The increase in LV mass over 12 months, after adjustment, was lower in the HIPA group compared to CON group (11.5 g; 90% CI, 2.0 to 21.0 g). This change was also lower in the FMS group compared to CON group (13.8 g; 90% CI, 4.6 to 23.1 g). The LV mass change score in the PASS group was also lower than control (9.9 g) but confidence intervals crossed zero. However, 9.9g was greater than the minimal clinically important difference (MCID; 6.2 g) (figure 7.8).

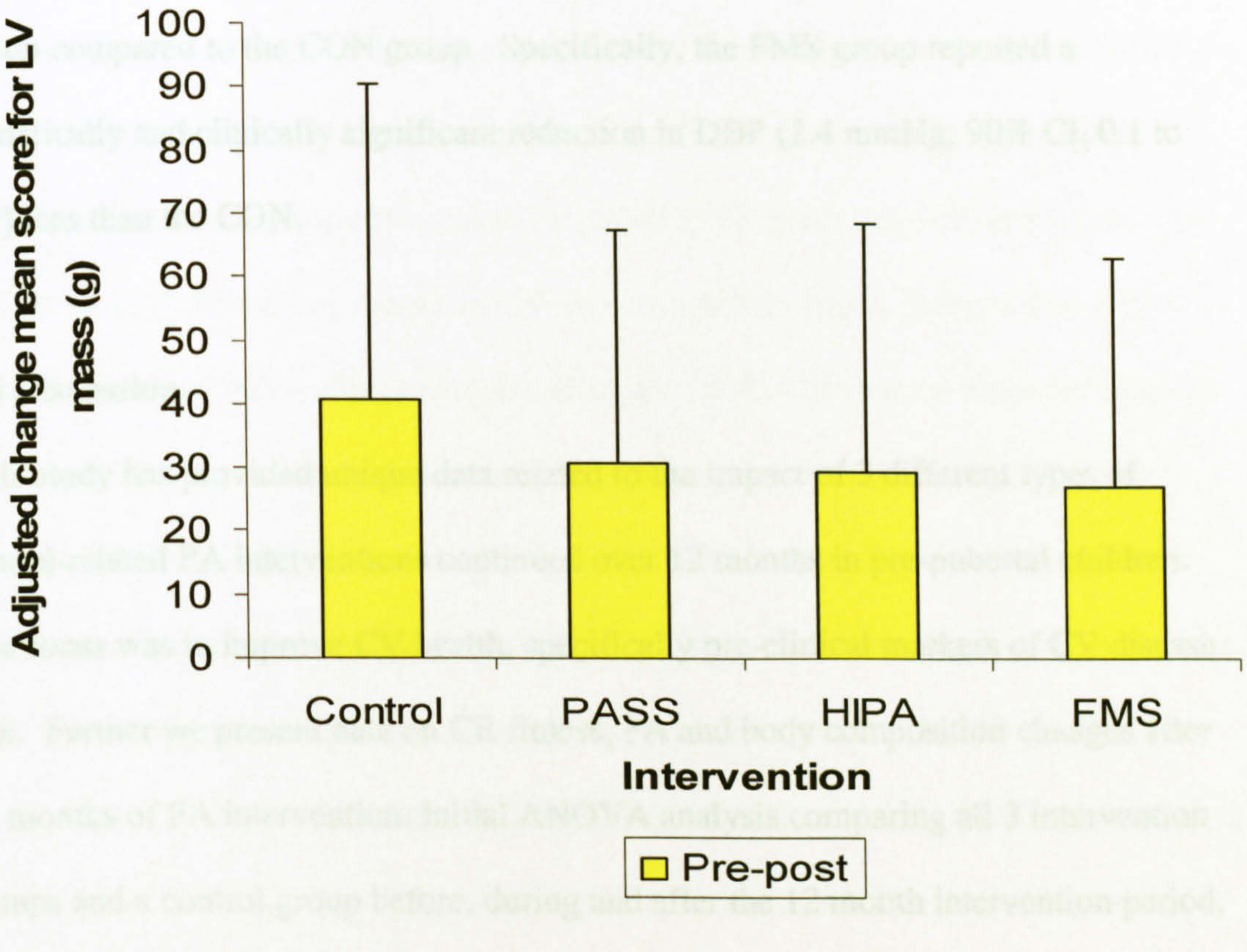

Figure 7.8 Adjusted mean change scores for LV mass when accounting for FM and peak height velocity changes in all groups.

ANCOVA analysis of the change scores for E'/A' demonstrated that the PASS group significantly improved their E'/A' (0.396; 90% CI, 0.707 to 0.084) compared to the CON group. No other between group differences were significant.

The ANCOVA adjusted change scores for both mean and max cIMT were smaller in the intervention groups compared to CON group but only in the PASS group were these differences significant ($P<0.05$). PASS increased its mean cIMT (-0.014mm less than control (90% CI, -0.002 to -0.030).

ANCOVA analysis of the change scores for diastolic BP were different in the FMS group compared to the CON group. Specifically, the FMS group reported a statistically and clinically significant reduction in DBP (2.4 mmHg; 90% CI, 0.1 to 4.7) less than the CON.

7.4 Discussion

This study has provided unique data related to the impact of 3 different types of school-related PA interventions continued over 12 months in pre-pubertal children. The focus was to improve CV health, specifically pre-clinical markers of CV disease risk. Further we present data on CR fitness, PA and body composition changes after 12 months of PA intervention. Initial ANOVA analysis comparing all 3 intervention groups and a control group before, during and after the 12 month intervention period, found limited statistically significant evidence for a positive impact of PA interventions compared to controls in pre-pubertal children. However, after adjusting for confounding variables in an ANCOVA analysis some, sporadic benefits of PA interventions on CV variables were uncovered. Somewhat surprisingly the

intervention programmes had no positive effect on CR fitness (indeed this decreased), PA measures and/or body composition over and above changes observed due to growth.

CV variables:

It is clear that over the study period all children grew. This partially explains the significant increase in LV mass observed over 12 months in all groups. This finding supports our exploratory trial (Henaghan *et al.*, 2008) and other training studies (George *et al.*, 2005). Indeed growth related changes in LV mass provide part of the necessity to appropriately scale or statistically analyse LV mass beyond simple absolute measures. When FM and peak height velocity changes were accounted for in the primary ANCOVA analysis a number of the PA interventions were found to significantly attenuate growth-related increases in LV mass which maybe beneficial to later or adult life as LV mass and LV hypertrophy are strong independent risk factors for CV events and disease (Savage *et al.*, 1990). It appears that over time all interventions played a role in this with FMS having the greatest impact. This is encouraging as it suggests by developing sufficient PA (possibly by adopting FMS skills) may help in the prevention of future CV risk factors. It could be suggested that taking part in physical activity such as those in the interventions, could prevent unwarranted increases in FM and thus reduce the increases in LV mass in pre-pubertal children.

The observation of an increase in E'/A' over the 1 year period was not entirely size or growth independent either. How body growth and/or maturation has an impact on diastolic function is difficult to directly explain except that with maturation comes

growth in heart size, mass and chamber cavity volume. An increased chamber volume requires greater filling in diastole and this likely occurs during early diastole and could serve to improve both E' and E'/A'. Whether the growth of the myocardial mass is also associated with more compliant tissue and thus impact early relaxation has never been full elucidated. After removing the effect of growth (FM and peak height velocity) the pre- to post-test increase in E'/A' was significantly higher in the PASS group than the control group and therefore may represent a positive response to increased PA through non-standard (HIPA) methods. Enticingly this would suggest that by increasing a child's exercise and health knowledge base changes in other factors (vascular health, diet etc.) may aid in the improvement of heart function irrespective of increases in total PA or absolute fitness levels. This could be mediated by factors such as diet and potentially changes in blood pressure but requires further study. Interestingly, those previous studies in children (pre-pubertal) that have investigated the impact of exercise training on diastolic function (George *et al.*, 2005; Obert *et al.*, 2007) have reported limited and equivocal findings. It may be that training really does have a limited impact on diastolic function of children at this age or it may reflect the limitations of previous research in the use of Doppler flow parameters of diastolic function compared to tissue-Doppler employed in the current study. Tissue-Doppler measures may be load-independent (George *et al.*, 2005), more sensitive to training influences and not affected by pseudo-normalisation (Khouri *et al.*, 2004).

Previously in the exploratory trail (Henaghan *et al.*, 2008) PA intervention groups had a reduction in mean and max cIMT over only a 9 week intervention. The small changes observed in that study provided a significant part of the rationale for this

longer intervention. Somewhat disappointingly we did not reproduce a reduction in mean or max cIMT with PA intervention in this study over a longer 12 month period. Again it is pertinent to note that increases in cIMT over time are associated with somatic growth and this likely explains part of the change in cIMT observed in all 4 groups. Nevertheless, despite not producing a decline in cIMT the intervention groups did appear to demonstrate a smaller increase in cIMT than the control group after adjusting for individual differences in growth and body size parameters. This suggests that although an increase in cIMT could not be totally prevented or reversed, the PA interventions helped to attenuate the changes seen in the PA intervention groups. Again this was without any improvements in PA or CR fitness, suggesting some local vascular adaption may have taken place. Any explanation for the exact cause or mechanism is purely speculative but changes in vascular health have been reported with training in children in other studies (Watts *et al.*, 2006).

Compared to the control group all PA intervention groups produced a slightly bigger change (decline) in DBP after adjustment for growth or body composition differences. However these differences were only significant in the FMS group pre- to post-test. The reduction in DBP in the face of an increase in LV mass in all groups again points to a beneficial vascular adaptation rather than something of note occurring in the myocardium itself. Whether the drop in DBP represents a PA intervention mediated change in arterial stiffness that would slow the propogation of a reflected pulse wave and thus reduce DBP is difficult to deduce. Certainly, further research should pay closer attention to vascular adaptation in PA interventions in pre-pubertal children. It could be that the vascular system, responding to the exercise stimuli of increased shear stress may adapt even without central cardiac, functional (peak oxygen uptake)

or noticeable changes in PA. Whatever the mechanism of change overall in the intervention groups, and the specific effect of the FMS group, with a drop in DBP the heart is working against a reduced afterload and this is a significant positive outcome..

Despite some positive, but sporadic significant, changes within the PA interventions one point of interest was the relative lack of impact of the HIPA intervention, compared to PASS and FMS, on CV variables. This maybe surprising to some when one considers that HIPA PA intervention are very common in the scientific literature, especially with children when attempting to modulate CV risk factors (Bacon *et al.*, 2004; Nottin *et al.*, 2004; Pela *et al.*, 2004; Tolfrey *et al.*, 2004; Woo *et al.*, 2004). The lack of efficacy of this intervention in producing no change in CV variables and concomitantly no alteration in VO_{2peak}, PA and body composition is hard to explain. Clearly the lack of training effect on fitness, PA and body size may underpin the lack of change in CV variables, although this did not prevent some changes in other groups. It may be that FMS and PASS may have provided a more dynamic, interesting and sociologically "current" approach to exercise in children. The relative "boredom" induced by repetitive HIPA exercise is somewhat at odds with the computer and "computer-game" age that today's children exist in. Specifically HIPA sessions may have led to a reduction in other forms of physical activity and potentially without session-by-session monitoring of all children's activity levels some may not have kept up with desired activities and intensities. With this in mind prescribing HIPA-type activity to pre-pubertal children in order to increase their PA level maybe "old-fashioned" and counter-productive. Newer modalities such as the supra-maximal intermittent trials run by Burgomaster *et al.* (2005) may be worth investigating in the future. Initial trials in adults suggest positive training adaptations

and it may more ecologically valid to apply to children and possibly replicates their natural activity patterns. .

Surprisingly no changes in PA, CR fitness and body composition were reported, nevertheless some, albeit small, changes in CV risk factors were apparent. An explanation for this is, as already discussed, difficult to clarify. What may be pertinent to discuss in terms of the overall response to the PA interventions, and specifically changes in CV disease risk, is that this was a 'healthy' population of children. Perhaps more "at-risk" groups with lower baseline PA, CR fitness and more individuals who were overweight/obese group may have shown more positive CV disease risk outcomes. Despite this we would support the outcomes from the preliminary trial and suggest that generally pre-pubertal children do not express widespread early, pre-clinical signs of CV disease and thus even if low PA, CR fitness and high body fat are present there remains a window of opportunity for PA interventions to help offset future CV disease risk.

As with all studies some limitations were present that must be acknowledged and provide goals for further research. Problems were encountered with some of the measuring tools. For example, PA monitoring through accelerometers meant that not all activity could be monitored. We could speculate that perhaps children taking part in the interventions did not appear to provide increased PA levels as the interventions just replaced previous or normal patterns of PA. Problems with participant compliance in the use of accelerometer monitors also meant participation numbers were lower for these measures. Similarly, CR fitness data was flawed with compliance issues as children often failed to reach peak due to lack of motivation. A

further limitation was that no dietary information was gathered for the body composition data. Further analysis of these children at a 6-month follow up after the cessation of the PA intervention programmes would have provided us with some information regarding the lifestyle impact of these interventions. In an ideal world these children should have been monitored over many years to assess for changes in maturation and its effects on the CV variables. This is a potential area of future research activity especially given the value of the Sportlinx data on Merseyside (SportsLinx *et al.*, 2004). Peri and post-pubertal children should also be observed to account for hormonal influences and its impact on CV risk factors in children.

A final point is worthy of note. The relative success of the PA interventions in terms of compliance and adherence should be noted, especially given the prolonged and complex nature of the trial and the logistical load this entailed. This at least suggests that PA interventions of this nature could be "rolled-out" into the primary school environment with a fairly sizeable chance of success. Adherence was high particularly in the PASS, which is likely due to the integration of this intervention into the normal class timetable. Despite FMS and HIPA being based in after school clubs, a relatively high compliance was also seen in these groups. Furthermore, in primary schools, the introduction of PASS into the compulsory school timetable could have some benefits for CV health. Further qualitative assessment could be used in future studies to assess for childrens enjoyment and changes in PA knowledge to help with maintaining high compliance levels and therefore successful interventions.

7.5 Conclusion

In conclusion, encouraging changes in CV variables were seen in all interventions albeit that these were sporadic in terms of pre-clinical variables an d interventions as well as being of a small absolute magnitude. These small but positive changes in CV disease risk factors occurred despite no significant and beneficial changes in CR fitness, PA levels and body composition. The mechanism of change for any CV variable is still undetermined as are the potential for the current interventions to be rolled out to other groups. Encouragingly, the compliance of children to these interventions was good and support the notion of further longitudinal work with paediatric populations.

Chapter 8

Synthesis of Findings

8.1 Thesis Recap

The general aim of this thesis was to understand and assess some of the 'pre-clinical' CV disease risk factors in pre-pubertal children in an attempt to recognise and offset future CV disease. Initially 'pre-clinical' markers of CV disease risk/development in pre-pubertal children were to be associated with body composition, PA and CR fitness in a broad cross-section of pre-pubertal children. Following this, an exploratory trial, aimed at introducing PA interventions and assess their effects on 'pre-clinical' markers, as well as body composition and CR fitness. Finally the impact of a 12-month long PA intervention period, spanning a full school year, was evaluated. Ultimately the feasibility of such interventions was to be assessed and their impact on CV 'pre-clinical' markers, body composition, CR fitness and PA levels. This programme of research provided a unique look at the current CV health of primary school children as well as developing strategies to combat future, adult, CV disease risk.

8.2 Recap of major findings

The cross-sectional study of 218 pre-pubertal children provided an in-depth look at the current CV health of children in Liverpool. The presence of 'pre-clinical' markers of CV disease risk in a normal 'healthy' population of pre-pubertal children was quite limited with the variables used in this thesis. The initial outcome of limited association between "pre-clinical" markers and PA, CR fitness and body composition should be viewed positively in that early markers of CV disease are largely absent in children of this age, irrespective of their CR fitness, PA and body composition. This could suggest that children in their pre-pubertal years are either relatively immune to lifestyle problems that would, later in life, lead to a rapid onset and development of

CV disease. Alternatively the data may be interpreted as showing that the chosen "pre-clinical" markers are not sensitive enough to register the early effects of reduced CR fitness, low levels of PA and high levels of body fat in pre-pubertal schoolchildren. Indeed, many might think that poor outcomes in CR fitness, PA monitoring and body composition assessment alone is cause for concern related to current and future disease risk. Certainly later in this synthesis we will consider other CV disease markers that could be assessed in similar population groups as well as before and after PA interventions.

A pertinent point related to all three studies is the nature of the population group studied. In all cases we attempted to investigate a "normal" cross-section of pre-pubertal Liverpool schoolchildren and whilst we reported significant variation and range in CR fitness, PA levels and body fatness we did not concentrate on the most unfit, the least active and the fattest section of this population. Notably in the cross-sectional study over 70% of the children were taking part in the required 60 minutes per day of MVPA (Biddle *et al.*,1998; Strong *et al.*, 2005) and over 80% of the children exceeded the proposed VO_{2peak} criteria (Ruiz *et al.*, 2007). With a high proportion of these children meeting the required PA and CR fitness criteria is it therefore less surprising that the prevalence of 'pre-clinical' CV disease risk factors was found to be so low. Interestingly even high levels of both PA and CR fitness were found to have little positive impact on the 'pre-clinical' CV disease risk markers and therefore again one might propose that at this early age children may be both immune from the direct negative or positive effect of poor lifestyle choices at this age. Whilst broadly beneficial in terms of physical capacity, psychology and pre-empting

lifelong health choice high levels of PA or CR fitness may not boost or protect the CV system at such an early age.

Admittedly a large proportion of the children in the cross-sectional study were overweight/obese (over 40% of them being classed as obese/overweight by BMI criteria; Chinn and Rona, 2004) but again no significant increases in 'pre-clinical' CV risk was identified. Clearly this should not be ignored as obesity is deemed as an independent risk factor for CV disease (Poirier and Eckel, 2002). Also notably with increasing FM both CR fitness and time spent in MVPA decreased. Nevertheless in the regression analyses the only large influence that FM appeared to exert was on LV mass in which LM also had a great impact. Given that LM represents a greater proportion of total mass it is likely that LM is the "driver" for changes in LV mass. Indeed both FM and LM increase with growth in pre-pubertal children and can be related to LV mass with LM likely the best theoretical and practical body size scalar for LV mass (Batterham and George, 1997).

Both intervention studies utilised differing PA interventions in an attempt to positively moderate early "pre-clinical" markers of CV disease risk. The introduction of PA interventions appeared to be promising in the exploratory trial but were not clearly supported by the longer term PA intervention trial. Although some potentially positive influences of the PA interventions were reported, after adjustment for covariate confounders, in the longer study further research is needed as this study also failed to demonstrate a beneficial influence on PA, CR fitness or body composition. Again it is pertinent to note that the subject groups recruited for the intervention trials

reflected a "normal" cross-section of pre-pubertal Liverpool schoolchildren and did not focus of the unfit, the inactive and those with the highest BMI.

Specifically, in the exploratory trial the only CV variable which appeared to clinically benefit from the PA intervention was cIMT. It appeared high intense (STEX) activity over 9 weeks reduced cIMT. These changes were small but substantial enough to suggest a clinically beneficial change compared to control subjects and warrant a more prolonged dose of PA intervention (study 3). Positive changes were also seen in the lifestyle intervention (PASS) but not to as great an extent as the structured exercise. One benefit of the short intervention is that the influence of maturational changes is likely small and it also provided an important "stepping-stone" to further studies. With these positive findings and the confirmation of the feasibility of implementing PA interventions in the school setting it was clear a more in-depth analysis was needed. From this initial trial the final study incorporated all of the lessons learned from the exploratory trial but with larger numbers, more interventions (inclusion of a skill-based session; FMS), some adjustments to PASS and STEX (HIPA) as well as for a greater length of time. An addition to PA intervention package was the introduction of a skill based session (FMS).

The year long interventions failed to improve PA levels, CR fitness and body composition variables of the children. Whilst this was not expected, nor deemed to be positive, it should again be considered that the participants, as in the other 2 studies, were a mix of high, moderate and low CR fitness, PA and BMI. Clearly, the interventions may not have had the same impact had we specifically recruited subjects who were deemed to be of low CR fitness, had low PA levels and/or where the

highest BMI. An intervention reduction in percent body fat associated with an increase in CR fitness and PA level would have been ideal but like other studies in children (Carrel *et al.*, 2005; Gutin *et al.*, 2008) is seemingly difficult to achieve particularly as children are growing and beginning to enter into puberty. Taking these issues into account future research may concentrate on lower CR fitness, PA and more obese populations and more substantive changes in 'pre-clinical' CV disease risk markers may be observed.

In the 12-month PA intervention study most CV variables that changed did so in line with normal maturation and growth. With LV mass, diastolic function and cIMT all increasing over the 12 month period it is likely this is all attributable to increasing body size but the relative contribution of maturational changes in LM and FM is still somewhat unclear. Again the fact that LM is larger and thus a larger proportion of total body mass may provide some indication of its relative importance. The lack of regression in cIMT in the 12-month compared to the 9-week trial would suggest that growth and maturation may be more important as a determinant of cIMT than PA or CR fitness at this age in these cohorts and thus masks a training effect. When analysis of cIMT (and other CV variables like LV mass) was conducted accounting for changes in FM and peak height velocity it appears that the PA interventions helped ameliorate to some extent the alterations in cIMT and LV mass and augment the positive change in BP and E'/A' although the influence of specific PA interventions varied to some degree for all the CV variables. Whilst small, these changes could have potential positive implications for future research in older children or for longer studies.

8.3. Overarching issues

The cohort

As we have already alluded to the cohorts in all three studies, children had relatively high CR fitness and most attained national goals for levels of MVPA. Despite this levels of overweight and obesity supported current local (Liverpool), national and international concerns about increasing prevalence of poor body composition. This does suggest a slight "dislocation" between body composition and other independent CV risk factors in pre-pubertal school children that may warrant further study and discussion. Overall the relative "health" of the cohorts presented a challenge in terms of observing or inducing positive health changes in CV variables. Indeed it also, seemingly, provided a challenge to alter CR fitness, PA and/or body composition even with the imposition of a 12-month PA intervention programme.

Trying to recruit large numbers of children to take part in PA interventions when they meet the criteria of low fitness, PA and poor body composition is likely a sensible way to move this research agenda forward. However, practically this is likely to be problematic as available populations from which to draw samples are reduced and some stigma may exist in such children associated with exercise and PA even before being placed in a research trial where they face repeated assessments. With this in mind perhaps a case study or small group numbers would be attainable for future research.

The early "pre-clinical" cardiovascular disease risk markers

The 'pre-clinical' CV disease risk markers used throughout this thesis were chosen because of their non-invasive nature (ethically more acceptable) and relative easy to

administer with young children as well as being quick to employ when dealing with mass-testing in children. However a combination of a lack of association with low PA, CR fitness and high body fat in the cross-sectional study and a general inability to detect differences due to a range of PA interventions places some question mark over the utility and sensitivity of the chosen markers.

Some research with similar cohorts, although often in adolescents, have reported improved vascular changes such as improved arterial stiffness and endothelial function through the implementation of similar PA interventions (Gates *et al.*, 2003; Woo *et al.*, 2004; Watts *et al.*, 2004). Green *et al.*, (2003) suggested that there are improvements in vascular variables even before any other improvements in other 'pre-clinical' CV markers. With this in mind perhaps the need for assessment of vascular function was needed within this thesis or could be adopted in future trials.

Furthermore analysis of CV markers in blood profiles has been shown to reproduce positive effects from previous PA interventions (Carrel *et al.*, 2005; Andersen *et al.*, 2008). This may be recommended for future studies in-conjunction with all the CV markers already discussed however this method is invasive and therefore increases the discomfort for children. Hence this may alter recruitment and compliance of children.

Role of Different PA interventions – Knowledge-base vs. Activity-base versus skills-base.

In the exploratory trial a positive response of cIMT to PA was only observed in the STEX programme and not in the PASS group. Further in the 12-month intervention

an increase in diastolic function (after adjustment for the effects of growth) was seen predominantly in the PASS group but not the HIPA group. Other examples of between intervention variability were presented in study 3. Whilst direct comparisons between the intervention studies is comprised by study length as well as more subtle changes in both STEX (HIPA) and PASS programmes these differences are interesting and worth following up. Some of the changes in the longer study would suggest that by implementing a knowledge based exercise intervention one can improve a pre-pubertal child's cardiac function irrespective of any changes in CR fitness, PA levels or body composition. Further studies are needed to support this as the effects of diet and vascular health should also be accounted for.

Feasability

The PA interventions introduced appeared to have some positive health-related impacts upon pre-pubertal schoolchildren. The feasibility and attendance records for all PA interventions was high, particularly that of PASS as it was incorporated into the normal school lesson timetable in study 3. This is beneficial to note as schools could easily adopt such practices and aid in the reduction of future CV risk factors in children. Brief qualitative questionnaires were distributed to the children and parents during the exploratory trial. All children appeared to enjoy the interventions which reflected in the high participation numbers. This was helped with the introduction of rewards given to the children following completion of tasks, assessments and attendance. Once the PA interventions were up and running the schools were very supportive of the studies and some teachers became very involved, even sometimes to the extent of joining in the sessions.

8.4 Implications for childhood health PA and policy

In children the current guidelines for PA, to maintain and/or promote CV health, are 60 minutes of moderate to vigorous physical activity (MVPA) daily (Biddle *et al.*,1998; Strong *et al.*, 2005). This thesis has provided data to support that a high percentage of children are meeting this criteria. Independent of attaining such criteria the cross-sectional study suggests that the prevalence of 'pre-clinical' markers of CV disease risk in this group is low but obesity prevalence is still quite high. As such one cannot clearly either support or alter the current guidelines for PA. Additionally this thesis would suggest that perhaps volume and intensity of PA in this age range is not as important as once thought but instead PA knowledge and skill-based activities could in-fact produce more desirable outcomes in children with adverse CV markers. Further research is needed to support these ideas such as exercise and health knowledge development impacts upon CV disease risk progression through puberty and adolescence as well as into adulthood.

8.5 Limitations and Problems encountered

The main limitations encountered were problems with measurement tools' of both PA and CR fitness, hence the lower numbers observed for analysis of these specific parameters. Accelerometer wear quite often did not meet regulation criteria for the full 9 hours a day or they were simply not worn at all. Wear problems were often due to the child taking part in contact or water based activities or simply forgetting to put the monitor on. Some of these issues were reduced by either re-monitoring children and/or introducing a reward system for meeting the wear time criteria. Additionally some monitors failed to receive any data due to technical faults.

Similarly technical issues did present themselves when using the on-line gas analyser for CR fitness that were primarily related to system breakdown and the use of, on occasion, different makes of on-line breath-by-breath analyser. Another issue with any test of maximal effort to volitional exhaustion is motivation on the part of the subject to push themselves to their physical limit. A number of children failed to reach maximal CR performance criteria (HR, RER data) due to either boredom or lack of motivation. Familiarisation sessions were used but in a small number of cases even this did not prevent sub-maximal effort.

8.6 Recommendations for further research

As has already been alluded too, further research is suggested in the more 'at risk' childhood groups. Previous research in overweight/obese and /or diabetic adolescents/children that have reported 'pre-clinical' CV risk factors to be elevated representing increased disease risk in these vulnerable populations (Chen *et al.*, 2005; Sharpe *et al.*, 2006; Maggio *et al.*, 2008). Furthermore the observation of children during (peri) puberty and post-puberty would provide a more in-depth analysis of CV risk as children develop into adults. Indeed following cohorts through this period of their life with multiple assessment points may be better than cross-sectional comparisons of children at different stages of pubertal development. The introduction of more intense PA interventions which are more likely to show improvements in PA, CR fitness and body composition are needed and potentially an extended range of early CV risk factors should then be assessed including measures of vascular endothelial health (Watts *et al.*, 2007).

Future intervention studies should also include some form of dietary analysis as this plays a large role in body composition variables. Finally, further research is needed with increased numbers in different geographical locations to assess global effects and impact and other factors such as seasonal variation in training, PA, fitness and health may need to be considered.

8.7 Conclusion

This thesis has provided a unique look at some of the 'pre-clinical' CV disease risk factors in a population of 'healthy' pre-pubertal children and the impact of differing PA interventions in this cohort. It appears there is a 'window of opportunity' for pre-pubertal children in whom these CV risk factors are not present irrespective of low PA levels, CR fitness and obesity. Whilst the introduction of PA interventions in this population is feasible and can produce high attendance records, improvements in PA levels, CR fitness and body composition were not observed. Nevertheless it appeared that compared to controls the interventions did produce some small and sporadic positive changes in CV variables. In the 12-month study PA interventions attenuated unwarranted increases in LV mass and cIMT associated with growth and also augmented diastolic function. In a 9-week PA intervention with a reduced maturation "contamination" a clinically relevant regression in cIMT was observed in the STEX PA intervention groups compare to controls. The exact mechanisms underpinning these changes are not clear but with diastolic BP also favourably altered it could be related to vascular endothelial health or large artery compliance.

At the beginning of this thesis the specific aims were;

(4) to document "pre-clinical" markers for CV disease risk/development in primary school children and to assess the relationship of these "pre-clinical" markers with body composition, physical activity and CR fitness.

(5) to assess the impact of short-term (9 weeks) physical activity interventions (traditional and lifestyle) on "pre-clinical" markers for CV disease, body composition and CR fitness.

(6) to assess the impact of long-term (52 weeks) physical activity interventions (traditional and lifestyle) on "pre-clinical" markers for CV disease, body composition, physical activity levels and CR fitness

The stated null hypothesises were;

Ho_1: Body composition, physical activity levels and CR fitness will not be significantly associated with "pre-clinical" CV disease markers in a "normal" population of prepubescent children.

Ho_2: The implementation of a short-term physical activity intervention will not alter "pre-clinical" markers of CV disease risk/development as well as body composition and CR fitness in prepubescent children.

Ho_3: The implementation of a long-term physical activity intervention will not alter "pre-clinical" markers of CV disease risk/development as well as body composition, physical activity levels and CR fitness in prepubescent children.

With these in mind this thesis has successfully answered these aims and can accept the first null hypothesis yet reject those associated with the interventions to some extent. This is because the exploratory trail appeared to have a positive influence on cIMT. The longer intervention failed to produce global increases in CR fitness, PA and reduced percent body fat and CV variables. Some small but positive findings were reported which warrant further investigation.

Chapter 9

References

9.1 References

Aadahl, M., Kjaer, M., and Jorgensen, T. (2007) Associations between overall physical activity level and cardiovascular risk factors in an adult population. European *Journal of Epidemiology,* **22,** 369-378.

Alpert, M.A. (2001). Obesity cardiomyopathy; pathophysiology and evolution of the clinical syndrome. *American Journal of Medical Science,* **321,** 225-236

American College of Sports Medicine (2000) *ACSM's guidelines for exercise testing and prescription; sixth edition.* USA; Lippincott Williams & Wilkins.

Andersen, L.B., Sardinha, L.B., Froberg, K., Riddoch. C.J., Page, A.S., Anderssen, S.A. (2008). Fitness, fatness and clustering of cardiovascular risk factors in children from Denmark, Estonia and Portugal: The European youth Heart Study. *International Journal of Pediatric Obesity,* **3,** 58-66.

Andersen, L.B., Wedderkopp, N., Hansen, H.S., Cooper, A.R., and Froberg, K. (2003). Biological cardiovascular risk factors cluster in Danish children and adolescences: The European Youth Heart Study. *Preventative Medicine,* **37,** 363-367.

Andersen, L.B., Harro, M., Sardinha, L.B., and Froberg, K. (2006). Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). *The Lancet,* **368,** 299-304

Anderssen, S.A., Cooper, A.R., Riddoch, C., Sardinha, L.B., Harro, M., Brage, S., and Andersen, L.B. (2007). Low Cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. *European Journal of Cardiovascular Prevention and Rehabilitation,* **14,** 526-531.

Armstrong, N., and Welsman, J.R. (1997). The physical activity patterns of European Youth with reference to methods of assessment. *Sports Medicine,* **36,** 1067-1086.

Armstrong, N., Welsman, J.R., and Kirby, B.J. (2000). Longitudinal changes in 11-13 year olds' physical activity. *Acta Paediatrica,* **89,** 775-780.

Armstrong, N., and Welsman, J.R. (2000). Aerobic fitness, In *Paediatric Exercise Science and Medicine* (Eds. N. Armstrong and W. van Mechelen), pp. 65-75. New York: Oxford University Press Inc.

Armstrong, N., Welsman, J.R., and Winsley, R. (1996). Is peak VO2 a maximal index of children's aerobic fitness? *International journal of Sports Medicine,* **17,** 356-359.

Armstrong, N., and Welsman, J.R. (1994). Assessment and interpretation of aerobic fitness in children and adolescents. *Exercise and Sports Science reviews,* **22,** 435-476.

Armstrong, N., and Simons-Morton, B. (1994). Physical activity and blood lipids in adolescence. *Pediatric Exercise,* **3,** 219-228.

Bacon, S.L., Sherwood, A., Hinderliter, A., and Blumenthal, J.A. (2004) Effects of exercise, diet and weight loss on high blood pressure. *Sports Medicine*, **34**, 307-16

Bandura, A (1986) *Social Foundations of Thought and Action: A Social Cognitive Theory*. Englewood Cliffs, NJ: Prentice Hall.

Baranowski, T., Cullen, K.W., Nicklas, T., Thompson, D., Baranowski, J. (2003). Are current health behavioural change models helpful in guiding prevention of weight gain effort? *Obesity Research,* **11**, 23S-43S

Baranowski, T. (1988). Validity and reliability of self-report measures of physical activity: An information-processing perspective. *Research Quarterly for Exercise and Sport, 59*, 314-32

Batterham, A.M. and George, K.P. (1997). Modeling the influence of body size and composition on M-mode echocardiographic dimensions. *American Journal of Physiology,* **274**, H701-708.

Batterham, A.M., George, K.P., Whyte, G., Sharma, S., and Mckenna, W. (1999). Scaling cardiac structural data by body dimensions: a review of theory, practice and problems. *International Journal of Sports Medicine,* **8**, 495-502.

Batterham, A.M., and Hopkins, W.G., (2006) Making meaningful inferences about magnitudes. *International Journal of Sports Physiology and Performance*, **1**, 50-57.

Berlin, J.A., and Colditz, A. (1990). A meta-analysis of physical activity in the prevention of coronary heart disease. *American Journal of Epidemiology,* **132**, 612-627.

Biddle, S., Cavill, N., and Sallis, J. (1998) Policy framework for young people and health-enhancing physical activity. *In Young and Active? Young people and Health-enhancing Physical Activity: Evidence and Implications.* (edited by S.Biddle, J.Sallis and N.Cavill), p3-16. London, Health Education Authority.

Blair, S. N., Clark, D. B., Cureton, K. J. and Powell, K.E. (1989). Exercise and Fitness in Childhood: Implications for a lifetime of health. In C. V. Gisolfi & D. L. & D. L. Lamb (eds.), *Perspectives in exercise science and sports medicine, vol. 2. youth, exercise and sport* (pp. 401-430). Indianapolis, IN: Bench Mark Press.

Boreham, C.A., Twisk, J., Savage, M.J., Cran, G.W., and Strain, J.J. (1997). Physical activity, sports participation and risk factors in adolescences. *Medicine and Science in Sports and Exercise*, **29**, 788-793.

Borodulin, K., Laatikainen, T., Lahti-Koski, M., Lakka, T.A., Laukkanen, R., Sarna, S., Jousilahti, P. (2005) Associations between estimated aerobic fitness and cardiovascular risk factors in adults with different levels of abdominal obesity.

European Journal of Cardiovascular Prevention and Rehabilitation, **12**, 126-131.

Bots, M.L. (2006). Carotid intima-media thickness as a surrogate marker for cardiovascular disease in intervention studies. *Current Medical Research and Opinion,* **22,** 2181-2190.

Burgomaster, K.A., Hughes, S.C., Heigenhauser, G.J., Bradwell, S.N., and Gibala, M.J. (2005). Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *Journal of Applied Physiology,* **98,** 1985-1990.

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A.L., Sandercock, P., Spiegelhalter, D., and Tyrer, P. (2000). Framework for design and evaluation of complex interventions to improve health. *British Medical Journal,* **321,** 694-696.

Carrel, A.L., Clark, R.R., Peterson, S.E., Nemeth, B.A., Sullivan, J., and Allen, D.B. (2005). Improvement of fitness, body composition, and insulin sensitivity in overweight children in a school-based exercise program: a randomized, controlled study. *Archives of Pediatrics and Adolescent Medicine,* **159,** 963-968.

Chen, W., Srinivasan, S.R., Li, S., Xu, J., and Berenson, G.S. (2005) Metabolic syndrome variables at low levels in childhood are beneficially associated with adulthood cardiovascular risk. *Diabetes Care,* **28,** 126-131.

Chinn, S., and Rona R.J. (2004). Letter to the editor re: International definitions of overweight and obesity for children: a lasting solution? *Annals of Human Biology,* **31,** 695-696.

Clarke, W.R. and Lauer, R.M. (1993). Does childhood obesity track into adulthood? *Critical Reviews in Food Science and Nutrition*, **33**, 423-430.

Cohen, J., (1988). Statistical Power Analysis for the Behavioral Sciences, 2nd edition. Hillsdale, NJ: Lawrence Erlbaum (pp. 24, 83).

Curran-Everett, D., Taylor, S., and Kafadar, K. (1998). Fundamental concepts in statistics: elucidation and illustration. *Journal of Applied Physiology*, **85**, 775-786.

Daniels, S.R., Morrison, J.A., Sprecher, D.L., Khoury, P., and Kimball, T.R. (1999). Association of body fat distribution and cardiovascular risk factors in children and adolescents. *Circulation*, **2**, 541-545

Daniels, S.R., Kimball, T.R., Morrison, J.A., Khoury, P., Witt, S., and Meyer, R.A. (1995). Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. *Circulation*, **92**, 3249-3254.

De Groot, E., Hovingh, G.K., Wiegman, A., Duriez, P., Smit, A.J., Fruchart, J-C., and Kastelein, J.J.P. (2004). Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation*, **109**, III-33-III-38.

Denker, M., Thorsson, O., Karlsson, M.K., Linden, C., Eiberg, S., Wollmer, P., and Andersen, L.B. (2007). Gender differences and determinants of aerobic fitness in children aged 8-11 years. *European Journal of Applied Physiology*, **99**, 19-26

Department of Health, (2002). Drug use, smoking and drinking among young people in England in 2001. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4010044

De Simone, G., Kizer, J.R., Chinali, M., Roman., M.J., Bella, J.N., Best, L.G., Lee, E.T., and Devereux, R.B. (2005). Normalization for body size and population-attributable risk of left ventricular hypertrophy: the Strong Heart Study. *American Journal of Hypertension*, **18**, 191-196

Devereux, R.B., Alonso, D.R., Lutas, E.M., Gottlieb, G.J., Campo, E., Sachs, I. And Reichek, N. (1986). Echocardiographic assessment of left ventricular hypertrophy: comparison of necropsy findings. *American Journal of Cardiology,* **57**, 450-458.

Diaz, V.A., Player, M.S., Mainous, A.G., Carek, P.J., and Geesey, M.E. (2006). Competing impact of excess weight versus cardiorespiratory fitness on cardiovascular risk. *American Journal of Cardiology,* **11**, 1468-1471

Di Bello, V., Santini, F., Di Cori, A., Pucci, A., Palagi, C., Delle Donne, M.G., Giannetti, M., Talini, E., Nardi, C., Pedrizzetti, G., Fierabracci, P., Vitti, P., Pinchera, A., and Balbarini, A (2006). Relationship between preclinical abnormalities of global and regional left ventricular function and insulin resistance in severe obesity: a color Doppler imaging study. *International Journal of Obesity,* **30**, 948-956.

Dollman, J., Norton, K., and Norton, L. (2005) Evidence for secular trends in children's physical activity behaviour. *British Medical Journal*, **39**, 892-897.

Eckel, R.H., York, D.A., Rossner, S., Hubbard, V., Caterson, I., St Jeor, S.T., Hayman, L.L., Mullis, R.M. and Blair, S.N. (2004) American Heart Association. Prevention Conference VII: obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation*, **110**, 2968-2975

Edmundson, E,W., Luton, S, C., McGraw, S, A., Kelder, S, H., Layman, A, K., Smyth, M, H., Bachman, K, J., Pedersen, S, A. and Stone, E, J. (1994). CATCH: Classroom Process Evaluation in a Multicenter Trial. *Education Quarterly,* **2**, S27 – S50.

Eiberg, S., Hasselstrom, H., Gronfeldt, V., Froberg, K., Svensson, J., and Andersen, L.B. (2005). Maximum oxygen uptake and objectively measured physical activity in Danish children 6-7 years of age: the Copenhagen school child intervention study. *British Journal of Sports Medicine,* **39**, 725-730

Eisenmann, J.C., Welk, G.J., Ihumels, M., and Dollman, J. (2007). Fatness, fitness and cardiovascular disease risk factors in children and adolescences. *Medical Science in Sports and Exercise*, **39**, 1251-1256.

Epstein, L. H., Paluch, R. A., Kalakanis, L. E., Goldfield, G. S., Cerny, F. J., & Roemmich, J. N. (2001). How much activity do youth get? A quantitative review of heart-rate measured activity. *Pediatrics,* **108**, e44-e54.

Farrell, S.W., Kampert, J.B., Kohl, H.W., Barlow, C.E., Macera,C.A., Paffenbarger, R.S. Jr, Gibbon, L.W. and Blair, S.N. (1998). Influences of cardiorespiratory fitness levels and other predictors on cardiovascular disease mortality in men. *Medicine and Science in Sports and Exercise,* **30,** 899-905

Feigenbaum, H., Armstrong, W.F., and Ryan, T. (2005). *Feigenbaum's Echocardiography,* USA; Lippincott Williams & Wilkins.

Floriani, V. and Kennedy, C. (2007) Promotion of physical activity in primary care for obesity treatment/prevention in children. *Current Opinion in Pediatrics,* **19,** 99-103

Foweather, L., McWhannell, N., Henaghan, J., Lees, A., Stratton, G., and Batterham, A. (2008), Effect of a 9-week after-school multiskills club on fundamental movement skill proficiency in 8 to 9 year old children: an exploratory trial. *Perceptual Motor Skills,* **106,** 745-754.

Freedman, D.S., Dietz, W.H., Tang, R., Mensah, G.A., Bond, M.G., Urbina, E.M., and Srinivasan, S. (2004). The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. *International Journal of Obesity*, **28**, 159-166

Faggard, R.H. (1997). Impact of different sports and training on cardiac structure and function. *Cardiology Clinics,* **15,** 397-412.

Froehlich G. (1999). What is the chance that this study is clinically significant? A proposal for Q values. *Effective Clinical Practice,* **2**, 234-239.

Gates, P.E., Tanaka, H., Graves, J., and Seals, D.R. (2003). Left ventricular structure and diastolic function with human ageing. Relation to habitual exercise and arterial stiffness. *European Heart Journal,* **24**, 2213-2220.

George, K.P., Gates, P.E., and Tolfrey, K. (2005). Impact of aerobic training upon left ventricular morphology and function in pre-pubescent children. *Ergonomics*, **11-14**, 1378-1389

Green, D.J., Walsh, J.H., Majorana, A., Best, M.J., Taylor, R.R., and O'Driscoll, J.G. (2003). Exercise-induced improvement in endothelial dysfunction is not mediated by changes in CV risk factors: pooled analysis of divers patient populations. *American Journal of Physiology. Heart and Circulatory Physiology,* **285**, H2679-H2687.

Green, D.J., and Cable, T. (2006). Physical activity to prevent obesity in young children: BMI in the BMJ. *British Medical Journal,* **333**, 1171.

Gutin, B., Islam, S., Manos, T., Cucuzzo, N., Smith, C., and Stachura, M. (1994). Relation of percentage body fat and maximal aerobic capacity to risk factors for atherosclerosis and diabetes in black and white seven to eleven year old children. *Journal of Pediatrics,* **125,** 847-852

Gutin, B., Owens, S., Treiber, F., Islam, S., Karp, W., and Slavens, G. (1997). Weight-independent cardiovascular fitness and coronary risk factors. *Archives of Pediatrics and Adolescent Medicine,* **151**, 462-465.

Gutin, B., Yin, Z., Humphries, M.C., and Barbeau, P. (2005). Relations of moderate and vigorous physical activity to fitness and fatness in adolescents. *American Journal of Clinical Nutrition,* **81**, 746-750.

Gutin, B., Yin, Z., Johnson, M., and Barbeau, P. (2008). Preliminary findings of the effect of a 3-year after school physical activity intervention on fitness and body fat: The Medical College of Georgia Fitkid Project. *International Journal of Pediatric Obesity,* **3**, 3-9.

Hanevold., C. Waller, j., Daniels, S., Portman, R., Sorof, J., and International Pediatric Hypertension Association (2004). The effects of obesity, gender and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. Pediatrics, **113**, 328-333.

Hansen, S.E., Hasselstrom, H., Gronfeldt, V., Froberg, K., and Andersen, L.B. (2005). Cardiovascular disease risk factors in 6-7 year old Danish children: the Copenhagen School Child Intervention Study. *Preventive Medicine,* **40,** 740-746.

Harrell, J. S., Pearce, P. F. and Hayman, L. L. (2003). Fostering Prevention in Paediatric Population. *Journal of Cardiovascular Nursing,* **18**, 144-149

Harro, M., & Riddoch, C. J. (2000). Physical activity. In N. Armstrong & W. van Mechelen (Eds.), *Pediatric Exercise Science and Medicine* (pp. 77-84). Oxford, UK: Oxford University Press.

Haywood, K., & Getchell, N. (2005). *Life span motor development*. Champaign, IL: Human Kinetics.

Henaghan, J., McWhannell, N., Foweather, L., Cable, N.T., Batterham, A.M., Stratton, G., and George, K.P. (2008). The effect of structured exercise classes and a lifestyle intervention on cardiovascular risk factors in primary school children: an exploratory trial (The A-CLASS Project). *Pediatric Exercise Science,* **20**, 169-180.

Hill, A.M., Buckley, J.D., Murphy, K.J., and Howe, P.R. (2007). Combining fish oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors. *American Journal of Clinical Nutrition*, **85**, 1267-1274.

Hodis, H.N., Mack, W.J., Labree, L., Selzer, R.H., Liu, C., and Stanley, P.A. (1998). The role of carotid intima-media thickness in predicting clinical coronary events. *Annals of Internal Medicine,* **128**, 262-269

Hu, G., Tuomilehto, J., Silventoinen, K., Barengo, N., and Jousilahti, P. (2004). Joint effects of physical activity, body mass index, waist circumference and waist-to-hip

ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *European Heart Journal,* **24**, 2212-2219

Humphries, M.C., Gutin, B., Barbeau, P., Vemulapalli, S., Allison, J., and Owens, S. (2002). Relations of adiposity and effects of training on the left ventricle in obese youths. *Medicine in Science of Sports and Exercise,* **34**, 1428-1435

Hurtig-Wennlof, A., Ruiz J.R., Harro, M and Sjostrom, M. (2007) Cardiorespiratory fitness relates more strongly than physical activity to cardiovascular disease risk factors in healthy children and adolescents: the European Youth Heart Study. *European Journal of Cardiovascular Prevention and Rehabilitation,* **14**, 575-581.

Iannuzzi, A., Licenziati, M.R., Acampora, C., Salvatore, V., Auriemma, L., Romano, M.L., Panico, S., Rubba, P., and Trevisan, M. (2004). Increased carotid intima-media thickness and stiffness in obese children. *Diabetes Care*, **27**, 2506-2508

Invitti, C., Maffeis, C., Gilardini, L., Pontiggia, B., Mazzilli, G., Gorola, A., Sartorio, A., Morabito, F. and Viberti, G.C. (2006). Metabolic syndrome in obese Caucasian children: prevalence using WHO-derived criteria and association with non-traditional cardiovascular risk factors. *International Journal of Obesity*, **30**, 627-633

Ishizu, T., Ishimitsu, T., Yanagi, H., Seo, Y., Obara, K., Moriyama, N., Watanabe, S., and Yamaguchi, I. (2004). Effect of age on carotid arterial intima-media thickness in childhood. *Heart Vessels,* **19**, 189-195.

Janz, K. F. (2002). Use of heart rate monitors to assess physical activity. In G. J. Welk (Ed.), *Physical Activity Assessments for Health-Related Research* (pp. 143-161). Champaign, IL: Human Kinetics.

Janz, K.F., Dawson, J.D., and Mahoney, L.T. (2000). Predicting heart growth during puberty: The Muscatine Study. *Pediatrics,* **105**, 63-80

Jones, F., Harris, P., Waller, H., and Coggins, A. (2005). Adherence to an exercise prescription scheme: the role of expectations, self efficacy, stage of change and psychological well-being. *British Journal of Health Psychology,* **10,** 359-378

Katzmarzyk, P.T., Srinivasan, A.R., Chen, W., Malina, R., Bouchard, C., and Berenson, G.S. (2004). Body mass index, waist circumference and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents. *Pediatrics*, **114**, e198-e205.

Khouri, S.J., Maly, G.T., Suh, D.D., and Walsh, T.E. (2004). A practical approach to the echocardiographic evaluation of diastolic function. *Journal of the American Society of Echocardiography,* **17,** 290-297

Kohl, H. W., Fulton, J. E., & Caspersen, C. J. (2000). Assessment of physical activity among children and adolescents: A review and synthesis. *Preventive Medicine, 31,* S54-S76.

Kwee, A., and Wilmore, J.H. (1990). Cardiorespiratory fitness and risk factors for coronary artery disease in 8-15 year old boys. *Pediatric Exercise Science,* **2,** 372-383.

Lang, R.M., Bierig, M., Devereux, R.B., Flachskampf, F.A., Foster, E., Pellikka, P.A., Picard, M.H., Roman, M.J., Seward, J., Shanewise, J., Solomon, S., Spencer, K.T., Sutton, M.S.J., and Stewart, W. (2006). Recommendations for chamber quantification. *European Journal of Echocardiography,* **7**, 79-108.

Leary, S.D., Ness, A.R., Smith, G.D., Mattocks, C., Deere, K., Blair, S.N., and Riddoch, C. (2008). Physical activity and blood pressure in childhood: findings from a population-based study. *Hypertension,* **51**, 92-98.

Lee, S., Kuk, J.L., Katzmarzyk, P.T., Blair, S.N., Church, T.S., and Ross, R. (2005). Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men. *Diabetes Care,* **28**, 895-901

Lesser, G.T., and Deutsch, S. (1967). Measurement of adipose tissue blood flow and perfusion in man by uptake of 85Kr. *Journal of Applied Physiology*, **23**, 621-630

Levy, D., Garrison, R.J., Savage, D.D., Kannel, W.B., and Castelli, W.P. (1989). Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. *Annals of Internal Medicine,* **15**, 101-107

Levy, D., Garrison, R.J., Savage, D.D., Kannel, W.P., and Castelli, W.P. (1990). Prognostic implications of echocardiography determined by left ventricular mass in the Framingham Heart Study. *New England Journal of Medicine*, **322**, 1561-1566

Liao, Y., Cooper, R.S., Durazo-Arvizu, R., Mensah, G.A., and Ghali, J.K. (1997). Prediction of mortality risk by different methods of indexation for left ventricular mass. *Journal of the American College of Cardiology,* **29**, 641-647

Lobstein, T., Baur, L., Uauy, R. (International Obesity Task Force) (2004). Obesity in children and young people: a crisis in public health, *Obesity Reviews,* **5**, 4-104

Lobstein, T., and Frulet, M.L. (2003). Prevalence of overweight among children in Europe, *Obesity Reviews,* **4**, 195-200

Lobstein, T.J., James, W.P.T., and Cole, T.J. (2003). Increasing levels of excess weight among children in England, *International Journal of Obesity,* **27**, 1136-11387.

Lorenz, M.W., Markus, H.S., Bots, M.L., Rosvall, M. and Sitzer, M. (2007). Prediction of clinical cardiovascular events with carotid intima-media thickness. A systematic review and meta-analysis. *Circulation,* **115,** 459-467.

Macarthur, D.G., and North, K.N. (2005). Genes and human elite athletic performance. *Human Genetics,* **116**, 331-339

Maggio, A.B., Aggoun, Y., Marchand, L.M., Martin, X.E., Herrmann, F., Beghetti, M., and Farpour-Lambert, N.J. (2008). Associations among obesity, blood pressure, and left ventricular mass. *Journal of Pediatrics,* **152**, 489-493.

Maziekas, M.T., LeMura, L.M., Stoddard, N.M., Kaercher, S., and Martucci, T. (2003). Follow up exercise studies in paediatric obesity: implications for long term effectiveness. *British Journal of Sports Medicine*, **37**, 425-429.

McGill, H.C., McMahan, A., Hererick, E.E., Tracy, R.E., Malcome, G.T., Zieske, A.W. and Strong, J.P. (2000) Effects of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. *Atherosclerotic and Thrombolitic Vascular Biology,* **20,** 836-845

McMurray R.G., Ainsworth, B.E., Harrell, J.S., Griggs, T.R., and Williams, O.D. (1998). Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors? *Medical Science in Sports and Exercise,* **30,** 1521-1529.

McMurray, R.G., Harrell, J.S., Bangdiwala, S.I., Bradley, C.B., Deng, S., and Levine, A. (2002). A school-based intervention can reduce body fat and blood pressure in young adolescents. *Journal of Adolescent Health*, **31,** 125-132

Merchant, A.T., Dehghan, M., Behnke-Cook, D., and Anand, S.S. (2007). Diet, physical activity, and adiposity in children in poor and rich neighbourhoods: a cross sectional comparison. *Nutrition Journal,* **6,** 1475

Mertens, D.J., Kavanagh, T., Campbell, R.B. and Shepard, R.J. (1998). Exercise without dietary restriction as a means to long term fat loss in the obese cardiac patient. *Journal of Sports Medicine and Physical Fitness,* **38,** 310-316.

Meyer, A.A., Kundt, G., Steiner, M., Schuff-Werner, P., and Kienast, W. (2006). Impaired flow-mediated vasodilation, carotid artery imtima-media thickening, and elevated endothelial plasma markers in obese children: The impact of cardiovascular risk factors. *Pediatrics*, **177**, p1560-1567

Meyer, A., Kundt, G., Lenschow, U., Schuff-Werner, P and Kienast, W. (2006). Improvement of early vascular changes and cardiovascular risk factors in obese children after a six month exercise program. *Journal of the American College of Cardiology*, **48**, 1865-1870.

Mitchell, B.M., Gutin, B., Kapuku, G., Barbeau, P., Humphries, M.C., Owens, S., Vemulapalli, S., and Allison, J. (2002). Left ventricular structure and function in obese adolescents: relations to cardiovascular fitness, percent body fat and visceral adiposity, and effects of physical training. *Pediatrics*, **109**, e73-e78

Moore, L.L., Gao, D., Bradlee, M.L., Cupples, L.A., Sundarajan-Ramamurti, A., Proctor, M.H., Hood, M.Y., Singer, M.R., and Ellison, R.C. (2003). Does early physical activity predict body fat change throughout childhood? *Preventive Medicine*, **37**, 10-17.

Nelson, M.C., Neumark-Stzainer, D., Hannan, P.J., Sirard, J.R., and Story, M. (2006). Longitudinal and secular trends in physical activity and sedentary behaviour during adolescence, *Pediatrics*, **118**, e1627-1634

Nilsson, A., Anderssen, S.A., Andersen, l.B., Froberg, K., Riddoch, C., Sardinha, L.B., and Ekeland, U. (2008). Between and within day variability in physical activity and inactivity in 9 and 15 year old European Children. *Scandinavian Journal of Medicine and Science in Sports,* **1,** in press.

Nottin, S., Nguyen, L-D., Terbah, M., and Obert, P. (2004). Left ventricular function in endurance trained children by tissue Doppler imaging. *Medicine and Science in Sports and Exercise*, **36**, 1507-1513

Obert, P., Nottin, S., Baquet, G., Thevenet, D., Gamelin, F.X., and Berthoin, S. (2007). Two months of endurance training does not alter diastolic function evaluated by TDI in 9-11 year old boys and girls. *British Journal of Sports Medicine*, **10**, in press.

Office of National Statistics (2005). General Register Office. Edinburgh, Scotland; http://www.heartstats.org/temp/Tabsp1.2spweb06.xls

Office of the Deputy Prime Minister [homepage] (2004). Indices of Deprivation 2000. Available at www.odpm.gov.uk. Accessed 9 June 2004.

Okely, A., Booth, M., and Patterson, J. (2001). Relationship of cardiorespiratory endurance to fundamental movement skill proficiency among adolescents. *Pediatric Exercise Science,* **13,** 380-391.

Okely, A. D., Booth, M. L., and Chey, T. (2004). Relationships between body composition and fundamental movement skills among children and adolescents. *Research Quarterly for Exercise and Sport,* **75**, 238-247.

Olds, T.S., Ridley, K., and Tomkinson, G.R. (2007). Declines in aerobic fitness: are they only due to increasing fatness? *Medicine and Sports Science,* **50**, 226-240

Ortega, F.B., Ruiz, J.R., and Sjostrom, M. (2007). Physical activity, overweight and central adiposity in Swedish children and adolescents: the European Youth Heart Study. *International Journal of Behaviour, Nutrition and Physical Activity,* **19**, 61.

Paffenbarger, R.S., Wing, A.L., Hyde, R.T., and Jung, D. (1983). Chronic disease in former college students: physical activity and incidence of hypertension of college alumni. *American Journal of Epidemiology,* **117**, 245-257.

Pate, R.R., Pratt. M., Blair, S.N., Haskell, W.L., Macera, C.A., Bouchard. C., Buchner, D., Ettinger, W., Heath, G.W., King A.C. et al. (1995) Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association,* **273**, 402-407.

Pela, G., Bruschi, G., Montagna, L., Manara, M., and Manca, C. (2004). Left and right ventricular adaptation assessed by Doppler tissue echocardiography in athletes. *Journal of the American Society of Echocardiography,* **17**, 205-211

Perneger, T.V. (1998). What's wrong with Bonferroni adjustments? *British Medical Journal*, **316**, 1236-1238.

Poirier, P., and Eckel, R.H. (2002). Obesity and cardiovascular disease. *Current Atherosclerosis Reports*, **4**, 448-453

Powell, K.E., Thompson, P.D., Caspersen, C.J., and Kendrick, K.S. (1987). Physical activity and the incidence of coronary heart disease. *Annual Review of Public Health*, **8**, 281-287.

Prentice, A.M., and Jebb, S.A. (1995). Obesity in Britain: gluttony or sloth? *British Medical Journal.*, **311**, 437-439.

Riddoch, C.J., Andersen, L.B., Wedderkopp, N., Harro, M., Klasson-Heggebo, l., Sardinha, L.B., Cooper, A.R. and Ekelund, U. (2004). Physical activity levels and patterns of 9 and 15 year old European Children. *Medicine and Science in Sports and Exericse*, **36**, 86-92.

Rizzo, N.S., Ruiz, J.R., Hurtig-Wennlof, A., Ortega, F.B., and Sjostrom, M. (2007). Relationship of physical activity, fitness and fatness with clustered metabolic risk in children and adolescents: The European Youth Heart Study. *Journal of Pediatrics*, **150**, 388-394.

Roberts, W.C., and Roberts, J.D. (1983). The floating heart or the heart too fat to sink: analysis of 55 necropsy patients. *American Journal of Cardiology*, **52**, 1286-1289

Ross, R., and Katzmarzyk, P.T. (2003). Cardiorespiratory fitness is associated with diminished total and abdominal obesity independent of body mass index. *International Journal of Obesity Related Metabolic Disorders,* **27**, 204-210.

Rowland, T.W. (2007). Evolution of maximal oxygen uptake in children. (2007). *Medicine in Sports Science,* **50**, 200–209.

Ruiz, J.R., Rizzo, N.S., Hurtig-Wennlof, A., Ortega, F.B., Warnberg, J., and Sjostrom, M. (2006). Relations of total physical activity and intensity to fitness and fatness in children: The European Youth Heart Study. *American Journal of Clinical Nutrition,* **84**, 299-303.

Ruiz, J.R., Ortega, F.B., Rizzo, N.S., Villa, I., Hurtig-Wennlof, A., Oja, L., and Sjostrom, M. (2007). High cardiovascular fitness is associated with low metabolic score in children: the European Youth heart Study. *Pediatric Research,* **61**, 350-355.

Sallis JF and Owen, N (1999) Ecological models, In K. Glanz, F.M Lewis and B.K. Rimmer (Eds.), Health behaviour and health education: theory, research, and practice (2nd ed., pp. 403-424). San Francisco: Jossey-Bass.

Salmon, J., Ball, K., Crawford, D., Booth, M., Telford, A., Hume, C., Jolley, D., and Worsley., A. (2005). Reducing sedentary behaviour and increasing physical activity among 10-year-old children: overview and process evaluation of the 'switch-play' intervention. *Health Promotion International,* **20**, 7-17,

Sass, C., Herbeth, B., Chapet, O., Siest, G., Visvikis, S., and Zannad, F. (1998). Intima-media thickness and diameter of carotid and femoral arteries in children, adolescences and adults from the Stanislas cohort: effect of age, sex, anthropometry and blood pressure. *Journal of Hypertension,* **16**, 1593-1602.

Savage, D.D., Levy, D., Dannenberg, A.L., Garrison, R.J., and Castelli, W.P. (1990). Association of echocardiographic left ventricular mass with body size, blood pressure and physical activity (the Framingham Study). *American Journal of Cardiology,* **65**, 371-376.

Savoye, M., Shaw, M., Dziura, J., Tamborlane, W.V., Rose, P., Guandalini, C., Goldberg-Gell, R., Burgert, T.S., Cali, A.M., Weiss, R., and Caprio, S. (2007). Effects of a weight management program on body composition and metabolic parameters in overweight children: a randomized controlled trial. *Journal of the American Medical Association,* **297**, 2697-2704

Schiel, R., Beltschikow, W., Radon, S., Kramer, G., Perenthaler, T., and Stein, G. (2007). Increased carotid intima-media thickness and associations with cardiovascular risk factors in obese and overweight children and adolescents. *European Journal of Medical Research,* **12**, 503-508.

Schiller, N.B., Shah, P.M., Crawford, M. DeMaria, A., Devereux, R., Feigenbaum, H,. Gutgesell, H., Reichek, N., Sahn, D., Schnittger, I. Et al (1989). Recommendations for quantitation of the left ventricle by two-dimensional

echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of two-dimensional echocardiograms. Journal of American Society of Echocardiography, **2**, 358-367

Schoeller, D.A., and van Santen E. (1982). Measurement of energy expenditure in humans by doubly labelled water method. *Journal of Applied Physiology*, **53**, 955-959

Serdula, M.K., Ivery, D., Coates, R.J., Freedman, D.S., Williamson, D.F., and Byer, T. (1993). Do obese children become obese adults? A review of literature. *Preventative Medicine*, **22**, 167-177

Shakespeare, T.P., Gebski, V.J., Veness, M.J., Simes, J. (2001). Improving interpretation of clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours. *Lancet*, **357**, 1349-1353.

Sharpe, J.A., Naylor, L.H., Jones, T.W., Davis, E.A., O'Driscoll, G., Ramsay, J.M., and Green, D.J. (2006). Impact of Obesity on diastolic function in subjects ≤ 16 years of age. *The American Journal of Cardiology*, **98**, p691-693

Sherar, L.B., Mirwald, R.L., Baxter-Jones, A.D.G., and Thomas, M. (2005). Prediction of adult height using maturity-based cumulative height velocity curves. *Journal of Pediatrics,* **147**, 508-514

Sirard, J. R., & Pate, R. R. (2001). Physical activity assessment in children and adolescents. *Sports Medicine,* **31**, 439-454.

Sorof, J.M. (2001). Systolic hypertension in children: benign or beware? *Pediatric Nephrology,* **16**, 517-525.

Sorof, J.M., Alexandrov, A.V., Garami, Z., Turner, J.L., Grafe, R.E., Lai, D., and Portman, R.J. (2003). Carotid ultrasonography for diction of vascular abnormalities in hypertensive children. *Pediatric Nephrology,* **18**, 1020-1024

Sorof, J.M., Lai, D., Turner, J., Poffenbarger, T., and Portman, R.J. (2004). Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*, **133**, 475-482.

SportsLinx. (2004). *Childhood obesity in Liverpool. Where do we go from here?* Liverpool City Council annual obesity report.

Sproston, K. and Primatesta, P. (2003). *Health Survey for England 2002; the health of children and young people.* London: The Stationery Office 2003

Stein, J.H., Douglas, P.S., Srinivasan, S.R., Bond, G., Tang, R., Li, S., Chen, W., and Berenson, G.S. (2004). Distribution and cross-sectional age-related increases of carotid artery intima-media thickness in young adults. The Bogalusa Heart Study. *Stroke*, **35**, 2782-2787.

Steinberger, J., Moran, A., Hong, C.P., Jacobs, D.R.Jr, and Sinaiko, A.R. (2001). Adiposity in childhood predicts obesity and insulin resistance in young adulthood. *Journal of Pediatrics,* **138,** 469-473

Stensel, D.J., Lin, F.P., Ho, T.F., and Aw, T.C. (2001). Serum lipids, serum insulin, plasma fibrinogen and aerobic capacity in obese and non-obese Singaporean boys. *International Journal of Obesity Related Metabolic Disorders,* **25,** 984-989.

Sterne, J.A, and Davey-Smith, G. (2001). Sifting the evidence – what's wrong with significance tests? *British Medical Journal*, **322**, 226-231.

Stratton, G., Ridgers, N.D., Fairclough, S.J., and Richardson, D.J. (2007). Physical activity levels of normal-weight and overweight girls and boys during primary school recess. *Obesity,* **15**, 1513-1519.

Strong, W.B., Malina, R.M., Blimkie, C.J., Daniels, S.R., Dishman, R.K., Gutin, B., Hergenroeder, A.C., Must, A., Nixon, P.A., Pivarnik, J.M., Rowland, T., Trost, S., and Trudeau, F. (2005). Evidence based physical activity for school age youth. *Journal of Pediatrics,* **146**, 732-737.

Sui, X., LeMonte, M.J., Laditka, J.N., Hardin, J.W., Chase, N., Hooker, S.P., and Blair, S.N. (2007). Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *Journal of the American Medical Association,* **298**, 2507-2516.

Talbot, L.A., Morrell, C.H., Metter, E.J., and Fleg, J.L. (2002). Comparison of cardiorespiratory fitness versus leisure time physical activity as predictors of coronary events in men aged < or = 65 years and > 65 years. *American Journal of Cardiology,* **15**, 1187-1192.

Taylor, M.J., Mazzone, M., and Wrotniak, B.H. (2005). Outcome of an exercise and educational intervention for children who are overweight. *Pediatric Physical Therapy,* **17**, 180-188

Tolfrey, K., Jones, A.M., and Campbell, I.G. (2004). Lipid-lipoproteins in children: an exercise dose-response study. *Medicine in Sports Science,* **36**, 418-427.

Tomkinson, G.R., and Olds, T.S. (2007). Secular changes in pediatric aerobic fitness test performance: the global picture. *Medicine in Sports Science,* **50**, 46-66

Tortora G.J., and Grabowski S.R. (2000). *Principles of Anatomy and Physiology (ninth edition).* USA: John Wiley and Sons Inc.

Tounian, P., Aggoun, Y., Dubern, B., Varille, V., Guy-Grand, B., Sidi, D., Girardet, J.P., and Bonnet, D. (2001). Presence of increased stiffness of the common caroti artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*, **27**, 1400-1404.

Treuth, M. S. (2002). Applying multiple methods to improve the accuracy of activity assessments. In G. J. Welk (Ed.), *Physical Activity Assessments for Health-Related Research* (pp. 213-225). Champaign, IL: Human Kinetics.

Trost, S.G. (2001). Objective measurement of physical activity in youth: current issues, future directions. *Exercise and Sports Sciences Reviews*, **29**, 32-36

Trost, S.G., Kerr, L.M., Ward, D.S. and Pate, R.R. (2001). PA and determinants of PA in obese and non-obese children. *International Journal of Obesity Related Metabolic Disorders*, **25**, 822-829

Trost, S.G., McIver, K., and Pate, R.R. (2005). Conducting accelerometer-based activity assessments in field-based research. *Medicine and Science in Sports and Exercise*, **37**, S531- S543.

U.S. Department of Health and Human Services. (2007) *Healthy people 2000: national health promotion and disease prevention objectives full report, with commentary.* Washington, DC: U.S. Department of Health and Human Services, Public Health Service, 1990. DHHS Publication 91–50212.

van Beurden, E., Barnett, L. M., Zask, A., Dietrich, U. C., Brooks, L. O., and Beard, J. (2003). Can we skill and activate children through primary school physical education lessons? "Move it Groove it"--a collaborative health promotion intervention. *Preventive Medicine*, **36**, 493-501.

van Sluijs, E.M., McMinn, A.M and Griffin, S.J. (2007). Effectiveness of interventions to promote physical activity in children and adolescents: systematic review of controlled trials. *British Medical Journal,* **335,** 703.

Vickers A.J., and Altman D.G. (2001). Statistics Notes: Analysing controlled trials with baseline and follow up measurements. *British Medical Journal,* **232,** 1123-1124.

Wang, M., Yip, G.W.K., Wang, A.Y.M., Zhang, Y., Ho, P.Y., Tse, M.K, Lam, P.K.W., and Sanderson, J.E. (2003). Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value, *Journal of the American College of Cardiology,* **41,** 820-826

Ward, D.S., Evenson, K.R., Vaughn, A., Rodgers, A.B., and Troiano, R.P. (2005). Accelerometer use in physical activity: best practices and research recommendations. *Medicine and Science in Sports and Exercise,* **37,** S582- S588.

Watts, K., Beye, P., Siafarikas, A., Davis, E.A., Jones, T.W., O'Driscoll, G., and Green, D.J. (2004). Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. *Journal of the American College of Cardiology,* **43,** 1823-1827.

Wei, M., Kampert, J.B., Barlow, C.E., Nichaman, M.Z., Gibbons, L.W., Paffenbarger, R.S. Jr., and Blair S.N. (1999). Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight and obese men. *Journal of the American Medical Association,* **282,** 1547-1553.

Wilfley, D.E., Stein, R.I., Saelens, B.E., Mockus, D.S., Matt, G.E., Hayden-Wade, H.A., Welch, R.R., Schechtman, K.B., Thompson, P.A., and Epstein, L.H. (2007). Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. *Journal of the American Medical Association,* **298**, 1661-1673.

Wilmore, J.H., Green, J.S., Stanforth, P.R., Gagnon, J., Rankinen, T., Leon, A.S., Rao, D.C., Skinner, J.S., and Bouchard, C. (2001) Relationship of changes in maximal and submaximal aerobic fitness to changes in cardiovascular disease and non-insulin-dependet diabetes mellitus risk factors with endurance training: the HERITAGE Family Study. *Metabolism,* **50**, 1255-1263

Woo, K.S., Chook, P., Yu, C.W., Sung, R.Y.T., Qiao, M., Leung, S.S.F., Lam, C.W.K., Metreweli, C., and Celermajer, D.S. (2004). Effects of diet and exercise on obesity related vascular dysfunction in children. *Circulation,* **109**, 1981-1986

World Health Organisation. (2000) Obesity: Preventing and managing the global epidemic. Geneva, WHO.

World Health Organisation. (2007) (feb) Cardiovascular diseases.

http://www.who.int/mediacentre/factsheets/fs317/en/index.html

World Health Organisation. (2007) Diabetes.

http://www.who.int/dietphysicalactivity/publications/facts/diabetes/en/

Wright, C.M., Parker, L., Lamont, D., and Craft, A.W. (2001). Implications of childhood obesity for adult health: findings from thousand families cohort study. *British Medical Journal,* 323, 1280-1284

Zhu, W., Huang, X., He, J., Li, M., and Neubauer, H. (2005). Arterial intima-media thickening and endothelial dysfunction in obese Chinese children. *European Journal of Pediatrics,* **164**, 337-344.