University of Alberta

The Association Between Physical Activity and Carotid Intima-Media Thickness in Children

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science
in
Epidemiology

Department of Public Health Sciences

Spring 2014
Edmonton, Alberta

Abstract

Modifiable cardiovascular disease (CVD) risk factors, such as adiposity, are already associated with atherosclerotic progression in childhood. Less is known about whether physical activity (PA) is associated with progression of atherosclerosis in non-clinical samples of children.

This cross-sectional study used baseline data from 426 eight- to ten-year-olds from the Quebec Adiposity and Lifestyle Investigation in Youth (QUALITY) Study to assess associations between PA and carotid intima media-thickness (cIMT) – a surrogate marker of atherosclerosis, and potential effect modification by adiposity and fitness. Results of this thesis should be interpreted with caution, as validity of cIMT measurement from the QUALITY Study is currently being investigated because of suboptimal reliability and precision of ultrasound equipment.

PA was not associated with cIMT in this at-risk sample. Analyses in adiposity or fitness categories showed potential differences by groups. More structured and high-intensity PA may be required to slow atherosclerotic progression between childhood and adulthood.

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List of Abbreviations

AGAHLS	Amsterdam Growth and Health Longitudinal Study
ANOVA	Analysis of Variance
ARIC	Atherosclerosis Risk in Communities
ARYA	Atherosclerosis Risk in Young Adults
BMI	body mass index
CAC	coronary artery calcification
CAD	coronary artery disease
CCHS	Canadian Community Health Survey
CDC	Centres for Disease Control and Prevention
CHD	coronary heart disease
CHMS	Canadian Health Measures Survey
CIHI	Canadian Institute for Health Information
cIMT	carotid intima-media thickness
cpm	counts per minute
CT	computed topography
CVD	cardiovascular disease
DEXA	dual energy x-ray absorptiometry
DBP	diastolic blood pressure
EYHS	European Youth Heart Study
FMI	fat mass index
IHD	ischemic heart disease
LDL	low-density lipoprotein

LVM	left ventricular mass
MetS	metabolic syndrome
MET	Metabolic Equivalent of Task
MI	myocardial infarction
MVPA	moderate-to-vigorous physical activity
PA	physical activity
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
PHAC	Public Health Agency of Canada
QUALITY	Quebec Adiposity and Lifestyle Investigation in Youth
rpm	revolutions per min
SBP	systolic blood pressure
SD	standard deviation
SLPA	sedentary-to-light physical activity
VO_2	volume of oxygen
VO_{2peak}	peak volume of oxygen
VO_{2max}	maximum volume of oxygen
VPA	vigorous physical activity
WC	waist circumference
WHtR	waist-to-height ratio
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Cardiovascular diseases (CVDs) are the major causes of mortality and morbidity around the world (1). CVD-related illnesses were the cause of 30% of deaths around the world in 2008 (2) and 28.7% of deaths in Canada in 2009 (3). A large proportion of CVDs and associated burdens can be prevented by targeting risk factors such as excess weight, low physical activity (PA), and fitness (2, 4-7). For example, increasing PA and reducing excess weight can prevent 30% and 23%, respectively, of the burden of global ischemic heart disease (IHD) (8). One third of coronary heart disease (CHD) deaths in Canada can be prevented if people engage in one hour of PA per day (9).

Atherosclerosis, the long-term thickening of arterial walls, leads to the development of CVD (1, 10). In adults, atherosclerotic lesions have been shown to be associated with CVD mortality (11). CVD risk factors such as smoking, high blood pressure, high cholesterol, and excess weight, or obesity, have also been associated with these lesions (12, 13). Although CVD manifests in adulthood, compelling evidence suggests that before symptoms show, the atherosclerotic process begins naturally in all children and progresses over the course of a lifetime (14, 15). For example, CVD risk factors such as high blood pressure, smoking, obesity, and high cholesterol are already associated with atherosclerotic lesions in children and adolescents (16-18). This long-term development of arterial thickening lends itself to early quantification and several surrogate markers can detect subclinical atherosclerosis such as: coronary artery calcification (CAC), left ventricular mass (LVM), and carotid intima-media

thickness (cIMT) (19). In both children and adults, surrogate markers have not only been associated with CVD mortality and morbidity (16, 18, 20, 21), but risk factors such as blood pressure and obesity have also been associated with these markers (21-28). This evidence shows that body fat, or adiposity, in particular, is a putative risk factor for the development of CVD later in life. It accelerates the atherosclerotic process and is associated with atherosclerotic markers in children and youth.

Since studies have shown that CVD risk factors are associated with surrogate markers of atherosclerosis, reducing the prevalence of these risk factors, especially in children, is important for public health. In particular, overweight and obese Canadian children and youth already present CVD risk factors such as high blood pressure and high cholesterol compared to those who have normal weights (29). Although deaths due to CVDs have decreased in Canada in the last five decades due to public health and medical interventions, such as smoking reductions and high blood pressure therapy (30), the prevalence of CVD risk factors remains high. A large proportion of Canadian children and youth are overweight or obese (31), physically inactive (32), and unfit (33). For example, according to Canadian Community Health Survey (CCHS) data, the percentage of overweight and obese 2- to 17-year-olds increased from 15% in 1978-1979, to 26% in 2004 (34). Canadian Health Measures Survey (CHMS) 2009-2011 data showed that 31.5% of Canadian children and adolescents aged 5 to 17 years were categorized as overweight or obese (31). Several studies have also shown that high adiposity in childhood can track into adulthood (35), and Canadian data from

the Physical Activity Longitudinal Study showed that 83% of overweight and obese children and adolescents continued to be overweight and obese even 22 years later (36).

In addition to obesity, low PA is also an important modifiable risk factor for CVD that is prevalent in children and contributes to excess weight gain (37). CHMS 2007-2011 data showed that only 3.4% of girls and 8.3% of boys aged 6 to 17 years achieved Canadian PA recommendations (38, 39). A recent analysis of longitudinal studies showed that PA levels decrease with age so that as children become adolescents, there is a 7% reduction in their PA per year (40). Physical activity behaviour can also track from childhood into adulthood (41-43); one Canadian study showed that 18% of physically inactive children and adolescents were still inactive in adulthood (36).

Fitness is another factor that is protective against CVD (4) and is associated with PA and obesity (44, 45). Low fitness, like obesity and physical inactivity, is prevalent in children. CHMS 2007-2009 data showed that in 15- to 19-year-olds, 20% and 32%, of girls and boys, respectively, were classified as having only fair fitness or needing improvement in their fitness (33). Comparing this data with Canadian Fitness Survey data showed that 8- to 19-year-olds had higher fitness in 1981 compared to 2007-2009, suggesting that children and adolescents have become less fit over time (46). Similar to PA, studies of fitness tracking have shown correlations between childhood and adolescence, and between childhood and adulthood (47-50).

Not only are risk factors such as obesity, low PA, and poor fitness prevalent in children, but they also have complex relationships with each other, which have shown associations into adulthood. The decrease in fitness and PA in childhood has also been shown to associate with obesity in adolescence and adulthood (45, 51, 52). Moreover, excess weight in childhood has been shown to associate with reduced fitness in adolescence, and participation in PA and weight loss in childhood can lead to better fitness in adolescence (48).

Taken together, research has shown that levels of obesity, PA, and fitness in children of the Canadian population are worrisome and can affect adolescent and adult health. The relationships between adiposity, PA, and fitness are complex. Adiposity is considered to be the strongest predictor of CVD risk, given its associations with other CVD risk factors and markers of atherosclerosis, and its high tracking from childhood to adulthood. Therefore, preventing the atherosclerotic process requires management of weight in childhood. Public health has widely encouraged increasing PA levels and consuming healthy foods to prevent and reduce obesity (37), however less is known about the direct effects of PA on atherosclerotic development in children. Therefore, the primary objective of this thesis is to investigate the association between PA and subclinical atherosclerosis in children, and the secondary objective is to assess how adiposity and fitness can modify this relationship.

CHAPTER 2: LITERATURE REVIEW

In order to situate this thesis' objectives in the scientific literature, the following sections summarize current knowledge on the following topics: 1) The epidemiology of cardiovascular disease and associated risk factors, 2) Evidence of the atherosclerotic process in young people, 3) The epidemiology of physical activity, and 4) The importance of adiposity and fitness in physical activity and carotid intima-media thickness studies.

2.1. The epidemiology of cardiovascular disease and associated risk factors

CVDs are conditions that affect the blood vessels and the heart (1). These include cerebrovascular disease which can lead to stroke, peripheral vascular disease, and CAD (coronary artery disease) and IHD which can lead to heart attack or myocardial infarction (MI) (1). CVD is the leading cause of death worldwide (2). It is predicted that in 2030, CVD will continue to be the number one cause of death, with 23.3 million people dying that year (2).

CVD is a major cause of death in Canada (53). According to Statistics Canada, 68,342 Canadians died from major CVDs in 2009, a drop of 10% from 76,046 in 2000 (54, 55). Although the absolute number of deaths due to CVD-related causes has declined over this time period, changes from year to year between 2000 and 2009 have fluctuated from a 3.7% reduction between 2005 and 2006, and an increase of 1.1% between 2006 and 2007 (55, 56). This shows that the decline is not consistent and has increased between certain years.

Not only can CVD lead to mortality, it is also a major cause of morbidity, and places a high burden on our health, social, and economic systems. According to the Public Health Agency of Canada (PHAC), the prevalence of people aged 12 years and above who reported that they were diagnosed with heart disease was 1.3 million or 4.8% of the population in 2007 (57, 58). Of these, 43.5% perceived their health, including physical, social, and mental factors, as fair or poor, and 30.3% reported that they were unable to partake in day-to-day activities without assistance (57, 58). Specifically, of those aged 15 years and older, 21.6% were undergoing stress, 59.9% had high blood pressure, and 24.0% had diabetes (57). In terms of the burden on the healthcare system, the economic cost of CVD from both direct and indirect costs totalled $22.2 billion in 2000, with mortality, hospital-associated costs, and chronic disability comprising most of the burden (57). According to the Canadian Institute for Health Information (CIHI), the number of hospitalizations for CVD-related causes has declined since the 1990s, however CVD continues to be a major reason for hospital use, and accounted for 16.9% of hospitalizations in 2005-2006 (57).

Reducing this burden of CVD through prevention requires an examination of the conditions that lead to disease. Risk factors for CVD include high blood pressure, obesity, high cholesterol, diabetes, alcohol use, smoking, unhealthy diet, and low PA (1). Of these, weight and PA are modifiable risk factors and therefore constitute important prevention targets for public health. Research has shown that these risk factors are prevalent in young people. Globally, 40 million children aged four years and younger were classified as overweight in 2011, according to

the World Health Organization (WHO) (37). Furthermore, the WHO prediction for overweight by 2015 is 1.5 billion people with at least half of the North American population being overweight (59). CCHS data showed that in 2007, 66.8% of adolescents aged 12 to 19 years had one or more CVD risk factor such as physical inactivity, smoking, stress, overweight or obese, diabetes, high blood pressure, or poor fruit and vegetable intake (57). Specifically, 2009-2011 CHMS data showed that 31.5% of Canadians aged 5 to 17 years were overweight or obese (31). Data from the Canadian Health Survey and the CCHS showed that the percentage of overweight and obese 2- to 17-year-olds increased from 15% in 1978-1979, to 26% in 2004 with changes mostly reflected in those aged 6 to 17 years (34). Moreover, comparisons between 1981 Canada Fitness Survey and 2007-2009 CHMS data showed that waist circumference (WC), a measure of central or abdominal obesity, increased by 5.4 cm in adolescents aged 12 to 19 years (60). This increase in weight is detrimental as overweight and obese Canadian children and adolescents already present CVD risk factors such as high blood pressure and high cholesterol compared to those who have normal weights (29). CCHS data from 2007 also showed that 23.8% and 33.9% of 12- to 14-year-olds and 15- to 19-year-olds, respectively, were physically inactive, based on self-reports (57). Furthermore, CHMS 2007-2011 data showed that only 3.4% of girls and 8.3% of boys aged 6 to 17 years achieved PA recommendations (38, 39). In terms of fitness, CHMS 2007-2009 data showed that in 15- to 19-year-olds, 20% and 32%, of girls and boys, respectively, were classified as having only fair fitness or needing improvement in their fitness (33). Compared to Canadian

Fitness Survey data from 1981, 8- to 19-year-olds had higher fitness in 1981 compared to 2007-2009 and this was significant in all boys, and in girls grouped into 8- to 10-year-olds, and 11- to 14-year-olds (46). In sum, this research suggests that children and youth are inactive and have become less fit over time.

In addition to the high prevalence of these risk factors in Canadian children and adolescents, the burden that these factors place on the healthcare system is enormous. According to the PHAC and CIHI, in Canada, the cost of obesity increased 19% from 2000 to 2008 with an estimated $4.6 billion spent in 2008 (61). Physical inactivity cost Canadians $6.8 billion, which was 3.7% of total spending in 2009 (62). The costs of CAD in 2001 due to low PA and obesity were $1.7 billion and $1.3 billion, respectively (63). American research has also shown that compared to those with low fitness, adults with high fitness have a lower percentage of overnight hospital stays and physician visits (64).

Since CVD places a major burden globally as well as in Canada, and the prevalence of CVD risk factors such as obesity, physical inactivity, and low fitness is high among children and youth, improving our understanding of the etiology of CVD and the important role that obesity, PA, and fitness play during the atherosclerotic process can inform prevention strategies that aim to reduce CVD burden from an early age.

2.2. Evidence of the atherosclerotic process in young people

2.2.1. The associations between cardiovascular disease, risk factors, and atherosclerosis from autopsy studies

The life-long atherosclerotic process, which can eventually cause CVD, refers to the accumulation of fatty streaks in the intima layer of major arteries, which develop into lesions (1, 10). These lesions then grow into fibrous plaques that can hinder blood flow inside arteries and lead to cardiovascular complications (1, 10). Three major groups of autopsy studies have demonstrated the presence of fatty streaks and plaque deposits in young people: New Orleans studies, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY), and the Bogalusa Heart Study. New Orleans autopsy studies in the 1950s and 1960s showed that fatty streaks were present in children as young as 7 years old (65). In one particular study with a sample of 548 individuals aged 1 to 69 years, adults aged 40 to 60 years who had died from CAD showed higher atherosclerotic lesions in their coronary arteries compared to those who died from external causes (11).

The PDAY study was a multi-centre study that autopsied 3,000 fifteen- to thirty-four-year-olds who died as a result of accidents, suicides, homicides, or other external causes (66). Research from PDAY was conducted in arteries and tissues to determine the associations between aortic or coronary atherosclerosis, and CVD risk factors determined from clinical charts, after death (13). High blood pressure and abdominal fat were associated with increased atherosclerotic lesions

in coronary arteries, and lesions in coronary arteries and abdominal aortas were greater in older individuals (66). In addition, body mass index (BMI), an indicator of adiposity, was positively associated with the accumulation of lesions of male coronary arteries (67).

The extent of atherosclerosis in autopsied aortas and coronary arteries was also examined in the Bogalusa Heart Study in 204 two- to thirty-nine-year-olds who died as a result of homicides, injuries, or other causes (17). Body mass index measured before death was correlated with the amount of fatty streaks and fibrous plaques found in the intima layer of the aorta and coronary arteries (17).

Taken together, these studies have shown that the atherosclerotic process which leads to CVD, begins years before the manifestation of disease, and that the effect of CVD risk factors such as BMI on the atherosclerotic process, begins in childhood and adolescence.

2.2.2. The associations between cardiovascular disease risk factors and carotid intima-media thickness: a surrogate marker of atherosclerosis in living children and adolescents

Using surrogate markers of atherosclerosis in living children and youth is an important way to assess risk and establish associations before CVD occurs. Several studies in children and adolescents have used magnetic resonance imaging (MRI), computed tomography (CT), echocardiography, ultrasound, and other diagnostic methods to study the associations of CVD risk factors with early markers of atherosclerosis, such as CAC, LVM, endothelial function, arterial

stiffness, and cIMT (18, 19, 68, 69). These markers are used in the following ways: CAC measurements are taken using CT scans to assess calcification in coronary artery walls (18, 19), LVM is frequently measured using echocardiography to assess the thickening of the walls of the left ventricle in the heart (19), endothelial function measurements test how the arteries react to different stimuli, arterial stiffness measurements indicate the elasticity of the arteries, and cIMT indicates the thickness of intima and media layers of the carotid artery (18). These markers are appropriate for use in living children as they are non-invasive and are therefore less harmful than invasive methods (18, 68). Several studies have shown that in children and adolescents, adiposity is associated with increased LVM, reduced endothelial function, and higher arterial stiffness, and that obese children and adolescents show increased atherosclerotic development based on these markers (70-76). Other investigations have shown that PA is associated with endothelial function and arterial stiffness, that fitness is associated with arterial stiffness, and that endothelial function is increased after PA interventions in obese children (77-80). Furthermore, childhood and adolescent adiposity has also been shown to associate with increased arterial stiffness and CAC in adulthood (25, 81). In sum, the use of surrogate markers in living children demonstrates that adiposity, PA, and fitness have important effects on the atherosclerotic process that can be assessed in early life.

From these surrogate markers, cIMT is a tool that has become valuable in the last two decades as advances in ultrasound technology have given rise to the direct visualization of the artery (18, 27). A study that compared intima-media

measurements from histological evaluations with ultrasound images from males in their twenties showed no differences between the two measures (82). Moreover, cIMT is considered to be an end point in several clinical trials in adults which have shown that therapy for CVD risk factors can reduce cIMT or slow its progression (18, 83, 84). Observational studies in adults have also shown that cIMT is associated with cardiovascular-related events such as stroke and MI, and that CVD risk factors such as BMI are associated with cIMT (69, 85, 86). The cIMT measurement is also useful because it assesses the early stages of the atherosclerotic process, which begin in the arterial wall's intima layer in childhood (69, 87). Therefore, in recent years, cIMT studies have emerged in children, which will be discussed in this chapter.

Investigators have assessed cIMT in millimetres, by measuring the distance from the echogenic borders of the arterial intima and media layers on a B-mode ultrasound image (88). Since cIMT can vary throughout life, it is time-specific assessment (88). Furthermore, the cIMT measurement in children has not been standardized, and there are several different methods to capture cIMT values, which depend on the following: the specific protocol undertaken, the particular carotid artery part selected (e.g. internal, common), the wall viewed (e.g. near, far), the angle viewed, the selection of mean or maximum values, the quality of equipment, the sonographer taking the image, and the reader analyzing the image (18, 21, 69, 88, 89). Moreover, differences may also be caused by the way images are examined which can be done manually by appropriately trained individuals who measure cIMT, or by automated edge detection by computers

(18, 88). Since this protocol can vary, there is also a range in how time consuming and expensive taking cIMT measurements can be (88). The great variability of cIMT measurements suggest that more research is required to determine the optimal procedures to measure cIMT, as previous studies have used different protocols, making it challenging to compare results from groups of studies (18, 88, 90). A review by Urbina et al. has emphasized these concerns regarding the measurement of cIMT in children, and has indicated that a standardization of protocols is required (18). The American Heart Association recommends that cIMT should be measured by calculating the mean of the maximum far wall cIMT values obtained from both the anterior-oblique and lateral angles of the carotid bulb, the proximal internal carotid, and the distal common carotid on the left and right sides (18).

Several studies have selected cIMT as an indicator of atherosclerotic development. Observational studies in samples of disease-free adults have shown evidence for the associations between cIMT and CVD, as well as between CVD risk factors and cIMT. Several of these studies included follow-up times, large sample sizes, and were done in disease-free individuals. For example, increased cIMT was shown to be associated with CVD, strokes, MIs, or deaths (85) in the following samples: 12,841 Americans aged 45 to 64 years from the Atherosclerosis Risk in Communities (ARIC) (91), 4,476 Americans aged 65 years and above from the Cardiovascular Health Study (92), 6,698 Americans aged 45 to 84 years from the Multi-Ethnic Study of Atherosclerosis (20), 1,565 Dutch individuals aged 55 years and above from the Rotterdam Study (93), 5,056

Germans aged 19 to 90 years who were part of the Carotid Atherosclerosis Progression Study (94), and 1,257 Finns that were part of the Kupio Ischemic Heart Disease Risk Factor Study (95). A meta-analysis containing some of these studies revealed that overall, a 0.1 mm increase in cIMT was associated with up to an 18% higher risk of stroke and a 15% higher risk of MI (85). Positive associations have also been found between CVD risk factors such as BMI, WC, or risk factor clustering, and cIMT, in the following samples: middle aged American adults as part of the ARIC study (23), the Bogalusa Heart study in young American adults (96, 97), and from the Atherosclerosis Risk in Young Adults (ARYA) study in young Dutch adults (86). In sum, observational studies in cohorts from several countries have given evidence to show that in adults, cIMT is a useful marker for indicating CVD risk since the number of cardiovascular events is greater in those with increased cIMT, and because established CVD risk factors such as BMI are associated with increased cIMT.

The association between CVD risk factors and cIMT has also been recently examined in groups of children and youth who present CVD risk factors. In a systematic review of 67 cross-sectional studies in children and youth up to 20 years old classified as cases with either high blood pressure, diabetes, chronic renal failure, dyslipidemia, metabolic syndrome (MetS), or obesity, and controls without these conditions, 55 studies found significantly higher cIMT in cases compared to controls, with cIMT ranging from 0.324 mm to 0.780 mm in cases and 0.266 mm to 0.649 mm in controls (24). This review shows that cIMT is

positively associated with CVD risk factors in children and youth, as cIMT was increased in samples of children and adolescents with known risk factors.

In contrast to studies in children and adolescents with medical conditions, epidemiologic studies in asymptomatic populations are especially important in understanding atherosclerosis and preventing CVD from childhood. Several cross-sectional studies have examined the associations between CVD risk factors and cIMT in disease-free populations. In children and adolescents, measures of adiposity such as BMI, waist-to-hip ratio, body weight, WC, waist-to-height ratio (WHtR), or height-adjusted abdominal fat, have been shown to be positively associated with cIMT in the following samples: 635 Americans aged 11 to 17 years from the Muscatine Offspring study (98), 599 Americans aged 6 to 20 years from Los Angeles County (99), 93 Brazilians aged 49 to 169 months (100), 52 Japanese children and adolescents aged 6 to 14 years (101), 247 Germans aged 10 to 20 years (75), and 306 Dutch children aged five years old (102). These cross-sectional studies in disease-free children and youth from different countries have shown that similar to studies in adults, measures of adiposity show associations with cIMT at young ages.

Not only have the associations between CVD risk factors and cIMT been studied in adults and children, separately, but prospective cohort studies have also shown that risk factors present in childhood and adolescence are associated with cIMT in adult life. A combined examination of four major cohort studies, namely the Muscatine Study, the Cardiovascular Risk in Young Finns Study, the Bogalusa Heart study, and the Childhood Determinants of Adult Health study in

4,380 children and adolescents, showed that BMI measured at ages 3, 9, 12, 15, and 18 years, was associated with cIMT measured between ages 20 to 45 years (103). Other analyses as part of the Cardiovascular Risk in Young Finns Study, the Bogalusa Heart study, the ARYA study, and the Amsterdam Growth and Health Longitudinal Study (AGAHLS), have shown that BMI, skinfold thickness, or the clustering of CVD risk factors in childhood and adolescence were positively associated with cIMT in adults whose ages ranged from 20 to 43 years (28, 104-108). Furthermore, childhood BMI and self-reported PA were associated with the change in cIMT measured between ages 24 to 45 years in 1,809 members of the Cardiovascular Risk in Young Finns cohort (109). In addition, change in weight classification to a higher BMI quartile from adolescence to adulthood was associated with higher cIMT between ages 27 to 30 years (107).

A systematic review examining the association between BMI in children and adult cIMT concluded that since many of these studies such as the Cardiovascular Risk in Young Finns study and the ARYA study showed that the independent association between childhood BMI and adult cIMT became non-significant after controlling for adult BMI, that childhood BMI was therefore not associated with adult cIMT (110). This, however, should be interpreted with caution as adiposity is known to associate with cIMT in the literature and other factors may account for attenuated effects when adjusting for adulthood BMI.

Taken together, the studies discussed show that the cIMT measurement is a useful marker of subclinical atherosclerosis in adults and recent studies have shown that it can also be evaluated in children from both clinical and non-clinical

populations, since CVD risk factors such as obesity in childhood are already associated with both childhood cIMT and adult cIMT. These studies show that cIMT can be considered an outcome variable to evaluate how risk factors can influence atherosclerotic progression before CVD symptoms appear. Based on these studies, adiposity has been shown to affect the development of atherosclerosis in childhood, but fewer studies have investigated how PA, another modifiable risk factor that is recommended in prevention programs for both obesity and CVD, influences cIMT directly. Investigating the relationship between PA and cIMT is the next step in assessing how atherosclerotic progression can be reduced through behaviour in early life.

2.3. The epidemiology of physical activity

Physical activity encompasses all movements made by the human body that use up energy (111). Physical activity is not limited to exercise, which is planned, organized, and regular, but rather includes any and all daily movements such as activities at work, during recreational time, at home, and while travelling (111, 112). Physical activity information can be expressed in terms of frequency, duration, setting, and intensity such as sedentary, light, moderate, moderate-to-vigorous (MVPA), or vigorous (VPA) (112-114). Moderate PA can include dancing and brisk walking while vigorous PA involves greater effort such as running, fast cycling, fast swimming, and competitive sports (115). Children can participate in PA through physical education, play time, sports, and games (112, 116).

Several methods of measuring PA have been used. Criterion standards include doubly labelled water, direct observation, and indirect calorimetry; secondary objective measures include pedometers, accelerometers and heart rate monitors; subjective measures include interviews, self-reports, proxy-reports and diaries (114, 117). Physical activity is challenging to measure in children because of their distinctive behavioural tendencies such as sporadic movements, the physical development of their bodies (112), issues in understanding and relaying PA information, or discrepancies in reporting compared to their parents (118). For example, when comparing child reports to parental reports, overweight and obese children have over-reported their levels of PA (118). Subjective measures have been widely used in children and adolescents because they are easy to implement and inexpensive (114), but are often critiqued as inaccurate (119) because children can have trouble recalling activities, or may be emotionally biased during the questioning process by proxies or interviewers, due to social desirability (112, 114). Furthermore, when describing activity through self-reports, descriptions of sports, for example, may be inaccurate as the actual intensity and length of time engaging in sport cannot be captured using these measures (120).

Objective measures such as accelerometers, pedometers and heart rate monitors, on the other hand, provide more detailed intensity, frequency, duration and time information (112). These measurements are also known to better associate with risk factors (120). In particular, there is emerging literature that VPA derived from objective measures is negatively associated with CVD risk factors such as central and total adiposity (121). Given these advantages, there are

still challenges when using this equipment due to device limitations or data use. For instance, activities such as climbing and cycling are difficult to detect by accelerometers and pedometers because there is limited movement above the waist or a lack of acceleration (122, 123). In addition, normal PA may not be captured if children change their behaviour because they are aware that they are being monitored or if they do not conform to accelerometer protocol (112). The use of accelerometers can also present inconsistencies in interpretation and standardization of data (120, 124). Physical activity intensity information can be described using cut-off points for MVPA and VPA, however there are no standardized cut-off points, leaving studies varied on intensity definitions (120). This may lead to misclassification of individuals based on intensity type and can question the comparability of PA variables between different investigations (120).

Taken together, PA is complex and difficult to measure in children. Various methods to measure PA have been employed including both subjective and objective evaluations. Although subjective measures are less expensive compared to objective measures (114), studies have shown that subjective and objective measures are not highly correlated (120). Recommendations for PA measurement favour objective measures with standardization (120) and within these measures, accelerometers are reliable, valid, and provide intensity information (125).

2.3.1. Prevalence of physical activity in young people

According to the WHO, in 2004, 3.2 million or 5.5% of global deaths were caused by physical inactivity (8), and in 2008, physical inactivity was seen globally in 31.3% of those aged 15 years and above (1). High-income countries, with a large 2004 gross national income per capita, such as Canada and the United States, listed physical inactivity as the fourth highest cause of death (8), and 2010 data showed that at least 25% of the population in these countries were not sufficiently active (1). Inactivity in high-income countries is thought to stem from urbanization, car use, and the increased use of technology (1, 126). This low PA can eventually lead to detrimental health conditions such as type 2 diabetes, cancer, and CVD (8). In addition, these chronic conditions put financial strains on the healthcare system. Physical inactivity cost Canadian adults $6.8 billion or 3.7% of total spending in 2009, due to the direct and indirect costs of conditions such as type 2 diabetes, high blood pressure, osteoporosis, colon cancer, breast cancer, stroke, and CAD (62).

In Canada, the PA recommendations from the Canadian Society for Exercise Physiology state that for 5- to 17-year-olds, a minimum of one hour of MVPA is required every day (127). However, 2007-2011 CHMS data showed that a mere 3.4% of girls and 8.3% of boys aged 6 to 17 years achieved this based on accelerometer data (38). Furthermore, boys had higher MVPA levels than girls, and older age groups showed lower MVPA levels compared to younger groups, suggesting that children engage in less PA as they become older (127). The percentage of children and youth meeting recommendations dropped between

age groups 6 to 11 years, and 12 to 17 years (38, 39). This decline in PA with age was also noted in the Canadian Physical Activity Levels Among Youth study 2009-2011 data which showed that pedometer step counts decreased between ages 5 to 19 years (128). In sum, the prevalence of physical inactivity is high, especially in Canadian children and adolescents, and this can lead to chronic diseases which amount to substantial health and economic burden.

2.3.2. The associations between physical activity, cardiovascular disease, and risk factors

Several studies have shown that PA is associated with CVD in adults. Observational studies as part of a systematic review for the American government's PA guidelines showed that in adults, self-reported PA was negatively associated with CVD mortality, CHD, and cerebrovascular disease (5). Moreover, adults who participated in more total PA or more intense PA had between a 30% to 40% lower risk of CVD than those who did not (5). In a meta-analysis of 21 cohort studies in adults who were disease-free at baseline, participating in high levels, either in duration, intensity or frequency, of objectively-measured PA during leisure time, versus low levels of PA during leisure time, resulted in a 24% lower risk of CVD in men and a 27% lower risk of CVD in women (6). In another meta-analysis of 33 cohort studies, there was a 14% reduced risk for CHD in disease-free adults achieving moderate intensity self-reported leisure time PA for 150 minutes per week versus no leisure time PA (129). These studies show the beneficial impact that PA, especially type of PA,

has in lowering CVD risk in adults, even with the high variability of measuring and defining PA in these studies.

Physical activity also has an effect on CVD risk factors in children and youth. For example, a systematic review in 5- to 17-year-olds showed that PA based on self-reports was moderately associated with obesity while PA measured using accelerometers or pedometers showed stronger associations with obesity (130). Furthermore, in studies where children and adolescents participated in exercise intervention programs lasting one month to two years, half of the studies showed that measures of adiposity such as total fat, abdominal fat, or BMI were significantly reduced (130). A recent literature review of the association between PA and CVD risk factors in children outlined that blood pressure decreased in hypertensive individuals who underwent intervention programs of 30 minutes or more of aerobic exercise, tri-weekly (131). This same review noted that in many studies, accelerometer-measured PA was negatively associated with MetS in children but that studies using self-reported PA had mixed findings about this relationship (131), stressing the importance of the selection of PA measure in epidemiologic studies. Overall, the literature shows that higher PA levels are associated with a reduced risk of CVD, and that this inverse relationship is also seen between PA and CVD risk factors.

2.3.3. The associations between physical activity and carotid intima-media thickness in adults

Although there is a clear association between PA and CVD, and between PA and CVD risk factors, two systematic reviews of studies investigating the independent effect of PA on cIMT specifically, have both concluded that the literature is inconclusive regarding this relationship, in the small number of studies that have been conducted so far (132, 133). For example, cross-sectional studies in disease-free adults have shown that self-reported PA was not significantly associated with cIMT in 800 fifty-six- to seventy-seven-year-olds who measured activity from playing sports (134), and in 137 eighteen- to seventy-seven-year-olds who participated in road running races and engaged in vigorous exercise six or seven times a week (135). In contrast, other studies have shown significant associations between PA and cIMT. Particularly, in 500 disease-free 40- to 60-year-olds from the Los Angeles Atherosclerosis study, engaging in greater amounts of high-intensity PA based on self-reports was associated with decreased cIMT progression so that the annual increase in cIMT in participants who participated in VPA was 0.0082 mm/year lower than those who were classified as sedentary (136). The Tromsø cohort study of 3,128 middle-aged adults showed that a higher PA level at baseline, based on self-reports, was negatively associated with cIMT 15 years later in men (137). Another cross-sectional analysis from the ARIC study in 14,430 disease-free 45- to 64-year-olds showed that only self-reported PA at work but not from time spent in leisure or playing sports, was inversely associated with cIMT (138). Taken together, these

results show that the literature examining the specific relationship between PA and cIMT is inconclusive. The authors of the two systematic reviews noted that the following were potential reasons for the discrepancies in results: the high number of observational studies and few intervention studies, differences in study populations and sizes, measurement issues previously discussed such as what protocol is undertaken to capture cIMT, the effects of other lifestyle interventions that were implemented alongside exercise, and the chance that either cIMT changes may not have enough follow-up time to be observed or may not be detectable from ultrasound imaging (132, 133). Therefore, the direct relationship between PA and cIMT needs to be further investigated in order to determine if changes in PA can affect atherosclerotic progression.

2.3.4. The associations between physical activity and carotid intima-media thickness in children and adolescents

Few studies have investigated the association between PA and cIMT in children and adolescents, and these have been predominantly intervention studies to reduce weight and improve CVD risk factors in small samples of high-risk individuals, such as those who are overweight or obese. Table 1 describes these investigations.

All intervention studies were performed in overweight or obese children and youth, and in two of these studies, participants also had polycystic ovarian syndrome (139) or non-alcoholic fatty liver disease (140). Intervention studies with sample sizes of less than 85 participants showed that PA programs which

ranged from 12 weeks to 1 year had a beneficial impact on cIMT, by reducing mean values between 0.006 mm to 0.100 mm (139, 141-149). In three of these studies, only those whose BMI standard deviation score was reduced by 0.5 or more (BMI reduced 2.2 kg/m^2) (142), whose BMI standard deviation score was reduced by more than 0.2 (BMI reduced 3.9 kg/m^2) (139), or those who were grouped in the third and fourth highest weight loss quartiles (greater than 10.90 kg lost) (141) showed these cIMT improvements, highlighting the influence of adiposity on cIMT which has been seen in the literature (139, 141, 142). Four intervention studies employed three or six month programs that focussed on exercise only as opposed to other lifestyle changes such as dieting, and all of these studies reported improvements in cIMT (146-149). This is an important finding as comprehensive intervention programs may not be able to highlight the specific impact of PA on cIMT, but only the combined effects of a group of different lifestyle changes. Overall, few intervention studies with mainly small sample sizes have evaluated changes in cIMT during exercise programs in overweight and obese children, and most have found that the mean cIMT in the intervention group decreased significantly after participating in programs with higher levels of structured PA.

In terms of observational studies investigating the association between PA and cIMT, three studies included children or adolescents with conditions such as cerebral palsy, type 1 diabetes, overweight, or high low-density lipoprotein (LDL) cholesterol. The observational studies, which did not find significant associations between PA and CIMT in childhood or adolescence, included three studies with

small sample sizes less than 150 participants of which only one used accelerometer data (150-152), and three studies with larger sample sizes between 250 to 350 participants which all used accelerometer information (13, 153-155). Of note, two of these investigations with larger sample sizes were also from the EYHS in children and youth from diverse European backgrounds, and showed that MVPA and VPA were not associated with cIMT in 336 adolescents assessed cross-sectionally (154), and that in 254 eight- to ten-year-olds, MVPA and VPA were not associated with cIMT measured six years later, in adolescence (155). These European studies included larger samples of disease-free children or adolescents compared to other PA and cIMT studies from the literature, and accelerometer-measured PA with intensity information, making them important in determining the association between PA and cIMT in children and youth from asymptomatic populations. However, more studies such as these are required in order to further clarify the relationship between PA and cIMT in larger samples of disease-free individuals. In addition, the important roles that adiposity and fitness play in understanding this relationship are required. This thesis will contribute to this gap in the literature concerning PA and cIMT in children.

Table 1. Studies on the effect of PA on cIMT in children and adolescents.

Authors	Study Design	Sample Size and Type	PA Intervention/ Assessment	Statistical Methodology Used	Results	Variables adjusted for
Meyer, A. A., G. Kundt, et al.(148)	Intervention	67 obese (11-16 year olds), intervention (n = 33) and control (n = 34); baseline lean group (n = 35)	6 months exercise	One-way ANOVA	Baseline cIMT significantly higher in obese group compared to lean group	
				Paired t-test	cIMT significantly decreased in intervention group after 6 months	
Farpour-Lambert, N. J., Y. Aggoun, et al.(147)	Intervention	44 obese (6-11 year olds), intervention (n = 22) and control (n = 22); baseline lean group (n = 22)	3 or 6 months exercise; 7-day accelerometer (total cpm), questionnaire for 12 month leisure activity (min/week)	ANOVA	Baseline PA variables significantly lower in obese groups compared to lean group, significantly lower cIMT in intervention group compared to control group after 6 months	Age, sex
Maggio, A. B., Y. Aggoun, et al.(149)	Intervention	20 obese (7-15 year olds)	2 years after 3 or 6 months exercise; 7-day accelerometer (total cpm, MVPA %, MVPA min/day), questionnaire for 12 month leisure activity (min/week)	Paired t-test	cIMT not significantly increased after 2 years	
Park, J. H., M. Miyashita, et al.(146)	Intervention	29 overweight or obese (12-13 year olds), intervention (n = 15) and control (n = 14)	12 weeks exercise	Two-way ANOVA	cIMT significantly decreased in intervention group compared to control group after 12 weeks	

Woo, K. S., P. Chook, et al.(145)	Intervention	82 overweight or obese (9-12 year olds), diet (n = 41), diet and exercise (n = 41)	6 weeks of diet only or diet and exercise intervention; 1 year of diet only, continued exercise or discontinued exercise	Paired t-test	cIMT significantly decreased in diet only and continued-exercise groups after 1 year	
Wunsch, R., G. de Sousa, et al.(142)	Intervention	56 obese (8-9 year olds); control (n = 10)	1 year exercise, diet, behavioural	Mann-Whitney *U* test, Wilcoxon test	cIMT significantly higher in obese group compared to non-obese group, cIMT significantly decreased in those whose BMI standard deviation score decreased by 0.5 or more after 1 year (n = 24)	
Kelishadi, R., M. Hashemi, et al.(156)	Intervention	35 obese (12-18 year olds)	6 weeks exercise and diet	Paired t-test, Mann-Whitney *U* test	cIMT decreased non-significantly after 6 weeks	
de Lima Sanches, P., M. T. de Mello, et al.(144)	Intervention	29 obese (14-19 year olds)	1 year exercise, diet, psychological, clinical	Wilcoxon signed rank test	cIMT significantly decreased after 1 year	
Lass, N., M. Kleber, et al.(139)	Intervention	59 obese girls (12-18 year olds) with polycystic ovarian syndrome	1 year exercise, diet, behavioural	Paired t-test, χ^2 test	cIMT significantly decreased in those whose BMI standard deviation score decreased by greater than 0.2 (n = 26) after 1 year	

Pacifico, L., M. Arca, et al.(140)	Intervention	120 obese (11-12 year olds) with non-alcoholic fatty liver disease	1 year exercise and diet; questionnaire for 1 week activity (METs/day)	Paired t-test, Wilcoxon's rank sum test	cIMT decreased non-significantly after 1 year	
				Linear regression	Change in PA was not significantly associated with change in cIMT	Age, sex, puberty status, baseline cIMT
Masquio, D. C., A. de Piano, et al.(141)	Intervention	77 obese (14-19 year olds)	1 year exercise, diet, psychological, clinical	Paired t-test	cIMT significantly decreased in the third and fourth highest weight loss quartiles after 1 year	
Poeta, L. S., F. Duarte Mde, et al.(143)	Intervention	32 obese Brazilian children (8 to 11 years); intervention (n = 16) and control (n = 16)	1 year exercise and diet	Wilcoxon test	cIMT significantly decreased in intervention group and significantly increased in control group after 1 year	
Martin, A. A., L. M. Cotie, et al.(150)	Observational (cross-sectional)	22 (9-16 year olds), cerebral palsy (n = 11) and control (n = 11)	Questionnaire for 1 week activity (total, light, moderate and vigorous min/week)	Unpaired t-test	VPA significantly lower in cerebral palsy group compared to control group, no significant differences in cIMT between groups	Age
Trigona, B., Y. Aggoun, et al.(152)	Observational (cross-sectional)	6-17 year olds, type 1 diabetes (n = 32), healthy controls (n = 42)	7-day accelerometer (total cpm, SLPA min/day, MVPA %, MVPA min/day)	Unpaired t-test, ANCOVA, χ^2 test, Mann-Whitney *U* test	Compared to control group: total PA significantly lower in type 1 diabetes group, MVPA significantly lower in type 1 diabetes group, SLPA significantly higher in type 1 diabetes group, cIMT significantly higher in type 1 diabetes group	PA variables adjusted for age
				Linear regression	PA variables not significantly associated with cIMT in type 1 diabetes group or in control group	Age, sex, self-reported Tanner stage

Morrison, K. M., L. Dyal, et al.(151)	Observational (cross-sectional)	148 (5-16 year olds), overweight (n = 44), high LDL cholesterol (n = 51), controls (n = 53)	Questionnaire for daily activity (hours/day)	Unpaired t-test	No significant differences in cIMT between overweight and control group, cIMT significantly higher in high LDL group compared to control group	Age, sex
				Linear regression	In univariate regression, PA not significantly associated with cIMT in all individuals	
Lamotte, C., C. Iliescu, et al.(153)	Observational (cross-sectional)	319 (12.5-17.5 year olds)	7-day accelerometer (total cpm)	Linear regression	PA not significantly associated with cIMT	Age, SBP, DBP, total fat intake from diet, family affluence, trunk to total skinfolds ratio
Ried-Larsen, M., A. Grontved, et al.(154)	Observational (cross-sectional)	336 (mean age 15.6 years)	7-day accelerometer (total cpm and sedentary, MVPA, VPA min/day)	Linear regression	MVPA and VPA not significantly associated with cIMT	Sex, Tanner stage, smoking status, sedentary activity time, WC; modification by sex

Ried-Larsen, M., A. Grontved, et al.(155)	Observational (cohort)	254 (8-10 year olds; 14-16 year olds)	5-day accelerometer (total cpm and sedentary, MVPA, VPA min/day)	Linear regression	Baseline, mean, and 6-year change in MVPA or VPA not significantly associated with cIMT measured 6 years later	Sex, Tanner stage, height, soft drink intake, TV-viewing time, mean arterial pressure; modification by sex; PA changes adjusted for intensity

2.4. The importance of adiposity and fitness in physical activity and carotid intima-media thickness studies

2.4.1. The role of adiposity

As the literature has shown, adiposity plays a crucial role in assessing CVD risk as it associates with CVD and atherosclerosis (8, 13, 17, 67, 69, 85, 86). Public health programs to reduce obesity and subsequent disease have recommended increased levels of PA to achieve this, implying that adiposity plays a mediating role in the link between PA and CVD risk (157). However, studies examining the relationship between PA and cIMT, a marker of atherosclerosis, have shown that a direct association between PA and cIMT exists even after controlling for adiposity measures such as BMI (136-138). This suggests that PA may also affect cIMT directly through other mechanisms (158), and that adiposity can also work through several pathways. Indeed, some studies have shown that overweight and obese children and youth already have lower PA levels compared to those with normal weights, which may in part be due to their physical capabilities (159-161). When determining the effect of PA on cIMT, adiposity is an important consideration in terms of its effect on cIMT (23, 24, 86, 96, 97) , but there is a need to further investigate its role in the context of PA. Since several studies have investigated the potential changes in CVD risk based on categories of adiposity (158, 162), there is a need to determine whether or not adiposity can modify the relationship between PA and cIMT.

Several methods of assessing adiposity can be employed in such studies, which also bring great variability. Direct measures of adiposity include densitometry and dual energy x-ray absorptiometry (DEXA) (163). Indirect measures include bioelectrical impedance, BMI, skinfold thickness, and WC (163). Adiposity measurements can also be expressed as total or central fat, and studies have shown that central fat is associated with CVD risk factors (163). This thesis will focus on five adiposity measures: BMI, total fat mass index (FMI), central FMI, central fat, and WHtR.

Body mass index is widely used to classify total adiposity in populations (164). It is calculated using anthropometric measures of weight divided by height squared, which are measurements that are non-invasive, easy to determine, reliable, and simple to interpret (164). The height adjustment is useful because it accounts for adiposity increases in taller individuals (165). Body mass index has been associated with mortality in adults, and with DEXA measurements, CVD risk factors, diabetes, and atherosclerotic lesions in children (165, 166). A challenge in BMI measurement is that it indicates the additional weight of an individual instead of body fat specifically (165). Further inaccuracies can occur based on what protocol is used to measure BMI, potential changes in children's bodies, selection of cut-offs for obesity categorization, and misclassification into these groups (164). Classification in children is especially challenging due to the differences by sex, age, and puberty and their influences on the growing body (163). Furthermore, several reference charts for BMI in children exist such as the Centres for Disease Control and Prevention (CDC), International Obesity Task

Force, WHO, and British standards (167). Self-reported BMI may also add to these inaccuracies and is a less valid assessment of adiposity compared to those measured by professionals (164). Overall, BMI is a popular and reliable measure of adiposity and associates well with risk factors, however BMI measurements should be undertaken by trained personnel with proper protocol and equipment, in order to reduce measurement errors (164).

Fat mass index and central fat are less widely used assessments of adiposity that include a measure of body fat mass, instead of body weight like the BMI measure (168). The body fat mass measurement can be assessed using bioelectrical impedance analysis or DEXA, for example (168). Fat mass index for total as well as central body fat using trunk fat mass can be evaluated (169). Fat mass index adjusts for height squared, to form a calculation in the same units as BMI (168, 170). Fat mass index has been considered in children (171, 172) and correlates with CVD risk factors such as blood pressure (172). The height adjustment is useful because it can distinguish differences in body fat between those who have different heights (168). Consequently, compared to BMI, FMI can more accurately categorize adiposity in individuals by differentiating between those who have normal BMI and increased fat, or high BMI but no increased fat (168). However, there are no accepted cut-offs for FMI in adults or children, although some studies have investigated potential values for them (168). Moreover, DEXA utilizes expensive equipment and requires more resources, making it difficult to access (173). Central fat is calculated as the percentage of trunk fat out of total body fat, from DEXA (174). A small number of studies have

used this particular variable to measure central adiposity (175). In sum, FMI and central fat are two measures of adiposity that can be derived from DEXA. Although FMI is not as widely used as BMI, it can provide a more accurate measure of body fat while also adjusting for height squared, and can therefore be compared to BMI.

Waist-to-height ratio uses anthropometric measurements of WC divided by height. It has recently been recognized as an important measure to assess central obesity and its subsequent risks (176). It can be easily measured and understood because age and sex-specific references do not need to be considered as they do with BMI (169). Furthermore, a cut-off value of 0.5 can be used for adults and children alike (176). Challenges in using WHtR include: inconsistencies in how WC is measured, high measurement error for WC, limited numbers of studies on the association between WHtR in early life compared to adult life, and the usefulness of WHtR in changing risk assessment when BMI measurements can already be used for classification (165). A systematic review of 78 cohort and cross-sectional studies in adults and children showed that compared to BMI, WHtR and WC, measures of central adiposity, were more strongly associated with CVD risk factors, CVD, or diabetes (177).

2.4.2. The role of fitness

Fitness indicates how well a person can complete physical activities and is comprised of cardiorespiratory or aerobic fitness, flexibility, muscular endurance, muscular strength, and body composition (178, 179). For the purposes

of this thesis, cardiorespiratory or aerobic fitness will be the main focus. Fitness is determined by sex, age, genetics, and health, but can be improved by increasing PA, making it an important consideration in PA studies (5, 44). Aerobic fitness levels are commonly captured objectively by measuring the rate of the volume of oxygen (VO_2) taken up by the body during high amounts of PA such as during exercise tests, and is measured in litres per minute, or millilitres per kilogram per minute (178-180). During these tests, the skeletal muscles, and the cardiovascular and respiratory systems work together to achieve PA and an individual's highest physical competence is noted (117). Different protocols can be used to measure VO_2 at maximum exhaustion: shuttle-run tests, treadmill tests, and bicycle tests (181). Studies in children have shown that VO_2 varies by age and sex (182). A major challenge when using VO_2 measurements is that studies differ regarding what variable to use when assessing fitness: the VO_{2peak} or the VO_{2max}. The VO_{2peak} has been measured in children and youth, and represents the greatest capacity achieved while exercising (183). The VO_{2max}, on the other hand, is measured only when a plateau of VO_2 occurs (184). Some studies have shown that it is difficult for children achieve this plateau even though they may perform exercise tests until they become fatigued (184). Moreover, there are no differences between children who can and cannot meet this criteria for VO_{2max} (184). Consequently, the use of VO_{2peak} over VO_{2max} has been recommended for fitness assessments (185).

Studies also differ regarding which equipment and protocol to use for exercise tests (182). The ergometers that may be used include cycle, step,

treadmill, and arm (182). Treadmills are easier to use for children under eight years old and VO_{2max} can be achieved, however they are expensive and can be unsafe (182). Cycles are cheaper and safer, but their use may be physically and mentally demanding for children, leading to a difficulty in achieving VO_{2max} (182). However, they are considered appropriate for children who are at least eight years old (182). According to this evidence, measuring VO_{2peak} is suitable and the safety and reduced costs of cycles warrants their use in children who are at least eight years old.

Fitness research has shown that a high percentage of children and youth are unfit, and that fitness levels have declined over time and with age (33, 46-50). Furthermore, a small number of studies have shown its relationship with healthcare burden. For example, in 6,679 twenty- to seventy-nine-year-old disease-free Americans, those categorized in the highest fitness quartiles based on a treadmill test, had a lower percentage of physician visits and a lower percentage of overnight stays in a hospital, compared to those in lower fitness quartiles (64).

Although fitness has not been considered as extensively as adiposity in PA and cIMT studies, it is an important consideration for this thesis because it is affected by PA (44). Studies have also shown that body size and VO_{2peak} are highly correlated in growing children (186) and increases in VO_{2peak} may be the result of a larger body size rather than fitness (180, 186, 187). Therefore, to take potential confounding due to body size into consideration, fitness is often described according to body mass (180, 186, 187). Fitness is also associated with atherosclerosis, CVD, stroke, and CVD mortality (7). For example, a meta-

analysis of 33 observational cohort studies in asymptomatic adults showed that the risk for CVD was 15% lower for those with higher fitness, compared to those with lower fitness (4). A systematic review of 42 studies that measured childhood and adolescence fitness showed that fitness in early life was associated with CVD risk factors in adulthood (50).

The relationship between fitness and CVD has been further investigated by studying the association between fitness and atherosclerosis, however this literature is mixed. Several observational studies in men have shown that when stratifying by VO_{2max} or VO_{2peak} fitness categories, those in higher fitness groups exhibit reduced cIMT or changes in cIMT over time, compared to those in lower fitness groups, suggesting that there is a beneficial effect of fitness on vasculature (188-190). Other research as part of AGAHLS showed that VO_{2max} was negatively associated with cIMT in 36 year old Dutch men but not women, that VO_{2max} measured from ages 13 to 16 years was negatively associated with cIMT only in men (191), and that in contrast, VO_{2max} change compared from adolescence to adulthood was not associated with the cIMT of 36-year-olds (192).

Given that fitness is a CVD risk factor that is largely influenced by PA (44) and has been shown to be associated with cIMT (188-190), it is an important consideration in PA and cIMT studies. Together with the literature on CVD risk based on stratification by fitness categories (158, 162), studies on the differences in cIMT based on VO_2 categories (188-190) suggest that understanding whether or not fitness can modify the relationship between PA and cIMT is necessary.

2.4.3. The relationships between physical activity, adiposity, and fitness

The relationships between PA, adiposity, and fitness are complex and not well understood. Each factor on its own has independent relations with CVD, but research regarding how these three risk factors work together to influence health is limited (44). Some research has investigated the interrelationships among these three factors only, while other research has attempted to describe how all three can simultaneously influence CVD risk factors or CVD-related conditions. This research will be discussed below.

In terms of the associations between these three factors, a systematic review of studies assessing PA, adiposity, and fitness in children and adolescents found that very few had investigated these associations and that further research was required due to mixed results (193). One systematic review found that out of 48 studies investigating the association between adiposity and objective measures of PA in children and youth, 38 showed that these two factors were inversely related (194). A literature review of 9 studies in children and adolescents determining the relationship between fitness measured by VO_{2peak} and PA assessed by accelerometer showed modest correlations between fitness and PA (195). PA studies using higher intensity measures have also investigated the relationships between PA, adiposity, and fitness, and a systematic review of 25 studies in 5- to 18-year-olds showed that engaging in VPA was associated with lower adiposity, and that after PA interventions, fitness increased and adiposity decreased (124). Taken together, there is limited research concerning the complex

relationships between PA, adiposity, and fitness, however it can be hypothesized that PA and fitness are inversely related to adiposity in children.

A small number of studies have attempted to assess the relationships between PA, adiposity, and fitness in the context of CVD risk. A literature review of PA, fitness, and CVD risk concluded that in adults, high PA or fitness was associated with lower CVD risk despite overweight status (162). Meta-analyses in adults have also shown that fitness and PA are negatively associated with CVD risk in a dose-response manner (162). Another literature review of a small number of studies considering PA, adiposity, and fitness in men concluded the following: that increased PA from self-reports reduced the risk of CHD regardless of weight status, that being unfit increased the risk of CVD mortality at an equivalent adiposity level, that being fit and having high adiposity was protective for CVD mortality compared to being unfit and having low adiposity, and that fit men still needed to have low adiposity to be at a lower risk for CVD mortality (196). These findings in adults lend importance to the categorization of fitness and adiposity in assessing risk.

The relationships between PA, adiposity, and fitness have also been investigated in young people. In a literature review in children and youth, PA was shown to be inversely related to metabolic risk, and research was inconclusive regarding whether or not adiposity was a mediator or confounder for this relationship (158). Furthermore, studies stratifying children and adolescents into fitness and adiposity groups have shown that fitness is associated with a reduction but not elimination of metabolic risk at the same adiposity level (158). This

finding is similar to studies of adiposity, fitness, and CVD discussed earlier in adults. Researchers of these reviews generally mentioned that studies exploring PA, fitness, and metabolic or CVD risk have potential limitations because subjective measurements of PA for example were used, which make it difficult to discern the relationships between these variables correctly (158).

As the abovementioned studies have shown, there are complex and important relationships between PA, adiposity, and fitness. A study investigating the association of PA specifically on cIMT would therefore benefit from including both adiposity and fitness in analyses to gain a better understanding of this association. Since the literature is inconclusive regarding the relationships between PA, adiposity, and fitness in relation to CVD risk, this thesis can add to the research in this area.

2.5. Summary of the literature review and significance of this study

Cardiovascular disease is a major cause of death (2), and CVD risk factors are associated with markers of the atherosclerotic process which leads to CVD (21-28). Carotid intima-media thickness is a surrogate marker of atherosclerotic burden that can indicate thickening in the intima layer of arterial walls, and has been shown to associate with CVD risk factors in adults and children (18, 69, 88, 197).

In Canada, the prevalence of childhood obesity is reaching epidemic levels (31) and there is a high prevalence of physical inactivity (38, 39) and low fitness (33, 46). This may accelerate the atherosclerotic process and contribute to CVD

burden. Increasing our understanding of the relationship between CVD risk factors such as obesity, PA, and fitness, and surrogate markers of subclinical atherosclerosis in populations of children, is important to inform public health approaches and to reduce CVD risk in early life. Many studies have shown that obesity is an important modifiable risk factor that is associated with markers of atherosclerosis in children and youth long before CVD symptoms show (21-28). Public health encourages greater participation in PA to reduce weight and subsequent CVD risk (37), and although PA is an established CVD risk factor (5), few studies have examined the specific associations between PA and cIMT to determine the direct effect of PA on atherosclerosis.

Studies that have assessed the effect of PA on cIMT in children and adolescents have yielded inconsistent results. They have focused on interventions to manage weight and improve CVD risk factor profiles in small clinical samples of obese individuals, with few observational studies in disease-free groups (109, 139-156). This indicates that there is a gap in the literature, and a need to expand research regarding the specific relationship between PA and cIMT in larger population-based samples of children. Although some studies have investigated these relations in larger samples, the use of different total and central adiposity measures, and the modification of this relationship by adiposity and fitness has not been studied before. Using objective measures for variables can also help reduce measurement errors that have caused discrepancies in previous research regarding PA (120) and adiposity (164). This thesis aims to add to the literature in this field by determining whether or not objectively-measured PA is associated

with cIMT in a large sample of at-risk children, and how measures of total and central adiposity, and fitness, can modify this relationship. This research can inform public health about the influence of PA behaviour on subclinical atherosclerosis in early life.

2.6. Objectives and hypotheses of this study

1) To examine the association between PA (total, MVPA, VPA) and cIMT. We hypothesize that there is an inverse relationship between each PA variable and cIMT.

2) To investigate the aforementioned association between PA and cIMT in different adiposity categories (BMI, total FMI, central FMI, central fat, WHtR) and fitness categories (VO_{2peak}) by considering adiposity and fitness as potential effect modifiers. We hypothesize that the relationship between PA and cIMT will vary in different adiposity and fitness categories so that adiposity and fitness modify the effect of PA on cIMT.

These relationships will be assessed using available data from QUALITY (Quebec Adipose and Lifestyle Investigation in Youth) Study which is based in a large population-based sample of at-risk children, as described in the Methods.

2.7. Conceptual model

Figure 1 shows the conceptual model of the potential relationships between the variables of interest in this study.

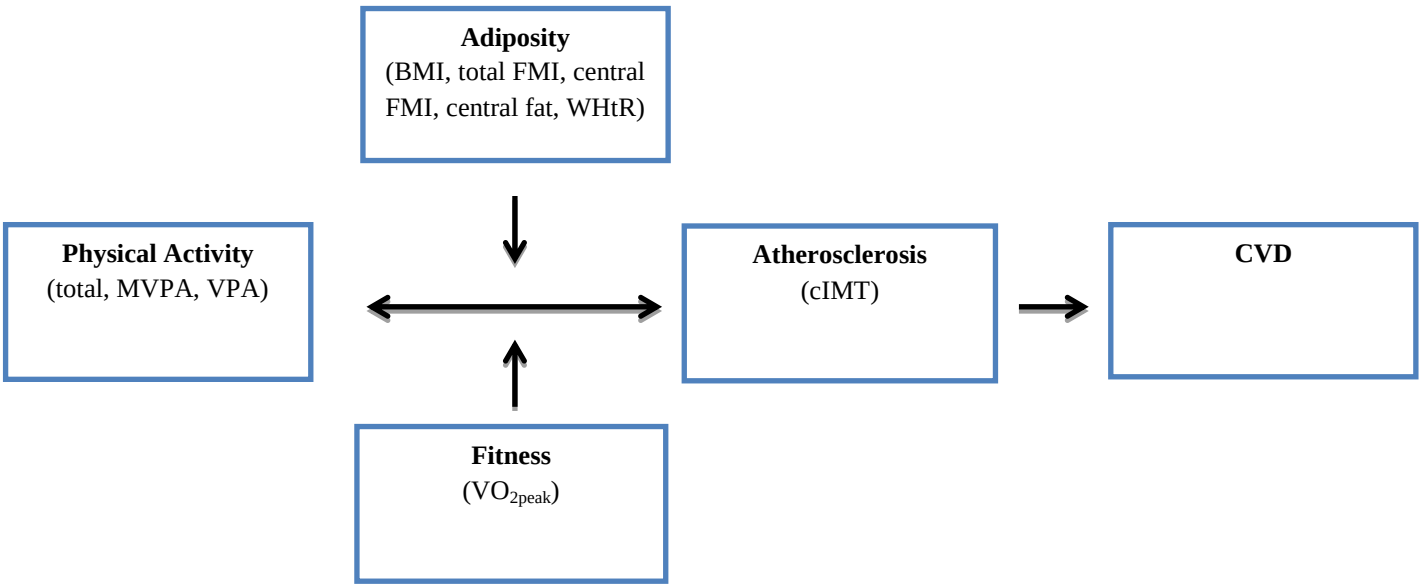

Figure 1. Conceptual model relating variables of interest in this study.

CHAPTER 3: METHODS

3.1. Study participants

The QUALITY Study cohort study aims to investigate the progression of obesity and cardiovascular outcomes in a community-based sample of at-risk children, which has been previously described (198). Further details of the study including the data collection procedures, measurements, and equipment used can be viewed in the QUALITY Study manuals (199-201). As part of this ongoing cohort study, child and parent data were collected at a baseline visit between September 2005 and December 2008 (198). Participants were initially recruited from Canadian primary schools using brochure circulation which targeted parents of Grades 2, 3, 4, and 5 students in and around 75 km of Montreal, Sherbrooke, and Quebec City (198). Baseline visit data were obtained for 634 children with the following inclusion criteria: Caucasian with Western European family lineage, aged 8 to 10 years, one or more obese parent classified as having a BMI at or above 30 kg/m^2, or a WC greater than 88 cm for mothers and greater than 102 cm for fathers (198). A child who had turned 11 years old in the previous two weeks was also included (199). Exclusion criteria included: a pregnant mother or a mother who was breastfeeding, families who would not be permanently residing in Quebec, children with health conditions rendering them unable to adequately contribute to the study, children who had a type 1 or type 2 diabetes diagnosis, children with a diet of less than 600 kilocalories per day, or children taking medication for high blood pressure (198).

The data used in this thesis were collected at the baseline visit which included physical evaluations at a test centre (Hôpital Laval, l'Unité de Recherche Clinique du Centre Hospitalier Universitaire Sainte-Justine) (198). Physical activity data were collected for the seven days following the baseline visit (198).

3.2. Study design

The cross-sectional study for this thesis was a secondary analysis of QUALITY Study data collected at a baseline visit between September 2005 and December 2008 (198).

3.3. Inclusion criteria

Since the primary aim of this thesis was to determine the association between the exposure, PA, and the outcome, cIMT, the original 634 observations were reduced to 461 observations that had values for the three PA variables (total, MVPA, VPA) and average cIMT. These variables are explained in detail in the next section of this chapter. The following inclusion criteria were used: a calculated value for average cIMT using original left and right cIMT measurements, a value for average total PA per day over one week when the accelerometer was worn for at least 10 hours for at least four days, a calculated value for average MVPA per day over one week when the accelerometer was worn for at least 10 hours for at least four days, and a calculated value for average VPA per day over one week when the accelerometer was worn for at least 10 hours for at least four days (201).

3.4. Variables of interest

3.4.1. Outcome variable

The outcome variable for this study was cIMT. cIMT measurements were performed with B-mode ultrasonography using the HDI 5000 (ATL, Phillips, Bothwell, WA) machine, a 7 to 12 MHz transducer, and a computer with Math-STD software (199). After device calibration, children were asked to lie in a supine position and angle their heads away from the side being measured (199). The ultrasound transducer, with a depth of field of 3.9 cm, was positioned behind the sternocleidomastoid muscle so that the posterior and anterior of the right and left common carotid arterial walls would be seen in a longitudinal view (199). The left and right common carotid artery walls, the carotid bulb, the carotid bifurcation and at least 2 cm below the bifurcation were located on the ultrasound image (199). With the transducer positioned perpendicular to the arterial inner wall, two 1.5 cm long parallel lines were used to mark the cIMT, between the border of the lumen and intima, and the border of the adventitia and media, on a fixed image (27, 198, 199). This was repeated 100 times by the computer (199). The measurement of the cIMT from the 2-D ultrasound image was taken for right and left carotid artery far walls (198, 199). Images were then analyzed off-site at Centre Hospitalier Universitaire Sainte-Justine with a computer (Eurequa, TSA Company, France) (198, 202). The secondary data provided included right and left cIMT measurements (mm).

The coefficient of variation for cIMT measured at baseline was reported by the QUALITY Study investigators to be 4.3% for the left artery and 6.8% for the right artery. However, cIMT measurement accuracy became uncertain after the first follow-up visit of the QUALITY Study between September 2008 and March 2011, when children were between 10 to 12 years old (198). Preliminary analyses conducted by the QUALITY Study team, showed that for many study participants, cIMT decreased by a median difference of 0.02 mm between the baseline visit and the first follow-up visit. This suggested that cIMT had decreased with age for the QUALITY Study participants, and contradicts the widely accepted notion that cIMT increases with age as arterial wall thickening develops over time (27). Following this finding, post-hoc accuracy evaluations of the cIMT measurement have been carried out by the QUALITY Study researchers and are currently in progress. Specifically, repeated measurements spanning two years between March 2011 and March 2013 on an adult nurse have revealed suboptimal precision and reliability of the cIMT measurement in the QUALITY Study. With regards to precision, the ultrasound transducer was only able to obtain precision within 0.40 mm. Given that mean cIMT values can range from 0.38 mm to 0.50 mm in children and youth between 10 to 20 years old (18, 75), and ranged from 0.42 mm to 0.73 mm in the QUALITY Study sample used in this thesis, the ultrasound transducer's precision of 0.40 mm calls into question the ability to capture true cIMT values. In terms of reliability, cIMT values ranged widely in the adult nurse, between 0.56 mm and 0.71 mm. Taken together, the aforementioned additional analyses revealing decreased median cIMT with age

and suboptimal accuracy with repeated assessments of cIMT on an adult nurse indicate that the results presented in this thesis, which used secondary QUALITY Study cIMT data, warrant interpretation using discretion.

Additional investigations are underway to re-examine the original ultrasound recordings obtained at the baseline and first follow-up visits, as these images were taken on a monitor and digitized permanently, making retrieval of records possible. In order to re-analyze the cIMT information, two measures will also be assessed using the original recordings to provide further information about arterial wall thickening: 1) vascular elasticity using elastography (203, 204), and 2) carotid diameter (205) to adjust the cIMT measurement. These examinations will entail a considerable amount of work spanning many years and at the time of writing this thesis, are in preliminary stages.

3.4.2. Exposure variables

The main exposure for this study was PA from accelerometer recordings. Three variables were used as measures of PA: average total PA per day, average MVPA per day, and average VPA per day. Children were given calibrated and validated accelerometers (Actigraph LS 7164 activity monitor, Actigraph LLC, Pensacola, FL, USA) (206) at the end of their baseline visit, and were instructed to wear the devices on the right side of their hip for one week, during the day, except when showering, bathing, sleeping, or swimming (198, 199). Children were also told to write down the times they put on and removed the device on a seven day log sheet which also included questions about when they played sports

or games, whether they had used a bicycle or taken a bath, and why they may not have been active (199). Children were instructed not to change their natural behaviour (199). After seven days of data capture, children returned the device and their log sheet to study investigators (199). When the accelerometer and log sheet were received, data was downloaded and organized by a study coordinator (199).

Adopting established validity criteria, this study used PA data from children who had four or more days of at least 10 hours of wear time per day (127). PA data was downloaded as one minute epochs. Non-wear time was noted when there were 60 or more consecutive minutes with zero counts with one to two minutes of 0 to 100 counts allowed (127). Wear time was calculated as: 24 hours minus non-wear time (127). The average of total PA per day over one week when at least four days of 10 hours were logged, was provided in the secondary data set as the total PA variable (counts per minute (cpm)) (201). For example, for a child who fulfilled five days of at least 10 hours of wear time per day, the average total PA per day was computed from the total PA for five days. MVPA and VPA variables (min/day) were provided for each individual day of the week with MVPA defined as activity at 2296 cpm and above, and VPA defined as activity at 4012 cpm and above (201).

3.4.3. Potential effect modifiers

3.4.3.1. Adiposity variables

Five adiposity variables were used in this study: BMI, total FMI, central FMI, central fat, and WHtR. Anthropometric measurements were evaluated using specific guidelines (207), with children wearing light clothing or a hospital gown, and no shoes or large items such as keys or cellphones (198, 199). All anthropometric measurements were recorded on paper by the research assistant or nurse and later captured electronically by the research assistant (199). Weight, height, and WC were measured using an electronic weighing scale, a stadiometer and measuring tape, respectively (198).

For weight measurements, the scale was made level and set at zero (199). The child was instructed to stand in the middle of the scale and look forward (199). The weight value in kilograms was rounded to one decimal place (199). The child was asked to step off of the scale and the process was repeated a second time (199). A third measurement was taken if discrepancies between the two values were greater than 0.2 kg (199).

For height measurements, children were instructed to remove hair accessories, and stand straight with their back, heels, shoulders, and bottom touching the stadiometer (199). The research assistant made sure that the child's feet were flat on the ground, that their cheekbones were parallel to the ground, that their arms were positioned loosely against their sides with their hands at their thighs, and that their shoulders were relaxed (199). The child was asked to stand

straight and take a deep breath, holding it at maximal inspiration (199). During this time, the research assistant, with their eyes level, measured height in centimetres and rounded to one decimal place (199). The child was asked to step away from the stadiometer and the process was repeated a second time (199). A third measurement was taken if discrepancies between the two values were greater than 0.2 cm (199).

For WC measurements, children were asked to stand straight and keep their feet still, abdomen relaxed, and arms on their chest area or close to their body (199). Following the child's natural expiration, the waist measurement was taken around the right and left sides, mid-distance from the iliac crest and the last floating rib (198, 199). Two separate measurements in centimetres were taken to the nearest decimal place (199). A third measurement was taken if discrepancies between the two values were greater than 0.2 cm (199).

The secondary data provided for anthropometrics included BMI (kg/m^2) and WHtR. BMI was calculated as: [weight (kilograms)]/ [height (meters squared)]. BMI percentile values based on CDC age and sex growth charts were also provided. BMI in original units (kg/m^2) was used in overall regression models for interpretation purposes, and CDC BMI percentile values were used to categorize children according to a ranking of American children of similar age and sex (208). WHtR values were calculated as: WC (centimetres)/height (centimetres).

Total body fat mass and trunk fat mass measurements for total FMI, central FMI and central fat calculations were determined using a calibrated

DEXA machine (Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation, Madison, WI, USA) (209) with children wearing hospital gowns and no shoes, tight clothing, or metals (198, 199). Children were asked first to fill out a questionnaire about their medical history (199). Children were then asked to lie supine with their back flat, their ankles secure, their palms facing down, and their arms by their sides (199). The child was asked not to move for the duration of the X-ray scan (199). The machine scanned at 1cm/sec, during which a generator underneath the child emitted x-rays with different energies, 30 cm into the body, and a detector above the child recorded the results (199). The scan recorded total and L2-L4 bone mass density in grams per centimetre squared as well as fat, fat-free, and bone mass in grams for legs, arms, and the trunk area (199). The secondary data provided from DEXA included total fat mass (kg), trunk fat mass (kg) and central fat (%). Central fat as a percentage was calculated as: [[trunk fat mass (kg)]/ [total fat mass (kg)]]*100.

3.4.3.2. Fitness

The fitness variable used in this study is VO_{2peak}. Children were asked to cycle on an electromagnetic bicycle (Oxycon Pro, Jaeger) until they were too fatigued, as part of a 12 stage incremental performance test based on McMaster protocol (182), which measured heartbeat, inspiration and expiration, and blood pressure (198, 199). Specifically, the VO_{2peak}, the peak amount of oxygen consumed, was noted during the test and used to indicate fitness (198).

Before the test, one of two different protocols with differing stage lengths (min), load (watts), and revolutions per minute (rpm), were selected based on the child's height: less than or equal to 160 centimetres, or greater than 160 centimetres (199). Electrocardiography electrodes were attached to the child's cleaned skin under the distal sections of the right and left clavicles, and between the right and left floating rib and hip (199). The electromagnetic bicycle was optimized by modifying the handlebar height to accommodate the child and allow them to view the rpm during pedalling (199). The seat height was modified so that the child's hips would be still during pedalling, the knees would be flexed to a small degree when the feet were positioned under the pedal, and the knees would stay below the waist (199). Masks that fully covered the nose and mouth were put on the child to detect breath measurements (199). An oximeter to measure oxygen saturation was clipped onto one of the fingers of the child's right hand (199). A sphygmomanometer cuff to measure blood pressure was attached on the child's left arm so that the sensor faced the brachial artery (199).

During the test, children were instructed to keep their arms and hands loose while pedalling and when prompted, to indicate that they were able to continue the test or when they wanted to stop (199). Children were told that pedal resistance would be increased every two minutes, that rates of 50 to 70 rpm were acceptable, and that they would have to indicate their exhaustion level, based on the OMNI scale, towards the end of each stage of the test (199). The child was monitored for the duration of the test, which continued until complete exhaustion (199). The test was terminated if the child: had an abnormal heart beat, felt ill,

was unable to pedal at least 40 rpm, had a diastolic blood pressure greater than 120 mmHg, had a systolic blood pressure greater than 250 mmHg, had no increase in systolic blood pressure even with inactivity from pedalling or, had a reduced systolic blood pressure even with more rigorous pedalling (199). In order to qualify as a maximum test, the following would need to be indicated: a respiratory exchange ratio greater than one, or the child's expected heart rate or 195 beats per minute, or a heart rate plateau even with a greater intensity of work, or a VO_2 plateau (199). After the 12 stages, a five minute recovery period at 40 rpm was conducted, followed by quadriceps stretching (199). All data were logged in a computer and printed after the test (199). Values for each test stage were entered manually into the database using information from the final 30 seconds of each stage (199). As part of the test protocol, blood pressure data were entered into the database using the sheet of paper from the equipment rather than the computer data which was delayed (199). The secondary data set included VO_2 during maximal O_2 consumption which was used as the VO_{2peak} variable (mL/min).

3.4.4. Other covariates

Age, sex, and Tanner stage (sexual maturation or puberty) are important considerations as children undergo developmental changes (75, 210, 211) and were considered to be biologically important variables in all of the regression analyses in this study, irrespective of their statistical significance. The child's birthday was manually recorded by their parents as part of a written questionnaire

with a research assistant present to provide clarification (199). Child's sex was noted electronically by an interviewer (198, 199). Tanner stage on a scale of one to five was reported after a visual assessment of sexual maturation (199, 212, 213). Children were assessed by a male professional if the child was male, or by a female professional if the child was female (199). Children were asked to wear hospital gowns and lie supine (199). In males, the penis, scrotum and pubic hair were assessed, and in females, the chest area and pubic hair were assessed (199). Tanner stage was recorded on paper by the research assistant or nurse (199). The secondary data set included age, sex, and Tanner stage values. Age was calculated as [baseline visit date - birth date]/365.25 (years) (200).

3.5. Statistical analyses

All statistical analyses were performed using Stata 12.1 for Windows. Significance was noted at $p \leq 0.05$.

3.5.1. Initial descriptive statistics and restricted cubic spline regression

Data were explored for the initial 461 observations and descriptive statistics were carried out for all variables of interest. Using lowess, non-linearity for observations with low PA was noted when plotting cIMT versus total PA, cIMT versus MVPA, and cIMT versus VPA. The observations at low PA were considered outliers and therefore, restricted cubic spline regression was run to determine which observations to exclude. Restricted cubic spline models with cIMT as the outcome variable and either total PA, MVPA, or VPA spline

covariates as the exposure variables were run using all 461 observations (214). Three, four, five, six, and seven knot models were explored (214). In total, 35 observations were identified as being outliers in either total PA, MVPA or VPA spline models, and were dropped. All further data management and statistical analyses in this thesis were done for the remaining 426 observations. Comparisons using one-way analysis of variance (ANOVA), between these 426 observations and the 208 observations that were dropped from the original sample due to inclusion criteria and outliers contributing to non-linearity, showed no significant differences in age, BMI, total FMI, central FMI, central fat, WHtR, and VO_{2peak} means.

3.5.2. Data management

The cIMT variable was calculated as the average of the right and left cIMT values (mm).

The same calculations used to create the total PA variable provided in the data set were also used to create the MVPA and VPA variables. Average MVPA per day over one week (min/day) and average VPA per day over one week (min/day) were calculated for children who fulfilled the criteria of at least four days of 10 hours of wear time per day. For example, for a child who fulfilled five days of at least 10 hours of wear time per day, the average MVPA per day was computed from the MVPA for five days. Total PA, MVPA and VPA tertiles were created for exploratory analyses with ANOVA.

Total FMI was calculated as: [total body fat mass (kilograms)/1000]/[height (metres squared)] to obtain values in kg/m^2, comparable to BMI. Central FMI was calculated as: [trunk fat mass (grams)/1000]/[height (metres) x height (metres)] to obtain values in kg/m^2, comparable to BMI.

Since one of the objectives of this thesis included examining the relationship between PA and cIMT by adiposity categories, categorical variables were created for each of the five adiposity variables. BMI was divided into four categories using CDC percentiles: underweight less than 5^{th} percentile, normal from the 5^{th} percentile to less than 85^{th} percentile, overweight from 85^{th} percentile to less than 95^{th} percentile, and obese at 95^{th} percentile and above (208). As there were only four observations in the underweight category, these observations were included with normal BMI to increase power, and three categories were considered for BMI: normal, overweight, and obese. Regression analyses that were performed with these four observations dropped showed minor changes in regression coefficients across adiposity and fitness categories.

Total FMI was divided into categories using cut-off values equivalent to BMI percentile cut-offs. A simple linear regression model was fitted with total FMI as the outcome variable and BMI percentile as the exposure variable. The equation total FMI = $\boldsymbol{\beta}_0 + \boldsymbol{\beta}_1$ BMI percentile was used to determine cut-off points for total FMI values equivalent to the 85^{th} percentile and 95^{th} percentile for BMI. The estimates of constant, $\boldsymbol{\beta}_0$, and regression coefficient for BMI percentile, $\boldsymbol{\beta}_1$, were used in the equation. BMI percentiles of 85 or 95 were used in the regression

equation to calculate the equivalent total FMI values at the 85^{th} percentile and 95^{th} percentile, respectively.

Total FMI value equivalent to 85^{th} BMI percentile was computed by:

$Y = \beta_0 + \beta_1 X = -0.9566044 + 0.0932757 (85) = 6.97.$

Total FMI value equivalent to 95^{th} BMI percentile was computed by:

$Y = \beta_0 + \beta_1 X = -0.9566044 + 0.0932757 (95) = 7.91.$

Total FMI was divided into three categories using these BMI equivalent cut-offs: less than 6.97 kg/m^2, from 6.97 kg/m^2 to less than 7.91 kg/m^2, and 7.91 kg/m^2 and above.

The same methods used to create total FMI categories were used to create central FMI categories (see Appendix A). Central FMI was divided into three categories using these BMI equivalent cut-offs: less than 3.10 kg/m^2, from 3.10 kg/m^2 to less than 3.55 kg/m^2, and 3.55 kg/m^2 and above.

WHtR was divided into less than 0.5 and at 0.5 and above, as has been done in previous research (177, 215, 216).

Central fat was divided using the median 40.40%, into less than 40.40%, and at 40.40% and above. Two groups were created in order to increase power.

Since one of the objectives of this thesis included examining the relationship between PA and cIMT by fitness categories, a categorical variable was created for VO_{2peak}. The same methods used to determine the cut-offs for total and central FMI were applied (see Appendix A). VO_{2peak} was divided into three categories using these BMI equivalent cut-offs: less than 1559.73 mL/min,

from 1559.73 mL/min to less than 1604.03 mL/min, and 1604.03 mL/min and above.

Tanner stage was recoded into two categories: stage one, and stages two and above, as some stages did not have enough observations.

Since VO_{2peak} and body composition can be correlated in children, and body size may confound the interpretation of fitness (186, 187), a VO_{2peak} residual variable was created (217, 218) by taking the residual from the simple linear regression of VO_{2peak} with BMI. VO_{2peak} residual was used as the fitness variable for statistical analyses.

3.5.3. Descriptive statistics for final sample

The categorical variables sex, Tanner stage, BMI categories, total FMI categories, central FMI categories, central fat categories, WHtR categories and VO_{2peak} categories were described using frequency tables. For the continuous variables age, cIMT, total PA, MVPA, VPA, BMI, total FMI, central FMI, central fat, WHtR, VO_{2peak}, and VO_{2peak} residual, the means, standard deviations and minimum to maximum ranges were explored. The data were described with histograms and boxplots. Pairwise correlations between variables were also determined, and the correlations between VO_{2peak} and adiposity variables were determined to take into account potential confounding of fitness by body composition. Scatterplots with lowess, comparing each variable with cIMT, were also visualized.

3.5.4. Exploratory analyses with one-way analysis of variance

Data were also explored with one-way ANOVA and post-hoc pairwise comparisons using Tukey's method. Differences in cIMT, total PA, MVPA and VPA means by adiposity and fitness categories, as well as differences in cIMT, VO_{2peak}, and VO_{2peak} residual means by total PA, MVPA, and VPA tertiles were noted.

3.5.5. Multiple linear regression

All models were run using the purposeful section approach. First, simple linear regression of cIMT was performed separately for each variable of interest to assess significant associations with cIMT. The magnitude and direction of the regression coefficient for each variable and its significance based on the p-value for t-test were determined.

Second, multiple linear regression models were conducted to determine the association of PA with cIMT (Objective 1). Base models included important covariates: age, sex, and Tanner stage. Table 2 shows models that were run to assess Objective 1 for all 426 observations.

Table 2. Models to assess the association between PA variables and cIMT (Objective 1).

Outcome variable	Exposure variable	Covariates
cIMT	total PA	age, sex, Tanner stage
cIMT	total PA	age, sex, Tanner stage, BMI
cIMT	total PA	age, sex, Tanner stage, total FMI

cIMT	total PA	age, sex, Tanner stage, central FMI
cIMT	total PA	age, sex, Tanner stage, central fat
cIMT	total PA	age, sex, Tanner stage, WHtR
cIMT	total PA	age, sex, Tanner stage, VO_{2peak} residual
cIMT	MVPA	age, sex, Tanner stage
cIMT	MVPA	age, sex, Tanner stage, BMI
cIMT	MVPA	age, sex, Tanner stage, total FMI
cIMT	MVPA	age, sex, Tanner stage, central FMI
cIMT	MVPA	age, sex, Tanner stage, central fat
cIMT	MVPA	age, sex, Tanner stage, WHtR
cIMT	MVPA	age, sex, Tanner stage, VO_{2peak} residual
cIMT	VPA	age, sex, Tanner stage
cIMT	VPA	age, sex, Tanner stage, BMI
cIMT	VPA	age, sex, Tanner stage, total FMI
cIMT	VPA	age, sex, Tanner stage, central FMI
cIMT	VPA	age, sex, Tanner stage, central fat
cIMT	VPA	age, sex, Tanner stage, WHtR
cIMT	VPA	age, sex, Tanner stage, VO_{2peak} residual

Final models included age, sex, Tanner stage, one PA variable, and one adiposity or fitness variable. Objective 1 was assessed by determining the magnitude and direction of the regression coefficient for the PA variable and its significance based on the p-value for t-test. Additional models with total PA were also assessed in boys and girls separately.

Third, effect modification by adiposity was assessed in two ways: by stratification and by adding interaction terms to regression models (Objective 2)

(219). For stratification, models were run separately by adiposity categories for BMI, total FMI, central FMI, central fat, and WHtR. Since total FMI and central FMI categories had 14 and 15 observations, respectively, in the greater than or equal to 85th to less than 95th BMI percentile equivalent category, these observations were added with the greater than or equal to 95th BMI percentile equivalent category to make the greater than or equal to 85th BMI percentile equivalent category. This was to improve statistical power in categories. To these models, total PA, MVPA and VPA were added separately. Tables 3 to 7 show the models that were run to assess Objective 2 by adiposity categories.

Table 3. Models to assess effect modification by BMI (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
Normal BMI	cIMT	total PA	age, sex, Tanner stage
Normal BMI	cIMT	MVPA	age, sex, Tanner stage
Normal BMI	cIMT	VPA	age, sex, Tanner stage
Overweight and Obese BMI	cIMT	total PA	age, sex, Tanner stage
Overweight and Obese BMI	cIMT	MVPA	age, sex, Tanner stage
Overweight and Obese BMI	cIMT	VPA	age, sex, Tanner stage
Overweight BMI	cIMT	total PA	age, sex, Tanner stage
Overweight BMI	cIMT	MVPA	age, sex, Tanner stage
Overweight BMI	cIMT	VPA	age, sex, Tanner stage
Obese BMI	cIMT	total PA	age, sex, Tanner stage
Obese BMI	cIMT	MVPA	age, sex, Tanner stage
Obese BMI	cIMT	VPA	age, sex, Tanner stage

Table 4. Models to assess effect modification by total FMI (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
Equivalent to Normal BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	VPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	VPA	age, sex, Tanner stage

Table 5. Models to assess effect modification by central FMI (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
Equivalent to Normal BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	VPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	VPA	age, sex, Tanner stage

Table 6. Models to assess effect modification by central fat (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
< Median	cIMT	total PA	age, sex, Tanner stage
< Median	cIMT	MVPA	age, sex, Tanner stage
< Median	cIMT	VPA	age, sex, Tanner stage
≥ Median	cIMT	total PA	age, sex, Tanner stage
≥ Median	cIMT	MVPA	age, sex, Tanner stage
≥ Median	cIMT	VPA	age, sex, Tanner stage

Table 7. Models to assess effect modification by WHtR (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
< 0.5	cIMT	total PA	age, sex, Tanner stage
< 0.5	cIMT	MVPA	age, sex, Tanner stage
< 0.5	cIMT	VPA	age, sex, Tanner stage
≥ 0.5	cIMT	total PA	age, sex, Tanner stage
≥ 0.5	cIMT	MVPA	age, sex, Tanner stage
≥ 0.5	cIMT	VPA	age, sex, Tanner stage

Final models for adiposity categories included age, sex, Tanner stage, and one PA variable. Objective 2 was assessed by determining the magnitude and direction of the regression coefficient for the PA variable and its significance based on the p-value for t-test, as well as differences by adiposity categories.

Effect modification by fitness categories was also assessed by stratification (Objective 2). Models were run independently for VO_{2peak} categories. Since greater than or equal to 85^{th} to less than 95^{th} BMI percentile

equivalent category had only 22 observations, observations these were added with the greater than or equal to 95th BMI percentile equivalent category to make the greater than or equal to 85th BMI percentile equivalent category. This was to improve statistical power in categories. To these models, total PA, MVPA and VPA were added separately. Table 8 shows the models that were run to assess Objective 2 by fitness categories.

Table 8. Models to assess effect modification by VO_{2peak} (Objective 2).

Category	Outcome variable	Exposure variable	Covariates
Equivalent to Normal BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Normal BMI	cIMT	VPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	total PA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	MVPA	age, sex, Tanner stage
Equivalent to Overweight and Obese BMI	cIMT	VPA	age, sex, Tanner stage

Final models by fitness categories included age, sex, Tanner stage, and one PA variable. Objective 2 was assessed by determining the magnitude and direction of the regression coefficient for the PA variable and its significance based on the p-value for t-test, as well as differences by fitness categories.

Effect modification was also assessed by adding an interaction term between the PA variable and the adiposity or fitness variable in regression models

(Objective 2). Table 9 shows interaction terms that were added to respective models.

Table 9. Interaction terms added to models (Objective 2).

Outcome variable	Exposure variable	Covariates	Interaction term
cIMT	total PA	age, sex, Tanner stage, BMI	total PA#BMI
cIMT	total PA	age, sex, Tanner stage, total FMI	total PA#total FMI
cIMT	total PA	age, sex, Tanner stage, central FMI	total PA#central FMI
cIMT	total PA	age, sex, Tanner stage, central fat	total PA#central fat
cIMT	total PA	age, sex, Tanner stage, WHtR	total PA#WHtR
cIMT	total PA	age, sex, Tanner stage, VO_{2peak} residual	total PA#VO_{2peak} residual
cIMT	MVPA	age, sex, Tanner stage, BMI	MVPA#BMI
cIMT	MVPA	age, sex, Tanner stage, total FMI	MVPA#total FMI
cIMT	MVPA	age, sex, Tanner stage, central FMI	MVPA#central FMI
cIMT	MVPA	age, sex, Tanner stage, central fat	MVPA#central fat
cIMT	MVPA	age, sex, Tanner stage, WHtR	MVPA#WHtR
cIMT	MVPA	age, sex, Tanner stage, VO_{2peak} residual	MVPA#VO_{2peak} residual

cIMT	VPA	age, sex, Tanner stage, BMI	VPA#BMI
cIMT	VPA	age, sex, Tanner stage, total FMI	VPA#total FMI
cIMT	VPA	age, sex, Tanner stage, central FMI	VPA#central FMI
cIMT	VPA	age, sex, Tanner stage, central fat	VPA#central fat
cIMT	VPA	age, sex, Tanner stage, WHtR	VPA#WHtR
cIMT	VPA	age, sex, Tanner stage, VO_{2peak} residual	VPA#VO_{2peak} residual

The R^2 value of each model was also noted to determine how well models explained the data.

3.5.6. Power analysis

PASS was used to conduct a power analysis with an F-test ($\alpha = 0.05$) to compare a multiple linear regression base model with age, sex, and Tanner stage and another multiple linear regression model with age, sex, Tanner stage, and total PA ($n = 426$ and $R^2 = 0.002$). The power to add total PA to the base model was noted.

CHAPTER 4: RESULTS

4.1. Detection of lower extreme observations for physical activity

The lowess curve for cIMT versus total PA is shown in Figure 2. A similar non-linear curve was also noted when exploring total FMI versus total PA, and this lowess curve is shown in Figure 3.

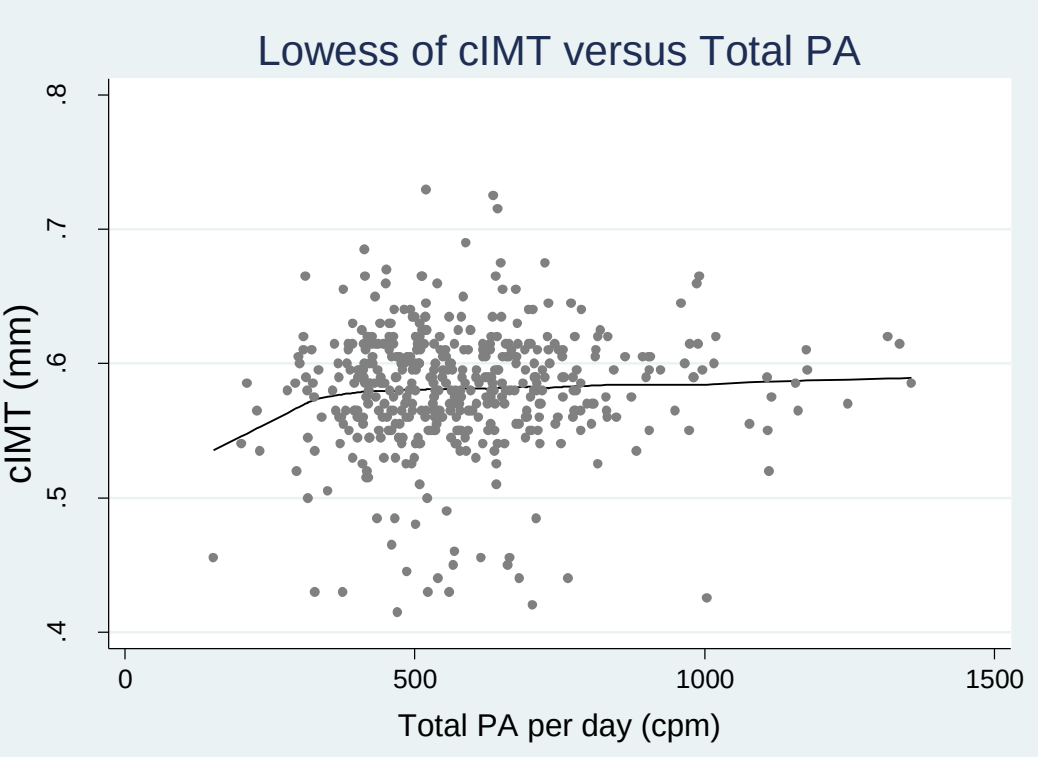

Figure 2. Lowess of cIMT versus Total PA.

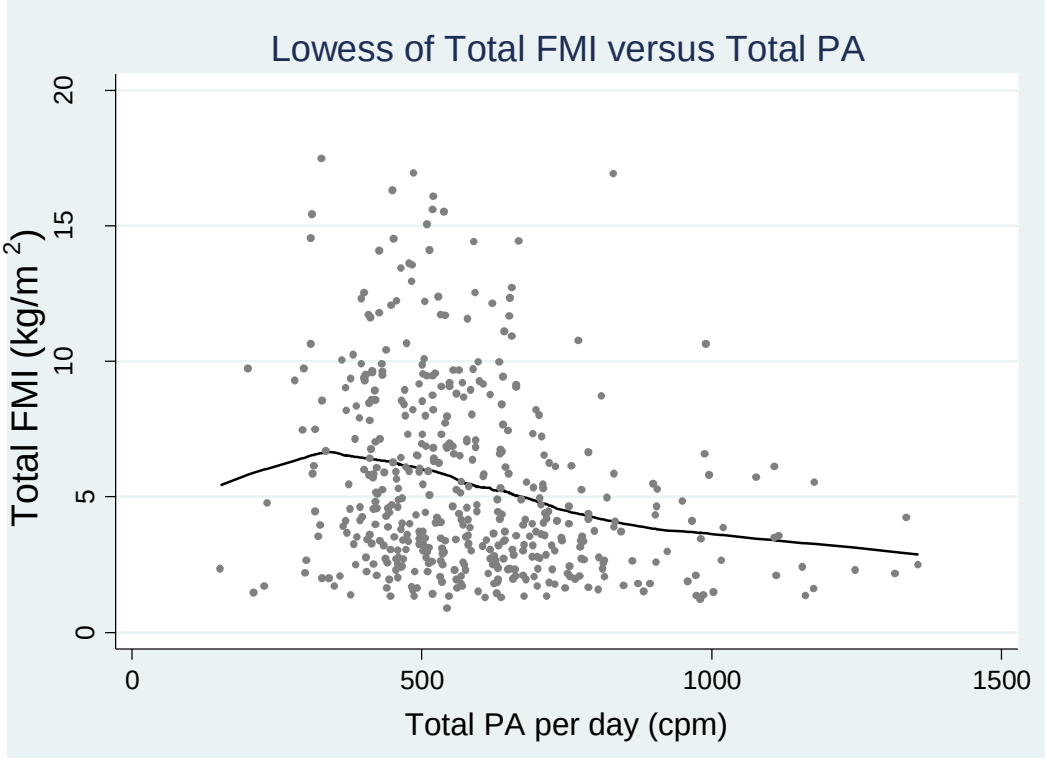

Figure 3. Lowess of Total FMI versus Total PA.

In restricted cubic spline models which were run to determine where outliers were located, the placement of the first knot for models with four, fix and six knots was 334.25 cpm for total PA, 17.29 min/day for MVPA and 2.01 min/day for VPA. These locations were used to mark the point at which extreme observations with low PA ended, and all observations with values less than these points were excluded. The remaining observations were assumed to follow a linear trend for regression analyses.

4.2. Descriptive statistics for final sample

Table 10 shows selected characteristics of the study sample (n = 426) by sex. The sample contained 238 boys (55.9%) and 188 girls (44.1%). The characteristics presented are for 238 boys and 188 girls unless otherwise stated.

In the total sample, cIMT values ranged from 0.42 mm to 0.73 mm, and 21.1% were obese, 18.1% were overweight, and 60.8% were normal weight. In addition, 32.9% had a WHtR greater than or equal to 0.5, and 67.1% had a WHtR less than 0.5.

Table 11 shows correlations between VO_{2peak} and adiposity variables in boys and girls. All correlations between VO_{2peak} and adiposity variables were positive and highly significant at $p < 0.001$. Since VO_{2peak} and adiposity variables were correlated, the VO_{2peak} residual, from the simple linear regression of VO_{2peak} with BMI, was used as the fitness variable in statistical analyses, to account for confounding of fitness by adiposity. In addition, as there were high correlations between adiposity variables (0.97 between BMI and total FMI, 0.96 between BMI and central FMI, 0.72 between BMI and central fat, 0.94 between BMI and WHtR, 0.99 between total FMI and central FMI, 0.74 between total FMI and central fat, 0.93 between total FMI, 0.80 between central FMI and central fat, 0.93 between central FMI and WHtR, and WHtR, 0.74 between central fat and WHtR), they were assessed separately in regression analyses.

Table 10. Characteristics of study sample by sex (n = 426).

Variable	Total (*n*)	Boys (*n* = 238)		Girls (*n* = 188)	
		Mean or No.	SD or %*	Mean or No.	SD or %*
Age (years)	426	9.59	0.91	9.59	0.93
Tanner stage	426				
>1	94	22	9.24%	72	38.30%
1	332	216	90.76%	116	61.70%
cIMT (mm)	426	0.58	0.05	0.58	0.04
PA					
Total PA (cpm)	426	652.42	192.35	548.46	140.54
MVPA (min/day)	426	62.49	26.71	42.35	16.69
VPA (min/day)	426	18.42	13.91	10.88	7.91
BMI (kg/m^2)	426	19.19	4.15	19.55	4.40
Obese	90	46	19.33%	44	23.40%
Overweight	77	46	19.33%	31	16.49%
Normal	259	146	61.34%	113	60.11%
Total FMI (kg/m^2)	424	4.87	3.29	6.00	3.43
Obese BMI equivalent	96	42	17.72%	54	28.88%
Overweight BMI equivalent	15	7	2.95%	8	4.28%
Normal BMI equivalent	313	188	79.32%	125	66.84%
Central FMI (kg/m^2)	424	2.06	1.61	2.63	1.75
Obese equivalent	89	39	16.46%	50	26.74%
Overweight equivalent	14	5	2.11%	9	4.81%
Normal BMI equivalent	321	193	81.43%	128	68.45%
Central fat (%)	424	39.78	5.14	41.41	5.48
≥ Median	212	107	45.15%	105	56.15%
< Median	212	130	54.85%	82	43.85%
WHtR	426	0.48	0.07	0.49	0.08
≥ 0.5	140	70	29.41%	70	37.23%
< 0.5	286	168	70.59%	118	62.77%
VO_{2peak} (mL/min)	413	1557.58	306.90	1389.25	303.01
Obese BMI equivalent	126	84	36.36%	42	23.08%
Overweight BMI equivalent	22	15	6.49%	7	3.85%
Normal BMI equivalent	265	132	57.14%	133	73.08%
VO_{2peak} residual (mL/min)¥	413	81.19	253.67	-103.05	242.28

Abbreviations: SD: standard deviation

* Percent out of participants with data ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

Table 11. Correlations between VO_{2peak} (mL/min) and adiposity measures in boys and girls.*

Adiposity Variable	Boys	Girls
BMI	0.5630	0.6007
Total FMI	0.4890	0.5247
Central FMI	0.4924	0.5220
Central fat	0.4228	0.4193
WHtR	0.4030	0.4171

* All correlation coefficients significant at $p < 0.001$

4.3. Comparison of carotid intima-media thickness and physical activity between adiposity and fitness categories, and carotid intima-media thickness and fitness by physical activity categories.

Table 12 shows comparisons of cIMT and PA means by adiposity and fitness categories. Children in the highest adiposity category had higher mean cIMT compared to those in the lowest adiposity category. There were no significant differences in mean cIMT across fitness categories. Children in the highest adiposity category had lower mean total PA, MVPA, and VPA compared to those in the lowest adiposity category. There were no significant differences in mean total PA, MVPA, and VPA across fitness categories.

Table 13 shows comparisons of cIMT, VO_{2peak}, and VO_{2peak} residual means by PA categories. There were significant differences in VO_{2peak} residual means between the highest and lowest MVPA and VPA categories, and the highest and middle MVPA and VPA categories. There were no significant differences in mean cIMT or VO_{2peak} by these categories.

Table 12. Comparison of cIMT (mm), Total PA (min/day), MVPA (min/day), VPA (min/day) means by adiposity and fitness categories.

	cIMT (mm)	Total PA (cpm)	MVPA (min/day)	VPA (min/day)
Groups	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BMI				
Obese	0.5909 (0.05)|	542.34 (108.16)|||	44.30 (15.86)|||	10.76 (7.21)|||
Overweight	0.5875 (0.04)	595.18 (177.32)	51.71 (22.72)	13.84 (10.74)
Normal	0.5775 (0.05)	632.23 (193.05)	57.39 (27.16)	16.97 (13.56)
Total FMI				
$\geq 85^{th}$ BMI percentile equivalent	0.5913 (0.05)*	529.76 (108.33)***	42.65 (15.86)***	10.14 (6.81)***
$< 85^{th}$ BMI percentile equivalent	0.5789 (0.04)	633.46 (191.18)	57.46 (26.39)	16.82 (13.22)
Central FMI				
$\geq 85^{th}$ BMI percentile equivalent	0.5931 (0.05)**	527.06 (109.78)***	42.15 (16.21)***	10.06 (7.00)***
$< 85^{th}$ BMI percentile equivalent	0.5787 (0.04)	631.74 (189.50)	57.25 (26.12)	16.68 (13.10)
Central fat (%)				
≥ Median	0.5867 (0.05)*	576.51 (152.57)***	49.46 (21.66)***	12.89 (9.83)***
< Median	0.5777 (0.04)	636.12 (198.18)	57.71 (27.25)	17.25 (13.92)
WHtR				
≥ 0.5	0.5910 (0.04)**	545.32 (118.85)***	44.80 (16.64)***	10.64 (7.11)***
< 0.5	0.5778 (0.04)	636.51 (195.14)	57.90 (27.09)	17.27 (13.56)
VO_{2peak}				
$\geq 85^{th}$ BMI percentile equivalent	0.5864 (0.04)	588.88 (172.73)	53.27 (24.20)	15.27 (12.26)
$< 85^{th}$ BMI percentile equivalent	0.5798 (0.05)	614.50 (181.24)	53.65 (25.28)	14.87 (12.18)

Abbreviations: SD: standard deviation

Post-Hoc pairwise comparison using Tukey's method:

p-value for mean difference between two categories: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$;

p-value for mean difference between obese and normal BMI: | $p \leq 0.05$, || $p \leq 0.01$, ||| $p \leq 0.001$

Table 13. Comparison of cIMT (mm) and VO_{2peak} (mL/min) means by PA categories.

	cIMT (mm)	VO_{2peak} (mL/min)	VO_{2peak} residual (mL/min)¥
Groups	Mean (SD)	Mean (SD)	Mean (SD)
Total PA Tertiles‡			
Highest	0.5834 (0.04)	1445.40 (273.80)	13.88 (232.55)
Middle	0.5818 (0.05)	1510.52 (334.34)	6.81 (277.62)
Lowest	0.5812 (0.04)	1492.93 (333.87)	-20.69 (281.17)
MVPA Tertiles‡			
Highest	0.5817 (0.05)	1482.07 (277.40)	53.75 (226.16)|*
Middle	0.5821 (0.05)	1494.44 (331.95)	-22.98 (274.20)
Lowest	0.5827 (0.04)	1473.68 (337.17)	-30.38 (283.71)
VPA Tertiles‡			
Highest	0.5840 (0.04)	1496.96 (278.28)	68.23 (229.24)|***
Middle	0.5840 (0.05)	1494.03 (320.51)	-18.40 (263.74)
Lowest	0.5785 (0.04)	1459.11 (346.05)	-48.30 (285.74)

Abbreviations: SD: standard deviation

‡ Created using groups of equal size (n = 142) ¥ Residual determined from simple linear regression of VO_{2peak} with BMI
Post-Hoc pairwise comparisons were performed using Tukey's method:
p-value for mean difference between highest and lowest categories: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$;
p-value for mean difference between highest and middle categories: | $p \leq 0.05$, || $p \leq 0.01$, ||| $p \leq 0.001$

4.4. Regression analysis of carotid intima-media thickness to investigate the associations between physical activity variables and carotid intima-media thickness, and effect modification by adiposity and fitness

Table 14 shows the results of the univariate analysis using the simple linear regression of cIMT by individual variables of interest in this study. Significant positive associations were found between cIMT and the following variables: BMI, total FMI, central FMI, central fat, and WHtR. No significant associations were found between cIMT and the following variables: age, sex, Tanner stage, total PA, MVPA, VPA, and VO_{2peak} residual.

Table 15 shows the results from the multiple linear regression of cIMT with total PA. Total PA was not significantly associated with cIMT in base models adjusted for BMI, total FMI, central FMI, central fat, WHtR, and VO_{2peak} residual. Adiposity variables showed significant positive associations with cIMT in all models. No significant association was found between cIMT and VO_{2peak} residual.

Tables 16 and 17 show the results from the multiple linear regression of cIMT with total PA, for boys and girls, respectively. In both boys and girls, total PA was not significantly associated with cIMT in base models adjusted for BMI, total FMI, central FMI, central fat, WHtR, and VO_{2peak} residual. Adiposity and variables showed significant positive associations with cIMT in all models for girls, but not for boys. No significant association was found between cIMT and VO_{2peak} residual in boys or girls.

Table 14. Results from the univariate analysis using simple linear regression of cIMT (mm).

Variable	Coeff.	SE	95% CI
Age (years)	0.00177	0.00239	(-0.00293,0.00647)
Sex (ref: male)	0.00232	0.00441	(-0.00634,0.01099)
Tanner stage (ref: stage 1)	0.00405	0.00528	(-0.00632, 0.01442)
Stages 2-4			
PA			
Total PA (cpm)	0.00001	0.00001	(-0.00002,0.00003)
MVPA (min/day)	0.00003	0.00009	(-0.00015, 0.00020)
VPA (min/day)	0.00018	0.00018	(-0.00018, 0.00053)
BMI (kg/m^2)	0.00179***	0.00051	(0.00079, 0.00278)
Total FMI (kg/m^2)	0.00191**	0.00064	(0.00065,0.00317)
Central FMI (kg/m^2)	0.00392**	0.00128	(0.00140, 0.00644)
Central fat (%)	0.00106**	0.00041	(0.00026, 0.00186)
WHtR	0.08971**	0.02984	(0.03106, 0.14835)
VO_{2peak} residual (mL/min)¥	0.0000019	0.00001	(-0.00001, 0.00002)

Abbreviations: Coeff.: regression coefficient; CI: confidence interval; ref: reference; SE: standard error

¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 15. Results from the regression of cIMT (mm) with Total PA (cpm) for various models.

Variable	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00001)	0.00002 (0.00001)	0.00002 (0.00001)	0.00002 (0.00001)	0.00002 (0.00001)	0.00002 (0.00001)	0.00002 (0.00001)
BMI (kg/m^2)	—	—	0.00194*** (0.00054)	—	—	—	—	—
Total FMI (kg/m^2)	—	—	—	0.00207** (0.00068)	—	—	—	—
Central FMI (kg/m^2)	—	—	—	—	0.00423** (0.00137)	—	—	—
Central fat (%)	—	—	—	—	—	0.00107* (0.00043)	—	—
WHtR	—	—	—	—	—	—	0.09591** (0.03075)	—
VO_{2peak} residual (mL/min)¥	—	—	—	—	—	—	—	0.0000003 (0.00001)
Age (years)	0.00137 (0.00270)	0.00181 (0.00273)	0.00020 (0.00273)	0.00078 (0.00273)	0.00071 (0.00273)	0.00087 (0.00274)	0.00165 (0.00270)	0.00222 (0.00322)
Sex (ref: male)	0.00173 (0.00478)	0.00288 (0.00492)	0.00366 (0.00486)	0.00220 (0.00491)	0.00210 (0.00491)	0.00209 (0.00493)	0.00375 (0.00488)	0.00497 (0.00535)
Tanner stage (ref: stage 1)								
Stage 2-4	0.00203 (0.00634)	0.00270 (0.00638)	0.00027 (0.00633)	0.00045 (0.00637)	0.00051 (0.00636)	0.00158 (0.00636)	0.00075 (0.00635)	0.00219 (0.00651)
R^2	0.0022	0.0045	0.0343	0.0258	0.0267	0.0194	0.0270	0.0067

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 16. Results from the regression of cIMT (mm) with Total PA (cpm) in boys, for various models.

Variable	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00001 (0.00002)
BMI (kg/m^2)	—	—	0.00152 (0.00080)	—	—	—	—	—
Total FMI (kg/m^2)	—	—	—	0.00155 (0.00102)	—	—	—	—
Central FMI (kg/m^2)	—	—	—	—	0.00304 (0.00209)	—	—	—
Central fat (%)	—	—	—	—	—	0.00104 (0.00063)	—	—
WHtR	—	—	—	—	—	—	0.07362 (0.04632)	—
VO_{2peak} residual (mL/min)¥	—	—	—	—	—	—	—	-0.0000044 (0.00001)
Age (years)	0.00092 (0.00361)	0.00141 (0.00368)	-0.00019 (0.00376)	0.00022 (0.00376)	0.00025 (0.00376)	0.00033 (0.00373)	0.00079 (0.00369)	0.00182 (0.00423)
Tanner stage (ref: stage 1)								
Stage 2-4	0.00635 (0.01130)	0.00667 (0.01132)	0.00501 (0.01129)	0.00546 (0.01134)	0.00564 (0.01134)	0.00597 (0.01131)	0.00526 (0.01132)	0.00773 (0.01150)
R^2	0.0022	0.0044	0.0195	0.0142	0.0134	0.0159	0.0151	0.0053

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 17. Results from the regression of cIMT (mm) with Total PA (cpm) in girls, for various models.

Variable	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)	0.00001 (0.00002)	0.00002 (0.00002)	0.00002 (0.00002)
BMI (kg/m^2)	—	—	0.00241*** (0.00071)	—	—	—	—	—
Total FMI (kg/m^2)	—	—	—	0.00269** (0.00091)	—	—	—	—
Central FMI (kg/m^2)	—	—	—	—	0.00551** (0.00178)	—	—	—
Central fat (%)	—	—	—	—	—	0.00113* (0.00057)	—	—
WHtR	—	—	—	—	—	—	0.12209** (0.04051)	—
VO_{2peak} residual (mL/min)¥	—	—	—	—	—	—	—	0.00001 (0.00002)
Age (years)	0.00222 (0.00407)	0.00252 (0.00410)	0.00141 (0.00400)	0.00237 (0.00402)	0.00221 (0.00401)	0.00187 (0.00409)	0.00365 (0.00403)	0.00268 (0.00508)
Tanner stage (ref: stage 1)								
Stage 2-4	-0.00065 (0.00775)	0.00045 (0.00795)	-0.00399 (0.00784)	-0.00423 (0.00794)	-0.00417 (0.00790)	-0.00158 (0.00795)	-0.00362 (0.00790)	-0.00120 (0.00811)
R^2	0.0021	0.0043	0.0636	0.0498	0.0542	0.0251	0.0514	0.0098

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Tables 18 and 19 show results from the multiple linear regression of cIMT with MVPA and VPA. MVPA and VPA were not significantly associated with cIMT in base models adjusted for BMI, total FMI, central FMI, central fat, WHtR, and VO_{2peak} residual. Adiposity variables showed significant positive associations with cIMT in all models. No significant associations were found between cIMT and VO_{2peak} residual.

Tables 20 to 26 show the results from the multiple linear regression of cIMT with total PA, MVPA, or VPA by comparing various adiposity and fitness categories. In base models with total PA, MVPA, or VPA, all PA variables were not significantly associated with cIMT in all adiposity and fitness categories. The magnitude and direction of the total PA, MVPA, and VPA regression coefficients changed between categories, however, PA remained non-significant in all models.

In models with interaction terms between a PA variable and the adiposity or fitness variable added, no significant interactions were found.

All models had very low R^2 values indicating that models did not explain the variance in cIMT well.

Table 18. Results from the regression of cIMT (mm) with MVPA (min/day) for various models.

Variable	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
MVPA (min/day)	—	0.00007 (0.00010)	0.00012 (0.00010)	0.00012 (0.00010)	0.00012 (0.00010)	0.00009 (0.00010)	0.00012 (0.00010)	0.00008 (0.00010)
BMI (kg/m^2)	—	—	0.00192*** (0.00054)	—	—	—	—	—
Total FMI (kg/m^2)	—	—	—	0.00205** (0.00069)	—	—	—	—
Central FMI (kg/m^2)	—	—	—	—	0.00419** (0.00137)	—	—	—
Central fat (%)	—	—	—	—	—	0.00106* (0.00043)	—	—
WHtR	—	—	—	—	—	—	0.09448** (0.03078)	—
VO_{2peak} residual (mL/min)¥	—	—	—	—	—	—	—	0.0000003 (0.00001)
Age (years)	0.00137 (0.00270)	0.00159 (0.00271)	-0.00007 (0.00272)	0.00052 (0.00272)	0.00045 (0.00272)	0.00063 (0.00273)	0.00136 (0.00269)	0.00195 (0.00320)
Sex (ref: male)	0.00173 (0.00478)	0.00303 (0.00513)	0.00418 (0.00507)	0.00275 (0.00510)	0.00264 (0.00510)	0.00235 (0.00513)	0.00424 (0.00510)	0.00522 (0.00551)
Tanner stage (ref: stage 1)								
Stage 2-4	0.00203 (0.00634)	0.00230 (0.00636)	-0.00026 (0.00631)	-0.00007 (0.00635)	-0.0000033 (0.00635)	0.00112 (0.00635)	0.00022 (0.00633)	0.00178 (0.00650)
R^2	0.0022	0.0034	0.0325	0.0242	0.0251	0.0179	0.0252	0.0054

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 19. Results from the regression of cIMT (mm) with VPA (min/day) for various models.

Variable	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
VPA (min/day)	—	0.00024 (0.00019)	0.00037 (0.00019)	0.00035 (0.00019)	0.00035 (0.00019)	0.00030 (0.00019)	0.00037 (0.00019)	0.00027 (0.00020)
BMI (km/m^2)	—	—	0.00200*** (0.00054)	—	—	—	—	—
Total FMI (kg/m^2)	—	—	—	0.00215** (0.00069)	—	—	—	—
Central FMI (kg/m^2)	—	—	—	—	0.00439** (0.00138)	—	—	—
Central fat (%)	—	—	—	—	—	0.00112** (0.00043)	—	—
WHtR	—	—	—	—	—	—	0.09991*** (0.03087)	—
VO_{2peak} residual (mL/min)¥	—	—	—	—	—	—	—	-0.0000008 (0.00001)
Age (years)	0.00137 (0.00270)	0.00162 (0.00270)	-0.00017 (0.00270)	0.00043 (0.00270)	0.00036 (0.00270)	0.00060 (0.00271)	0.00132 (0.00267)	0.00210 (0.00318)
Sex (ref: male)	0.00173 (0.00478)	0.00350 (0.00497)	0.00457 (0.00491)	0.00296 (0.00495)	0.00287 (0.00495)	0.00282 (0.00497)	0.00465 (0.00493)	0.00538 (0.00537)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00203 (0.00634)	0.00222 (0.00634)	-0.00058 (0.00629)	-0.00038 (0.00633)	-0.00030 (0.00633)	0.00096 (0.00632)	-0.00010 (0.00631)	0.00166 (0.00648)
R^2	0.0022	0.0061	0.0377	0.0287	0.0296	0.0220	0.0303	0.0082

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model ¥ Residual determined from simple linear regression of VO_{2peak} with BMI

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 20. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by Normal BMI, and Overweight and Obese BMI categories.

Variable	Normal BMI category (n = 259)				Overweight and Obese BMI category (n = 167)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00002 (0.00002)	—	—	—	0.00002 (0.00002)	—	—
MVPA (min/day)	—	—	0.00010 (0.00012)	—	—	—	0.00008 (0.00019)	—
VPA (min/day)	—	—	—	0.00036 (0.00022)	—	—	—	0.00021 (0.00039)
Age (years)	-0.00210 (0.00338)	-0.00161 (0.00341)	-0.00181 (0.00340)	-0.00197 (0.00337)	0.00782 (0.00445)	0.00832 (0.00453)	0.00795 (0.00448)	0.00812 (0.00450)
Sex (ref: male)	-0.00340 (0.00600)	-0.00164 (0.00621)	-0.00115 (0.00657)	-0.00020 (0.00629)	0.01194 (0.00774)	0.01312 (0.00797)	0.01298 (0.00817)	0.01305 (0.00802)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00123 (0.00886)	0.00279 (0.00898)	0.00212 (0.00893)	0.00218 (0.00885)	-0.00378 (0.00911)	-0.00374 (0.00912)	-0.00394 (0.00914)	-0.00417 (0.00916)
R^2	0.0028	0.0075	0.0056	0.0133	0.0326	0.0350	0.0335	0.0343

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 21. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by Overweight BMI, and Obese BMI categories.

Variable	Overweight BMI category (*n* = 77)				Obese BMI category (*n* = 90)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	-0.00001 (0.00003)	—	—	—	0.00003 (0.00005)	—	—
MVPA (min/day)	—	—	0.00001 (0.00022)	—	—	—	-0.00002 (0.00035)	—
VPA (min/day)	—	—	—	0.00008 (0.00044)	—	—	—	0.00004 (0.00077)
Age (years)	0.00258 (0.00584)	0.00203 (0.00624)	0.00266 (0.00612)	0.00291 (0.00618)	0.01209 (0.00661)	0.01181 (0.00665)	0.01218 (0.00679)	0.01204 (0.00672)
Sex (ref: male)	0.00673 (0.00967)	0.00591 (0.01021)	0.00693 (0.01073)	0.00733 (0.01034)	0.01775 (0.01189)	0.01846 (0.01197)	0.01763 (0.01210)	0.01782 (0.01203)
Tanner stage (ref: stage 1)								
Stages 2-4	-0.00399 (0.01199)	-0.00390 (0.01207)	-0.00402 (0.01209)	-0.00417 (0.01212)	-0.00335 (0.01329)	-0.00311 (0.01333)	-0.00331 (0.01338)	-0.00343 (0.01343)
R^2	0.0089	0.0099	0.0090	0.0093	0.0582	0.0632	0.0583	0.0582

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 22. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by Total FMI categories.

Variable	Total FMI equivalent to Normal BMI category (*n* = 313)				Total FMI equivalent to Overweight and Obese BMI category (*n* = 111)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00001)	—	—	—	0.00004 (0.00004)	—	—
MVPA (min/day)	—	—	0.00007 (0.00011)	—	—	—	0.00016 (0.00030)	—
VPA (min/day)	—	—	—	0.00029 (0.00020)	—	—	—	0.00031 (0.00068)
Age (years)	-0.00224 (0.00305)	-0.00181 (0.00309)	-0.00199 (0.00307)	-0.00196 (0.00305)	0.01155 (0.00585)	0.01129 (0.00586)	0.01104 (0.00595)	0.01119 (0.00593)
Sex (ref: male)	-0.00259 (0.00536)	-0.00138 (0.00555)	-0.00106 (0.00583)	-0.00014 (0.00561)	0.01632 (0.01045)	0.01708 (0.01047)	0.01728 (0.01063)	0.01663 (0.01051)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00451 (0.00793)	0.00533 (0.00799)	0.00493 (0.00796)	0.00483 (0.00792)	-0.01283 (0.01124)	-0.01199 (0.01127)	-0.01272 (0.01128)	-0.01286 (0.01128)
R^2	0.0023	0.0046	0.0037	0.0090	0.0440	0.0535	0.0467	0.0458

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 23. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by Central FMI categories.

Variable	Central FMI equivalent to Normal BMI category (n = 321)				Central FMI equivalent to Overweight and Obese BMI category (n = 103)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00001)	—	—	—	0.00007 (0.00004)	—	—
MVPA (min/day)	—	—	0.00006 (0.00011)	—	—	—	0.00027 (0.00031)	—
VPA (min/day)	—	—	—	0.00027 (0.00020)	—	—	—	0.00047 (0.00069)
Age (years)	-0.00152 (0.00299)	-0.00117 (0.00304)	-0.00131 (0.00302)	-0.00124 (0.00299)	0.01084 (0.00616)	0.01006 (0.00614)	0.00989 (0.00626)	0.01025 (0.00624)
Sex (ref: male)	-0.00281 (0.00529)	-0.00190 (0.00547)	-0.00161 (0.00574)	-0.00059 (0.00552)	0.01713 (0.01102)	0.01783 (0.01095)	0.01863 (0.01116)	0.01776 (0.01109)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00134 (0.00762)	0.00191 (0.00767)	0.00164 (0.00765)	0.00161 (0.00761)	-0.00906 (0.01200)	-0.00681 (0.01201)	-0.00846 (0.01203)	-0.00894 (0.01203)
R^2	0.0016	0.0030	0.0026	0.0076	0.0428	0.0651	0.0505	0.0473

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 24. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by Central fat categories.

Variable	Central fat < Median category (n = 212)				Central fat ≥ Median category (n = 212)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00002 (0.00002)	—	—	—	0.00001 (0.00002)	—	—
MVPA (min/day)	—	—	0.00018 (0.00013)	—	—	—	-0.00004 (0.00015)	—
VPA (min/day)	—	—	—	0.00040 (0.00023)	—	—	—	0.00014 (0.00033)
Age (years)	-0.00406 (0.00381)	-0.00333 (0.00384)	-0.00347 (0.00383)	-0.00390 (0.00380)	0.00611 (0.00395)	0.00627 (0.00401)	0.00605 (0.00397)	0.00624 (0.00397)
Sex (ref: male)	0.00241 (0.00669)	0.00515 (0.00700)	0.00683 (0.00741)	0.00624 (0.00703)	0.00069 (0.00688)	0.00096 (0.00697)	0.00024 (0.00712)	0.00130 (0.00703)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00051 (0.01027)	0.00121 (0.01027)	0.00095 (0.01025)	0.00597 (0.01023)	0.00173 (0.00813)	0.00212 (0.00828)	0.00151 (0.00820)	0.00192 (0.00816)
R^2	0.0077	0.0159	0.0167	0.0214	0.0153	0.0156	0.0156	0.0162

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 25. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by WHtR categories.

Variable	WHtR < 0.5 category (*n* = 286)				WHtR ≥ 0.5 category (*n* = 140)			
	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)	Reg. Coeff. (SE)
Total PA (cpm)	—	0.00002 (0.00001)	—	—	—	0.00001 (0.00003)	—	—
MVPA (min/day)	—	—	0.00011 (0.00011)	—	—	—	0.00003 (0.00024)	—
VPA (min/day)	—	—	—	0.00038 (0.00021)	—	—	—	-0.00001 (0.00054)
Age (years)	-0.00268 (0.00322)	-0.00200 (0.00327)	-0.00227 (0.00325)	-0.00231 (0.00321)	0.01030* (0.00498)	0.01025* (0.00500)	0.01021* (0.00504)	0.01031* (0.00503)
Sex (ref: male)	-0.00280 (0.00568)	-0.00087 (0.00591)	-0.00034 (0.00626)	0.00075 (0.00598)	0.01313 (0.00865)	0.01340 (0.00872)	0.01335 (0.00882)	0.01312 (0.00874)
Tanner stage (ref: stage 1)								
Stages 2-4	0.00407 (0.00836)	0.00520 (0.00840)	0.00464 (0.00838)	0.00460 (0.00833)	-0.00863 (0.00984)	-0.00820 (0.00995)	-0.00852 (0.00990)	-0.00863 (0.00987)
R^2	0.0030	0.0079	0.0061	0.0147	0.0381	0.0389	0.0382	0.0381

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Table 26. Results from the regression of cIMT (mm) with Total PA (cpm), MVPA (min/day) or VPA (min/day) by VO_{2peak} categories.

Variable	VO_{2peak} equivalent to Normal BMI category (n = 265)				VO_{2peak} equivalent to Overweight and Obese BMI category (n = 148)			
	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)	Coeff. (SE)
Total PA (cpm)	—	0.00001 (0.00002)	—	—	—	0.00002 (0.00002)	—	—
MVPA (min/day)	—	—	0.00004 (0.00013)	—	—	—	0.00015 (0.00016)	—
VPA (min/day)	—	—	—	0.00022 (0.00025)	—	—	—	0.00031 (0.00031)
Age (years)	-0.00064 (0.00381)	-0.00023 (0.00386)	-0.00052 (0.00384)	-0.00043 (0.00382)	0.00222 (0.00537)	0.00281 (0.00543)	0.00253 (0.00539)	0.00239 (0.00538)
Sex (ref: male)	0.00372 (0.00612)	0.00482 (0.00630)	0.00448 (0.00662)	0.00526 (0.00637)	0.00672 (0.00859)	0.00859 (0.00889)	0.00940 (0.00908)	0.00918 (0.00893)
Tanner stage (ref: stage 1)								
Stages 2-4	-0.00129 (0.00908)	-0.00030 (0.00918)	-0.00097 (0.00915)	-0.00057 (0.00912)	0.00365 (0.00924)	0.00392 (0.00926)	0.00357 (0.00925)	0.00300 (0.00926)
R^2	0.0016	0.0037	0.0020	0.0045	0.0125	0.0172	0.0182	0.0194

Abbreviations: Coeff.: regression coefficient; ref: reference; SE: standard error

— Variable not in model

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

4.5. Power results

Power analyses revealed that the addition of total PA to a base model with age, sex, and Tanner stage, had 15% power with $n = 426$ and $R^2 = 0.002$.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1. Summary of results

The primary objective of this study was to assess the association between PA (total PA, MVPA, VPA) and subclinical atherosclerosis in children. We hypothesized that there would be an inverse relationship between PA and cIMT, a surrogate marker of atherosclerosis. This cross-sectional investigation showed that in 426 eight- to-ten-year-old at-risk children, PA was not associated with cIMT.

The secondary objective was to examine whether adiposity and fitness could modify the relationship between PA and cIMT. Analyses in adiposity or fitness categories revealed that there were potential differences in the relationship between PA and cIMT in certain adiposity or fitness groups; however PA showed no association with cIMT.

5.2. Discussion

The main finding that PA was not associated with cIMT from this study is contrary to our original hypothesis, but corroborates results from the EYHS which was conducted in a large population-based sample of children and adolescents (154, 155). These studies showed the following: that in a cross-sectional analysis in adolescents with a mean age of 15.6 years, MVPA and VPA were not associated with cIMT (154), and that in a cohort analysis, MVPA and VPA measured in 8- to 10-year-olds were not associated with cIMT measured between

ages 14 to 16 years (155). Four reasons why PA may not appear to have an effect on cIMT have been hypothesized in the literature including: 1) the age at which surrogate markers of atherosclerosis are assessed, 2) the type of population studied, 3) the amount and intensity of PA required to detect associations with cIMT, and 4) the artery selected for intima-media thickness measurements (154, 155, 157). These reasons will be further explored below.

Analyses in this thesis showed that in 8- to 10-year-olds, PA was not associated with cIMT. The age of the QUALITY Study participants (8- to 10-year-olds) may be one reason why PA was not associated with cIMT, as the direct effect that PA has on cIMT may not be detectable at young ages when the atherosclerotic process is beginning. Other observational studies have also shown that PA is not associated with cIMT in groups of children and adolescents ranging from 5- to 17-years-old (151-155). However, two longitudinal observational studies in non-clinical samples have shown that that PA measured in children and adolescents was associated with cIMT measured in adulthood, although the direction of this relationship was not consistent between these two studies, with one study showing a negative association (109) and one study showing a positive association (220). In one of these studies in 1,809 children and adolescents aged 3 to 18 years, PA was negatively associated with a 0.006 mm change in cIMT measured in young adulthood, 21 to 27 years later, (109). However, the results should be interpreted with caution as PA was assessed using questionnaires, and PA intensity, frequency, and duration information was not individually expressed in statistical analyses, making the interpretation of this measure difficult (109). In

the other investigation from the European Youth Heart Study (EYHS) in 277 adolescents with a mean age of 15.7 years, MVPA measured by accelerometer in adolescence was positively associated with cIMT measured 6 or 12 years later, in young adulthood (220). Taken together, these findings suggest that the PA attained by children may not be associated with cIMT until young adulthood, when more lesions are present in the arteries.

A second reason why PA was not associated with cIMT in this study may be due to the type of population studied, such as whether or not samples of children are clinical or non-clinical. Comparable research that has also assessed cIMT in large non-clinical samples of children and adolescents include: a study in 599 six- to twenty-year-olds from Los Angeles County which found that adiposity was associated with cIMT (99), a study in 319 twelve- to seventeen-year-olds from the Healthy Lifestyle in Europe by Nutrition in Adolescence Cross-Sectional Study which found that PA was not associated with cIMT (153), and a study in 635 eleven- to seventeen-year-olds from the Muscatine Offspring cohort which also found that adiposity was associated with cIMT (98). As mentioned, research from the EYHS in 336 adolescents with a mean age of 15.6 years, and in 254 eight- to sixteen-year-olds, did not find associations between PA and cIMT in adolescence (154), or between childhood PA and adolescent cIMT (155). In contrast, interventions in small samples of already overweight and obese children and adolescents have shown that three or six months of programs focussing on exercise can lower cIMT (146-148). These mixed results indicate that it is unclear whether or not the detection of an association between modifiable CVD risk

factors and cIMT depends on the type of population studied. This calls for further studies comparing populations of children at different levels of CVD risk.

A third reason why an association may not have been found relates to the amount and intensity of PA that children undertake. Most intervention studies found reductions in cIMT after 12 weeks to 1 year of structured programs involving exercise (139, 141-149). Of those interventions which only included exercise, children and adolescents participated in activities ranging from walking to competitive sports, which encompass moderate and vigorous PA (115). These studies all showed reductions in cIMT for those engaging in this PA for at least one hour, three times weekly (146-148). Our study, like other observational studies which measured PA of different intensities in those not undergoing exercise programs (150-155), did not find associations with cIMT. This suggests that perhaps it is through exercise interventions encouraging PA of higher intensities, beyond normal levels, that an impact on cIMT can be made, rather than from ordinary activity. In our sample, only 18 children (4%) achieved the recommended one hour of MVPA every day which may not have been enough higher intensity activity to associate with cIMT. As with the type of population studied discussed above, it is unknown whether the relationship between PA and cIMT can only be detected when greater intensities of PA are carried out. Since intervention studies have included only clinical samples undergoing exercise programs, future studies should investigate how type of population and amount of higher intensity PA influence the PA and cIMT relationship separately. This has also been suggested in recent literature (157).

The artery selected for intima-media thickness measurement may be the fourth reason why an association between PA and cIMT was not detected in our study. Research has suggested that in adults, it may be the intima-media of peripheral arteries like the brachial and femoral arteries, that responds to exercise before the carotid arteries do (132, 157). This means that in children, it may take higher intensity exercise of longer durations to see differences the intima-media of the carotid artery (157). As suggested before, future research in this area should examine how high-intensity and long-term exercise can impact cIMT in childhood as higher PA levels may be able to impact the carotid arteries earlier.

The secondary finding that the relationship between PA and cIMT differed by adiposity or fitness categories suggests that adiposity and fitness may modify the relationship between PA and cIMT; however PA was not associated with cIMT in all of our analyses. Future research can be conducted to determine in what specific ways the relationship between PA and cIMT may be changed by adiposity and fitness.

5.3. Strengths

The strengths of this study included: 1) a large sample size, 2) the use of different objective measures of PA such as total, MVPA and VPA, 3) the use of multiple measures of adiposity, and 4) the assessment of effect modification by adiposity and fitness.

The first strength was the sample size. Previous studies investigating the effect of PA on cIMT in children and youth have used smaller sample sizes.

Intervention studies have used sample sizes of 120 or less, and observational studies have used samples less than 350. This study included data from 426 children which is to our knowledge, the greatest sample size that has been used in a study investigating the relationship between PA and cIMT in children.

A second strength of this study was the use of objective measures of PA such as total, MVPA, and VPA. Using objective measures eliminated further biases that may be present when using PA questionnaires, for example. Furthermore, since PA recommendations for Canadian children and youth involve higher intensity activity, specifically an hour of MVPA per day (127), defining PA of varying intensities could help identify whether certain types of PA had an effect on cIMT.

A third strength of this study was the use of multiple adiposity measures including: widely used and easy to interpret measures such as BMI, more direct assessments of fat obtained from DEXA measurements such as FMI, and a variety of both total and central measures of adiposity. Previous studies have either not controlled for adiposity, which is known to be associated with cIMT (75, 98-102), or adjusted for only an indirect measure such as BMI (109), trunk-to-total skinfolds ratio (153), or WC (154).

A fourth strength of this study was that it is the first to our knowledge that has investigated the potential modification of the association between PA and cIMT by adiposity or fitness in children, and that has grouped observations into lower and higher risk adiposity or fitness categories.

5.4. Limitations

The limitations of this study include: 1) the validity of the cIMT measurement, 2) PA, adiposity, and fitness measurement challenges, 3) issues in study design, 4) external generalizability of the study, 5) the capture of high-intensity PA data, 6) the categorization of adiposity and fitness, 7) the power of the study, 8) the detection of a non-linear curve in the data, and 9) confounders that were not controlled for.

The validity of the cIMT measurement presents a key limitation of the current study. As discussed previously, the age of the study sample (8- to 10-year-olds) and the type of population of the QUALITY Study participants (non-clinical) may partially explain the results of this thesis. Since vascular changes may be easier to detect in adults or high-risk populations of children at more advanced stages of the atherosclerotic process, the assessment of cIMT in the QUALITY Study may not be as accurate. Furthermore, mean cIMT for the sample used in this thesis was 0.58 mm (Table 10) and values ranged from 0.42 mm to 0.73 mm. As explained in the Methods (Chapter 3), post-hoc analyses for accuracy of the cIMT measurement in the QUALITY Study using an adult nurse showed ultrasound precision within 0.40 mm and poor reliability due to a wide range of cIMT values from 0.56 mm to 0.71 mm. This indicates limited ability of the ultrasound equipment to accurately measure cIMT and suboptimal validity of the cIMT measurement in the QUALITY Study.

Moreover, the lack of standard measurement protocols for cIMT in children and youth, and the great variability of cIMT measurements in published

research studies, have been emphasized in the literature as a major challenge in the assessment of subclinical atherosclerosis in pediatric populations (18). This variability in methods, as discussed in the Literature Review (Chapter 2), include: the protocol being used, the angle viewed, the wall selected, the carotid artery part selected, the maximum or mean values measured, the quality of equipment, and the personnel involved in taking and interpreting the image (18, 21, 69, 88, 89). There is also a lack of information regarding how reliable or quantifiable the thickness of the carotid is in different groups of children based on age, sex, development, risk status, race, body size, or artery size (18). Taken together, the findings from accuracy assessments for cIMT in the QUALITY Study and the variability of cIMT measurements in children, warrant caution when interpreting the results of this thesis.

The second limitation may have been due to potential challenges in the measurement and interpretation of data regarding PA measured by accelerometer, BMI, adiposity measures derived from DEXA, WHtR, and VO_{2peak}. These challenges have been addressed in the literature review, however there may have been additional limitations based on this study due to the protocol undertaken. In particular, using PA data from one week may not have accurately depicted the type of PA of the particular child during the course of the year. Indeed, PA in children may change at different points in the year (112).

The third limitation was the study design. Due to the cross-sectional nature of this study, the exposure, PA, and the outcome, cIMT, were not assessed

longitudinally; therefore the temporal nature of the association could not be determined.

A fourth limitation was the external generalizability of this study. The QUALITY Study sample contained only Caucasian children with at least one obese parent. This limits our findings to groups of children with these characteristics. This is reflected in the average cIMT which was 0.58 mm, a value that is higher compared to normative values in children and adolescents (18, 75).

The fifth limitation was that MVPA and VPA values for children were low and may not have been high enough to detect changes in cIMT. Boys averaged 62.49 min/day of MVPA, and girls averaged 42.35 min/day, however only 18 children (4%) achieved one hour of MVPA every day, the current PA recommendation.

The sixth limitation of this study was that the methods used to define the total FMI, central FMI, and VO_{2peak} categories that were comparable to BMI categories may have affected the validity of the study. As these measures had no universal cut-offs, the data points from this study were used to define cut-off points for FMI and VO_{2peak} that corresponded with BMI percentiles. These categories may not have accurately defined those in higher risk groups causing misclassification, and may not be applicable outside of this study. Furthermore, stratification of the data by these groups resulted in regression models being run for smaller samples which may have affected statistical power (221).

The seventh limitation was due to the power of the study. With 426 observations, there was only 15% power for the addition of PA to a base model with age, sex, and Tanner stage.

The eighth limitation of this study was the non-linear curve detected during initial descriptive analyses and subsequent removal of outliers, which may have resulted in selection bias. Eliminating the 35 outliers may have removed information that could have added to the study. Furthermore, linear regression may not have been the most appropriate statistical method for data that were inherently non-linear.

The ninth limitation may be due to other variables that were not controlled for in this study which may have been important. For example, smoking, cholesterol, blood pressure, and diet are considered confounders and were controlled for in other studies determining the association between PA and cIMT in children and youth (109, 153-155). In particular, diet was not adjusted for in order to reduce the number of variables in our models, as there are several components of diet that can be recalled, and models would already be adjusted for biologically important covariates (age, sex, Tanner stage) and effect modifiers of interest (adiposity and fitness). However, any of the aforementioned confounders that were not assessed may have contributed to the results that were seen in our study.

5.5. Directions for future research

Future studies need to examine the association between PA and subclinical atherosclerosis longitudinally in order to establish the temporal nature of the relationship. Evaluating the relationship at different time points during childhood and adolescence will also help understand critical periods during which childhood PA levels can impact the carotid artery. Exercise intervention studies in children from the general population may also shed light on whether or not long-term and structured high-intensity PA programs can reduce the progression of atherosclerosis, given that most interventions have focussed on high-risk groups. Since public health has already encouraged MVPA in children and adolescents, new studies may inform these groups about the amount and intensity of PA required to impact arterial health.

Moreover, the assessment of whether adiposity and fitness can modify the relationship between PA and cIMT needs to be explored further as this is the only study to our knowledge that has addressed adiposity and fitness as modifiers of the association between PA and cIMT in children. This study has shown potential changes in the relationship between PA and cIMT based on adiposity and fitness, and future studies may be able to increase knowledge in this area to see if the impact of PA on cIMT varies in groups of children classified into different adiposity or fitness groups.

5.6. Importance to public health

The results from this study may inform public health by suggesting that the current levels of PA in children from an at-risk population may not be enough to delay the progression of atherosclerosis in early life. Given that less than 10% of Canadian children and adolescents meet PA guidelines (38, 39), that PA levels decrease with age (40), and that PA in childhood has been shown to associate with cIMT in adulthood (109, 220), encouraging more frequent, high-intensity and long-term PA may be required to see changes in cIMT in childhood and adulthood. Future studies should investigate the degree of PA that may be required to slow the atherosclerotic process and whether there may be important periods in childhood and adolescence during which PA may be associated with cIMT. This may better inform public health strategies that recommend PA in early life to reduce future cardiovascular burden, by providing more information about the ages at which certain types of PA can prevent damage to arterial health.

5.7. Conclusion

This study has shown that in 8- to 10-year-olds from an at-risk population, PA was not associated with cIMT. The results are in agreement with some of the previous observational studies in population-based samples of children and adolescents which have found no associations between PA and cIMT, contradict findings in intervention studies, and provide new information regarding the potential modification of this relationship by adiposity or fitness. Future studies investigating the long-term effects of high-intensity structured PA in the general

population may explain what type of PA is required to affect cIMT in asymptomatic children, and at what time between childhood and young adulthood that these changes can take place. Together, this research can inform public health by indicating at what ages higher intensity PA can impact subclinical atherosclerosis in the carotid artery, and if this relationship differs for children and adolescents classified into certain adiposity or fitness categories.

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Appendix A - Creation of central FMI and VO_{2peak} categories

Linear regression was run in Stata with central FMI as the outcome variable and BMI percentile as the exposure variable. The equation $Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X$ was used to determine cut-off points for central FMI values equivalent to the 85th percentile and 95th percentiles for BMI. From the Stata output, the constant, $\boldsymbol{\beta}_0$, and the regression coefficient for BMI percentile, $\boldsymbol{\beta}_1$, were used in the equation. X = 85 or X =95 were used to calculate the equivalent central FMI values at the 85th percentile and 95th percentile, respectively.

Central FMI value equivalent to 85th BMI percentile was computed by:

$Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X = - 0.7922964 + 0.0457348 (85) = 3.10.$

Central FMI value equivalent to 95th BMI percentile was computed by:

$Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X = -0.7922964 + 0.0457348 (95) = 3.55.$

Linear regression was run in Stata with VO_{2peak} as the outcome variable and BMI percentile as the exposure variable. The equation $Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X$ was used to determine cut-off points for VO_{2peak} values equivalent to the 85th percentile and 95th percentiles for BMI. From the Stata output, the constant, $\boldsymbol{\beta}_0$, and the regression coefficient for BMI percentile, $\boldsymbol{\beta}_1$, were used in the equation. X = 85 or X = 95 were used to calculate the equivalent VO_{2peak} values at the 85th percentile and 95th percentile, respectively.

VO_{2peak} value equivalent to 85th BMI percentile:

$Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X = 1183.206 + 4.429684 (85) = 1559.73.$

VO_{2peak} value equivalent to 95th BMI percentile:

$Y = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 X = 1183.206 + 4.429684 (95) = 1604.03.$

Appendix B - Ethics approval

Notification of Approval

Date:	July 11, 2012
Study ID:	Pro00031800
Principal Investigator:	Nazia Darvesh
Study Supervisor:	Katerina Maximova
Study Title:	Investigating the Association between Physical Activity and Carotid Intima-Media Thickness in 8 to 10 year old Children
Approval Expiry Date:	10 July 2013
RSO-Managed Funding:	Project ID Project Title Speed Code Other Information There are no items to display

Thank you for submitting the above study to the Research Ethics Board 2 . Your application has been reviewed and approved on behalf of the committee.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Research Ethics Board does not encompass authorization to access the staff, students, facilities or resources of local institutions for the purposes of the research.

Sincerely,

Dr. Stanley Varnhagen
Chair, Research Ethics Board 2

Note: This correspondence includes an electronic signature (validation and approval via an online system).