Physical Activity Intensity and Visceral Adiposity in Youth: A Randomized Controlled Trial

by

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A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfilment of the requirements of the degree of

MASTER OF SCIENCE

Faculty of Kinesiology and Recreation Management

University of Manitoba

Winnipeg

ABSTRACT

Background: Physical activity (PA) reduces visceral adipose tissue (VAT) in adults; however, the dose to reduce VAT in youth is unclear.

Objective: To examine whether high intensity PA preferentially reduces waist circumference (WC) and VAT compared to lower intensity PA.

Design: Randomized controlled trial.

Participants: Youth were 13-18yrs, overweight, with one additional risk factor for type 2 diabetes (T2DM).

Intervention: 6-months, exercising 3 times/week at a high intensity (70-85% of Heart Rate Reserve HRR), or low intensity (40-55% HRR).

Primary outcome: VAT (cm^2) measured by MRI at L4-L5, and WC at the height of the iliac crest (cm).

Results: 94 Youth were randomized to either high intensity (n=30); low intensity (n=32) or control (n=32). Changes in WC and VAT were not significant across groups. A trend towards a reduction in VAT in the training groups, compared to controls was demonstrated in sub-analysis (-14.3 ± 9.6 % vs. +0.01 ± 0.4 %, p= 0.059). Peak fitness increased significantly in both the high and low intensity arms (1.3 ± 0.6 and 1.4 ± 0.6 ml/kg/min, $p < 0.05$).

Conclusions: Training at 55-65% HRR improves fitness by ~10%, and ~2 days/week elicits modest non-significant reductions in VAT in overweight youth.

ACKNOWLEDGEMENTS

First, I would like to acknowledge my advisors Dr. Jon McGavock, and Dr. Elizabeth Ready. Jon, you demonstrated the effort, teamwork, and passion required to succeed in research. You work extremely hard so the research we do makes a difference. Thanks for giving me both the independence and guidance I needed to accomplish my goals. Dr. Ready, thank you for providing great support and encouragement throughout this process. I would also like to thank the rest of my committee. Dr. Todd Duhamel, thank you for taking the time to open my eyes to basic science research, and demonstrating how it can translate clinically. I am also very fortunate to have Dr. John Walker as my external committee member. You have provided great perspective and further sparked my interest in mixed method design.

Second, I would like to acknowledge the rest of the team in the lab. My experience would not have been the same without their support and humour. Pinar, Anita, Andrea, Meaghan, Martin, Catherine and Becky, thank you for all for everything. You all helped edit, re-read, enter data, and most of all made me laugh when I needed it most. I would also like to acknowledge Kristy and Darolyn who helped me tremendously when I first started out. Thank you to all the POWER trainers, your enthusiasm, and effort made a difference in many lives. I would also like to acknowledge the generous support I received from the Ruth Asper Scholarship, the Manitoba Health Research Council, the Manitoba Institute of Child Health, and CIHR for funding the study. Thanks to my family and friends for their endless support of all my endeavours. Most of all, I would like to thank the parents and youth who volunteered their time to complete the study.

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INTRODUCTION

Statement of the Problem

Pediatric obesity and overweight are major public health concerns in Canada (Shields, 2006). However, recent evidence suggests the compartmentalization of adipose tissue surrounding visceral organs is of greater consequence than overall obesity. Studies in youth have demonstrated a strong relationship between visceral adipose tissue (VAT) and risk factors for T2DM, cardiovascular disease, and the metabolic syndrome (Bacha, Saad, Gungor, Janosky, & Arslanian, 2003; Lee, Gungor, Bacha, & Arslanian, 2007; Taksali et al., 2008). In adults, numerous studies have demonstrated physical activity (PA) significantly reduces VAT, often independent of weight loss (Lee et al., 2005; Ross et al., 2004; Slentz et al., 2005). On the other hand, a paucity of evidence exists examining the association between PA and VAT, specifically the dose of PA required to reduce VAT in youth remains unclear (Kim & Lee, 2009).

Purpose

The purpose of this study was to address this limitation in the literature and determine the effect of exercise intensity on VAT among overweight adolescents. The research question guiding this thesis was: "Does high intensity PA preferentially reduce waist circumference (WC) and VAT mass to a greater extent than lower intensity PA?"

Strengths

We employed a randomized controlled trial to test this research question and VAT was measured using the gold standard, magnetic resonance imaging (MRI). In

addition, few experimental studies have attempted to address the effect of PA intensity specifically on VAT, and the sample size for our study is larger than previous studies. Furthermore, we believe the use of the 2-week run in period prior to randomization increased adherence, and reduced the rates of attrition seen in similar experimental trials.

Limitations

The study has some limitations as individual differences in participants may affect their desire or ability to attend the lifestyle intervention. However, by using Canadian Society for Exercise Physiology (CSEP) Certified Personal Trainers (with experience working with youth) to supervise training, we hoped to have overcome this limitation. The length of the intervention may have led to participant attrition, however, to combat this we employed a variety of adherence strategies including group activities, and continued communication. Another limitation includes the confounding effect of pubertal development on the primary outcome measure, as the population included youth aged 13-18.

Hypothesis

We hypothesized that youth randomized to 6 months of high intensity PA will experience a more significant reduction in VAT and WC than youth randomized to a lower intensity PA intervention.

REVIEW OF THE LITERATURE

Prevalence of Obesity

Over the past decade in Canada, pediatric obesity has become a significant public health concern. According to the Canadian Health Measures Survey (CHMS), as of 2004, 1.1 million or 26% of children age 2-17 years are overweight or obese (Shields, 2006). The prevalence of has increased ~75% since 1978 when rates of overweight and obesity were only 15%. Adolescents aged 12-17 years represent the population most affected by this trend, as the prevalence of overweight has doubled, and the rates of obesity have tripled (Shields, 2006). The trend is troublesome as obesity in youth tracks into adulthood (Freedman et al., 2005) and is associated with cardiometabolic risk factor clustering (Taksali et al., 2008). Similar trends in overweight and obesity are occurring worldwide; therefore, expert panels and the World Health Organization have called for effective policies and programs to prevent this concerning trend (Wang & Lobstein, 2006).

Measurement of Obesity

In clinical and epidemiological settings, obesity is defined as an excessive amount of weight relative to height. Overweight (25-29.9 kg/m^2) and obesity ($\geq$ 30 kg/m^2) are classified in adults using thresholds for body mass index (BMI) that are associated with incremental health risk and mortality (Calle, Thun, Petrelli, Rodriguez, & Heath, 1999). The classification of overweight (BMI 85-94.9th percentile) and obesity (BMI $\geq$ 95th percentile) (Centers for Disease Control and Prevention, 2012) among youth are more arbitrary for a number of reasons. First, youth rarely experience obesity-related end-

points (i.e. T2DM and myocardial infarction), and therefore cut-points cannot be established according to inflections of disease risk. Second, as children and adolescents grow rapidly throughout childhood, BMI values change over time and are sex-dependant. Despite these limitations, the International Obesity Task Force (IOTF) has created age and sex based BMI cut-points for overweight and obesity that reflect BMI cut-points of 25 and 30 kg/m^2 at 18 years of age (Cole, Bellizzi, Flegal, & Dietz, 2000).

Figure 1. The age and sex specific BMI cut-points for overweight and obesity set by the International Obesity Task Force (Cole et al., 2000).

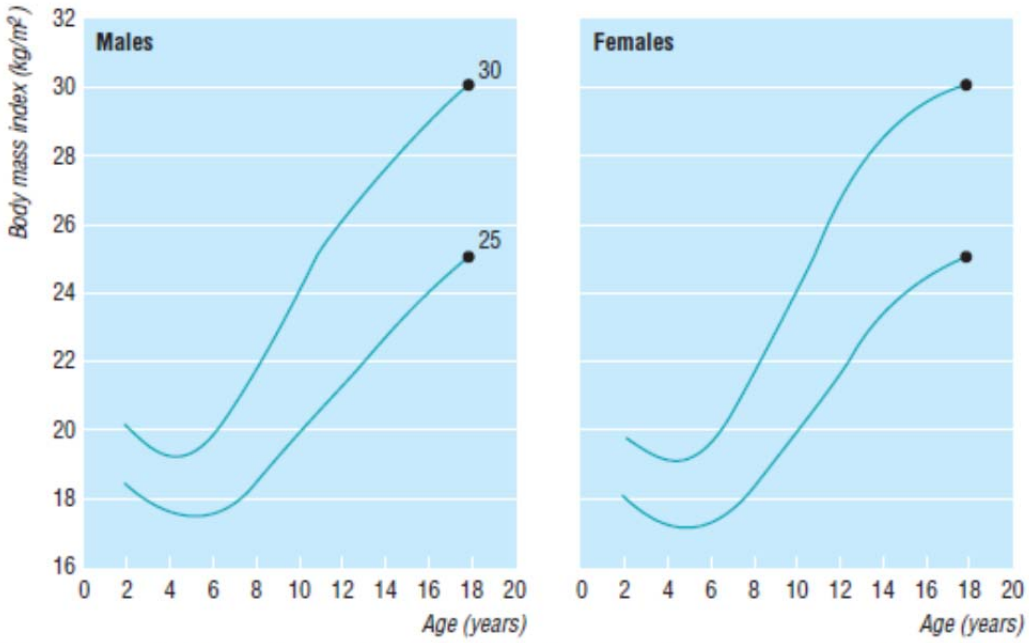


Fig 6 International cut off points for body mass index by sex for overweight and obesity, passing through body mass index 25 and 30 kg/m² at age 18 (data from Brazil, Britain, Hong Kong, Netherlands, Singapore, and United States)

The utilization of BMI itself has limitations, as it does not distinguish between fat mass, and fat free mass, or describe the distribution of fat (Janssen, Katzmarzyk, & Ross, 2004). Visceral obesity is a condition of excess adipose tissue surrounding visceral

organs that is associated with an increased risk of cardiometabolic diseases. As in adults, studies in youth have documented robust associations between the compartmentalization of adipose tissue viscerally and the risk factors for T2DM, and cardiovascular disease (Bacha et al., 2003; Lee et al., 2007; Taksali et al., 2008) .

Measurement of visceral adipose tissue

There are several methods to measure VAT and define visceral obesity (summarized in Table 1). The easiest, most cost effective and clinically relevant method is a measure of WC (McCarthy, Jarrett, & Crawley, 2001). In a review of studies in youth, aged 6-17 years, anthropometric measures such as BMI, and WC were validated against the gold standard MRI derived measures of VAT (Brambilla et al., 2006). The measurement of WC was found to be the best predictor of objectively measured VAT in youth by explaining 64.8% of the variance, while BMI was the best predictor of subcutaneous adipose tissue (Brambilla et al., 2006).

The measurement of WC has limitations, as it does not distinguish between subcutaneous adipose tissue and VAT. In addition, no standardized technique for measuring WC exists for the pediatric population (Katzmarzyk, 2004). Ross and colleagues (2008) conducted a systematic review to determine whether the protocol used for measurement affects the association of WC with cardiovascular disease (CVD), T2DM, and all-cause mortality from CVD. The protocols examined included both measurement of WC using bony landmarks (iliac crest, rib, midpoint between the rib and iliac crest), as well as external references (umbilicus, the minimal waist). No statistically significant differences were found between the measurement protocols (Ross et al.,

2008). These data suggest that regardless of the methods used, a larger WC is a predictor of morbidity and mortality in adults.

In Canada, the prevalence of visceral obesity measured by WC has increased in both youth and adults since 1981 (Janssen, Shields, Craig, & Tremblay, 2011). The cut-points defining high risk abdominal obesity in adults are $\geq$ 102cm and $\geq$ 88cm for men and women respectively (National Institute of Diabetes and Digestive and Kidney Diseases (U.S.) & National Heart, Lung,and Blood Institute, 1998). Although, the adult cut-points were established based on their correlation with disease risk, no such cut-points exist in youth. Simply, a higher WC represents a higher risk (Janssen et al., 2011). Several efforts have been made to come up with age-specific cut-points. Janssen and Jolliffe (2007) recently developed a series of thresholds that reflect the adult cut-points using a model similar to the one used by the IOTF to define overweight and obesity.

Other methods are also used to assess the amount of adipose in the viscera; these include dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). DXA absorptiometry estimates VAT indirectly via a measure of total trunk fat mass. However, the major limitation of the DXA is the inability to distinguish between subcutaneous and VAT depots. Both MRI and CT provide high resolutions images allowing for the direct quantification of adipose tissue volumes around visceral organs. MRI is increasingly utilized in the pediatric population due to the decreased exposure to radiation. Whole body scans provide greater accuracy for quantifying tissue compartments; however due to higher cost associated with MRI, scientists generally use a single slice taken at the 4th-5th lumbar vertebrae (L4-L5) level to estimate total VAT (Shen et al., 2003). To prevent the misclassification of VAT tissue,

the inner edges of the abdominal muscles can be used to constrain the VAT tissue compartment (Shen et al., 2003). While this is the gold standard, it is difficult to apply to large epidemiological studies due to the time and cost associated with MRI use (See Table 1).

Although CT scans and MRI images provide the most accurate and reproducible quantifications of VAT, other factors such as cost, radiation, and utility must also be taken into consideration. As a result, the measurement of WC may be an important proxy measure of VAT for large-scale population health studies. Comparisons of the methods used to measure visceral adiposity are summarized in the following table.

Table 1: Comparison of Measures of Visceral Adiposity

Measurement	Type	Advantages	Disadvantages	Association with MRI measure
BMI	indirect	-low cost -association with disease risk	-cannot distinguish between subcutaneous and VAT -does not distinguish between muscle, bone, or adipose -does not provide indication of adipose distribution	-explains 56% of the variance in VAT in youth age 7-16 (Brambilla et al., 2006)
WC	indirect	-low cost -good predictor of VAT	-cannot distinguish between subcutaneous and VAT -multiple measurement sites	-explains 64% of the variance in VAT in youth age 7-16 (Brambilla et al., 2006)
DXA	indirect	-low radiation -good reproducibility	-cannot distinguish between subcutaneous and VAT	
MRI	direct	-no radiation -ability to distinguish between subcutaneous and VAT -multiple slices better than single	-cost -utility as mainly used in research	
CT	direct	-ability to distinguish between subcutaneous and VAT	-cost -utility as mainly used in research -radiation	

Obesity and Disease

Overweight in youth is associated with diseases such as T2DM, cardiovascular, and respiratory disease (McCargar & Ball, 2003; Reilly et al., 2003). However, more recent studies suggest that adipose deposited viscerally may be a better biomarker of health than overall obesity (Després & Lemieux, 2006). Dr. Jean Vague was one of the first to identify the differential adipose deposition and the association with disease risk. He demonstrated that android obesity (i.e. upper body obesity) was more closely associated with diabetes and atherosclerosis, than gynoid obesity (i.e. lower body obesity) (Vague, 1999).

Among obese adolescents, those with the highest ratio of VAT to subcutaneous adipose were found to be at 5 times greater risk for developing metabolic syndrome compared with adolescents with the lowest ratio of VAT to subcutaneous adipose tissue (Taksali et al., 2008). Therefore, even among obese or overweight youth, higher VAT accumulation is associated with a more deleterious cardiometabolic profile. While the WC and fat percentage were similar in all patients; the amount of VAT area varied considerably within the cohort studied. More importantly, measures of insulin resistance, dyslipidemia and glucose tolerance worsened in a dose-response manner with increasing VAT mass, despite similar BMI, total body fat and WC (Taksali et al. 2008).

Currently, it remains unclear why certain youth are predisposed to adipose deposition within the viscera while others are likely to experience accumulation subcutaneously. A review of the possible mechanisms may shed light on possible strategies to reduce VAT in adolescents.

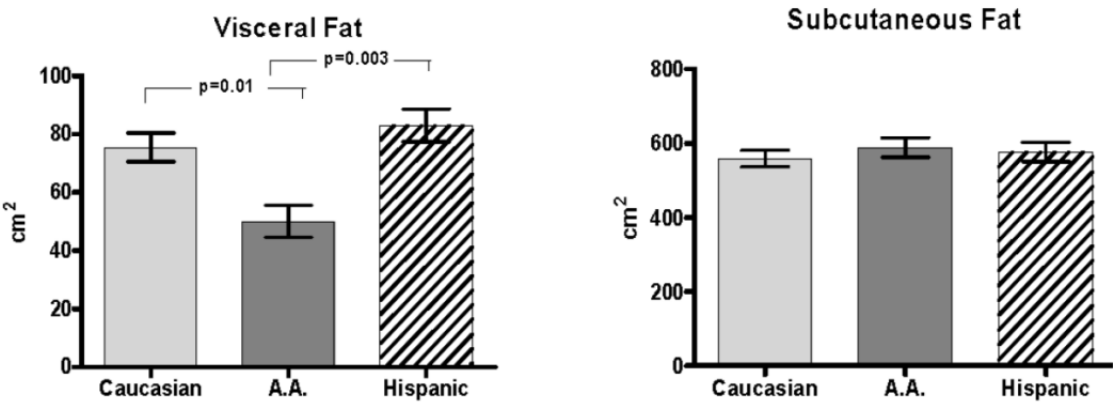
Factors Influencing Visceral Adipose Tissue

There are several purported factors influencing VAT deposition (Goran, 1998). Among youth, hormones, age, sex, genetics, stress, race, sleep and nutrition play a role in the differential deposition of adipose tissue (Goran, 1998). Some of the hormones influencing adipose distribution include growth hormone (GH), sex steroids, and cortisol (Roemmich & Rogol, 1999). Males tend to have higher levels of VAT tissue then females (Brambilla et al., 2006); however differences do not emerge until adolescence (Goran, 1998). It has been suggested that an increase in female sex steroids causes an increase in GH secretion and is protective against the deposition of adipose viscerally among adolescent girls (Björntorp, 1996).

Race is also an important factor influencing the deposition of adipose tissue. Asians tend to have more VAT at all levels adiposity when compared to Caucasians (Park, Allison, Heymsfield & Gallagher, 2001), as do Hispanics (Liska et al., 2007). A study using a MRI derived measure of visceral adiposity at the L4-L5 level examined ethnic differences in overweight and obese adolescents (Liska et al., 2007). After matching adolescents for BMI and total fat mass, obese African American adolescents demonstrate significantly lower levels of visceral adiposity compared with Caucasian adolescents (41.5 cm^2 vs. 65.2 cm^2 , $p = 0.01$) while Hispanic adolescents displayed the highest degree of VAT (41.5 cm^2 vs. 70.5 cm^2 , $p=0.003$). Interestingly, subcutaneous adipose did not differ across groups, suggesting that ethnic differences are restricted to weight gain specifically in the visceral space (Figure 2 Liska et al., 2007). It is possible that this predilection for VAT accumulation explains ethnic differences in the rates of metabolic syndrome and the distribution of individual risk factors.

Figure 2. Racial differences in visceral adipose tissue accumulation**.**

As depicted overweight and obese African American (N=17) youth display significantly lower levels of VAT as compared with Caucasians (N=21), and Hispanic youth (N=17). It is important to note that no significant differences exist in the subcutaneous depots (Liska et al., 2007).



Genetic factors are also important in determining obesity status and fat deposition. A study found that children with two obese parents have an 18.3-fold (95%CI: 9.0-37.4) greater likelihood of becoming obese in adulthood compared to those born to non-obese parents. Having only one obese parent increased the likelihood of obesity in the child by a factor of 6.3 (95%CI: 3.2-13.2) (Jacobson et al., 2007). When foster parents were studied, the BMI of the parent had no correlation with the child, which strengthens the argument for the strong role that genetics plays in the development of obesity (Jacobson et al., 2007). The role of genetics in the differential deposition of adipose tissue was also demonstrated in an overfeeding study involving monozygotic twins (Bouchard et al., 1990). In the study, 12 sets of sedentary male twins between the ages of 19 and 27 were

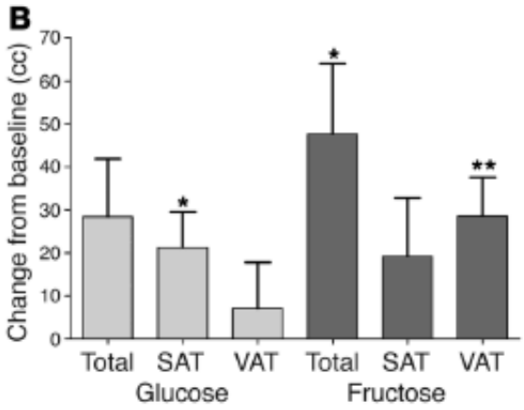
overfed 6000 calories weekly for 100 days. All participants experienced a mean 8.1 kg increase in body mass ($p < 0.001$). Significant heterogeneity existed in regional adipose distribution in response to the overfeeding. All participants experienced a significant increase in CT assessed VAT (34 ± 9 cm^2 to 58 ± 15 cm^2 $p < 0.001$); however there existed significantly similar responses within twin pairs represented by an intra-class correlation coefficient (ICC) of 0.56, $p < 0.05$). This relationship was further strengthened (an ICC of 0.72, $p < 0.01$) when the analysis was adjusted for increases in fat mass in the twin pairs. The results of the study support the role of genetics in the deposition of VAT; however as some heterogeneity did exist within the twin pairs therefore, the interplay between genetics and other environmental factors cannot be overlooked.

In addition to these non-modifiable factors, several lifestyle factors are associated with VAT deposition. Dietary patterns are an important modifiable behaviour that contributes to VAT mass in youth. Within large population-based surveillance studies, sugar sweetened beverage intake is associated with higher levels of VAT (Berkey, Rockett, Field, Gillman, & Colditz, 2004; Ludwig, Peterson, & Gortmaker, 2001). Smaller cohort studies have revealed associations between higher fiber intake, and breakfast consumption with lower VAT (Alexander et al., 2009; Davis, Alexander, Ventura, Toledo-Corral, & Goran, 2009). While robust associations have been noted in observational studies, the causal nature of these associations remains unclear.

An experimental trial recently demonstrated that the consumption of fructose is an important causal factor for the deposition of adipose viscerally (Stanhope et al., 2009). A 10-week intervention randomly assigned 32 overweight and obese adults to increase

their daily energy intake by 25% with either a fructose- or a glucose-based beverage. Over the course of 10 weeks, participants in both groups experienced a significant increase in body weight, WC, and total fat mass. A CT scan performed at the level of the umbilicus quantified VAT mass, however revealed a significant increase in VAT in only the fructose group. Participants consuming fructose increased VAT mass by 14% ± 5.5% over the 10-week period (Figure 3, $p<0.01$), while individual consuming glucose demonstrated no significant increases in VAT mass of 3.2% ± 4.4% (Stanhope et al., 2009). The results from this experimental trial strongly support the concept that dietary factors play a role in the development of visceral obesity. In agreement with these findings, positive associations between VAT and total fructose consumption have been recently demonstrated in an observational study of youth 14-18 years (Pollock et al., 2012).

Figure 3. Changes from baseline in adipose depots after consuming 25% of daily energy requirements from either a glucose or fructose beverage. Consuming glucose significantly increased subcutaneous adipose stores, while consuming fructose led to significant increases in both total fat, and VAT (Stanhope et al., 2009).



Other dietary factors associated with visceral adiposity in youth include low dietary fiber and skipping breakfast. A recent prospective cohort study found that a higher intake of fiber was associated with lower levels of MRI derived measures of visceral adiposity in youth 11-17 years of age (Davis et al., 2009). At baseline, youth consumed approximately 9 g/ 1000kcal/ day of fiber, and those who increased their fiber intake by 3 g/ 1000kcal/ day over a year decreased their VAT by 4%, while those who decreased their intake by 3 g/ 1000kcal/ day demonstrated a 21% increase in VAT ($p=0.02$) (Davis et al., 2009). A study of the same cohort of youth determined those who reported eating breakfast consistently (two days), or occasionally (one of two days) demonstrated significantly lower levels of MRI derived VAT compared to youth who never ate breakfast (Alexander et al., 2009). These data strongly suggest that diet plays an important role in the differential distribution of adipose tissue.

Recent evidence is also linking reduced sleep duration with higher levels of obesity. Population statistics reveal that nightly sleep duration has decreased by more than one hour over the past few decades (National Sleep Foundation, 2006). Short sleep duration relates to increased risk of being overweight, due to its impact on recovery of a hormonal profile facilitating appetite control (Hart & Jelalian, 2008). Experimental evidence has found a causal relationship between shorter sleep duration and disruptions in neuroendocrine control, including higher levels of ghrelin that increases hunger and lower levels of leptin that promote satiety (Hart & Jelalian, 2008). In addition, several epidemiological studies have revealed a strong association between shorter sleep duration and the increased risk of overweight. For example, Chaput and colleagues (2006) found a 3.5 greater likelihood of overweight in children 5-10 years old who slept 8-10 hours compared to peers sleeping 12-13 hours per night; similar results were found in adolescents.

It is possible that all of these modifiable risk factors share a common biological mechanism that would lead to a preferential distribution of adipose around the visceral organs. Important insight into the possible mechanisms that lead to excessive central adipose distribution can be gained by examining extreme medical conditions of visceral adiposity. Cushing syndrome is the hallmark example of visceral obesity. This condition is caused by excessive exposure to glucocorticoids, either exogenously secondary to medical treatment, or in conditions that cause excessive release of adrenocorticotropic hormone (ACTH) or cortisol such as pituitary tumours (Fitzgerald, 2012). Clinical manifestations include central obesity, and metabolic complications such as insulin resistance (Fitzgerald, 2012).

In support of a role for cortisol in the development of visceral obesity, several studies have shown that cortisol within the normal range is positively associated with VAT mass among otherwise healthy individuals (Alvarez, Beske, Ballard, & Davy, 2002; Goldbacher et al, 1998). Cortisol is a hormone released from the hypothalamic-pituitary-adrenal axis (HPAA) in response to various stressors. It is possible that changes in lifestyle factors like sleep, and dietary patterns lead to higher levels of stress, increasing the activity of the HPAA and the sympathetic nervous system (SNS), resulting in the development of visceral obesity (Tsatsoulis & Fountoulakis, 2006). Activities that can reduce the burden of excessive activation of the HPA axis and/or lower daily cortisol levels may be an effective strategy to reduce visceral obesity in youth and increasing PA may be one such approach (Yin, Davis, Moore, & Treiber, 2005).

Current Physical Activity Trends in Youth

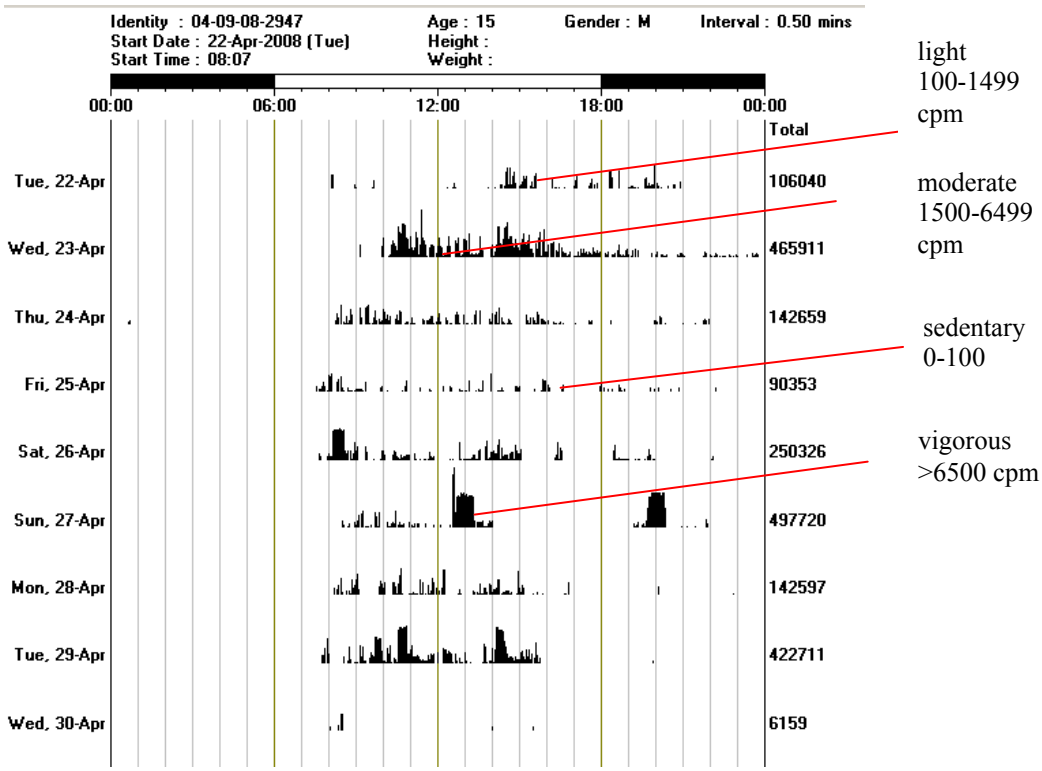
The CSEP and the World Health Organization (WHO) suggest children 12-17 years of age accumulate 60 minutes of moderate - to vigorous intensity PA (MVPA) most/all days of the week, and incorporate vigorous activity 3 days/week for optimal growth and health (Canadian Society of Exercise Physiology, 2011; World Health Organization, 2012). However, few are meeting the current PA guidelines in North America (Troiano et al., 2008). Epidemiological studies suggest that PA levels are decreasing or have declined significantly over the past 2 decades in parallel with increasing rates of obesity (Colley et al., 2011). For example, in Canada, only 7% of youth met the guidelines, and only 4% accumulate 20 minutes or more of vigorous activity 3 times a week in 2007 (Colley et al., 2011) . The low rates of PA are similar in

the United States with 6-8% of adolescents meeting the current guidelines (Troiano et al., 2008). The secular trends in PA have accompanied the increased rates of obesity, suggesting a possible association between the two.

Until recently, PA in youth was determined for the most part from self-report, using validated questionnaires. As of 2000, large population-based surveys or cohort studies have begun to assess PA using either pedometers or accelerometers (Colley et al., 2011; Troiano et al., 2008). These tools provide a reliable and valid estimate of total ambulatory PA levels (Esliger & Tremblay, 2007). Data is collected at various time points (i.e. epochs) that reflect movement in a certain plane, and PA intensity can then be estimated from the number of counts achieved over the course of a minute (Butte, Ekelund, & Westerterp, 2012). For example, counts per minute (cpm) accumulated at a rate of 100 or less are considered sedentary behaviour and >2000 would be considered MVPA, while everything in between would be quantified as light PA (Andersen et al., 2006). There is no current consensus regarding the most valid accelerometer thresholds to classify PA intensity in youth, as studies have used a variety of methods to define intensity including prediction equations, PA energy expenditures, and receiver operator characteristic curves (Butte et al., 2012). Other limitations of accelerometers include variations in model algorithms, lack of standards in converting raw data into cpm, and inability to quantify non-ambulatory activities such as resistance training (Matthew, 2005).

Figure 4. An example of a daily accelerometer physical activity file.

The lines represent various intensities of activities, with the higher the deflections representing more intense the activity.



Canadian population based studies have adopted the following cut points to classify PA intensity: sedentary time (<100 cpm), light (100-1499 cpm), moderate (1500-6499 cpm) and vigorous (>6500 cpm) PA intensities (Colley et al., 2011). These were adopted from a validation study by Puyau, which suggested that these cut-points closely approximate the energy expenditure rates of 1.5, 3.0 and 6.0 Metabolic Equivalents (METS) (Puyau, Adolph, Vohra, Zakeri, & Butte, 2004). Table 2 provides specific PA intensity examples, and summarizes the METS, as well as the cpm associated with each intensity.

Table 2. Physical activity intensity cut-points for Actical accelerometers adapted from (Colley et al., 2011).

Intensity	Metabolic Equivalents (METS)	Example	Accelerometer count range (counts per minute)
Sedentary	1 to less than 2	sitting, standing	< 100
Light	2 to less than 3	walking less than 3.2km/hr	100 to <1500
Moderate	3 to less than 6	walking faster than 3.2km/hr	1500 to < 6500
Vigorous	6 or greater	playing sports, running	>6500

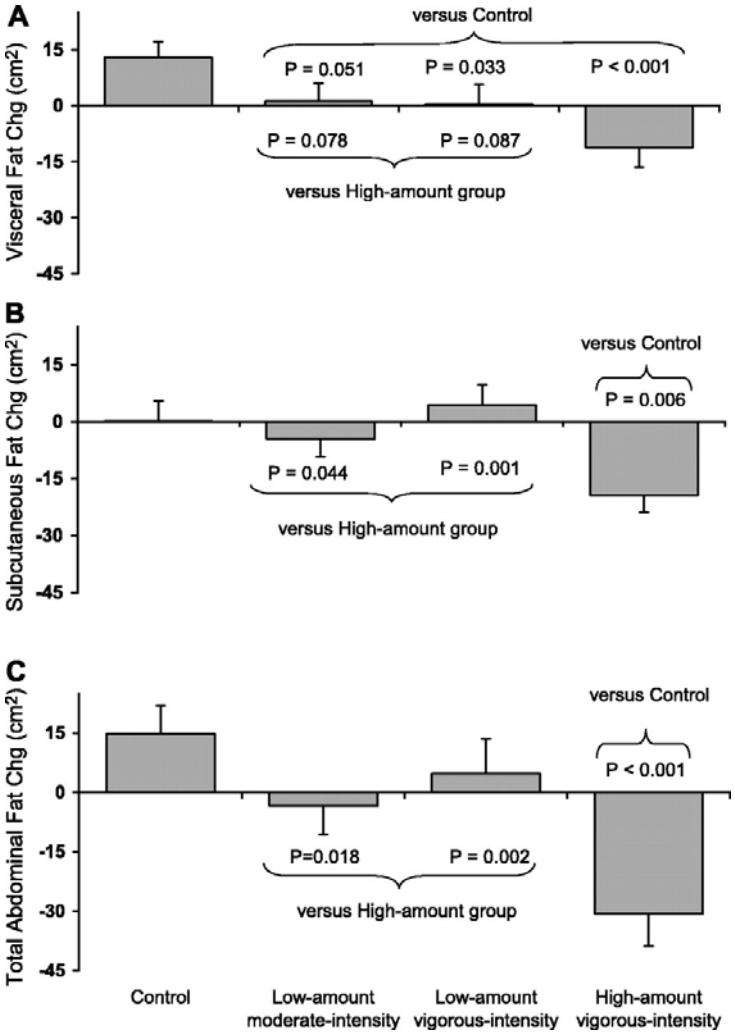
Large population-based studies that relied on accelerometer determined PA intensity demonstrated that children who participate in higher intensity activity are characterized by a more favorable (low risk) cardiometabolic risk profile (Ekelund et al., 2012; Wedderkopp, Hansen, Riddoch, Andersen, & Froberg, 2003). In European Youth Heart Study, a large cross sectional study of youth aged 9-15 years, cardiometabolic risk factor clustering (systolic blood pressure, insulin resistance, serum lipoprotein profile and adiposity) declined with increasing time spent in MVPA (Wedderkopp et al., 2003). Interestingly, this association was not found with lower intensity PA or total PA. This landmark study led to a growing body of research related to the importance of PA intensity in regulating adiposity and body fat distribution in youth. Collectively, these data suggest that the time spent in more vigorous PA may confer additive protection against risk factor clustering. This may relate in part to favorable effects of vigorous PA on VAT mass.

Physical Activity Intensity and Visceral Adipose Tissue

The body of experimental evidence regarding the dose of PA associated with VAT reduction is extensive in adults. Studies have revealed that PA (3-7days/week of 30-60 minutes duration) leads to significant decreases in VAT independent of changes in diet (Ross & Bradshaw, 2009). Randomized controlled trials in adults have demonstrated increased PA is associated with lower levels of central obesity (VAT and WC) without any corresponding change in body weight, and these changes occur regardless of age, or sex (Lee et al., 2005; Ross et al., 2004). The STRIDDE (Study of Targeted Risk Reduction Interventions through Defined Exercise design) randomized controlled trial provided some of the most conclusive evidence for a dose response relationship between exercise and VAT in adults (Slentz et al., 2005). The 8-month trial randomized 175 participants to either (1) high amounts of vigorous PA (~20miles per week at 65-80% of peak oxygen consumption); (2) low amounts of vigorous PA (~12miles per week at 65-80% of peak oxygen consumption); (3) low amount of moderate PA (~12miles per week at 40-55% of peak oxygen consumption); or (4) a control group. As demonstrated in Figure 5, CT-derived VAT increased in the control group by 8.6%, did not significantly change in either the low vigorous or low moderate groups, but decreased 6.9% in the high amount of vigorous activity group (Slentz et al., 2005). The results highlight the benefit of PA in attenuating VAT accumulation with vigorous activity.

Figure 5. Dose response reduction in visceral adipose tissue (Slentz et al., 2005).

While PA attenuated the increase in VAT in both the low-amount of moderate and low amount of vigorous activity groups, only high amounts of vigorous intensity was associated with a significant reductions in all adipose depots.



Unfortunately, a similar body of experimental data is not available in children. However, a number of recent observational studies support the concept that higher intensity activity is preferentially associated with lower central obesity in youth. For example, a series of

cross-sectional studies using accelerometers to assess PA intensity documented robust associations between the time spent in vigorous PA and measures of adiposity in youth (Gutin, Yin, Humphries, & Barbeau, 2005; Ruiz et al., 2006; Ulf Ekelund, Luis B Sardinha, Sigmund A Anderssen, Marike Harro, & et al, 2004; Wittmeier, Mollard, & Kriellaars, 2008). Wittmeier and colleagues found a dose response negative relationship between time spent in vigorous PA and measures of adiposity in a sample of 250 children aged 8-10. After controlling for age and sex, only increasing time spent in vigorous PA was inversely associated with both BMI ($r = -0.26$, $p < 0.001$) and skinfold measured body fat ($r = -0.35$, $p < 0.001$) (Wittmeier et al., 2008). Similarly, in a sample of 780 youth aged 9-15 from the European Youth Heart Study, only vigorous PA was associated with lower levels of adiposity (body fat calculated from the sum of five skinfolds) after adjusting for age, sex, and study location (Ruiz et al., 2006). Correspondingly, in a sample of adolescents vigorous PA, but not moderate PA was associated with lower levels of DXA measured body fat, ($\beta = -4.19$ $p = 0.001$ Gutin et al., 2005)). Kim and Lee (2009) recently reviewed all cross-sectional studies that tested for an association between visceral adiposity and either PA or cardiorespiratory fitness. Among the limited number of studies that used objective measures for both variables, they found that increased time spent in MVPA was negatively associated with abdominal obesity. Additionally they found that "increased time spent in vigorous physical activities (>6 METs) is independently associated with lower waist circumference and visceral fat" (Kim & Lee, 2009, p.572).

The same systematic review also examined the effect of PA-based interventions directed at reducing VAT in youth (Kim & Lee, 2009). They reviewed 15 experimental

trials of either aerobic exercise alone (n=11) or combined resistance and aerobic exercise (n=4). Among the aerobic exercise interventions, 6 were randomized controlled trials, while 5 were not randomized. Among the randomized controlled trials sample sizes varied between 11 and 80 per intervention arm. The exercise durations ranged between 40 minutes and 2.5 hours daily. Overall, the authors found that aerobic exercise either attenuated the age-related increase or led to a modest decrease in VAT or WC. The wide range of participants (as some focused on overweight youth while others did not), the wide range of exercise prescriptions, and the infrequent use of the gold-standard MRI-derived measures of visceral fat limited the studies. A paucity of experimental trials in children have attempted to define a dose of PA associated with optimal reductions in VAT. Therefore, the optimal/minimal intensity for decreasing visceral obesity in youth has yet to be elucidated, as few studies have examined the relationship between exercise intensity and VAT (Kim & Lee, 2009).

An efficacy study examined the effect of structured aerobic training on body composition in 74 obese youth aged 7-11 years (Owens et al., 1999). The youth were randomly assigned to either a physical training group or a control group for 4-months. The training group exercised 5 times/week, 40 minutes per session, at an intensity of approximately 70-75% of their maximum heart rate (MHR). The authors did not perform an intention to treat analysis and only participants that attended $\geq$ 3 sessions/week were included in the final analysis. Although both groups demonstrated an increase in MRI measured VAT over the 4-month period, the gain was attenuated in those randomized to physical training compared to the control group (+0.5% vs +8.1%, p= 0.02) (Owens et al., 1999).

To the best of our knowledge, Gutin and colleagues performed the only experimental trial that directly compared the effects of low and high intensity exercise on measures of adiposity in youth. Specifically, 80 overweight adolescents (13-16yrs) were randomized to either moderate intensity exercise (55-60% of VO_2peak) with lifestyle education (LSE), high intensity exercise (75-80% of VO_2peak) with LSE, and a comparison group who received LSE only condition (Gutin et al., 2002). The youth in the PA intervention arms were asked to train 5 times/week, with a LSE session occurring once every 2 weeks over the 8-month intervention. The LSE only arm attended sessions twice a week over the intervention period. LSE sessions included information regarding diet, exercise, coping strategies, and behaviour modification. The duration of the training sessions in the high and moderate intensity groups were controlled to elicit an approximate energy expenditure of 350kcal/session. Visceral adipose was quantified directly using multiple slice MRI acquired at the 5th lumbar vertebrae level (Gutin et al., 2002). The authors did not find an effect of vigorous activity on measures of central adiposity among overweight youth.

Major limitations to this study include a lack of adherence to the prescribed training intensity and poor attendance. The high intensity group did not achieve the prescribed intensity (average heart rate was 154 beats/min vs. the prescribed 167 beats/min). In addition, both groups suffered low attendance (51% in the moderate intensity and 56% in the high intensity groups respectively) and only 71% of youth returned for follow-up testing. As a result, the intention to treat analysis was unable to detect any differences in VAT between the 3 groups. The high intensity group did experience a statistically significant increase in cardiovascular fitness regardless of their

adherence to the intervention (Gutin et al., 2002). In a post-hoc efficacy analysis restricted to participants who adhered to $\geq$ 40% of the prescribed intervention, VAT decreased significantly in those who trained compared to controls receiving the LSE only (-42.0 cm^3 ± 9.3 vs. -11.0 cm^3 ± 10, respectively $p < 0.05$). The authors were unable to detect a difference in the high or moderate intensity groups as only 17 youth (9 moderate and 8 in the high intensity) trained at a heart rate within 10 beats per minute of the prescribed intensity (Gutin et al., 2002). Therefore, the effect of intensity on VAT tissue reduction in youth remains unclear.

Summary

The prevalence of obesity is increasing in youth, and little evidence is available describing the intensity of PA needed to reduce visceral adiposity. Recent cross sectional studies suggest that higher intensity PA is associated with lower levels of VAT in youth. The dose of PA intensity associated with a reduction in VAT, and WC remains unknown. In their recent systematic review, Kim and Lee gave the following recommendations: (1) "Further studies are needed to examine the role of PA (e.g., types and frequency) in the prevention and treatment of abdominal obesity"; and (2) "Currently, the minimal and optimal levels of PA required for abdominal obesity reduction in the pediatric age group are unknown and this warrants investigation" (Kim & Lee, 2009, p.572). This thesis is designed specifically to address the clinically relevant gaps in the literature related to the prevention of visceral obesity in youth. The information gathered from this study will be important for PA recommendations and programs designed to reduce visceral adiposity in the growing number overweight and obese youth in Canada. To address the limitations

of the previous studies outlined above we have designed a randomized control design of youth from the POWER (Physical activity for OverWEight youth at Risk for T2DM) Trial to determine the association between PA intensity and measures of VAT in youth.

METHODS

Aims and Hypothesis:

The primary aim of this study was to examine the effect of 6 months of high and low intensity aerobic exercise on measures of central adiposity (WC and VAT measured by MRI) in overweight youth between the ages 13-18 years. Based on current cross-sectional data in youth, and randomized controlled trials conducted in adults we hypothesized that youth randomized to high intensity activity (> 70% of HRR) would elicit more significant reductions in WC and VAT than youth randomized to lower intensity activity (40-55% of HRR).

Study Design:

The Biomedical Research Ethics Board from the University of Manitoba approved the POWER trial, a 6 month randomized controlled clinical trial (See Appendix A). Both parents and participants provided written consent to participate in the study (See Appendix B). We randomized participants to either: (1) high intensity PA (70-85% of HRR); (2) low intensity PA (40-55% of HRR); or (3) a control group for a period of 6 months (Figure 6 illustrates the flow of participants through the study). To overcome the previous adherence limitations experienced by Gutin and colleagues (2002), prior to randomization participants first completed a 2-week run-in phase. During the run-in phase, participants were required to attend at least 4 out of 6 prescribed sessions in order to be randomized. In order to increase adherence, participants and their parents signed a contract that outlined their individual responsibilities (See Appendix C). An online

number generator created an unbiased randomization. Allocation was performed using an opaque envelope by an investigator unfamiliar with the randomization scheme.

To control for the potential confounding effects of differences in energy expenditure, the duration of each training session was adjusted to ensure equal caloric expenditure between the groups. A sub-maximal steady state treadmill protocol with expired gases was used to determine oxygen consumption at different exercise intensities. Energy expenditure was estimated for each individual based on the linear association of heart rate and oxygen consumption, and that for each litre of oxygen consumed 5 kcals are expended (McArdle, Katch, & Katch, 2007b). The baseline measurements occurred prior to the intervention, and excluding the sub-maximal treadmill protocol, all measures were repeated after 6 months.

Study Population:

Recruitment:

Participants were recruited from May 2008 - September 2012 through POWER Trial posters placed in the offices of doctors, physiotherapists, and dieticians. Posters were also placed in community centers, and the schools approved by the Director of Research, Planning and Systems Management for the Winnipeg School Division number one. Print advertisements were placed in the Winnipeg Free Press, Leisure Guide, and other local community papers. Radio advertisements were placed on several different radio stations in order to reach a greater number of the target audience, and included HOT 103.1FM, QX104.1FM, and Curve 94.3FM.

Inclusion Criteria

Eligible youth were 13-18 years and considered overweight, or obese for their age and sex based on the BMI standards created by the IOTF (Cole et al. 2000). As the trial was originally designed to determine the effects of PA on the risk of T2DM in overweight youth, we selected youth that were at an increased risk for T2DM based on the following criteria: a family history of T2DM, ethnicity, fetal exposure to gestational diabetes, or evidence of non-alcoholic fatty liver disease (NAFLD) measured by spectroscopy (Kaufman, 2002). Exposure to gestational diabetes mellitus has been found to be associated with an increased risk for T2DM (Young et al., 2002) and increased VAT and total adiposity in youth (Crume et al, 2011). The presence of NAFLD is associated with the presence of central obesity, insulin resistance, and the metabolic syndrome in youth (Schwimmer, Pardee, Lavine, Blumkin, & Cook, 2008).

Eligible youth were screened for T2DM and impaired fasting glucose with a 75 gram Oral Glucose Tolerance Test (OGTT). T2DM and impaired fasting glucose diagnosis were determined according to the guidelines established by the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

Exclusion Criteria

Participants were excluded if they presented with a condition that may confound the results of the study. These included: (1) diagnosis of T2DM or impaired glucose tolerance; (2) severe obesity or an injury that would prevent them from exercising; (3) significant weight loss in the past 6 months (4) current intake of corticosteroids, or

atypical antipsychotics, because they can influence metabolism (Luna & Feinglos, 2001); or (5) pregnancy.

Intervention:

The target components of the training intervention are summarized in Table 3. The exercise training occurred at 4 Winnipeg YMCA locations (Downtown, South, West Portage, Elmwood Kildonan). For both intervention arms, training was offered three times per week at intensities of either 40-55% (low intensity arm) or >70% of peak fitness (high intensity arm) for 30-45 minutes/session. The duration of exercise was adjusted to ensure an equal caloric expenditure of approximately 350kcal/session, a daily target used previously in other intervention trials in both youth and adults (Slentz et al., 2005; Gutin et al., 2002) .

Table 3. Training Targets for Intervention Groups.

	Low Intensity	**High Intensity**
Frequency	3x/week	3xweek
Intensity	40-55% HRR	70-85% HRR
Time	40 minutes	30 minutes
Type	Aerobic	Aerobic
Duration	6 months	6 months

Experienced CSEP Certified Personal Trainers supervised the training sessions. Each training session began with a 5-minute warm up and ended with a 5-minute cool down. Weather permitting, the training occurred outdoors and included co-operative low organized games (Ultimate Frisbee, soccer). Co-operative games were offered every

week or other week as they were an attractive option for youth in the trial to increase attendance. Heart rate and duration of exercise were recorded with a Polar heart rate monitor (Polar RS200). The participant selected their mode of exercise; however, walking and running were encouraged. A written record was kept of the activities, duration, and average heart rate.

Data Collection:

Setting:

All baseline and follow up measurements were obtained at the Manitoba Institute of Child Health, except for MRI data which was collected at either the St. Boniface Hospital, Health Science Centre, or National Research Council in Winnipeg, MB. Intervention data was collected at the YMCA locations.

Main Outcome Measures:

Primary outcome:

Visceral Fat:

VAT was measured by a single axial slice using a 1.5-T whole body magnet. Subcutaneous adipose tissue and VAT was assessed at approximately the level of the 4th lumbar vertebrae (L4). A standard MRI imaging technique was used in accordance with the method previously described (Abate, Garg, Peshock, Stray-Gundersen, & Grundy, 1995; Levine et al., 2007). Previous studies in youth have relied on multiple slices to estimate a volume of VAT (cm^3) (Owens et al., 1999; Gutin et al., 2002; Barbeau et al., 2007). However, Ross and others have demonstrated that quantifying VAT in a single

slice at the level of L4-L5 is highly correlated with total VAT volume ($r = 0.95$, $p < 0.01$ and $r = 0.93$, $p<0.001$ respectively) (Ross, Leger, Morris, de Guise, & Guardo, 1992; Han, Kelly, Walsh, Greene, & Lean, 1997). Based on these findings and the fact that VAT was a secondary outcome of the larger trial, we decided to rely on a single slice to quantify VAT. 3D Slicer software quantified VAT and subcutaneous fat offline. In brief, tissue compartments were mapped, the pixels in each compartment were then counted and converted to an area (cm^2).

Secondary outcome measure:

Waist circumference

WC was measured in duplicate at the height of the iliac crest in accordance with the protocol set by CSEP (McGuire & Ross, 2008). The average of the 2 measures was analyzed.

Exploratory outcomes and confounding variables

Total body fat:

Dual energy x-ray absorptiometry (DXA) quantified fat mass, fat free mass (FFM), and the percent body fat.

Cardiorespiratory Fitness:

A graded maximal exercise test using cycle ergometry to volitional exhaustion was used to determine cardiorespiratory fitness. The ParvoMedics True One Metabolic System (OUSW 4.2 cx – 20061010) measured ventilation and expired gases every fifteen

seconds. Blood pressure and the Borg Scale Ratings of Perceived Exertion (RPE) were measured every two minutes. Cardiorespiratory fitness was reported as a VO_2 peak.

Physical activity:

To control for the possible differences in PA participants wore a waist-mounted pedometer for seven consecutive days, objectively measuring daily activity levels. The participants tracked daily step counts and activities using a log prior to randomization.

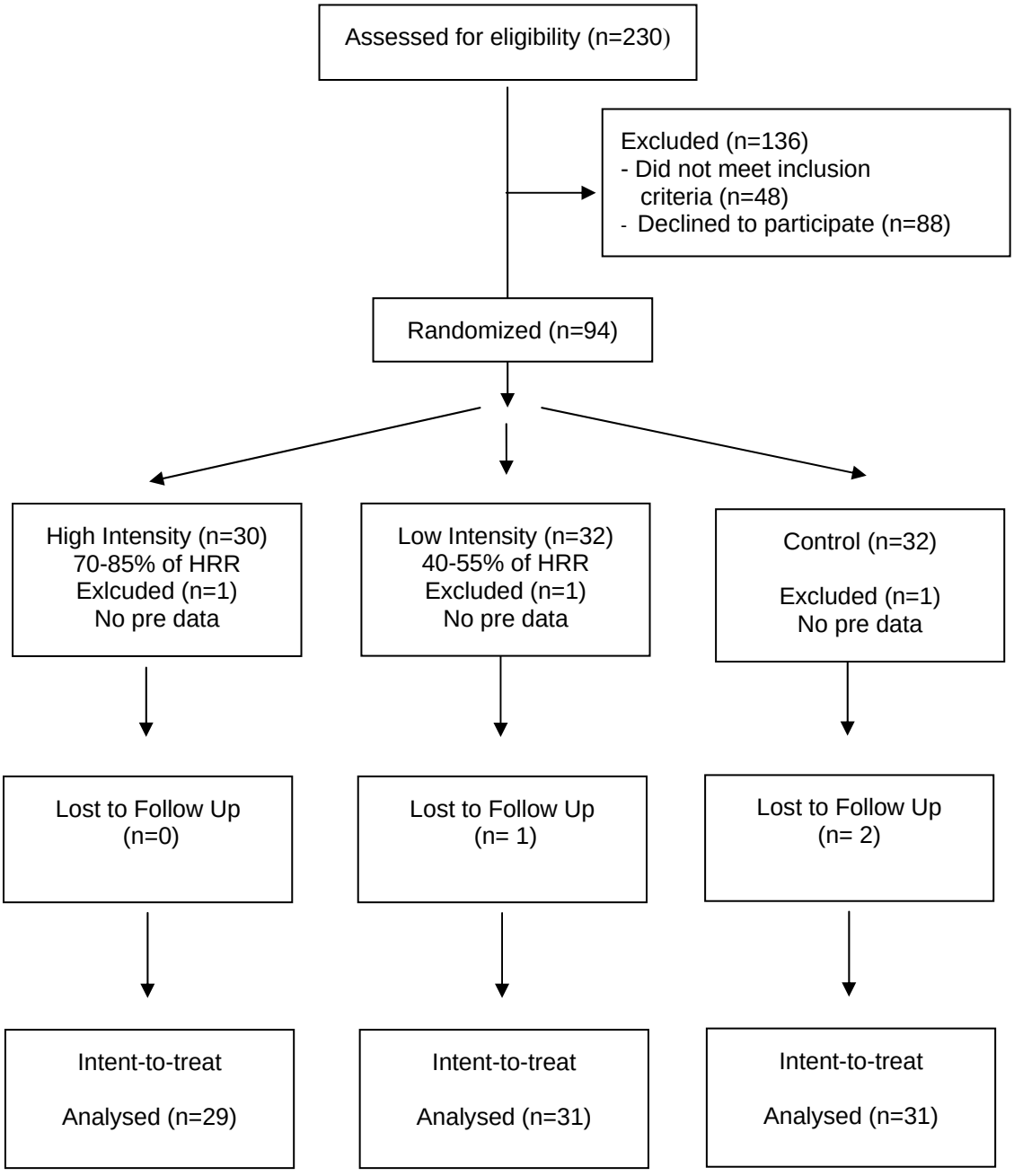
Puberty:

In order to control for the confounding effects of maturation, puberty stage was measured using a self-reported Tanner staging instrument. Tanner staging is a method used to describe the stages of maturation along a scale of 1-5 (Marshall & Tanner, 1969; Marshall & Tanner, 1970). Stage 1 refers to pre-pubertal stage characterized by no external development of genitalia and the absence of pubic hair. Stages 2-4 refer to advancing development of the external genitalia and pubic hair growth between pre-pubertal status and complete formation of external genitalia. Stage 5 refers to adult genitalia and pubic hair length and distribution (Marshall & Tanner, 1969; Marshall & Tanner, 1970). Self-reporting Tanner staging in adolescents has been found previously to be both reliable and consistent with physician determined staging (Desmangles, Lappe, Lipaczewski, & Haynatzki, 2006).

Statistical Analyses

All statistical analyses were conducted using SAS software version 9.3, and SPSS version 19. Data are presented as means and standard error unless otherwise stated. All data were tested for normality using Kolmogorov-Smirnov tests. One-way ANOVAs were used to examine group differences in continuous variables at baseline and chi-square tests were used to examine differences in categorical variables. Independent t-tests were used to test for differences in exercise training variables between the high and low intensity training arms. Paired t-tests were used to analyze within groups changes over time, and repeated-measures ANOVA were used to test for group, time, and group-time interaction effects on outcomes. In the primary analyses, data were analyzed according to the intention-to-treat principle to preserve the randomization process. In brief, pre-data was carried forward for participants with missing post values. To facilitate the comparison of our results with previous interventions conducted in youth (Barbeau et al., 2007; Gutin et al., 2002) separate efficacy analysis were conducted within a sub-group of participants who attended at least 50% of the training sessions, and comparing training with the control condition. Bivariate analyses were used to examine the continuous association between changes in VAT with exercise intensity and intervention attendance. An alpha level of 0.05 was considered statistically significant, except in the case of the paired t-tests. The Bonferroni method was used to account for multiple comparisons (0.05/3), the p level was adjusted to $p < 0.017$.

Figure 6. Flow diagram of participants based on randomization for the primary outcome of VAT. All randomized participants were included in the intent-to-treat analyses with missing values carried forward.



RESULTS

Demographics

We screened 230 individuals by telephone, 48 did not meet the inclusion criteria and were excluded, 88 declined participation (generally citing incompatibility with the training schedule or fear of needles) and 4 failed the run-in phase. The data presented here represents an interim analysis of the first 94 of 120 participants randomized. Of the 94 participants randomized, 3 were lost to follow up, and the baseline data for the primary outcome was unavailable for 3 participants (Figure 6). Youth were on average 15 ± 1.7 years of age, the majority were female (77%) and Caucasian (63%) (Table 4). The average BMI-Z was 2.04 ± 0.41 indicating youth were considered obese for their age and sex (BMI $\geq$ 95th percentile). The baseline fitness for the entire cohort was 24.6 ± 1.7 ml/kg/min, and the average steps per day were 6808 ± 2682. Following randomization, there were no significant group differences in age, pubertal development, fitness, PA levels, or adiposity at baseline. However, there was trend towards a lower WC in the low intensity group (Table 4). Differences in sex and ethnicity existed between groups (Table 4). A greater proportion of males (p= 0.04), and non-First Nation and non-Causasians were randomized to the control and low intensity groups (p= 0.01).

Table 4. Baseline characteristics of the study population.

Variable	High Intensity N= 30	Low Intensity N=32	Control N=32	P value
Age	15 ± 1.6	15 ± 1.8	15 ± 1.8	0.88
Sex (M/F)	3 /27	7/25	12/20	**0.04**
Ethnicity (N)				
Caucasian	23	20	16	0.10
First Nations	7	4	9	0.30
Other	0	8	7	**0.01**
Tanner (2/3/4/5)*	4/3/10/7	0/5/10/10	3/6/5/11	0.53
Height (cm)	165	165	167	0.18
Weight (kg)	89.3 ± 15.4	86.8 ± 15.7	93.7 ± 17.5	0.24
BMI (kg/m^2)	32.8 ± 4.8	31.9 ± 4.7	33.1 ± 5.5	0.62
BMI z score	2.01 ± 0.40	1.99 ± 0.43	2.11 ± 0.42	0.52
Waist (cm)	107.4 ± 13.3	101.2 ± 13.0	108.8 ± 13.5	0.06
Hip (cm)	113 ± 11.2	112 ± 10.6	113.6 ± 11.3	0.85
VAT (cm^2)*	81.3 ± 32.1	75.6 ± 39.1	80.9 ± 32	0.77
SAT (cm^2)*	336 ± 133.8	328 ± 103.0	329 ± 104.1	0.96
% fat*	40.1 ± 4.6	38.8 ± 5.2	38.8 ± 5.2	0.49
FFM (kg)*	50.9 ± 6.3	50.8 ± 8.0	53.3 ± 8.6	0.37
Rest HR (bpm)	74 ± 10	74 ± 11	74 ± 14	0.99
Systolic BP (mmHg)	115 ± 7.4	115 ± 9.9	117 ± 14	0.60
Diastolic BP	64 ± 5.9	64 ± 6.3	63 ± 8.3	0.82
VO_2 (ml/kg/min)	24.6 ± 3.7	25.3 ± 4.4	24.2 ± 4.4	0.57
Total Steps (per/day)	6865 ± 2703	6162 ± 1915	7398 ± 3429	0.29

Data presented as mean and standard deviation.* Sample sizes different: Tanner = 74, VAT = 91 (3 had no pre data), SAT = 78 (image cut off), % fat and FFM = 92 (obesity levels of 2 participants were too significant to perform the scan).

Training data

The average energy expended per session did not differ between the high and low intensity intervention arms (334 ± 15 kcals/session vs. 315 ±78 kcals/session, p= 0.17) (Table 5). Attendance decreased similarly in both groups over the 6 month intervention

(Table 5). No difference existed in the average monthly attendance between the high and low intensity arms (60% vs. 55%, $p = 0.23$). As per the study design, youth randomized to the high intensity arm trained at a greater percentage of their peak fitness compared to youth randomized to the low intensity arm (66 vs. 55%, $p < 0.001$) (Table 5). Youth in the low intensity intervention arm exercised on average 6 minutes longer to match energy expenditure between groups.

Changes in VAT and WC

Group-wise differences in the primary outcome measure of VAT, and waist circumference in response to training are presented in Tables 6a and 6b. Compared to the control group, the changes in WC and VAT were not significantly different for youth randomized to either low or high intensity exercise training. To determine the efficacy of the intervention, we performed a sub-group analysis of youth that attended at least 50% of the prescribed exercise sessions (N=68). A trend towards a group-by-time interaction was observed for VAT (Table 6a; $p= 0.059$ and Figure 7). No significant differences or trends towards significance were observed for waist circumference in the efficacy sub-group analyses. To determine if being randomized to exercise at either intensity was associated with a significant changes in visceral adiposity we performed a second subgroup analysis. In this analysis, we combined youth in both intervention arms and compared them to the control group. No differences in either WC or VAT were observed between the training and control group (Tables 6a and 6b).

Table 5. Average Monthly Training Data**.**

High Intensity							
Average/Session	1	2	3	4	5	6	average
E.E. (Kcals)	342 ± 80	330 ± 68	320 ± 69	325 ± 67	344 ± 103*	320 ± 77*	334 ± 63
Intensity (HRR%)	65 ± 10**	65 ± 9**	65 ± 10**	66 ± 7**	65 ± 9**	66 ± 11**	66 ± 7 **
Duration (mins)	41 ± 7*	40 ± 8	37 ± 6**	38 ± 8	40 ± 9	38 ± 6	39 ± 6 **
Attendance (%)	77 ± 20	62 ± 26	60 ± 28	60 ± 27	58 ± 33*	53 ± 31	60 ± 23
Low Intensity							
Average/Session	1	2	3	4	5	6	average
E.E. (Kcals)	312 ± 91	322 ± 96	309 ± 84	323 ± 78	303 ± 72	290 ± 48	315 ± 78
Intensity (HRR%)	54 ± 8	55 ± 9	53 ± 9	57 ± 11	55 ± 10	53 ± 11	55 ± 7
Duration (mins)	44 ± 8	45 ± 7	43 ± 7	46 ± 9	44 ± 8	43 ± 8	45 ± 6
Attendance (%)	71 ± 27	63 ± 26	60 ± 28	50 ± 31	47 ± 36	48 ± 35	55 ± 24

Data presented as mean ± standard deviation E.E. = energy expenditure. ** $p < 0.01$, and * $p < 0.05$ denote a difference between the high and low intensity groups.

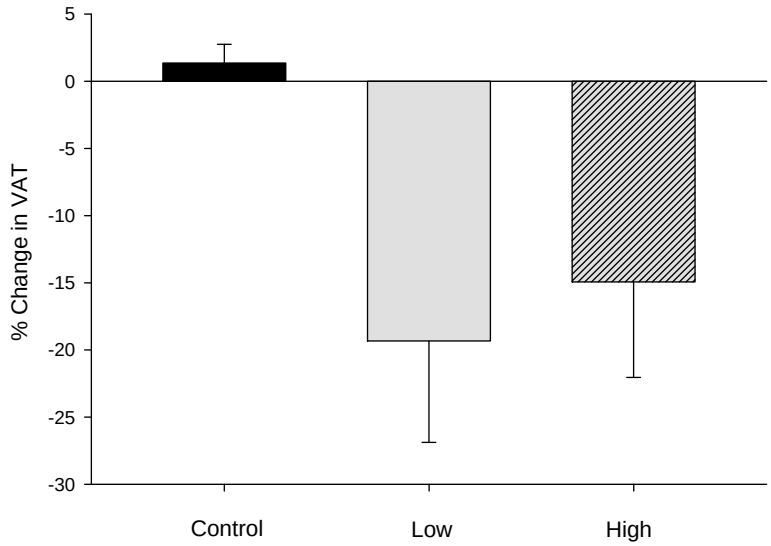
Table 6a. Baseline, Follow up, and Changes in VAT (cm^2).

		Mean (SE)		Mean (95% CI)	P Value		
Group	**N**	**Baseline Value**	**Follow-up Value**	**Within-Group Changes**	**Time**	**Group**	**T x G**
Intention-to-Treat Analysis (n=91)							
Control	31	80.9 (6.1)	82.0 (6.1)	+1.1 (-13.1 to 15.2)			
Low	31	75.6 (6.1)	67.8 (6.1)	-7.8 (-22.0 to 6.3)	0.06	0.48	0.27
High	29	81.3 (6.3)	71.8 (6.3)	-9.5 (-24.1 to 5.1)			
Efficacy Analysis Limited to Participants Attending> 50% of the Intervention (n=68)							
Control	31	80.9 (6.3)	82.0 (6.3)	+1.1 (-13.7 to 15.9)			
Low	15	95.7 (9.1)	77.2 (9.1)	-18.5 (-39.8 to 2.7)	0.01	0.74	0.06
High	22	84.4 (7.5)	71.9 (7.5)	-12.6 (-30.1 to 5.0)			
Training vs. Control (n=91)							
Control	31	80.9 (6.1)	82.0 (6.1)	+1.1 (-11.6 o 13.7)	0.21	0.29	0.11
Training	60	78.4 (4.4)	69.7 (4.4)	-8.6 (-17.7 to 0.45)			

Table 6b. Baseline, Follow up, and Changes in WC (cm).

		Mean (SE)		Mean (95% CI)	P Value		
Group	**N**	**Baseline Value**	**Follow-up Value**	**Within-Group Changes**	**Time**	**Group**	**T x G**
Intention-to-Treat Analysis (n=94)							
Control	32	108.8 (2.4)	109.7 (2.4)	+0.94 (-3.2 to 5.0)			
Low	32	101.2 (2.4)	103.1 (2.4)	+1.9 (-2.2 to 6.0)	0.76	0.10	0.14
High	30	107.4 (2.5)	105.3 (2.5)	-2.1 (-6.3 to 2.2)			
Efficacy Analysis Limited to Participants Attending > 50% of the Intervention (n=70)							
Control	32	108.8 (2.4)	109.7 (2.4)	+0.94 (-2.1 to 4.0)			
Low	16	105.8 (3.4)	107.7 (3.4)	+1.9 (-2.4 to 6.1)	0.95	0.69	0.21
High	22	107.7 (2.9)	105.1 (2.9)	-2.6 (-6.3 to 1.0)			
Training vs. Control (n=94)							
Control	32	108.8 (2.4)	109.7 (2.4)	0.94 (-2.8 to 4.7)	0.61	0.08	0.58
Training	62	104.2 (1.7)	104.2 (1.7)	-0.03 (-2.7 to 2.7)			

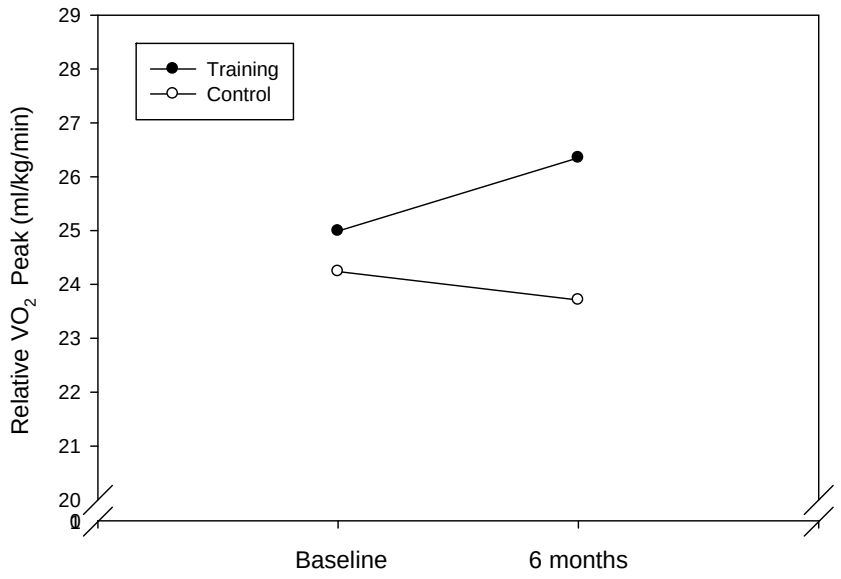
Figure 7. Group-wise differences in changes in VAT with the intervention restricted to participants attending ≥ 50% of the intervention (N=68, p= 0.06).



Changes in fitness

The intention to treat analysis and efficacy analysis revealed significant group-by -time interactions for both absolute (L/min) and relative oxygen uptake (ml/kg/min) (Table 7a and 7b). Peak oxygen uptake increased significantly in both exercise training groups, compared to controls (Table 7a & 7b). With the training groups combined, improvements were seen in both relative (1.4 ± 0.4 vs. -0.54 ± 0.6 ml/kg/min, p = 0.01 Figure 8) and absolute fitness (0.13 ± 0.03 vs. -0.01 ± 0.04 L/min, p = 0.01) when compared with controls (Table 7c).

Figure 8. Changes in relative VO_2 peak (ml/kg/min) following a 6 month intervention (N=93, p=0.01).



Changes in other measures of body composition

In the intent-to-treat analysis youth in the control group gained 2.1± 1.0 kg, and despite a promising tendency towards weight loss in the high intensity arm of the trial (-0.33 ± 1.0 kg), these differences were not statistically different between groups (Table 7a, $p = 0.24$). No significant group-wise differences were seen in the VAT/SAT ratio. All groups demonstrated mean reductions (-0.01 in the controls, -0.02 in the low intensity and -0.04 in the high intensity group respectively) (Table 7a). Similar results were found in the both sub-group analyses (Table 7b and 7c). Fat free mass (FFM) increased in the control and low intensity groups, $p < 0.01$. There were no significant group-wise differences for any other measure of adiposity and the changes were not significantly different between the exercise and control arms (Table 7a, 7b, 7c).

Table 7a. Changes in Exploratory Outcomes after 6 months (intent-to-treat).

		Mean (SE)			P Value
	N	**Control**	**Low**	**High**	**T x G**
Weight (kg)	94	2.1 (1.0)	0.41 (1.0)	-0.33 (1.0)	0.24
BMI-Z	94	-0.03 (0.04)	-0.07 (0.04)	-0.07 (0.4)	0.68
DXA % Fat	92	-0.15 (0.39)	-0.83 (0.38)	-0.64 (0.39)	0.44
Hip (cm)	94	0.68 (1.2)	-0.42 (1.2)	1.6 (1.2)	0.50
SAT (cm^2)	78	1.8 (20.8)	-2.4 (18.9)	3.0 (20.3)	0.98
VAT/SAT ratio	78	-0.01 (0.02)	-0.02 (0.02)	-0.04 (0.02)	0.32
FFM (kg)	92	1.6 (0.46)*	1.1 (0.45)*	0.76 (0.46)	<0.01
VO_2 (L/min)	93	-0.01 (0.04)	0.13 (0.04)*	0.12 (0.04)*	0.04
VO_2(ml/kg/min)	93	-0.54 (0.56)	1.4 (0.56)*	1.3 (0.57)	0.02

* Indicates a significant within group difference $p < 0.017$ to adjust for multiple comparisons.

Table 7b. Changes in Exploratory Outcomes after 6 months (participants who attended >50%).

		Mean (SE)			P Value
	N	**Control**	**Low**	**High**	**T x G**
Weight (kg)	70	2.1 (1.0)	0.01 (1.4)	-0.22 (1.2)	0.28
BMI-Z	70	-0.02 (0.03)	-0.04 (0.04)	-0.07 (0.04)	0.68
DXA % Fat	68	-0.15 (0.35)	-0.93 (0.48)	-0.86 (0.40)	0.29
Hip (cm)	70	0.68 (1.1)	-1.0 (1.6)	0.80 (1.3)	0.63
SAT (cm^2)	57	1.8 (19.6)	-4.9 (25.6)	-3.8 (22.0)	0.97
VAT/SAT ratio	57	-0.01 (0.01)	-0.04 (0.03)	-0.04 (0.02)	0.36
FFM (kg)	68	1.6 (0.45)	1.7 (0.62)	0.93 (0.53)	0.54
VO_2 (L/min)	69	-0.01 (0.05)	0.18 (0.07)	0.12 (0.06)	0.05
VO_2(ml/kg/min)	69	-0.54 (54)	1.9 (0.78)*	1.4 (0.65)*	0.02

* Indicates a significant within group difference $p < 0.017$ to adjust for multiple comparisons

Table 7c. Changes in Exploratory Outcomes after 6 months (Training Vs. Control).				
		Mean (SE)		**P Value**
	N	**Control**	**Training**	**T x G**
Weight (kg)	94	2.1 (1.0)	0.05 (0.72)	0.11
BMI-Z	94	-0.03 (0.04)	-0.07 (0.03)	0.38
DXA % Fat	92	-0.15 (0.39)	-0.74 (27)	0.21
Hip (cm)	94	0.68 (1.1)	0.54 (83)	0.92
SAT (cm^2)	78	1.8 (20.6)	0.12 (13.8)	0.94
VAT/SAT ratio	78	-0.01 (0.01)	-0.03 (0.03)	0.23
FFM (kg)	92	1.6 (0.5)	0.96 (0.3)	0.23
VO_2 (L/min)	93	-0.01 (0.04)	0.13 (0.03)*	0.01
VO_2(ml/kg/min)	93	-0.54 (0.56)	1.4 (0.41)*	0.01

* Indicates a significant within groups difference $p < 0.017$ to adjust for multiple comparisons.

Associations

Bivariate analyses revealed no associations between changes in VAT and exercise intensity ($r=-0.01$, $p=0.90$) (Figure 9a.). However, a moderate negative relationship was found between changes in VAT and intervention attendance (%), ($r = -0.3$, $p< 0.05$)(Figure 9b).

Figure 9a. Association between changes in VAT and exercise intensity (%HRR).

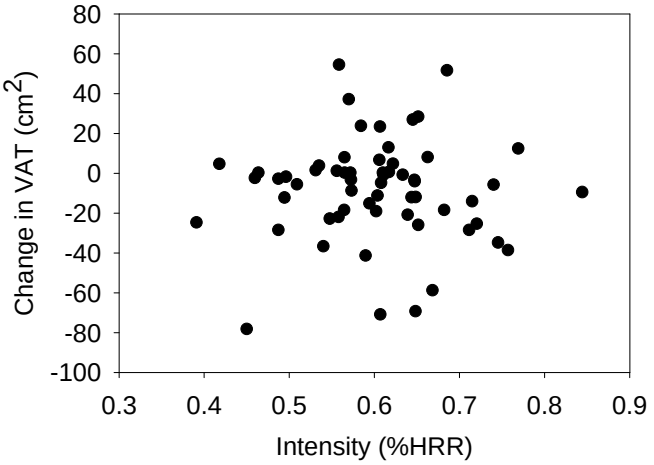
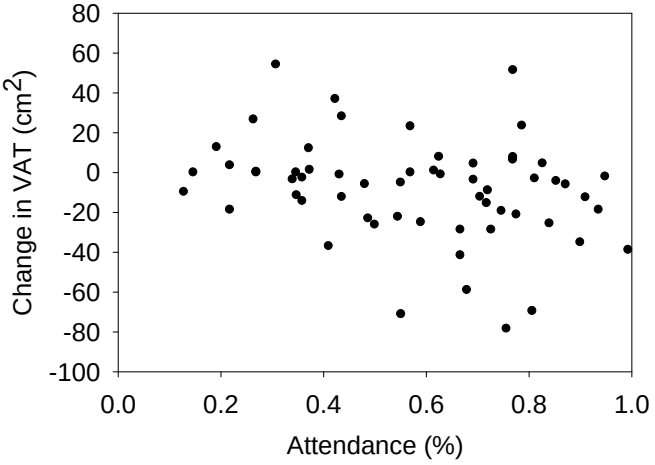


Figure 9b. Association between changes in VAT and intervention attendance (%).



DISCUSSION

Summary of Findings

We examined the effect of high intensity aerobic exercise (>70%HRR) on measures of VAT, WC, and other measures of adiposity in overweight and obese youth aged 13-18 years. We hypothesized that higher intensity exercise would elicit preferential reductions in VAT, as cross-sectional studies in youth have previously demonstrated stronger negative associations between time spent in higher intensity PA (> 6 METS or 6500 cpm) and adiposity, compared to time spent in lower intensity PA (< 3 METS or < 1500 cpm) (Ekelund et al., 2012; Hay et al, 2012; Ruiz et al., 2006). A recent cross-sectional study published by our group further supports the growing body of evidence demonstrating the benefit of higher intensity PA. In a cohort of ~ 600 youth, we demonstrated that time spent in vigorous activity (>6500 cpm) was negatively associated with BMI-Z, and WC, while no associations were found with time spent in low (100-1500 cpm) or moderate intensity activity (1500-6500 cpm) (Hay et al, 2012, See Appendix F). The results of our randomized controlled trial are in contrast with these latest findings, as we found no differences between the high and low intensity training protocols on any measures of adiposity. We also found that randomizing youth to an exercise regime targeting PA intensities <70% of HRR is not associated with greater improvements in fitness than randomizing youth to exercise > 50% of HRR.

Studies in adults have demonstrated that regular PA (3-7days/week of 30-60 minutes duration) leads to significant reductions in VAT independent of changes in diet (Lee et al., 2005; Ross et al., 2004). For example, Ross et al found that obese women randomized to 14 weeks of daily aerobic exercise at 80% of their maximum heart rate

experienced a significant mean reduction in their CT measured VAT, compared to women randomized to the control group (Ross et al., 2004). The exercise combined with weight loss arm experienced a mean reduction of 0.7 ± 0.8 kg in VAT, the exercise alone arm experienced a mean reduction of 0.4 ± 0.7 kg, while no significant change occurred in the control group (Ross et al., 2004). These findings have been replicated in other cohorts of older and middle aged adults living with and without T2DM (Lee et al., 2005). Overall, these data provide convincing evidence that exercise alone is capable of reducing VAT among overweight individuals that were previously sedentary. Our data in overweight youth do not support these findings. Although there existed a tendency towards reductions in VAT with training compared with the controls (-14.3 % vs. +0.1%), group-wise differences were not statistically different (p=0.11).

Reductions in VAT in overweight individuals may occur in a dose response manner, with favorable effects observed with higher volumes and intensities of PA. A randomized controlled trial designed to determine the dose response effects of PA on VAT in adults determined that only a high volumes of PA at vigorous intensities (~20miles per week at 65-80% of peak oxygen consumption) elicited significant reductions in total adiposity (Slentz et al., 2005). In addition, their results demonstrated a trend towards a preferential effect of high volume (~ 20 miles/week) vigorous intensity PA (65-80% of peak fitness) reducing VAT. Both the high and low amounts of vigorous PA significantly reduced VAT in comparison to the control group (See Figure 5). However, only a trend existed towards a greater benefit of the high amount of vigorous PA in comparison with the low-amount of moderate PA (~12miles/week, 40-55% of peak fitness, p=0.078) and the low-amount of vigorous PA (~12miles/week 65-80% of peak

fitness, p=0.087) (See Figure 5, Slentz et al., 2005). The data we present here does not support the findings of Slentz. Studies that achieve higher intensity exercise (i.e. > 70% of HRR) are needed to determine if these effects seen in adults with vigorous intensity training are possible in youth.

Very often, the reductions in VAT observed with exercise training alone are achieved without any changes in body weight (Lee et al., 2005; Ross et al., 2004). The data presented here appear to support these findings. The tendency towards reductions in VAT was observed with minimal changes in body mass in those who exercised. Specifically, in our efficacy analysis those randomized to high intensity and low intensity experienced no change in body mass over the 6 month intervention (-0.22 ± 1.2 kg and +0.1 ± 1.4 kg respectively, p= 0.28). In addition, there was a trend for reductions in VAT in our intervention groups (p= 0.06), overweight youth randomized to the low and high intensity exercise experienced a mean 18.5 cm^2 and 12.6 cm^2 absolute reductions in VAT respectively, while the control group experienced a 1.1 cm^2 increase in VAT. Although these trends appear promising, overall the variability in the response to training was vast (Figure 10, Appendix D & Figure 11, Appendix E) and therefore these differences were not statistically significant.

In contrast to studies in adults, there are very few randomized controlled trials of exercise alone on measures of VAT in youth. In a recent comprehensive review of PA on VAT in youth, 6 aerobic randomized control trials were identified (Kim & Lee, 2009). As there existed heterogeneity in the study groups in terms of age, obesity status, and exercise prescription, the results were inconsistent. While some studies showed improvements in VAT with training, others demonstrated attenuation. Overall, the

authors concluded regular PA is associated with attenuating VAT accumulation in youth (Kim & Lee, 2009). One study of overweight youth 7-11 years found an attenuation of VAT with training a minimum of 3 days/week at 70-75% of maximum heart rate (Owens et al., 1999). Although both the intervention and control groups demonstrated an increase in MRI measured VAT over the 4-month period (+0.5 ± 3.2 % compared with +8.1 ± 1.7 %, p= 0.02) the increase was significantly attenuated in the intervention group. On the contrary, we found a non-significant reduction in VAT in our training group compared with controls (-14.3 ± 9.6 % vs. +0.01 ± 0.4 % respectively). Discrepancy between our results and theirs may be due to differences in age and maturation, as it has been reported that VAT increases with age, and differences in deposition do not emerge until adolescence (Goran, 1998). In addition, our mean VAT values at baseline were consistent with directly measured VAT in a like cohort of obese adolescents (Bacha et al., 2003).

To the best of our knowledge, only one other trial has examined the association between higher intensity PA and VAT in youth. Gutin and colleagues (2002) enrolled overweight youth into one of two aerobic-based exercise arms that differed in exercise intensity (55-60% vs. 75-80% of VO_2 peak) or a lifestyle education only arm. The exercise interventions were delivered over the course of 8 months within their clinical laboratory setting. They were unable to detect differences in the exercise groups, as the study suffered from low rates of adherence and poor follow-up, so the training groups were pooled. In the training group VAT decreased significantly (-42.0 ± 9.3 cm^3, p <0.05), but did not significantly change in the lifestyle only group (-11.0 ± 10 cm^3). In comparison, our study enrolled more participants (N= 94 vs. 80), our average attendance

was higher (57 vs. 54%), and we lost fewer participants to follow up (3 vs. 29%). Although, we successfully overcame some of the previous limitations experienced by Gutin (larger sample size, lower loss to follow-up, and greater attendance), no differences between exercise intensities were detected.

A potential difference leading to the contrast of our results with the cross-sectional data suggesting preferential reductions in VAT with higher intensity PA, may be related to the lack of separation in exercise intensity between the exercise training arms. Similar to the previous randomized controlled trial conducted with overweight youth (Gutin et al., 2002), the intended intensity was not achieved in this current study. Specifically, the high intensity group in our study did not reach the 70% of HRR intended, and on average only reached 66% of their HRR, while the low intensity group reached the peak of the desired intensity at 55% of their HRR. The 11% difference in exercise intensity between the groups may not be sufficient to detect group-wise differences in measures of central adiposity. In addition to a lack of separation in exercise intensity between the study arms, the high inter-individual response to training may also account for the lack of an observed effect.

Inter-individual variation in the response to training is a common finding in exercise-based randomized controlled trials. Ross and colleagues (2009) have demonstrated the changes in VAT in response to exercise are mixed. Therefore regardless of exercise intensity some individuals may experience significantly greater reductions in VAT, despite performing a similar relative dose of exercise. This was mirrored in our own data, with a vast variability in response to exercise evident in both intervention arms (See Appendix D and E). Additionally, the cross-sectional studies may suffer from

confounding bias, as it is possible that youth who participate in more vigorous intensity PA may also consume healthier diets.

Interestingly, we found that attendance to the exercise sessions, but not the exercise intensity achieved during the trial, was negatively associated with the change in VAT observed in the youth randomized to either intervention arm. This association suggests that the frequency of exercise may be more important than the intensity achieved during an exercise intervention. Barbeau and colleagues (2007) found a similar negative association with intervention attendance and measures of adiposity. In their efficacy analysis of girls (aged 8-12), training at least 2 days per week was negatively associated with BMI (β = -0.011, p= 0.02), body fat percentage (β = - 0.04, $p < 0.01$), and a non-significant reduction in VAT (β =- 0.17). Our findings were similar, as our sub-analysis limited to participants attending ~2days/week revealed a greater reduction in VAT than the intention to treat analysis. In addition, these group-wise differences in VAT nearly reached statistical significance (p=0.059). Therefore, increased frequency of exercise training is likely associated with an increased reduction in VAT among overweight youth.

A recent study examining the dose-response effect of increased exercise duration supports this concept (Davis et al, 2012). Davis and colleagues enrolled 222 overweight youth (BMI-Z 2.1 ± 0.4), aged 7-11 to a low dose PA (20 minutes), a high dose PA (40 minutes), or a control group. Youth trained 5 days a week for 10-15 weeks at a heart rate >150 beats/min. Compared to the control group, both exercising at 20 mins/day, and 40mins/day led to significant reductions in VAT (-2.7 cm^3 , p= 0.01 and -3.9 cm^3, p <0.001 respectively). However no significant differences existed between exercise doses

(p=0.78). Taken together, these data suggest that the duration of PA is may not be as important as the frequency of PA in reducing VAT in overweight youth.

Our results found significant increases in FFM in the control and low intensity groups, with no significant change found in the high intensity intervention arm. We expected to find no difference in FFM between groups, as a previous large cross-sectional study in youth found no relationship between objectively measured PA at any intensity and FFM (Moliner-Urdiales et al., 2010), nor did a similar aerobic interventions demonstrate any significant group-wise difference in response to training (Gutin et al., 2002). Males are known to have greater proportion of FFM than females (McArdle, Katch, & Katch, 2007a). Therefore, we believe the results may be spurious, and related to the larger proportion of males randomized to the control and low intensity arms.

Studies in youth have previously demonstrated cardiorespiratory fitness is negatively associated with gold standard measures of VAT (Barbeau et al., 2007; Lee & Arslanian, 2006). While factors such as age, sex, and genetics influence fitness, greater improvements in fitness are generally associated with higher intensity activity (McArdle, Katch et al., 2007b). The separation in exercise intensities between our high and low intensity groups may not have been large enough to elicit differences in peak oxygen uptake in response to training. In our study, exercise training increased peak oxygen uptake similarly in both high and low intensity exercise groups (1.3 ± 0.6 and 1.4 ± 0.6 ml/kg/min respectively) and did not significantly change in the control group. Similar improvements in fitness were demonstrated in a comparable cohort of youth. Specifically, overweight youth who trained $\geq$ 2 days per week for 8 months significantly increased

their fitness compared to the lifestyle education alone group (group-wise difference = 1.7 ± 0.6 ml/kg/min, $p < 0.05$) (Gutin et al., 2002).

Clinical Significance

Although the results of the study may not be statistically significant, the changes observed in the various measures of visceral adiposity may be considered clinically relevant. For example, youth randomized to the high and low intensity groups experienced a mean reduction in their ratio of visceral to subcutaneous fat mass of 0.04 and 0.02 respectively. In a similar cohort of overweight youth, with every 0.05 difference in this ratio, the risk of metabolic syndrome was 3-fold lower (Taksali et al., 2008). In addition, compared to the control group, the mean change in WC observed in youth randomized to high intensity PA was -3.04 cm. Previous observational studies have demonstrated that for every 1 cm difference in WC the odds of the metabolic syndrome decreases by 6% (Janssen et al., 2004). Therefore, we would theoretically observe an 18% reduced risk of the metabolic syndrome for youth that experience a 3 cm decline in WC, compared to those not exercising. Taken together, these data suggest that if the effect sizes observed here remained the same in a larger adequately powered trial, overweight and obese youth may experience beneficial improvements in cardiometabolic risk in response to high intensity exercise training.

Strengths and Limitations

The study had several strengths that need to be mentioned. First, we used a randomized controlled trial design to test our study hypothesis. Second, we used gold

standard tools (MRI) to assess clinically relevant measures of central adiposity in a population of youth at risk for cardiometabolic disease. Third, we retained a greater proportion of our sample with 97% returning for follow up testing, and achieved greater attendance rates than the previous study examining the effect of PA intensity on VAT. However, there were some limitations to our design as well that may limit the external validity of our results. First, the exercise session durations in the trial were relatively short. Previous intervention studies have demonstrated longer durations may be required for normal weight adolescents to achieve reductions in VAT (Barbeau et al., 2007). Barbeau and colleges found 80 minutes of PA, with a minimum of 35 minutes of MVPA 5 days per week, significantly reduced adiposity in normal weight youth (Barbeau et al., 2007). Secondly, as our study was a lifestyle intervention, the youth were not blinded to their intervention, and an attention control program was not given to the control group. Therefore the adolescents may have changed their behaviour outside the intervention that could have influenced the study findings. In addition, seasonal variation has been demonstrated to influence PA in adolescents (Bélanger, Gray-Donald, O'loughlin, Paradis, & Hanley, 2009). However, we have tried to control for this by assessing changes in PA using pedometry. Additionally, our sample was mainly female and Caucasian, therefore further limiting the generalizability of our findings. On the other hand, the uniformity of our sample increases the internal validity of our results. Information on diet was not collected and therefore is a limitation. Studies in youth have linked higher fiber intake (Davis et al., 2009), and eating breakfast to lower levels of visceral adiposity (Alexander et al., 2009). However, previous randomized controlled trials have revealed regular exercise leads to significant decreases in VAT independent of

any changes in diet (Lee et al., 2005; Ross et al., 2004). Finally, the variability in response to the training was significantly greater than we originally anticipated which contributed to the negative findings. Based on the effect size and variation in the response to training observed in this trial, we would require a sample size of 125 overweight youth in each intervention arm to achieve statistical significance for the effect sizes we observed in this trial. Finally, as the adolescents in this trial did not achieve the attendance or intensities of exercise that we had originally proposed, the final dose of exercise achieved was quite similar between the groups and may have limited our ability to detect a different between the intensity arms.

CONCLUSIONS

Exercise training at an intensity of 55-65% of HRR for 35-40 minutes is sufficient to improve cardiorespiratory fitness by ~10% in overweight and obese youth. Training ~2days/week at 55-65% of HRR elicits modest and clinically significant reductions in VAT in overweight and obese youth. Although not statistically significant, the improvements in adiposity may have clinical relevance and therefore, PA that improves fitness and decreases WC and VAT should be recommended in overweight and obese youth.

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APPENDIX A

Ethics Approval

UNIVERSITY OF MANITOBA

BANNATYNE CAMPUS
Research Ethics Boards

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
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APPROVAL FORM

Principal Investigator: Dr. J. McGavock
Sponsor: Manitoba Childrens Hospital Foundation And Sick Kids Foundation

Protocol Reference Number: B2006:091
Date of Approval: March 19, 2007

Protocol Title: **"The Role of Fitness and Muscle Lipid Content in the Development of Insulin Resistance in Adolescents with Type 2 Diabetes"**

The following is/are approved for use:

- **Protocol Version 3 dated March 16, 2007**
- **Research Participant Information and Consent Form-Cardiorespiratory fitness, steatosis and insulin resistance in overweight adolescents with/without type 2 diabetes-Version 4 dated March 16, 2007**
- **Research Participant Information and Consent Form-Cardiorespiratory fitness, steatosis and insulin resistance in adolescents with type 2 diabetes – Exercise Training Intervention-Version 4 dated March 16, 2007**
- **Poster submitted March 15, 2007**

The above was approved by Dr. Nicholas Anthonisen, Chair, Biomedical Research Board, Bannatyne Campus, University of Manitoba on behalf of the committee as per your letter dated March 15, 2007. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations.*

A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval should be sought from the relevant institution, if required.

Sincerely yours,

[redacted]

Nicholas Anthonisen, MD, Ph.D
Chair,
Biomedical Research Ethics Board
Bannatyne Campus

Please quote the above protocol reference number on all correspondence.
Inquiries should be directed to the REB Secretary
Telephone: (204) 789-3255/ **Fax:** (204) 789-3414

APPENDIX B

Consent Form

Study Date:_____

Participant #: _____

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: "Cardiorespiratory fitness, steatosis and insulin resistance in adolescents at risk for and diagnosed with T2DM"
- Physical Activity Intervention.

PROTOCOL #: **B2006:091**

SPONSOR: **Manitoba Children's Hospital Foundation**

INVESTIGATORS:

Jonathan McGavock, PhD	Pediatrics	480-1359
Dean Kriellaars, PhD	Rehab. Medicine	787-3505
Heather Dean, MD	Pediatrics	787-7435
Elizabeth Sellers, MD	Pediatrics	787-7435
Lawrence Ryner, PhD	Radiology	984-7693
Phillip Gardiner, PhD	Physiology	474-7087

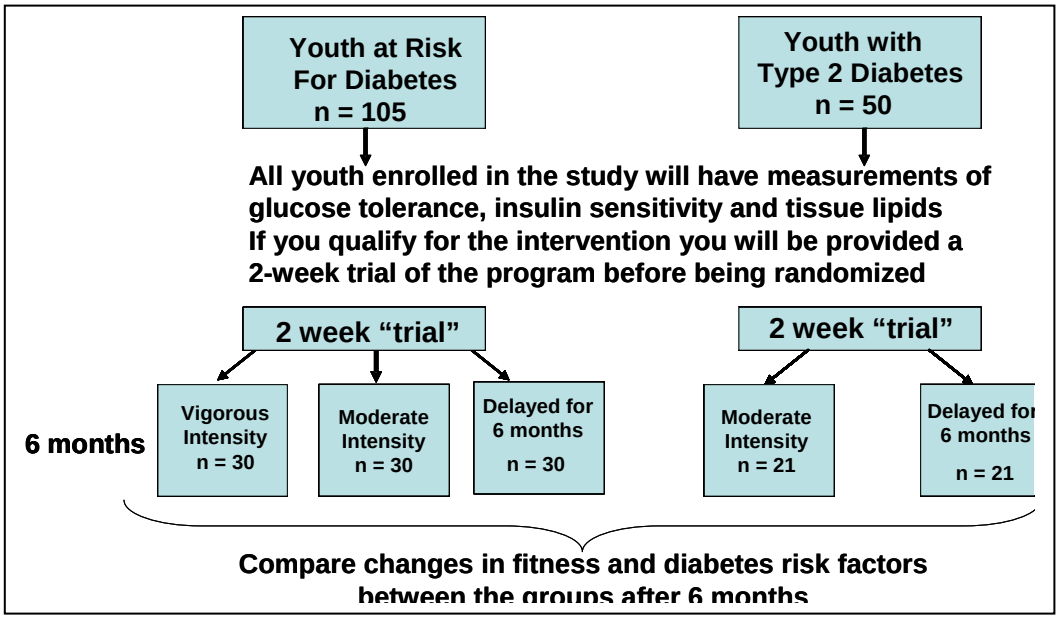
You are being asked to participate in a research study involving several visits to determine if increased physical activity changes certain risk factors for T2DM. Before you agree to participate we will also require that your parent or guardian consent to your participation. Please take your time to review this consent form with your parent or guardian and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your parents, friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study

Physical activity is an important lifestyle factor in the treatment and prevention of T2DM. Studies in adults show that increased activity reduces the risk for diabetes and improves the body's ability to manage blood sugar. Little information is available describing the dose of exercise on diabetes risk or blood sugar control in adolescents. If you agree to participate in this study we will do two tests for diabetes risk, a test of exercise ability and an MRI of your muscle and liver before and after a 6 month physical activity intervention. MRI is a large magnet that we use to take pictures of muscles and organs inside your body. It is not harmful to you and will not require any needles. The MRI of the muscle is a new method to

measure fat inside muscle and the liver without using a needle and may provide information about your risk for diabetes.

Am I Eligible to Participate? We plan to study approximately 50 youth with T2DM and 90 youth without diabetes but who are considered at risk for T2DM. After the preliminary measurements, all youth will be randomly assigned to one of three physical activity intervention groups: (1) Delayed start (control); (2) vigorous intensity or (3) moderate intensity.



The study is purely voluntary and if you decide not to participate or withdraw, your normal medical care will not be affected in any way.

For all groups, all subjects who participate in this research study must be between 13 and 18 yrs of age and must pass a medical screen by his/her physician. If any of the following applies to you, you may not participate in the study:

1. You have metal objects inside your body. MRI may be dangerous for anyone with metal implants or metal objects inside their body.
2. You, in the opinion of the screening physician or investigators, have a medical condition that could be made worse by any stress associated with participation in a research protocol. These conditions include heart and circulatory problems, seizure disorders, anxiety disorders, and mental disorders.
3. You are unable to exercise on a daily basis.
4. You have claustrophobia.
5. You are or may be pregnant.
6. You weigh more than 350 pounds.

Study procedures

Schedule of Study Visits

Visit	Purpose	Duration	Location
#1	Baseline Assessment of Diabetes risk (OGTT) Exercise Tolerance, and muscle mass (DXA).	3 hours (week day)	Manitoba Institute of Child Health 5th Floor John Buhler Research Center 715 McDermot Ave. Phone: 480-1359 or 789-3591 And the National Research Council building, 435 Ellice Avenue
#2	Arterial stiffness Insulin sensitivity, Sleep Habits Questionnaire, and Food Frequency Questionnaire	4 hours	
#3	MRI imaging of muscle and liver	1 hour	
	Physical activity intervention started immediately or delayed for six months.	3 one-hour visits/week for a period of 6 monthsths	
#4	Follow-up assessment of exercise tolerance, and muscle mass.	3 hours (week day)	
#5	Arterial stiffness and Insulin sensitivity	4 hours	
#6	Follow-up MRI imaging of muscle and liver	1 hour	
#7	Long-term Follow-up – 12-36 months after completing the intervention	1 hour	

The primary goal of this study is to see if physical activity changes the levels of fat inside the muscles and liver of youth at risk for or diagnosed with T2DM. We will also measure insulin sensitivity, which is a term we use to describe how well your body handles sugar after a meal and it gives us information about your risk for diabetes. We can test insulin sensitivity using a glucose test described below. If you agree to participate you will be placed into one of three groups: (1) vigorous physical activity; (2) moderate intensity physical activity or (3) delayed Physical activity of your choice after 6 months of regular activities of daily living (control). The choice of study group is not up to you or your study doctor, but will be determined by chance (i.e. drawing straws). Regardless of when you start, you will receive a structured, supervised exercise program tailored to your needs.

What will I have to do if I participate?

Visit #1 – Exercise test / Diabetes Screening visit.

You will arrive at the John Buhler Research Centre at a time scheduled by the research coordinator which is typically between 7:30 and 9:00am. You cannot eat anything before arriving to the University and we ask that you not eat any food after 10 pm the night before. Someone will meet you at the front doors of the centre and escort you up to the lab. We will explain the study in detail and ask any questions you may have. After you and

your parent/guardian have signed the consent form a nurse will insert a catheter (a needle and plastic tube) into a vein in your arm. You will have the option of using a special cream (called EMLA) used to numb the area where we will insert the needle. A small plastic tube will remain in your arm and be used to sample blood in small amounts during the test. We will use these samples to measure blood sugar levels, cholesterol, insulin, and the activity of energy producing cells (known as mitochondria) work in your system. After collecting a few samples you will consume a sugar drink. After finishing the drink, we will collect blood samples at 15, 30, 60, 90 and 120 minutes, from the tube that will remain in your arm. After the test we will provide you with a light lunch then escort you to the exercise lab, where you will change into clothes appropriate for exercising.

Once changed, we will escort you to a quiet room where we will perform a scan of your body that measures the amount of muscle, fat and bone inside your body. This test takes approximately 10 minutes to perform and all you have to do is lie still while a scan moves across your body. The machine takes an x-ray (picture) of your body that we can use to measure the size of your muscles. The amount of x-ray used in this test amounts to less than a regular chest x-ray and is similar to the amount of radiation a person is exposed to in the environment on a daily basis. Some researchers equate this to one commercial flight across Canada or living for one day in the city. **This test is completely safe and no needles are involved.**

The exercise test will be performed on a stationary bicycle. We will measure your heart rate and blood pressure throughout the test. Heart rate is measured with a small black band around your chest and blood pressure is measured with a cuff on your arm. We will also measure the air you exhale (breath out) during the exercise. After you start pedaling, we will increase the resistance on the pedals every two minutes. As the exercise becomes more difficult we will encourage you to continue until you are no longer able to pedal. When you can no longer keep pedaling we will stop the exercise test. You will be the one who decides when to stop exercising, the study doctors will only encourage you to continue as long as you can. The amount of oxygen in your breath at the end of the test will give us an estimate of your current fitness level. After completing the exercise test we will monitor you for a period of 20 minutes and you will be free to go.

Visit #2 - You will arrive at the John Buhler Research Centre between 7 and 7:30 am. You cannot eat anything before arriving to the University and we ask that you not eat any food after 10 pm the night before. We will explain the study in detail and answer any questions you may have. A trained nurse will insert a catheter into a vein in your arm and another into your arm. One small tube will be used for collecting blood and the other will be used to inject a small amount of sugar into your body. We will start by taking one blood sample -5 min) before injecting the sugar and at 8:00

am we will inject a sugar solution into one of the small tubes. The amount of sugar is very small and contains the same number of calories that are in an apple. This test will provide information about how the various systems in your body react to sugar, which will help us understand your risk for diabetes. After injecting glucose we will take small blood samples at 2,3,4,5,6,8,10,14 and 19 min than we will inject a very small amount of insulin to help return your blood sugar to normal levels (the amount injected will be a small fraction of the amount of insulin a child with diabetes would inject to control their blood sugar). After the injection of insulin we will take blood samples at 22,25,26,30,40,50,70,100, 140 and 180 min. The amount of blood removed for each sample is no bigger than a teaspoon and total amount of blood we take will be less than half of the size of a small (250 mL) juice box.

During the blood sampling one of the research assistants will make repeated measurements of the pressure in a blood vessel in your wrist and your neck. This test does not involve a needle. Instead we will place a small metal device the size of a pen against your skin. This device will estimate the pressure in your blood vessel and provide us with information about the stiffness of your blood vessels. You will not experience any pain or discomfort during the measurements. We will make the measurements every 15 minutes during the test. After this test we will provide a light breakfast and you will change into clothes appropriate for an exercise test. You will also be asked to fill out a sleep habits survey during this visit. The survey consists of questions regarding your day to day activities, your usual sleep and wake times, and other general health related questions.

Visit #3 – Will likely take place on a Saturday as this is the only time we will have access to the MRI machine at the National Research Council building. You do not have to fast overnight for this visit. A member of our staff will meet you inside the front door of the National Research Council building. The MRI will take approximately 1 hour and all you have to do is lie still and listen to music. ***This test is completely non-invasive (i.e. there will be no needles involved).*** At your appointment for the MR scan, an investigator will go through the Screening Form with you, give you information about the study and show you the MRI system (see the picture).

You should make sure that all your questions are answered and you and your parent/guardian agree to participate in the study before signing the consent form. Before you enter the magnet room, we will ask you to remove all metal objects, such as keys, coins, since they could be attracted to the MRI scanner with great force. If a metal object hit anyone in the way, it could cause serious injury. You will be asked to change into clothing which does not contain metal. You have a choice of wearing your own clothing, if it is metal-free (e.g., jogging suit) or the hospital gowns that we can provide.

For the first scan, you will be positioned comfortably on your back for the scan of your lower leg and for the second scan you will be positioned on your stomach for a scan of your liver. You will be provided with soft earplugs to reduce the noise from the MRI scanner (the sound it produces is a loud knocking noise). For the scan of your lower leg, a special receiver will be placed just below your knee and padded to ensure that your leg does not move while we image it. You will then be slid into the large, tunnel-shaped scanner until your leg or stomach is at the centre of the magnet. The scanner at the National Research Council has a field-strength of 3.0T (similar to most hospital MRI scanners). The tunnel is 60 cm (about 2 feet) across and is open at both ends. During the scan, the MR operator will talk with you regularly through a two-way intercom to let you know what to do. At times you will be asked to remain very still so that the images will be sharp. After the scan has been completed and you have left the magnet room, we will ask you to fill out a questionnaire about how the study went for you.

These two visits will be repeated at the end of a six month intervention period to determine if there were any changes in these variables during that time frame.

Physical Activity Intervention – After the first two visits all youth will receive two weeks of structured physical activity provided by the study doctors. Members of the study team will supervise exercise visits on treadmills and stationary bicycles located at one of the four YMCA facilities three days per week. You are required to attend a minimum of four visits over the course of this “run-in” phase to be considered eligible for the study. After the two week phase you will be placed into one of three groups: (1) vigorous intensity; (2) moderate intensity or (3) delayed start (control). The choice of when you start is “random”, meaning that we have a computer decide and neither you or your doctor can influence the decision. The order is determined by a statistician at the University of Manitoba to ensure fairness to all participants. Children in the vigorous or moderate intensity groups will begin exercise immediately, while those in the delayed phase will begin exercise six months after the run-in phase (they will be considered as “controls”). Regardless of the phase of the study you enter, you will be asked to return for follow-up measurements described above six months after the initial visit.

The physical activity intervention is a 3 days/week program that involves walking on a treadmill (or outside if weather permits) and cycling on a stationary bicycle. Three days of the week, you will come to one of the four YMCA locations in Winnipeg to perform the exercise under the supervision of a trained professional. We will provide you with a heart rate monitor to wear to record each of the home-based activity sessions. The daily exercise sessions will initially last 30 minutes and progressively increase to 60 minutes. The intensity will also increase gradually over the

six-month period. For youth in the vigorous intensity group, they will perform 30 minutes of activity with brief increases in the speed or hill on the treadmill which will increase your heart rate. The youth in the moderate intensity group will not get their heart rate up as high but will exercise a little longer to burn the same number of calories. Adolescents in the delayed-intervention group will receive six months of supervised exercise training at the YMCA which will be supervised by the research team and you will get to choose the regime you want. Follow-up measurements of your risk for diabetes will be available at six months after starting the training regime to determine the effectiveness of the activity on your risk for T2DM.

Participation in the study will be for a period of approximately 7 months. We will also ask you to return 12-36 months following the end of the trial to see how you are doing. We would like to repeat some of the measurements that do not involve a needle, including the X-Ray of your body, the physical activity measurements, your waist circumference and the MRI of your liver.

The researcher may decide to take you off this study if the funding for the study is stopped, if there is a change in your medical condition that would prevent you from exercising or requiring you to receive additional therapy that would exclude you from the study. You *can withdraw from the study at any time. However, if you decide to stop participating, we encourage you to talk to the study staff first.*

Risks and Discomforts

Blood samples: Some people experience slight discomfort, bleeding and/or bruising during collection of blood samples. Sometimes people feel dizzy or even faint occasionally. An infection in your arm can develop if the testing site is not kept clean. Medical personnel will insert a catheter (needle and tube) into the forearm vein one time and the plastic tube will remain in your arm for the remaining blood samples (total 6-8 tablespoons). Every effort will be made to reduce these risks. We will have trained nurses who work with children everyday and are very comfortable with inserting needles.

Arterial Stiffness: Arterial stiffness is measured with a device called a "tonometer". This is a small piece of metal at the end of a device shaped like a pencil. A researcher will place the metal against your skin on the top of a blood vessel. We will make measurements on a vessel in your wrist and a vessel in your neck. There are no risks associated with this procedure.

Cardiopulmonary Exercise Testing and Training: There exists the possibility of certain changes occurring during the exercise test. Serious complications of exercise testing occur in approximately 1 in 10,000 tests in adults. These may include abnormal blood pressure, fainting, disorders of heart rate and, in rare instances heart attack, stroke and death. Exercise may also cause slight injury to muscles and joints that will go away within three days after the test. Every effort will be made to minimize these risks by reviewing information about your health and fitness before the test and by closely monitoring how your body responds to the exercise. We will reduce these risks by closely monitoring your condition throughout the exercise test and training. If you experience an abnormal response, to exercise, the session will be stopped. Emergency equipment and trained personnel are available to deal with any situations that may arise.

Dual Energy X-ray Absorptiometry (DXA): The physical risks associated with the scan of your whole body are considered to be low. The device uses an x-ray source to measure bone density. However, the amount of radiation is much less than a regular chest x-ray and equivalent to the radiation accumulated during one normal day.

Potential Risks to your Insurance: There is a possibility that a diagnosis of T2DM, high cholesterol or blood pressure may have a negative impact on the cost of medical insurance for you in the future. This risk would be the same if you were diagnosed at your doctors office or within a hospital setting.

Magnetic resonance imaging and spectroscopy: You may experience some discomfort as you will be asked to remain relatively motionless for periods of up to 45 minutes. It is not always possible to predict whether you will have these problems or not. You may experience nervousness from confinement in a tight space (claustrophobia) and if you do become anxious, you can stop the procedure at any time using a panic button. It will help that your head will remain outside the scanner during muscle imaging and lying on your back during liver imaging. There are no known side effects from exposure to magnetic fields but if you have any metal clips or plates or any devices listed below in your body, you should tell the investigator about it as you will not be eligible to take part in this phase of the study. Also, MRI may not be appropriate if you have permanent eyeliner or eyebrows or if you are pregnant.

List of implanted body devices and metallic parts inappropriate for magnetic resonance experiments:-

- Heart pacemaker,
- Heart valve replacement,

• Aortic clips,
• Metal fragments in body
• Brain clips or pieces of metal used in brain surgery
• Pieces of metal in the body resulting from work as a sheet-metal worker or welder
• Clips placed in an internal organ
• Prosthetic devices, such as middle ear, eye, joint, or penile implants
• Joint replacement.
• Hearing aid that cannot be removed
• Insulin pump
• Intrauterine device (IUD)
• Shunts or stents
• Metal mesh or coil implants
• Metal plate, pin, screws, or wires, or any other metal implants.

RISKS TO AN EMBRYO, FETUS, OR BREAST-FED INFANT: A female who is pregnant or is breast-feeding an infant should not participate in this research. It is not known whether MRI&S may harm an embryo or fetus or an infant who is breast-feeding. It is also not known whether MRI&S may lead to birth defects.

Pregnancy test: A pregnancy test will be performed for any female who is able to have children and wishes to participate in this research. A pregnancy test may be repeated later. A study doctor will ask for the date when a female's last monthly period started.

Pregnancy during participation in this research: If you are able to have children, and you suspect pregnancy during this research, you must tell your study doctor immediately. Your participation in the research will stop if you become pregnant.

Unforeseen Risks

A previously unknown side effect may occur. It is not possible to estimate the chances of such occurrences or their severity.

How you can help reduce risks:

During your participation in this study, research personnel will watch closely to determine whether there are complications that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the doctors' recommendations.
- Contact us if your telephone number changes.
- Tell the research personnel if any other medical condition develops or if you begin new medication.
- Have your parent or guardian inform your regular doctor about your participation in this study.

- Talk to a family member or a friend about your participation in this research.
- Carry information about the research in your purse or wallet.

What to do if you have any problems: If you have any problems, such as unusual symptoms or pain, at any time during your participation in the research, your study doctor can recommend treatment. Please report the problem to your study doctor promptly. Telephone numbers where he/she may be reached are listed on the first page of this consent form.

POSSIBLE BENEFITS

Benefit to you: Your study doctor cannot guarantee that you will directly benefit from participation in this research. You will receive information about your risk for diabetes that would not routinely be measured during a regular visit to the doctor. You will also receive information regarding your fitness and recommendations regarding physical activity if you are interested. The physical activity intervention will be provided at no cost to you and may help lower your risk for T2DM. You will be provided with access to an exercise facility and learn important life skills regarding the benefits of daily physical activity. You will also receive your test results so that your parent/guardian can give them to your primary care physician**.**

Benefit to youth who are at risk for or currently have T2DM: There are a growing number of youth who are considered at risk for T2DM and doctors need more information regarding risk factors that will help them prevent the disease. The information gathered in this study will help provide information regarding new risk factors that could be used to identify youth who may be at an increased risk for progressing to T2DM. The information gathered here will provide physicians with important information regarding the benefit of physical activity in the treatment and prevention of T2DM. The findings may help reduce the number of youth diagnosed with diabetes in Canada.

Costs All the procedures, which will be performed as part of this study, are provided at no cost to you or your parent/guardian. None of the study doctors, the University or the Manitoba Institute of Child health are receiving professional fees or personal financial support to conduct this study.

Payment for participation

You will be given $25.00 per completed testing visit to a maximum of $150.00 upon termination of your participation in this research study to cover costs associated with participating such as parking fees. You will not be compensated for the physical activity intervention visits. You will receive payment upon completion of the entire study. If you decide not to participate in the study after visit #1 we will process the payment for Visit #1 after confirming with you and your parent/guardian that you would like to withdraw from the investigation.

Confidentiality

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. All study documents will refer to you with a number and your initials to protect your privacy

Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The study doctors will need to have access to your medical records to keep track of any events that may occur during the study. This is a very common practice at the University and is done for the protection of youth participating in research.

Normally, only people directly involved with the research procedure are allowed in the study area. Because the study takes place at the Health Sciences Center which is a clinical facility, people not involved in the research study may occasionally require access. All staff at the Health Sciences Centre are required to keep health information confidential, in accordance with the Health Information Act of Manitoba.

All data obtained during your MRI scan will be stored with an alpha-numerical code instead of your name. Only your file, which is kept in Dr. McGavock's office in a locked filing cabinet, will have information which relates your name to the code. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:
Organizations that may inspect and / or copy your research results for quality assurance and data analysis, including; the SickKids Foundation and the Canadian Diabetes Association who may help fund the study. In addition, the National Research Council Research Ethics Board and The

University of Manitoba Health/Biomedical Research Ethics Board have the right to inspect / copy the data collected.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary and also depends upon your willingness to provide informed assent to participate. You may refuse to participate or you may withdraw from the study at any time. Your decision not to participate will not affect your care at this centre. If the study staff feel that it is in your best interest to withdraw from the study, we will remove you from the study without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Medical Care for Injury Related to the Study

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you.

What else should I know?

Although the MRI for this study is not a diagnostic scan and any images obtained are for research purposes only, it is possible that the MR scan may disclose an unknown abnormality. Should this occur, you have a choice of whether you would like your doctor to be informed or not. The sooner your doctor knows, the earlier a proper follow-up may begin. If you choose to have your physician informed, a medical imaging specialist will review the images and we would send a report to your physician. On the other hand, because this research is not a diagnostic examination, you may prefer not to have any problems investigated. You have every right not to let your doctor know should an abnormality be detected in your scan.

In summary, if we observe a possible abnormality during our routine processing of the research images and you have indicated on the enclosed consent form that you wish your doctor to be informed, we will then have a medical imaging specialist review the images. If the specialist agrees that further follow-up is advisable, we will contact your doctor, who in turn will contact you for follow-up with the necessary proper diagnostic tests. If you have indicated that you don't want your doctor to be informed, we will not have the image reviewed by a medical imaging specialist and neither you nor your doctor will be contacted regarding a possible abnormality.

Please contact us if you would like any more information about the study. Please let us know if you would like copies of any published scientific reports about the research project.

Questions

You are free to ask any questions that you may have about this investigation and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study doctor and the study staff:

Name	**Phone**
Jonathan McGavock, PhD	480-1359
Heather Dean, MD	787-7435
Elizabeth Sellers, MD	787-7435
Dean Kriellaars, PhD	787-3505
Phillip Gardiner, PhD	474-7087
Lawrence Ryner, PhD	984-7693

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

In case of a possible abnormality showing up on the MR scan,
☐ I wish my doctor, Dr. _____, be informed.
☐ I do not wish my doctor be informed.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Jonathan McGavock and or his/her study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statements or implied statements. Any relationship (such as employer, supervisor or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of any of my health records that relate to this study by The University of Manitoba Research Ethics Board, for quality assurance purposes.

By signing this consent form, I have not waived any of my legal rights as a participant in a research study.

I agree to be contacted for future follow-up in relation to this study,
Yes _ No _

Participant signature_____ Date _____

(day/month/year)

Participant printed name: _____

Parent/legal guardian's signature_____Date _____

(day/month/year)

Parent/legal guardian's printed name: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____Date _____

(day/month/year)

Signature: _____

“Role in the study: _____

Relationship (if any) to study team members:_____

APPENDIX C

POWER Contract

Welcome to the POWER Trial! This form explains what will be expected of you during the next six months. You will be asked to sign this form to indicate that you understand and agree to the guidelines and expectations of the POWER Trial.

Run-in Phase:

To be eligible for the full POWER Trial, you need to complete 4 supervised training sessions within a 2 week period. Your run-in phase starts on: _____, and must be completed by: _____.

Once you successfully complete your run-in phase, you will be randomized to either:

1. low intensity exercise
2. high intensity exercise
3. control group

Every one who completes the run-in phase receives a POWER Trial hoodie, a logbook with study information and invitations to holiday events. You will also be granted access to our website www.thepowertrial.com .

If you are **randomized to control**, continue to participate in your usual physical activities. Study staff will contact you to invite you to fun events the study puts on. After 6 months you have the option of joining the exercise group.

If you are **randomized to low or high intensity exercise group**, the study staff will purchase your 6 month YMCA pass, and together you will establish your training schedule (days / location) for the next 6 months. You will be provided with a heart rate monitor to track your exercise during the trial. You will be booked for one additional session in the lab to exercise on the treadmill with the metabolic cart for an "energy expenditure test". At this time you will also agree on a 6 month training goal.

In the exercise groups you are expected to:

1. Attend the YMCA 3x/week
2. Bring your heart rate monitor and logbook to each workout session.
3. Wear appropriate clothes and footwear to exercise in (indoor/outdoor as appropriate).
4. Contact study staff in advance if you will miss a scheduled exercise session.
5. Record your exercise data in your logbook.

You will be shown how to use your HR monitor and logbook to record your exercise.

Missed sessions:

It is very important both for achieving your goals and for the outcome of this study that you attend all scheduled workouts.

If you miss one exercise session you will be contacted by a trainer to arrange a good time to make up the session.

If you miss several sessions, we will discuss attendance strategies with you and your parents in person or over the phone.
If you still are not attending sessions regularly, we will have a meeting with you, your family and study staff to develop a plan to get your workouts back on track.

As a parent/guardian of a teen in the POWER Trial, you are expected to:

1. Support your child's participation in the study by providing transportation, a bus schedule, or simply encouraging your child to attend all the training sessions
2. Communicate with study staff if your child is going to miss a session PRIOR to the session date
3. Be available for regular contact from your child's trainer for progress updates

<u>Statement of Agreement</u>

We have read the guidelines and expectations and agree to the conditions as listed. We have had the opportunity to discuss the POWER Trial with study staff.

Signatures:

_____ _____ _____

(participant signature) **(participant name printed)** **(date)**

_____ _____ _____

(parent/guardian signature) **(parent/guardian printed)** **(date)**

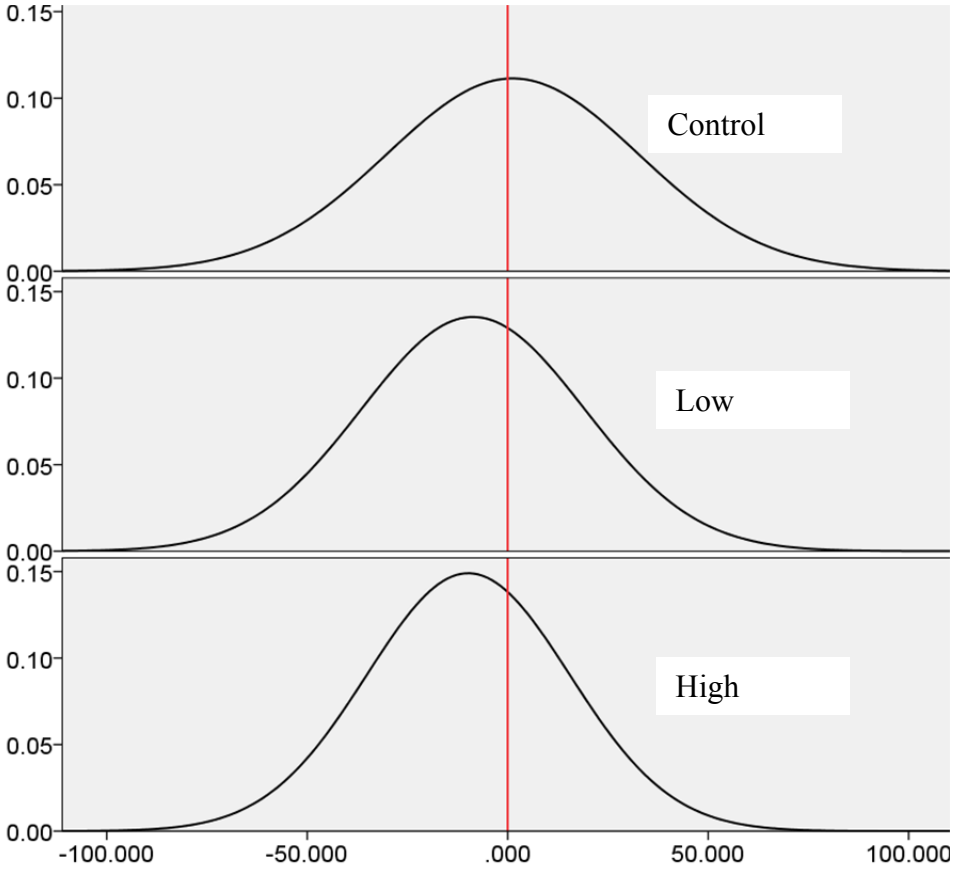
_____ _____ _____

(witness signature) **(witness name printed)** **(date)**

APPENDIX D

Normal Distribution Curves for Changes in VAT

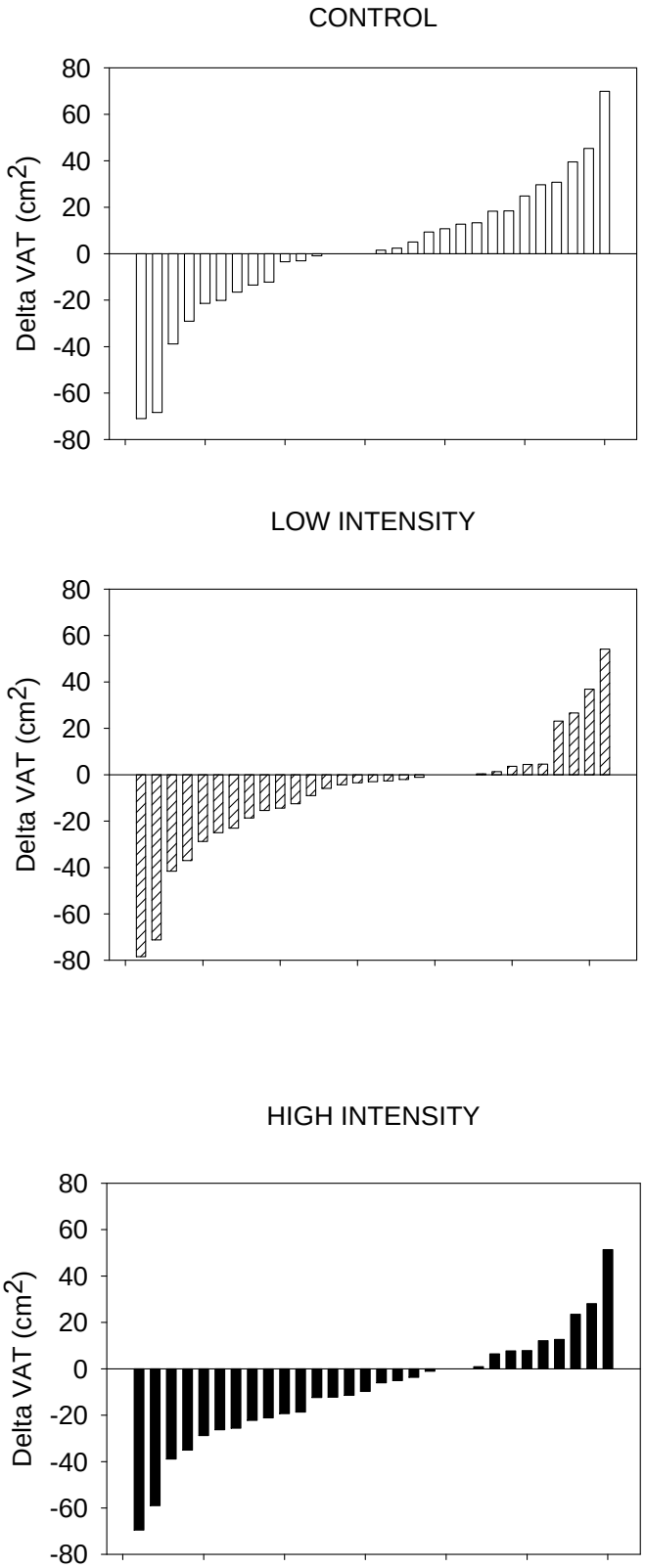
Figure 10. Normal distribution curves: changes in VAT by group.



APPENDIX E

Individual Responses to the 6 month Intervention by Group

Figure 11. Individual responses to the 6 month intervention by group.



APPENDIX F

Physical Activity Intensity and Cardiometabolic Risk in Youth

ARTICLE

Physical Activity Intensity and Cardiometabolic Risk in Youth

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Objective: To determine the association between physical activity (PA) intensities and cardiometabolic risk factors in youth.

Design: Cross-sectional study using data from the 2008 Healthy Hearts Prospective Cohort Study of Physical Activity and Cardiometabolic Health in Youth.

Setting: Rural and urban communities in Alberta, Canada.

Participants: A convenience sample of 605 youth aged 9 to 17 years. Youth were on average aged 12.1 years, 248 were boys (41%), and 157 were overweight or obese (26%).

Main Exposure: Actical accelerometer–measured PA intensity.

Main Outcomes Measures: The primary outcome was body mass index (calculated as weight in kilograms divided by height in meters squared) *z* score. Secondary outcome measures included waist circumference, systolic blood pressure, and cardiorespiratory fitness (maximal oxygen consumption [$\dot{V}O_{2max}$]).

Results: Body mass index *z* score, waist circumference, and systolic blood pressure decreased and $\dot{V}O_{2max}$ increased in a dose-response manner across tertiles of vigorous PA (adjusted $P < .001$). No significant differences in cardiometabolic risk factors were seen across tertiles of moderate or light PA in multivariable analyses. Achieving more than 7 minutes of vigorous PA daily was associated with a reduced adjusted odds ratio of overweight status (0.56; 95% CI, 0.33-0.95) and elevated systolic blood pressure (0.36; 95% CI, 0.16-0.79). The odds of overweight status and elevated blood pressure decreased with increasing time and intensity of PA.

Conclusions: Only vigorous PA was consistently associated with lower levels of waist circumference, body mass index *z* score, systolic blood pressure, and increased cardiorespiratory fitness in youth. These findings underscore the importance of vigorous PA in guidelines for children and adolescents.

Arch Pediatr Adolesc Med. 2012;166(11):1022-1029. Published online September 10, 2012. doi:10.1001/archpediatrics.2012.1028

IT IS WIDELY ACCEPTED THAT PHYSICAL activity (PA) confers significant health benefits among children and adolescents.[1] Observational and experimental studies have consistently demonstrated that youth who engage in regular moderate to vigorous (MV) PA display lower visceral fat mass,[2,3] lower systolic blood pressure (SBP),[4,5] enhanced vascular function,[6] lower serum triglycerides,[5] and heightened insulin sensitivity.[7,8] Based in large part on these observations, current PA guidelines from various expert groups call for a minimum of 60 minutes of MVPA daily to achieve optimal growth and reduce cardiometabolic risk factors in youth.[9,10] Unfortunately, the data informing these guidelines were based largely on observational studies that relied on self-reported PA, a measure limited because of subjectivity and recall bias.[9]

Recent studies using objective measurements suggest that the association between PA and cardiometabolic risk factors in youth may be more complex than previously believed.[11,12] Population-based studies using accelerometer-derived measures of PA demonstrate that cardiometabolic risk factors are more closely associated with vigorous PA than lower-intensity PA.[2,11,12] Furthermore, sedentary time has become widely recognized as an important determinant of cardiometabolic risk factors in youth, independent of PA levels.[11,13] However, these studies had several limitations that restricted their interpretation into policy. First, past studies and subsequent analyses failed to control for key confounding variables, in particular dietary intake and sedentary time.[2] Second, few investigations distinguished between moderate vs

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vigorous PA on study end points.[2,4,5] Finally, most studies failed to explore the association between light PA and health outcomes, despite the observation that youth spend most of their time in this form of activity.[14]

In the context of this cross-sectional school-based study, we hypothesized that a negative association would exist between vigorous PA and cardiometabolic risk factors. We also hypothesized that the strength of the association between PA and cardiometabolic risk would be attenuated for light-intensity and moderate-intensity PA. Finally, we hypothesized that the prevalence of overweight status and elevated SBP would be lower in students who accumulated relatively high levels of vigorous PA compared with students who accumulated low levels of vigorous PA.

METHODS

STUDY DESIGN AND POPULATION

This is a cross-sectional analysis of data collected in the first year of the Healthy Hearts Prospective Cohort Study of Physical Activity and Cardiometabolic Health in Youth.[15] The procedures were approved by the biomedical research ethics board at the University of Alberta. Among the 2189 students who participated in a survey conducted in 2008,[15] we recruited a convenience sample of 841 students in grades 5 through 11 (aged 9-17 years) within 8 middle or high schools in the Black Gold School District to wear an accelerometer. Six hundred five of these students returned the accelerometer with sufficient wear time and were included in the study. The school district serves approximately 8900 students within 27 schools from 5 rural and 2 urban communities.

Every school offered a classroom and gymnasium space each spring semester for a 3-day data collection period. All data were collected within the school environment and within a defined window of time that spanned 2 weeks.

MAIN OUTCOME MEASURES

Primary Outcome Measure

The primary outcome measure of interest was body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) *z* score (BMI-*z*). Body mass index was calculated from height and weight obtained with children in their physical education clothing (T-shirt and shorts) and without shoes. Body weight was measured to the nearest 0.1 kg in duplicate using a digital scale that was calibrated each morning (Seca 882 Digital Floor Scale). Height was measured in duplicate to the nearest 0.1 cm using a medical standard stadiometer (Seca Portable Model 214). Absolute BMI values were converted to a *z* score for age in months and sex using Epi Info software.[16] Participants were categorized as healthy weight, overweight, or obese according to the International Obesity Task Force guidelines.[17]

Secondary Outcome Measures

Waist circumference was measured in duplicate at the level of the iliac crest to the nearest 0.5 cm according to guidelines established by McCarthy et al.[18] Blood pressure was assessed in triplicate according to the American Heart Association guidelines for children and adolescents.[19,20] In brief, students laid quietly on a portable bed for 5 minutes prior to measurements, then sat quietly in an appropriately sized chair with feet flat on the ground and arm at the level of the heart. High normal SBP was classified as greater than the 90th percentile for age, sex, and height.[21]

Cardiorespiratory fitness was determined using the Leger shuttle run,[15,22] a field test that was validated in large international samples of children across a range of BMI values.[23] The protocol began with each student walking briskly back and forth over a 20-m distance. The pace of the run increased by 0.5 km/h each minute until the student was unable to run at the required pace. The final stage achieved was used to calculate a rate of maximal oxygen consumption ($\dot{V}O_{2max}$) using a validated regression equation.[22]

EXPOSURES OF INTEREST

Physical activity was measured objectively using waist-mounted accelerometers during a period of 7 days (Actical, serials B101270-B101375; Respironics). Raw PA counts were acquired in 15-second epochs and converted into minutes of PA using a specially designed software program (KineSoft).[14,24] As have others, we classified raw counts per minute (cpm) into sedentary time (<100 cpm) and light (100-1499 cpm), moderate (1500-6499 cpm), and vigorous (>6500 cpm) PA intensities.[25,26] Sedentary time translated to standing or reclining; light activity to walking less than 3.2 km/h; moderate activity to walking more than 3.2 km/h, and jogging is representative of vigorous activity.[24,25,27] Sequences of consecutive zero counts 60 minutes or longer were deemed nonwear and excluded from analyses. Inclusion criteria for estimating PA in the final analyses were a minimum of 3 days of wear, with at least 480 registered minutes (8 hours) per day. Sensitivity analyses were conducted using a cohort of students who achieved 4 days and 8 hours of wear, and the results were similar. Therefore, to increase external validity and maximize power, we included data from students who provided a minimum of 8 hours of data on at least 3 days in the final analysis. Similar criteria have been used in previous cohort studies of youth to estimate habitual PA.[2,5,28]

POTENTIAL CONFOUNDING VARIABLES

Dietary intake was assessed using a validated web-based 24-hour recall instrument (Web-Survey of Physical Activity and Nutrition).[29] We previously validated and used this tool to study dietary patterns among school-aged children in Alberta.[29,30] Children were prompted to list everything they had to eat and drink during the previous 24 hours. The food record was analyzed using Food Processor SQL for Windows version 7.9 (ESHA Research) and the Canadian Nutrient File for estimates of daily energy, macronutrient and micronutrient content, and fraction of daily recommended intake. A composite measure of diet quality was quantified according to the recommendations for Eating Well with Canada's Food Guide.[31]

STATISTICAL ANALYSES

Data are presented as means and 95% confidence intervals, unless otherwise stated. All data were tested for normality using the Kolmogorov-Smirnoff test. Nonnormally distributed variables were either log transformed or nonparametric tests were used to test for groupwise differences. Cross-sectional comparisons were initially performed using standard independent *t* tests and Mann-Whitney *U* tests, as appropriate. Generalized linear regressions were used to test for differences in the demographic and outcome measures across tertiles of PA while controlling for age, sex, and sedentary time. Multiple comparisons were adjusted for with a Bonferroni correction. Multiple logistic regression tests were used

Table 1. Association Between Vigorous PA and Selected Cardiometabolic Risk Factors in Youth

Variable	Mean (95% CI)			*P* Value
	Tertile I, Low	Tertile II, Moderate	Tertile III, High	
Demographic				
Age, y	12.2 (12.0-12.4)	12.0 (11.8-12.2)	12.2 (11.9-12.4)	.10
Sex, No.				
Male	74	81	91	.32
Female	120	125	111	
Waist circumference, cm	73.1 (71.5-74.7)	70.2 (68.8-71.5)	68.0 (66.7-69.2)	<.001
BMI *z* score	0.67 (0.53-0.80)	0.44 (0.32-0.57)	0.23 (0.11-0.34)	<.001
Overweight/obese, %	33.0	26.7	17.3	.002
High SBP, %	20.2	16.6	8.0	.002
PA data				
Sedentary time, min/d	562 (549-575)	550 (539-561)	539 (529-550)	.03
Light PA, min/d	170 (164-176)	177 (171-183)	185 (179-190)	.003
Moderate PA, min/d	40.5 (38.1-42.8)	53.5 (50.9-56.2)	64.1 (61.1-67.2)	<.001
Vigorous PA, min/d	1.39 (1.31-1.48)	3.59 (3.49-3.70)	8.74 (8.17-9.32)	<.001
Valid duration of wear time, d	4.63 (4.48-4.79)	4.76 (4.61-4.91)	4.71 (4.56-4.86)	.50
Valid duration of wear time, mean min/d	774 (760-787)	784 (772-796)	797 (784-809)	.04
Valid duration of wear time, mean min/weekday	796 (783-810)	807 (795-810)	817 (804-830)	.08
Valid duration of wear time, mean min/weekend d	722 (703-742)	723 (702-744)	736 (713-760)	.61
Dietary pattern				
Diet quality	1.49 (1.38-1.60)	1.58 (1.48-1.69)	1.73 (1.62-1.84)	.01
Sodium intake, mg	2512 (2181-2843)	2463 (2205-2721)	2462 (2199-2724)	.97
Total daily calorie intake, kcal	1838 (1665-2011)	1912 (1743-2081)	1886 (1730-2041)	.82

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PA, physical activity; SBP, systolic blood pressure.

to determine the odds of overweight status and elevated SBP across PA tertiles after adjusting for sedentary time and PA intensities. Multiple linear regression analyses were performed to test for independent continuous associations between cardiometabolic risk factors and intensities of PA. Based on eigenvalues, we did not observe any statistically significant collinearity between PA intensities; therefore, we included them as independent variables in regression analyses. Additional logistic regression tests were used to determine the odds of overweight status and high normal SBP according to graded intensities of PA (1500-6500 cpm). All odds ratios were adjusted for age, sex, sedentary behavior, and diet quality. All data were analyzed using SPSS version 19 (SPSS Inc). A $P<.05$ was considered statistically significant.

RESULTS

PARTICIPANT DEMOGRAPHICS

Data from the 605 students included in our study sample are provided in the eTable (http://www.archpediatrics.com). Compared with those who provided a valid accelerometer file, those who did not were (1) more likely to be boys ($P=.005$), (2) less likely to be sedentary (505 vs 554 minutes, $P<.001$), and (3) achieved greater levels of daily MVPA (62.8 vs 57.1 minutes, $P=.04$). No differences in BMI-*z* or waist circumference were noted between those who provided valid data compared with those who did not.

Students spent 69.6% of their accelerometer wear time in sedentary behavior, 22.9% in light PA, 6.8% in moderate PA, and 0.6% in vigorous PA (eTable). Compared with girls, boys spent a greater proportion of their time in light (24% vs 22%, $P<.001$) and moderate PA (7.4% vs 6.4%, $P<.001$) and less time in sedentary behavior (67.9% vs 70.9%, $P=.007$). No interaction effect was observed between sex and PA for any of the outcome measures; therefore, boys and girls were pooled for all analyses. Three separate analyses were run to test for differences in the outcome variables according to tertiles of PA intensity.

PA INTENSITY AND CARDIOMETABOLIC RISK IN YOUTH

Participant characteristics for the primary analyses are restricted to tertiles of vigorous PA in **Table 1**. No differences in age, sex, minutes of accelerometer wear time, or valid days of data were noted across tertiles of vigorous PA (Table 1). After adjusting for age, sex, sedentary time, and BMI-*z* where applicable, students in the highest tertile of vigorous PA (mean [SD], 8.7 [1.5] min/d) compared with those in the lowest tertile of vigorous PA (mean [SD], 1.4 [0.4] min/d) displayed lower BMI-*z* (0.2 vs 0.7, $P<.001$), lower waist circumference (68 cm vs 73 cm, $P<.001$), and higher cardiorespiratory fitness (51 mL/kg/min vs 46 mL/kg/min, $P<.001$) (**Figure 1**). No statistically significant difference in SBP was seen after adjusting for BMI-*z* (111 mm Hg vs 112 mm Hg, $P=.74$). Body mass index *z* score increased across tertiles of light PA, and fitness increased across tertiles of moderate PA (Figure 1). No other notable associations were made between the outcome variables and tertiles of light or moderate PA.

In a separate series of logistic regressions, we found that the odds of being overweight declined with in-

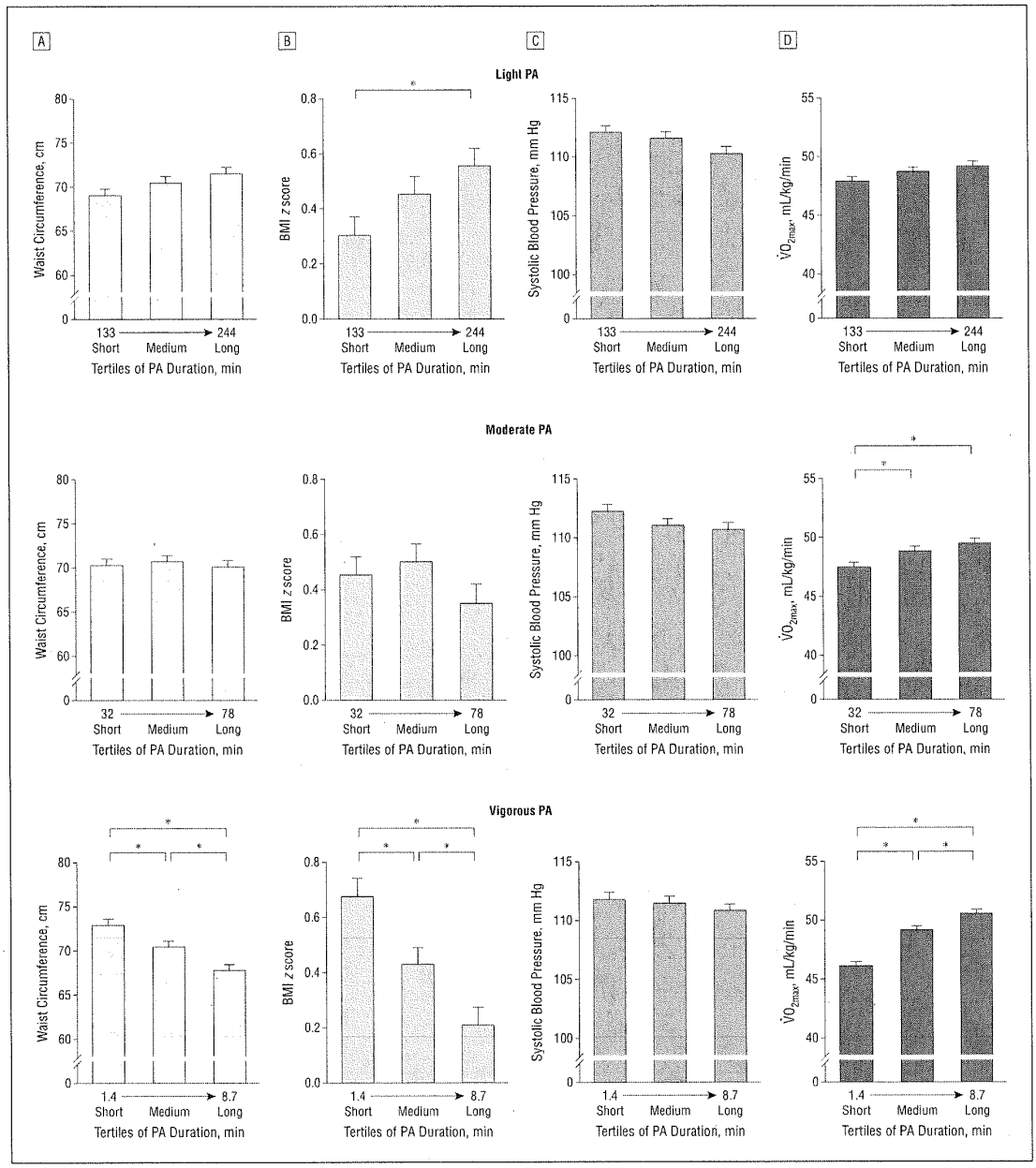

Figure 1. Cardiometabolic risk factors are associated with vigorous but not moderate or light physical activity (PA). Waist circumference (A), body mass index (BMI) *z* score (B), systolic blood pressure (C), and $\dot{V}O_{2max}$ (D) according to tertiles of light, moderate, and vigorous PA. Physical activity tertiles: short, medium, and long. Means are adjusted for age, sex, sedentary time, and BMI *z* score, where applicable. Error bars are standard error of the mean. * $P < .05$. Numbers on the x-axis denote the mean number of minutes spent in that form of PA within the particular tertile.

creased time greater than 2000 cpm, while the odds of high normal SBP declined with increased time greater than 1500 cpm (**Figure 2**). The slope of the association became steeper with increased intensity for both end points. For example, 50% reduced odds of being overweight were achieved with less than 10 minutes of greater than 6500 cpm of PA, 20 to 25 minutes of greater than 4000 cpm, and more than 60 minutes of greater than 2000 cpm. The same risk reduction for high normal SBP would be achieved with less than 5 minutes of greater than 6500 cpm of PA, less than 10 minutes of greater than 4000 cpm, approximately 15 minutes of greater than 2000 cpm, and more than 25 minutes of greater than 1500 cpm.

Rates of overweight status/obesity and high normal SBP declined in a dose-response manner across tertiles of vigorous PA (Table 1; $P = .002$ and $P = .002$, respectively).

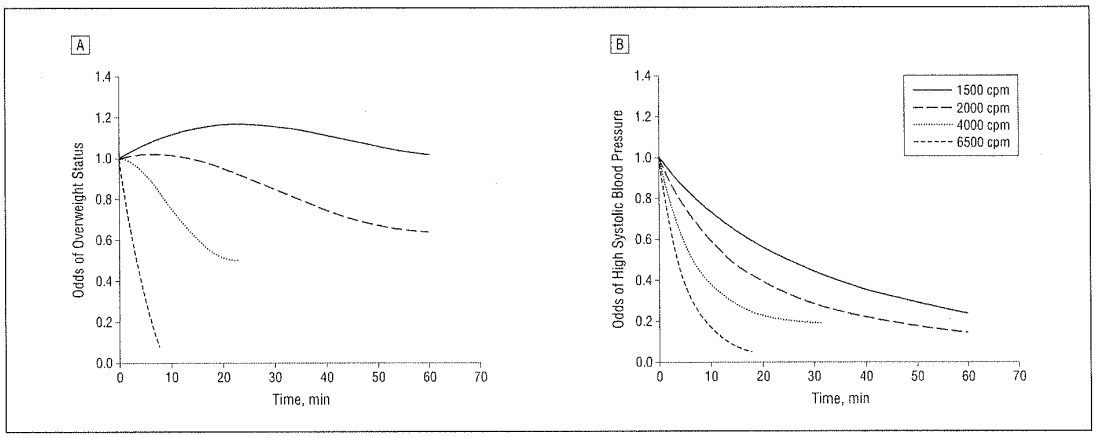

Figure 2. The association between the odds of overweight status and high normal systolic blood pressure across various intensities of physical activity. This graphic representation of the results of a series of logistic regression analyses depicts the slope of the association between the time spent being physically active at various accelerometer cutpoints (ie, physical activity intensities) and the odds of overweight status (A) and high normal systolic blood pressure (B). cpm indicates counts per minute.

Compared with students in the lowest tertile of vigorous PA, the odds of overweight status/obesity and high normal SBP were reduced by 57% (odds ratio, 0.43; 95% CI, 0.27-0.68) and 64% (odds ratio, 0.36; 95% CI, 0.19-0.66), respectively, in youth within the upper tertile of vigorous PA. Rates of overweight status/obesity and high normal SBP did not differ across tertiles of light PA.

PA INTENSITY AND CARDIOMETABOLIC RISK IN OVERWEIGHT YOUTH

We repeated all analyses within the subgroup of overweight and obese youth (n = 156; **Figure 3**). Among overweight youth, waist circumference and BMI-*z* decreased, while fitness levels increased in a dose-response manner across vigorous PA tertiles, after adjusting for confounders (Figure 3). However, the degree of adiposity and fitness levels seen in the highest tertile of overweight youth were still significantly different from healthy-weight youth (Figure 3).

Results from the multivariate linear regression analyses are presented in **Table 2**. After adjusting for all confounders, only vigorous PA was independently associated with all cardiometabolic risk factors.

COMMENT

This cross-sectional study of PA and cardiometabolic risk factors revealed 4 novel findings, while confirming previously published research.[2,4,5,8] First, measures of cardiometabolic risk declined in a dose-dependent manner with increasing vigorous PA but not with increasing light or moderate PA. Second, the odds of elevated SBP and overweight status declined in a dose-dependent manner only with increasing time in vigorous PA. Third, a minimal intensity threshold existed above which the risk of overweight status (>2000 cpm) and high normal SBP (>1500 cpm) began to decline with increasing time spent being physically active. Finally, among overweight youth, measures of adiposity decrease and fitness levels increased with increasing vigorous PA. The key finding from these analyses is that the independent associations observed between vigorous PA and cardiometabolic risk factors were noted across a narrow range of PA duration (approximately 7 minutes). In contrast, no differences in cardiometabolic risk factors were noted despite large differences in light PA (approximately 110 min/d) and moderate PA (approximately 46 min/d). These findings provide novel insight into the value of vigorous PA as a determinant of cardiometabolic risk in adolescents. These data strongly support the importance of including vigorous PA targets within current PA guidelines for youth.

In a landmark paper by the European Youth Heart Study Group, cardiometabolic risk factor clustering (SBP, insulin resistance, serum lipoprotein profile, and adiposity) declined in a dose-response manner, with increasing time spent in MVPA (>2000 cpm).[2] Follow-up studies from this same cohort[32,33] and others[11,12,34] extended these findings, demonstrating that vigorous PA is a robust predictor of waist circumference, BMI-*z*, and body fat. Our data extend these observations in several ways. First, after adjusting for all PA intensities, we found that vigorous PA was the single best predictor of measures of adiposity. Second, we found that the odds of being overweight/obese were significantly reduced across tertiles of vigorous but not moderate PA. Third, we found that vigorous PA is also the most robust PA intensity associated with cardiorespiratory fitness. Finally, the dose-response increase in cardiorespiratory fitness and declines in waist circumference and BMI-*z* were observed within the cohort of overweight and obese youth, suggesting the benefits of vigorous PA can be achieved among this high-risk group. While experimental trials are needed to confirm these observations, they suggest that vigorous PA confers greater protection from overweight status/obesity than lower intensity activity in youth.

Interestingly, in contrast to some studies, sedentary time was not associated with cardiometabolic risk fac-

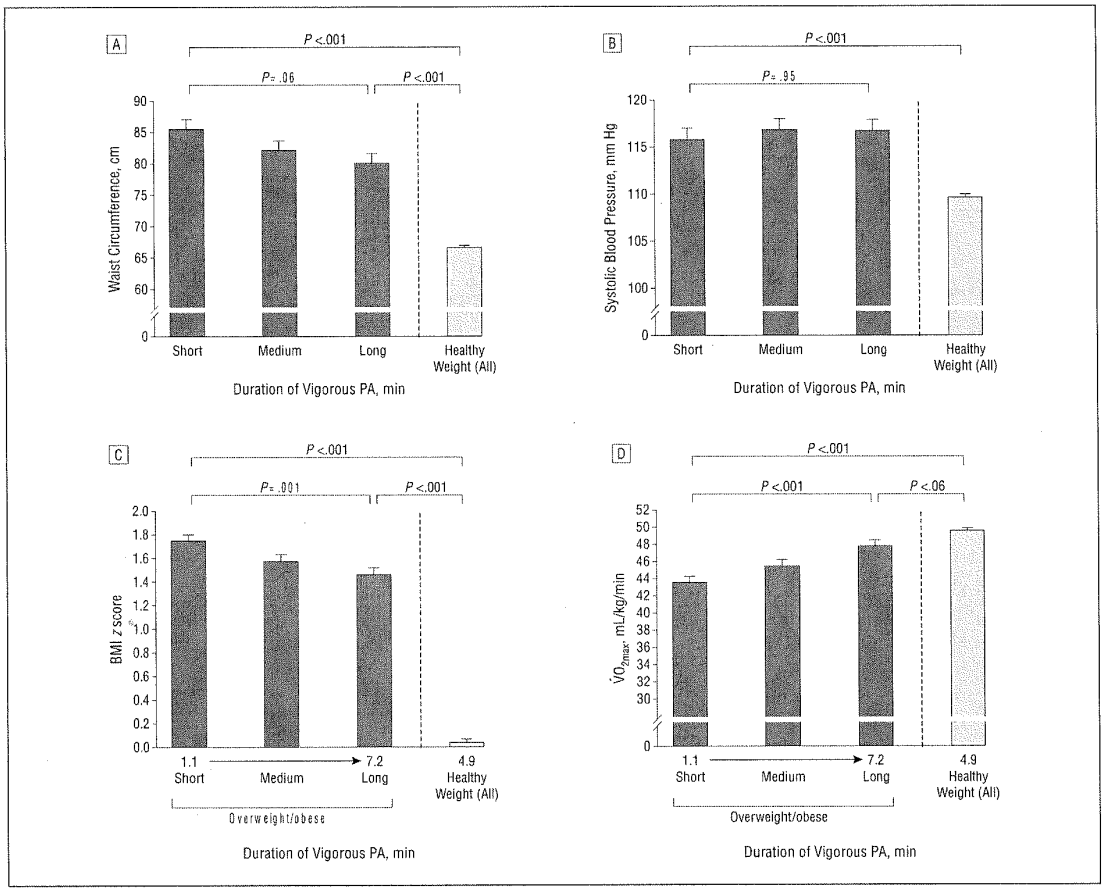

Figure 3. Vigorous physical activity attenuates cardiometabolic risk factor clustering in overweight youth. Values for waist circumference (A), systolic blood pressure (B), body mass index (BMI) *z* score (C), and $\dot{V}O_{2max}$ (D) according to tertiles of vigorous physical activity in overweight students compared with normal-weight students. Physical activity tertiles: short, medium, and long. Means are adjusted for age and sex. Error bars are standard error of the mean. Numbers on the x-axis denote the mean number of minutes spent in that form of physical activity within the particular tertile.

Table 2. Continuous Association Between Minutes Spent at PA Intensities and Selected Cardiometabolic Risk Factors

	Waist Circumference		BMI *Z* Score		Systolic Blood Pressure		$\dot{V}O_{2max}$	
Variable	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Age, y	0.33	<.001	−0.03	.66	0.18	.001	−0.04	.52
Sex	0.005	.93	0.04	.44	0.10	.07	0.19	.002
Sedentary time, min/d	0.03	.56	0.05	.35	0.04	.45	0.05	.47
Light PA, min/d	0.14	.02	0.19	.003	−0.02	.73	−0.01	.89
Moderate PA, min/d	0.003	.97	0.04	.56	0.04	.56	0.02	.79
Vigorous PA, min/d	−0.11	.05	−0.15	.009	−0.19	.001	0.17	.007
Diet quality, AU	0.03	.55	−0.02	.74	0.05	.38	0.06	.29

Abbreviations: AU, arbitrary unit; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PA, physical activity.

tor clustering in youth after adjusting for all intensities of PA. Previous studies have documented modest associations between sedentary behavior and adiposity.[11,35] Stronger associations are noted in observational and experimental trials of screen time and the risk for obesity[36,37] and high normal SBP.[38] The discrepancy between our study and others may be the inclusion of light PA in the analysis, which may be closely associated with sedentary time considering the cutpoints for stratification. Of note, previous studies that measured sedentary time with accelerometers did not observe associations with SBP[38] or cardiometabolic risk.[13]

Although no consensus has been reached regarding the thresholds of PA intensity in youth,[39] previous studies have validated the thresholds of intensity with energy expenditure.[25,26] To our knowledge, no study has

compared the association between cutpoints (ie, intensity) of PA and the risk for cardiometabolic outcomes in youth. The results presented in Figure 2 were created in an attempt to resolve this issue and determine an appropriate dose (duration and intensity) of PA associated with reduced odds for specific cardiometabolic end points. Similar to other dose-response studies,[40] we found that the odds of overweight status and high normal SBP declined with both increasing time and intensity of PA. Interestingly, the minimal intensity threshold associated with reduced odds of being overweight (>2000 cpm) was significantly higher than that for high normal SBP (>1500 cpm). Additional studies with larger sample sizes are required to determine a more precise threshold for achieving a reduction in cardiometabolic outcomes in youth.

The study offers several strengths, including the high-resolution (15-second epochs) objective measurement of PA. Shorter epoch durations prevented the misclassification of PA intensity and were in accordance with current best practice recommendations.[41] Further strengths included the addition of dietary information, the direct comparison of various intensities of PA, and the subgroup analyses within a cohort of overweight youth. Despite these strengths, there were some limitations. First, the cross-sectional nature of the study precluded the determination of a direction or a causal nature of these associations. Cross-sectional studies are efficient and frequently used to test hypotheses that focus on the dose-response association between PA and health outcomes.[2,11,40] Second, accelerometers do not account for the increased relative intensity experienced by overweight and obese youth at all thresholds of activity.[42] To overcome this limitation, we conducted subgroup analyses restricted to overweight or obese students and found that the associations with vigorous PA extended to this group of youth. We did not assess puberty and were unable to control for differences in maturation between the groups. Lastly, the ethnic diversity was limited within this cohort from urban and rural Canada, limiting the generalizability of these findings. However, limited ethnic diversity minimizes ethnic stratification, thereby increasing the internal validity of this study.

In conclusion, vigorous PA is superior to light and moderate PA for attenuating cardiometabolic risk factors in youth. These data support the concept that vigorous types of PA should be encouraged to reduce cardiometabolic risk factors in youth. The current targets for PA in youth may need to be reexamined, and the inclusion of specific targets for vigorous PA emphasized.

Accepted for Publication: April 13, 2012.
Published Online: September 10, 2012. doi:10.1001/archpediatrics.2012.1028
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Financial Disclosure: None reported.
Funding/Support: This study was supported by operating grants from the Canadian Diabetes Association and the Alberta Centre for Child, Family, and Community Research. Ms Hay's work is supported by a Manitoba Institute of Child Health/Manitoba Health Research Council studentship. Dr Ball is a Canadian Institutes of Health Research new investigator and a health scholar supported by Alberta Innovates. Dr Majumdar is an endowed chair in patient health management (supported by the Departments of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences, University of Alberta) and a health scholar (supported by the Alberta Heritage Foundation for Medical Research and Alberta Innovates–Health Solutions). Dr Veugelers holds a tier II Canada research chair in school-based child health. Dr McGavock is a Canadian Institutes of Health Research new investigator and holds the Robert Wallace Cameron chair in evidence-based child health.
Online-Only Material: The eTable is available at http://www.archpediatrics.com.

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