THE ROLE OF EXERCISE IN MODULATING VASCULAR FUNCTION IN CHILDHOOD AND ADOLESCENT OBESITY

by

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MPH, University of Washington, 2005

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate and Postdoctoral Studies (Kinesiology)

THE UNIVERSITY OF BRITISH COLUMBIA (Vancouver)

July 2019

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Abstract

Purpose: Overweight children and adolescents have increased aortic stiffness conferring an increased risk of future cardiovascular events. This thesis evaluated exercise training as a means to modify aortic stiffness in obese youth. An institutional treadmill protocol (British Columbia Children’s Hospital, BCCH) for assessing metabolic gas exchange parameters (minute ventilation, tidal volume, breathing frequency, oxygen consumption, carbon dioxide production) was validated using a healthy cohort (study 1, Chapter 3). This protocol was used to test obese children and adolescents before and after an exercise intervention. Echocardiography was used to study changes to vascular properties pre- and post- training (study 2, Chapter 4). Pulmonary function tests were used to assess lung function pre- and post- training (study 3, Chapter 5).

Study 1: A scaled institutional (BCCH) protocol was validated using 70 healthy boys and girls. This validated protocol was used in the subsequent training study to individually adjust intensity to VO2 capacity, in keeping with exercise intervention recommendations.

Study 2: Ten to 18 year old children and adolescents (BMI ≥ 97th percentile for age) were recruited to undergo a 12-week exercise program in a randomized cross-over study. Standard echocardiographic dimensions and measures of systolic and diastolic cardiac function were recorded before and after both a 12-week exercise intervention and 12-week control phase. Biophysical properties of the aorta including pulsewave velocity were calculated using an echocardiographic-Doppler method. Treadmill exercise tests were also performed before and after each study phase.
Study 3: The same participants that underwent the exercise training in study 2 were measured for resting pulmonary function and exercise spirometry as per the protocol described in the second study.

Results: The institutional treadmill protocol produced similar peak exercises responses compared to the traditional protocol and was validated as an alternate for pediatric exercise testing. Ten participants completed the exercise intervention (age 14.3±3.2 yrs). Training showed a significant reduction in PWV (p=0.003), a modest reduction in body mass (p=0.0135), and exercise tolerance improved (METs, p=0.003; total exercise time, p=0.015). A reduction of aortic pulsewave velocity can be achieved with exercise training in obese children and adolescents and cardiovascular fitness can be modestly improved.
Lay Summary

The adaptation of the aorta – the central artery leaving the heart – to exercise in obese children and adolescents is unclear. Likewise, changes to their lung function with progressively high intensity training are also poorly understood. The aims of this dissertation were (i.) to describe a method for assessing exercise capacity by treadmill testing in children and adolescents with obesity, (ii.) to describe cardiorespiratory responses before and after a 12-week, supervised, exercise training program. Changes to the aorta was assessed by taking ultrasound pictures. Changes to lung function testing was assessed using various lung function tests. It was determined that exercise can improve properties of the aorta and improve aerobic fitness in the obese child and adolescent. As well, difficulty breathing does not appear to limit exercise in this group.
Preface

This thesis describes work carried out at the Exercise Physiology Lab in the Heart Centre at BCCH, Vancouver, Canada under the guidance of Drs. William Sheel and James Potts. All studies were approved by The University of British Columbia, Children and Women’s Health Centre (UBC C&W) Research Ethics Board.

Chapter 2 is based on work conducted in the Exercise Physiology Lab in the Heart Centre at BCCH, Vancouver, Canada under the guidance of Drs. William Sheel and James Potts. Duff DK was responsible for participant recruitment, testing and data analysis.

A version of chapter 3 has been published: D. Kathryn Duff, Derek G. Human, Astrid M. De Souza, James E. Potts, Kevin C. Harris A novel treadmill protocol for exercise testing in children: The BCCH Protocol. BMJ Open Sport Exerc Med 2017;3:e000197. doi: 10.1136/bmjsem-2016-000197. Duff DK conducted all the testing and wrote most of the manuscript with revisions provided by James Potts, Kevin Harris, and Astrid De Souza.

The UBC C&W Research Ethics Board certificate no.: H13-02218
Douglas College Research Ethics Board approval: Date of letter 12th March, 2013 (no certificate no. provided)

Chapter 4 and 5 are also based on work conducted in the Exercise Physiology Lab in the Heart Centre at BCCH under the guidance of Drs. William Sheel and James Potts. Duff DK was responsible for participant recruitment, testing, and data analysis. Duff DK conducted all exercise training sessions and prepared manuscripts (in progress) for peer reviewed submission.

UBC C&W Research Ethics Board certificate no.: H12-03385
Douglas College Research Ethics Board approval: Date of letter 11th March, 2014 (no certificate no. provided).
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<th>Description</th>
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<tbody>
<tr>
<td>ACSM</td>
<td>American college of sport medicine</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>Ao</td>
<td>Peak aortic flow</td>
</tr>
<tr>
<td>AoPWV</td>
<td>Aortic pulse wave velocity</td>
</tr>
<tr>
<td>APHV</td>
<td>Age at peak height velocity</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>dBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Dd</td>
<td>End diastolic dimension</td>
</tr>
<tr>
<td>DS</td>
<td>Maximal systolic dimension</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>EELV</td>
<td>End-expiratory lung volume</td>
</tr>
<tr>
<td>EILV</td>
<td>End-inspiratory lung volume</td>
</tr>
<tr>
<td>Ep</td>
<td>Arterial pressure-strain elastic modulus</td>
</tr>
<tr>
<td>ERV</td>
<td>Expiratory reserve volume</td>
</tr>
<tr>
<td>Fb</td>
<td>Frequency of breath</td>
</tr>
<tr>
<td>FEV1.0</td>
<td>Forced expiratory volume in the first second</td>
</tr>
<tr>
<td>FMD</td>
<td>Flow-mediated dilation</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>HDL-c</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HIIT</td>
<td>High intensity intermittent (or interval) training</td>
</tr>
<tr>
<td>HIT</td>
<td>High intensity training</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HRR</td>
<td>Heart rate reserve</td>
</tr>
<tr>
<td>IOTF</td>
<td>International obesity task force</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LDL-c</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LOA</td>
<td>Limit of Agreement</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MET</td>
<td>Metabolic equivalent task</td>
</tr>
<tr>
<td>MIIT</td>
<td>Moderate intensity intermittent (or interval) training</td>
</tr>
<tr>
<td>MIT</td>
<td>Moderate intensity training</td>
</tr>
<tr>
<td>MVPA</td>
<td>Moderate to vigorous physical activity</td>
</tr>
<tr>
<td>MVV</td>
<td>Maximum voluntary ventilation</td>
</tr>
<tr>
<td>NHANES</td>
<td>National health and nutrition examination survey</td>
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**List of Abbreviations - continued**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>NO</td>
<td>Nitric-oxide</td>
</tr>
<tr>
<td>Ob</td>
<td>Obesity</td>
</tr>
<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary function testing</td>
</tr>
<tr>
<td>PNS</td>
<td>Parasympathetic nervous system</td>
</tr>
<tr>
<td>PP</td>
<td>Pulse Pressure</td>
</tr>
<tr>
<td>RER</td>
<td>Respiratory exchange ratio</td>
</tr>
<tr>
<td>RPE</td>
<td>Rating of perceived exertion</td>
</tr>
<tr>
<td>RV</td>
<td>Reserve volume</td>
</tr>
<tr>
<td>SA</td>
<td>Sino-Atrial</td>
</tr>
<tr>
<td>sBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>TG</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>T&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Inspiratory time</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>V&lt;sub&gt;D&lt;/sub&gt;</td>
<td>Ventilatory dead-space</td>
</tr>
<tr>
<td>V&lt;sub&gt;E&lt;/sub&gt;</td>
<td>Minute ventilation</td>
</tr>
<tr>
<td>VCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Volume of carbon dioxide production</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Volume of oxygen uptake</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt;R</td>
<td>Reserve volume of oxygen uptake</td>
</tr>
<tr>
<td>V&lt;sub&gt;T&lt;/sub&gt;</td>
<td>Tidal Volume</td>
</tr>
<tr>
<td>Zc</td>
<td>Characteristic impedance</td>
</tr>
<tr>
<td>Zi</td>
<td>Input impedance</td>
</tr>
<tr>
<td>β-index</td>
<td>Arterial wall stiffness index</td>
</tr>
</tbody>
</table>
Acknowledgements

This thesis describes the methods and results of my recent research, but more importantly, it reflects a process of collaboration and support between many exceptional people. I would like to thank all the study participants for volunteering their time to complete the studies contained in this dissertation. I would also like to thank the following individuals for their time and expertise: my supervisors, Dr. William Sheel, Director of UBC Health and Integrated Physiology Lab, and Dr. James Potts, Director of the Exercise Physiology Lab in the Heart Centre at BCCH, and my other committee members, Dr. Kevin Harris and Dr. Jean-Pierre Chanoine (intellectual support and academic rigour); Astrid De Souza, Barb Morrison (exercise physiology support); Christine Voss, Boris Kuzeljevic (statistical analysis support); Raman Gill and Lindsey Williams (sonographers); Dr. George Sandor, Pediatric Cardiologist (Echocardiography) and Professor Emeritus, Department of Pediatrics, Faculty of Medicine, UBC; Undergraduate students from UBC Kinesiology and Douglas College Sport Science program (assistance with exercise sessions). I would also like to acknowledge the various funding partners that allowed this research to take place: BC Telethon Projects Fund, the Douglas College Research and Scholarly Activity Fund, and the UBC Graduate Students Travel Fund.
Dedication

This dissertation is dedicated to the very wide support team that was unwavering in providing backbone to the process. To William Sheel, James Potts, Kevin Harris, and Jean-Pierre Chanoine, a special thank you for your patience, understanding, and tremendous guidance of a mature student. To George Sandor, a Pediatric Cardiologist and Professor Emeritus of Pediatrics, thank you for your wisdom and insight and time spent teaching me the practical skills. To Astrid De Souza, for so many things, thank you for offering support for exercise sessions, lab testing, data interpretation and discussion, all above and beyond your regular work load.

To the Sport Science faculty and students at Douglas College, thank you for the support, inspiration, and periodic progress checks. A special thanks to Lara Duke and Brian Storey who took turns chairing the department during this process, creating a tenable schedule, course coverage where needed, and above all, kind wisdom and friendship. To the Sport Science students that volunteered their time, completed field work, and engaged in a playful, sensitive way with the study participants, thank you.

To the support of my family, I ultimately dedicate this thesis; to my beautiful mother who passed away during the process, although never saw it come to fruition, made her pride endlessly communicated. To my dad who came to live with us, and to Troy, Tomas, and Natalee, without whose love, support and tolerance, this endeavour would not have happened, thank you.
CHAPTER 1: Overview of the Literature

1.1. Introduction

Obesity (Ob) has placed a huge burden on the pediatric population over the last 40 years due to its association with a higher risk for disease morbidity (1) and premature mortality (1,2,3). Similarly, the association of childhood obesity with adult obesity, foretells an increased likelihood of obesity-related morbidity in adulthood (4,5). The later into adolescence overweight persists and the more severe the Ob, the greater the likelihood of persistence (6,7,8,9,10). Ob adversely affects almost all the cardiovascular (CV) disease risk factors, particularly those related to the metabolic syndrome (11,12), including blood pressure (BP) (11), lipids (13), and increasing blood glucose (eventually leading to type 2 diabetes) (13,14,15). In addition, because adipocytes release cytokines that increase inflammatory proteins, Ob is generally associated with increased inflammation (16,17). Given these co-morbidities, increased fat accumulation has adverse effects on cardiac structure (18) and function (19,20,21). Unsurprisingly then, almost all CV disease is increased in the setting of Ob (14,15,22). With CV disease as one of the greatest causes of poor health and mortality, programs aimed at preventing CV disease have been designed mainly focusing on modifiable risk factors such as lifestyle of which physical activity (PA) is considered a key component (23). Indeed, one of the reported determinants of childhood Ob and associated chronic disease is a lack of adequate PA (24), especially in the adolescent period (25), which seems to be important amongst an age group where habitual PA is known to be decreasing (26,27,28). It has been suggested that healthy-living children and youth, 5-17 years of age, accumulate an average of at least 60 minutes per day of moderate to vigorous intensity PA.
Using data from the first cycle of the Canadian Health Measures Survey (CHMS), Colley et al. (2011) examined accelerometer-measured PA and sedentary behaviour in a nationally representative sample of Canadian children and youth (27). According to results of the CHMS, 7% of Canadian children and youth (9% of boys and 4% of girls) aged 6-19 accumulate at least 60 minutes of MVPA at least 6 days a week (27). Almost all MVPA (97%) is accumulated at moderate intensity (27). More than half of boys (53%) and a third (35%) of girls do so at least 3 days a week and the percentages accumulating 60 minutes of MVPA decline with increasing age with more elementary school children than middle and high school students achieving the goal (27). Overweight and obese boys accumulate less MVPA (51 and 44 minutes a day, respectively), compared with boys who are neither overweight nor obese (65 minutes) (27). This gradient is not evident in girls—regardless of their BMI, girls average 44 to 48 minutes of MVPA a day (27).

The 2007-2009 CHMS demonstrated inadequate PA levels, revealing that youth have greater mean body mass index (BMI), waist circumference and skinfold measurements, as well as, lower levels of fitness than they did in 1981 (27,30). Of great concern is that overweight adolescents very often maintain overweight in adulthood (8). Despite some excellent longitudinal, prospective, population-based, cohort studies such as the Bogalusa Heart Study (25) and Cardiovascular Risk in Young Finns Study (31) demonstrating the relationship between the early development of PA and physical fitness on health outcomes later in life, the understanding of the types and amounts of PA relevant to health and health outcomes is still growing.
Endurance training using moderate exercise is cited as one of the best strategies for Ob management (29). Recently, the impact of intense interval training has been studied and has shown promising results in Ob management (32,33,34). A high intensity training model may improve lipid metabolism and other health markers in obese individuals, and by a shorter time than conventional training (35). Previous training programs have relied on exercise geared towards adults such as walking, cycling, or daily activities involving low to moderate intensity training of long duration (>60 minute sessions; 225 and 420 min-week\(^{-1}\)) designed with a focus on weight loss (36,37,38,39), where the volume of exercise needed is greater than that which is necessary to improve fitness or derive health outcomes (39).

Even though clinical symptoms of chronic diseases do not become apparent until much later in life, it is known that the origin of many chronic diseases lie in early childhood (40), maybe even in fetal life (41). Impaired vascular function, for example, contributes to increased CV risk as atherosclerosis begins in childhood (41, 42). Endothelial dysfunction has been identified as an early event contributing to development of atherosclerosis (42). Strong evidence shows that obese children and adolescents have impaired endothelial function marked by lower arterial compliance and distensibility (43). It stands to reason that retarding atherosclerosis with early preventive measures that enhance vascular function will reduce CV risk. Therefore, the prevention of chronic diseases should start as early in life as possible and investigating interventions for health-related outcomes is important especially in adolescents who are at an age where PA is known to be declining.

The focus of this PhD work is to understand the role exercise plays in modulating properties of vascular and respiratory function in obese children and adolescents. The
implication for this work is primarily to inform health care providers and exercise scientists in British Columbia to improve clinical practices for pediatric Ob management. This current chapter introduces the concepts for understanding cardiovascular health in children and youth with Ob and considerations for providing exercise prescription to them. Chapter two will discuss the general methods used in three original studies that I have undertaken to document the role of exercise in cardiovascular function in children and adolescents. Chapter three is the first of the original studies validating a treadmill protocol for assessing cardiorespiratory fitness in youth. This chapter has been published in manuscript format. The second original study is presented in Chapter 4 providing an exercise intervention aimed at modulating the biophysical properties of the heart to assess vascular health. Biophysical properties of the aorta are measured before and after the intervention and implications for the findings are discussed. Chapter 5 distinguishes changes to the respiratory system from the exercise intervention as measured through spirometry and exercise respiratory responses. In chapter 6, a summary of the findings is provided and a commentary addressing why the focus on the physiological health consequences has complicated the notion of reversing or quelling the Ob trend. The commentary will also address the challenges associated with this population in terms of implementing health initiatives and their recruitment for study in an exercise context in the pursuit of advancing their care. The document will conclude with recommendations for future study.
1.2. Literature Review

1.2.1. Adiposity in Childhood and Adolescence

In children and adolescents, Ob and overweight are defined on the basis of established age- and sex-specific BMI reference values (BMI = mass (kgs) / height (m)^2) (44).

A number of reference data sets are available, often based on representative data from a given country (i.e. in North America, the National Health Examination Surveys II and III from the 1960’s, the National Health and Nutrition Examination Survey (NHANES I and II) from the 1970’s and NHANES III from the late 1980’s to early 1990’s have been used) (45) or from global data (The World Health Organization, WHO (46,47) and Centre for Disease Control, CDC (48)) for representative, normal clinical growth. From this representative data, an individual child can be measured and compared as part of monitoring growth clinically or data may be used specifically to define childhood overweight based on risk-based fixed values or to examine population trends. Although there are differing definitions in the literature, to define risk-based fixed values, prevalence has had to be measured against stable cut-points and transformed in order to define statistically (i.e. translating BMI-for-age to a percentile relative to some specified distribution of BMI-for-age as a BMI value alone may be arbitrary in children with little frank disease) (49). One reference set of BMI values that has been widely used for defining overweight and Ob consists of smoothed sex-specific 85th and 95th percentiles from 1971-1974 (NHANES I) when the distribution of BMI values were constant (49,50). Collecting new data has been considered problematic because including an increasing prevalence of overweight and obese in the dataset, redefines healthy normal with overinflated values. In 2000, Cole et al. (51) published a set of smoothed sex-specific BMI cut-
off values based on 5 representative data sets from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore and the United States (from NHANES I and II only). These values are referred to as the International Obesity Task Force (IOTF) cut-off values, providing a common basis for prevalence estimates internationally. This method incorporated adult morbidity cut-points to address Ob at the extremes (cut-off values chosen as the percentiles that matched the adult cut-offs of a BMI of 25 and 30 at age 18 years) (52). Although there is currently no well-accepted standard of body fatness for children and youth, the IOTF recommends a BMI cut-point at or above the 97th BMI percentile for age and sex to be used to define Ob (53).

The obvious criticism of using BMI to assess pediatric body composition is that it does not provide any information on total body fat nor fatness across all pediatric groups when boys and girls are considered separately (54,55,56). The use of BMI within each sex assumes that equivalent BMIs represent similar relative degrees of fatness at all ages and does not account for relative leanness. At any given BMI there can be widely varying degrees of body fatness and fat-free mass (55). In terms of efficacy for estimating adiposity, it is widely used and validated as safe, inexpensive to obtain and characterizes childhood fatness in large-scale epidemiologic studies (56). When used in conjunction with other markers of health, such as waist circumference (57) or blood pressure (58), BMI reliably reflects fatness on a population level and, in turn, BMI has been associated with various adverse biochemical and physiologic effects of excessive adiposity (53,59).

Rates of childhood Ob have undeniably increased dramatically both globally (60,61,62,63) and especially in North America (64,65,66) over the past 40 years. In the US, between 1980 and 2006 the prevalence of high BMI (>95th percentile of sex-specific 2000 CDC
growth charts measured at regular intervals) increased from 6% to 16% among children and teenagers aged 2 through 19 years (66). This represents an increase from 4.6% in 1966-1970 (67). Skinner (2016) recently reported, in a study of children from 1999-2014, no indication of a decline in childhood Ob prevalence and a linear, upward trend in the severity of Ob (68). In the 2013-2014 sample, 33.4% of youth met the criteria for overweight, including 17.4% for class I Ob (BMI ≥95th percentile), 6.3% for class II Ob (BMI ≥120% of the 95th percentile or BMI ≥35 whichever was lower) and 2.4% for class III Ob (BMI >140% of the 95th percentile or BMI ≥40 whichever was lower) and older children had greater prevalence of all classes of Ob compared with younger children (69). Although the rates in the US still remain higher, trends in Canada show a similar trajectory. In 2004, 26% of Canadian children and adolescents 2-17 years were overweight or obese and 8% were considered obese (70). The prevalence of overweight using the IOTF definition (51) in 7-13 year old girls doubled in Canada between 1981 and 1996 and tripled in boys (70). Although there are geographical and cultural differences reported in rates throughout North America, similar increases are reported in children in British Columbia (71).

Recently, it has been predicted that childhood Ob will lead to the first ever decline in life expectancy in the developed world (72). Much of the morbidity and early mortality attributable to childhood Ob is due to its association with an increased risk of adverse CV events. For example, Engeland et al. (2003) conducted a 32-year longitudinal study of 227,000 Norwegian males and females who took part in a compulsory tuberculosis screening program from 1963-1975 as teenagers (73). Among males, mortality rates from all causes, especially CV disease, were increased by 30% when BMI at baseline was between the 85th and 95th
percentile (using CDC definition) and by 80% when BMI at baseline exceeded the 95th percentile (73). The corresponding rates among females showed a 30% increase in all-cause mortality when baseline BMI was between the 85th and 95th percentiles and 100% when BMI at baseline exceeded the 95th percentile (73). In another landmark longitudinal study, Twig et al. (2016) analyzed data from 2.3 million Israeli men and women (mean age at baseline, 17.3±0.4 years) measured from 1967 through 2010, and reported adolescents with a BMI in the 50th to 74th percentiles (considered acceptable healthy range) had a 49% increased risk of CV disease as adults (74). Teenagers in the 75th to 84th percentile at baseline were at more than twice the risk of future CV disease (74). The excess mortality among adolescents whose BMI was high in both the Norwegian and Israeli groups was not clearly manifested before they reached their thirties, therefore, evidence supports that BMI in adolescence is predictive of adult mortality.

Ob is an important independent risk factor for CV disease in adults and these same risks have been documented in obese children and adolescents (75,76). Freedman et al. (2007) used results from the Bogalusa Heart Study to compare six CV risk factors, triglycerides, low-density lipoprotein, high-density lipoprotein, fasting insulin, systolic BP (sBP), and diastolic BP (dBP) in 5-10 year old obese children based on BMI percentile (77). The results showed that 39% of children ≥95th percentile and 59% of children ≥99th percentile had ≥ two risk factors, respectively, which was significantly greater than children in the 85th to 95th percentile. They also showed that both of the higher BMI groups were much more likely to become obese as adults (77).
There is strong evidence that weight reduction in overweight and obese individuals, including children, improves risk factors for CV disease (78,79,80,81,82,83,84). Studies by Ford et al. (2010) (85) and more recently Reinehr et al. (2016) (86) found an improvement in body composition and cardiometabolic risk (improved hypertension, hypertriglyceridemia, and lower HDL-c) can be seen with standardized BMI (BMI-SDS percentile) reductions of ≥0.25 in obese adolescents, whereas a BMI-SDS greater than 0.5 doubled the effect. Ford et al. (2010) followed 88 adolescents (40 males, 86% Caucasian) of median age 12.4 years (range 9.1–17.4) and mean (SD) BMI SDS 3.23 (0.49) for 12 months (85). Reinher et al. studied 388 overweight children (using IOTF criteria) (mean BMI 27.9 ± 0.1 kg/m2, mean age 11.4 ± 0.1 y, 43.8% male, 45.5% prepubertal) (86). They also found that the most insulin-sensitive individuals seem best able to effect these changes (86). Weight management programs usually include: diet restriction, bariatric surgery or exercise interventions or some combination. Although weight loss has been reported to be minimal when considering interventions of exercise alone, weight reduction alongside exercise has been shown to improve risk factors for CV disease in both adults and youth (29,87,88,89). Therefore, the effects of exercise may not be mediated through body composition. While these increased risks in terms of hypertension, dyslipidemia and glucose metabolism are documented in obese pediatric cohorts (90), few studies have quantified change in these parameters secondary to weight loss.

Janssen and LeBlanc (2010) completed a systematic review limited to seven health indicators: high blood cholesterol, high BP, the metabolic syndrome, Ob, low bone density, depression, and musculoskeletal injuries citing 86 eligible papers and found that PA is
associated with numerous health benefits in school-aged children and youth (29). The dose-response relations between PA and health that were observed suggested that the more PA, the greater the health benefit, however, the exact magnitude of the additional reduction in risk remains uncertain (29,91,92). The results from the Janssen and LeBlanc (2010) review did show that even modest amount of PA can have tremendous health benefits in obese youngsters and should be of moderate intensity, suggesting that even if weight loss is minimal, obese, fit individuals are at reduced risk for CV mortality than their lean, but unfit, counterpart (29).

PA is generally conceptualized as all leisure and non-leisure body movements resulting in an increased energy output from rest (93). Classically defined, exercise refers to the structured and repetitive leisure-time PA whose main objective is to maintain or improve physical fitness, exercise performance, health status, or more than one of these (94,95). Within the exercise literature, numerous studies have evaluated the relationship between health status and one or more components of health related physical fitness such as cardiorespiratory fitness (96,97,98), motor fitness (99,100), body composition (101), and metabolism (102) for children and youth. It is important to note there are various components of PA and exercise across a continuum, ranging from being inactive to being very physically active. It is also important to distinguish that someone who is inactive may not be completely sedentary because people engage in some level of PA throughout the day unless confined to bedrest or reliant on others to move (93). Accordingly, sedentary behaviour may be considered waking behaviour that requires very low levels of energy expenditure (≤ 1.5 METs) (103). All tasks that require more energy than sedentary behaviours but are not at
least of moderate intensity are categorized as light activity (<3 METs) (29,104) with moderate activity being considered as 3-6 METs and vigorous >6 METs (29). According to specific PA guidelines (32), a child is described as inactive if they are not performing sufficient MVPA (104,105), however, relatively little is known about the effects that changes in sedentary behaviours and non-exercise PA will have on health status.

The CHMS is the most comprehensive direct health measures survey conducted in Canada. According to results of the CHMS, only 7% of Canadian children and youth (9% of boys and 4% of girls) aged 6-19 accumulate at least 60 minutes of MVPA at least 6 days a week to meet the PA guidelines (27). More than half of boys (53%) and a third (35%) of girls do so at least 3 days a week and the percentages accumulating 60 minutes of MVPA decline with increasing age with more elementary school children (aged 5-11 years) than middle and high school (aged 12-17 years) students achieving the goal (27). A much higher percentage—44%—have 60 minutes of MVPA at least 3 days a week, which suggests that young Canadians tend to have long within-day sessions of activity rather than shorter episodes spread across more days of the week (27). Overweight and obese boys accumulate less MVPA (51 and 44 minutes a day, respectively), compared with boys who are neither overweight nor obese (65 minutes) (27). This gradient is not evident in girls—regardless of their BMI, girls average 44 to 48 minutes of MVPA a day (27). This shows that girls are less active than their male counterparts overall and differences in sex require consideration. In follow up study, these rates have stayed consistent, results from the 2014 and 2015 CHMS indicate fewer than 1 in every 10 (8%) of Canadian children and youth are getting 60 minutes of PA every day (103).
The CHMS study has also shed light on the declining levels of fitness observed in Canadian youth over the past few decades. Estimates of body composition (body mass index, waist circumference, waist-to-hip ratio and skinfolds), aerobic fitness and musculoskeletal fitness (including muscular strength, endurance and flexibility) were reported by Tremblay (30), showing a population decline in fitness since 1981, regardless of sex or age. For boys and girls in all age groups, flexibility and muscular strength scores, in particular, were lower in 2007-2009, and mean BMI, waist circumference and the sum of five skinfolds were higher. Age-related declines may reflect less overall PA, a less-optimal pattern of PA, increased adiposity, or changes in hemodynamic and/or metabolic functions associated with growth and development (106), but what may not be reflected is that children are still getting health benefits by moving their mass and that the 60 minutes per day requirement of MVPA may over-estimate the amount required to derive health outcomes.

Levine and Kotz (2005) used the Non-Exercise Activity Thermogenesis (NEAT) hypothesis of energy generation to examine the interaction of energy expenditure and environment (107). NEAT is the energy expenditure of all physical activities other than volitional sporting-like exercise that provides a crucial thermoregulatory switch between energy storage and dissipation that is biologically regulated and influenced, and perhaps over-ridden, by environment (107). They explained that all energy expenditure makes an impact on adult weight maintenance—the planned as well as the unplanned or non-exercise activity thermogenesis—and that there is potential individual variance in this expenditure. Levine et al. (2005) were able to show that lean sedentary people are standing and ambulatory for 152 min longer per day than obese participants (108). Obese participants
were seated for 164 min per day more than lean participants. If the obese subjects adopted the same posture allocation as the lean subjects, they might expend an additional 350 kcal per day because of the energy cost of standing/ambulating (108). This demonstrates the magnitude of the formal exercise level that obese people need to adopt to promote negative energy balance and weight loss. Thus, NEAT and specifically standing/ambulating time are of substantial energetic importance in Ob.

Further to this, Hamilton (2007) used the physiological inactivity paradigm to discuss the role of sedentary behavior, especially sitting, on mortality, CV disease, type 2 diabetes, metabolic syndrome risk factors, and Ob (109). Evidence from early controlled laboratory studies (110,111) including Hamilton’s own work (112) examining the cellular regulation of skeletal muscle lipoprotein lipase (LPL) (a protein important for controlling plasma triglyceride catabolism, HDL cholesterol, and other metabolic risk factors) had shown that reducing normal spontaneous standing and ambulatory time had a much greater effect on LPL regulation than adding vigorous exercise training on top of the normal level of nonexercise activity. Because non-exercise activity makes up a much larger component of daily total energy expenditure than exercise, Hamilton (2006) argued that the average nonexercising person may become even more metabolically unfit in the coming years if they sit too much, thereby limiting the normally high volume of intermittent nonexercise PA in everyday life (109). Hamilton therefore advocates for maintaining or increasing non-exercise activity to control health status (109).

Many factors may underlie lower PA levels including: greater access to sedentary ways to enjoy leisure time (e.g. audio-visual screen entertainment), lower rates of active
transportation, which may be partially due to the built environment, perceived unsafe environments of outdoor play, contrived play due to constrictive built apparatus, and pressures on schools to place a greater emphasis on academic achievement at the expense of PA opportunities, as examples (113,114,115). Additionally, low rates of physical literacy and motor competence among school-aged children is impairing PA participation (116,117). As such, implementation of multi-factorial solutions offer the best chance at combating the Ob trend. Health care providers can encourage and promote appropriate PA in children with a better understanding of the role of exercise in CV health and appropriate programs designed to improve it. Failure to provide PA opportunities will increase the likelihood that the children and youth on the Ob trajectory will live less healthy, possibly shorter, lives than their parents (118).

1.2.2. Adiposity and Cardiovascular Health

Ob, particularly with excess visceral adiposity (119), is associated with numerous co-morbidities that may affect vascular health through its influence on known risk factors such as: dyslipidemia, elevated BP, impaired glucose tolerance, inflammatory markers, and hypoventilation (16,42,78). Although subcutaneous and visceral adipose tissue show functional differences (17), elevated BP, low plasma high-density lipoprotein cholesterol (HDL-c), and elevated triglyceride, all independent of vascular risk factors (120,121), are most closely associated with abdominal Ob due to its effect on and proximity to vital body organs (119, 122). The Young Finns cohort showed that risk factors identified in adolescence predict increased intima-media thickness (IMT) two decades later in adulthood independently of the adult risk factor status (123). This suggests that risk factors operating in early life may be
associated with permanent damage to the arterial wall (124). Without over-simplifying the complex etiology of CV disease, the many risk factors are interrelated, ultimately creating a vicious cycle of inflammation-mediated vascular damage.

Evidence demonstrates that adipocytes (fat cells) release adipokines and other pro-inflammatory molecules such as: cytokines (tumor necrosis factor TNF-α, interleukins IL-1β or IL-6, C-reactive protein CRP, vascular adhesion molecules VAM) affecting platelet aggregation and the clotting cascade (17,125); oxidative enzymes (MPO, NADPH-oxidase) increasing free radicals harmful to the endothelium, DNA, lipids and sub-endothelial vascular tissues (126); leptin, a signaling molecule affecting lipolysis (17); or substrate mediators (such as adiponectin) altering insulin sensitivity (17), that all have deleterious effect on the vascular wall (127) and promote a systemic inflammatory state. Systemic and local inflammation is associated with oxidative stress, adipokine dysregulation and increased sympathetic nervous system (SNS) action (especially via γ-aminobutyric acid (GABA) which contributes to the pathogenesis of Ob-induced hypertension) (128,129,130,131), and is implicated in endothelial dysfunction, providing a key mechanism to explain increased vascular tone associated with Ob (127,131,132,133). The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self-regulate tone and to adjust blood flow and distribution in response to changes in the local environment (134). Many blood vessels respond to an increase in flow, or shear stress, by dilating. This phenomenon is designated flow-mediated dilation (FMD) (134). Thus, overall endothelial function is altered in Ob disrupting the mechanism of vascular homeostasis regulation which may lead to reductions in FMD predisposing the vessel wall leukocyte adhesion, platelet activation,
oxidative stress, thrombosis, coagulation, and inflammation, hence leading to the pathogenesis of CV disease (134). This has structural, subclinical, atherogenic implications as seen through increased thickness to the sub-endothelial layers contributing to overall arterial stiffness (84,135).

Arterial stiffness, also known as the loss of arterial elasticity, has been regarded as a reliable marker of adverse structural and functional alterations to the vascular wall, impacting overall vascular structure, vascular function and BP (136,137). BP is a well-defined stress to the arterial wall, as pressurizing a vessel distends the wall, and increase of IMT is an adaptative response to tensile stress (137,138). Along with the factors of inflammation and oxide stress, the renin-angiotensin-aldosterone system (RAAS) (altering the volume of extracellular fluid in the body, leading to increases in BP, systemic vascular resistance, and changes to chamber morphology) and genetic factors that influence the function of the vascular system in short term or the structure in long term, can induce arterial stiffness (139). In fact, there might exist a vicious circle between endothelial dysfunction and arterial stiffness. That is, endothelial dysfunction could aggravate structural stiffening and, in turn, worsen endothelial function (140), linking arterial stiffness to CV disease risk in children and adolescence with Ob (141,142,143).

Endothelial dysfunction can be studied at the macro- or micro-vascular level but only non-invasive assessment techniques are widely accepted in children, limiting micro-vascular inquiry in particular. Its association with Ob in children and adolescents is widely established at the macro-vascular level (144,145,146) even in the absence of comorbidities (147). Correlations between some inflammatory markers and endothelial dysfunction in obese
children have been reported but less is known about oxidative stress markers and endothelial function in children with Ob. Kapiotis et al. (2006) showed that obese children have higher CRP levels compared with lean children and that CRP levels are correlated with functional, structural, and biochemical signs of vascular dysfunction and low grade systemic inflammation (144). In a cross-sectional study, they compared early markers of endothelial dysfunction (FMD of the brachial artery) and morphological arterial changes (carotid intima-media thickness, cIMT) measured by high-frequency ultrasound and biochemical markers of inflammation (hsCRP, hsIL-6) and cell adhesion molecules (CAMs), including the endothelial cell specific adhesion molecule E-selectin between 145 severely obese (BMI 32.2±5.8 kg/m²) and 54 lean children (BMI 18.9±3.2 kg/m²) 12±4 years old. Obese children had significantly higher levels of hsCRP, hsIL-6, and E-selectin than healthy controls (P<0.001 for hsCRP; P<0.05 for hsIL-6; P<0.01 for E-selectin). There were no differences in the levels of ICAM-1 and VCAM-1 between groups. Obese children had lower peak FMD response (P<0.006) and increased IMT (P<0.03) compared with controls. Morbidly obese children (BMI>40 kg/m²) had the highest levels providing evidence that abnormalities of vascular function (FMD) and structure (IMT) are detectable in obese children (144).

While FMD impairment evaluates endothelial vasomotor function in large vessels (131), a principal mediator of FMD is endothelium-derived nitric oxide (NO), which possesses a number of anti-atherogenic properties (148). A lack of NO production induces vasoconstriction, leukocyte adhesion, platelet activation, oxidative stress and thrombosis (148). An impairment of nitrate-dependent vasodilation would demonstrate smooth muscle dysfunction (148). In some studies, both FMD and nitrate-dependent vasodilation have been
found to be lower in obese than in lean control children (132,149,150), but the relative role of endothelial and vascular smooth muscle dysfunction remains uncertain. In a cross-sectional study, Pena et al. (2006) measured vascular function by FMD but also by glyceryl trinitrate-mediated dilatation in 270 children (140 males, mean age 13.7±2.8 yr) including 58 obese, 53 nonobese, and 159 type 1 diabetic children (149). Glyceryl trinitrate is a NO donor that induces an increase in vessel diameter independent of the endothelium and, therefore, assesses vascular smooth muscle response (151). They found children with mild to moderate Ob had a similar degree of endothelial and vascular smooth muscle dysfunction to those with type 1 diabetes compared with nonobese youth (P<0.001) (149).

Greater arterial stiffness, IMT and endothelial dysfunction have all been reported in children with Ob at the carotid artery (20,152), pulmonary artery (153) and in the central aorta (154), although the strength of the association and mechanisms by which these effects are mediated are not fully understood including the effect of pubertal status. Puberty alters some of the inflammatory markers associated with endothelial dysfunction in obese children. Codoner-Franchet et al. (2011) reported increased serum and blood metabolites of NO and L-arginine, respectively, associated with oxidative stress and inflammation in pre-pubertal obese children (7-14 years), with higher values found in children with the greater metabolic risk (155). Gruber et al. (2008) showed lower NO bio-synthesis in pubertal obese children (156). They investigated 57 obese (BMI 30.21±5.09 and BMI SDS 5.53±2.31) and 57 normal weight (BMI 20.03±2.81 and BMI SDS 0.42±0.97) age- and gender-matched juveniles (mean age 14 years) (156). Aggoun et al. (2008) measured arterial IMT, FMD and nitroglycerin-mediated dilation by high-resolution ultrasound in 48 obese and 23 lean pre-pubertal
children (8.8+1.5 years old) and found that both central pulse pressure and IMT of the common carotid artery are not modified in pre-pubertal children with obesity, though the arterial wall properties change independently of geometry (147). Arterial wall remodelling may be emergent in pre-pubertal obese children, being sufficiently advanced to increase vessel stiffness but not enough to increase IMT (147). The persistence of adiposity during puberty may reach the state of arterial thickening, hence, endothelial dysfunction may worsen as obese children pass through puberty, accelerating the process of atherosclerosis. However, there are sex differences; the upsurge of sex hormones such as estrogen in pubertal girls may counteract impairment (157). As well, besides changes in inflammation and oxidative stress markers, in both lean and obese children, puberty is known to reduce insulin insensitivity and consequently triggers hyperinsulinaemia (106), both having a reciprocal relationship with endothelial dysfunction (158).

As a whole, overweight and Ob predisposes or is associated with numerous vascular complications such as CV disease, increasing morbidity and mortality through its impact on the macro-vascular system. Although CV disease should be rare among children, with the rise in childhood Ob, these same problems are being seen in obese children. Modifying clinical indicators of vascular dysfunction such as arterial stiffness in children is of great importance in reducing disease burden. Interventions such as exercise that can influence BP, arterial function or structure in either the short or long term, has been shown to be promising de-stiffening therapy for brachial and carotid arteries (146,159,160) but its effect on the central aorta has not been studied. Since the aorta makes the largest contribution to buffering blood
flow, and given that adolescence is a critical period associated with onset and progression of vascular complications, it is important to evaluate central vascular changes.

1.2.2.1. Vascular Structure and Function

Information on relationships between cardiac structure and function has been determined echocardiographically, with clinical expressions of disease and with clinical outcome (161). Vascular structure is a major determinant of arterial stiffness. Vessel wall compliance is dependent on the status of two major scaffolding proteins: collagen and elastin (162). When Shirwany and Zou (2010) examined stiffened vessels microscopically, they observed increased collagen and matrix metalloproteinases, fragmented and diminished elastin, abnormal and disorganised endothelium, infiltration of smooth muscle cells, macrophages and mononuclear cells (136), indicating the scaffolding changes. In addition, increased luminal pressure (such as in hypertension) also tends to favour collagen production at the expense of elastin (163), leading to hemodynamic adaptation impacting structure. In response to hemodynamic influences, a variety of adaptations or alteration in cardiac geometry (structural) and function occur in obese individuals altering preload and afterload, including aortic stiffness, LV mass and altered diastolic properties (16,132).

Left atrium and LV dimensions are significantly greater in children with Ob compared with children with a healthy BMI (164,165,166), some detecting changes as early as 2 years of age (18). Dhuper et al. (2011) collected echocardiographic data on a sample of predominantly African-American youth (213 obese, BMI of 36.53 ± 0.53 kg/m² and 130 normal-weight subjects, BMI of 19.73 ± 0.21 kg/m²) and found the obese subjects had significantly higher LV mass index (LVMI; 49.6 ± 0.9 vs. 46.0 ± 1.0 g/m2.7, P = 0.01) (166).
Greater epicardial fat (adipose tissue deposited around the heart between the pericardium and outer wall of the myocardium) (167) has also been reported in children with Ob compared to sex-matched children with healthy BMI, and is positively associated with LV mass (165), and significantly higher in pubertal obese youth (168).

The adaptive increase in LV mass is to normalize the increased wall tension (169,170) which impacts pre-load and afterload to the heart. Ob in children and adolescents is associated with an elevated blood volume (due to expanded vascular tree) (170). LV hypertrophy might represent a compensatory response to increased cardiac workload: the higher hemodynamic load, reduces LV myocardial performance, with greater force developed by the left atrium to complete LV filling. These alterations can be seen in chamber size, myocardial contractile properties (chamber strain and strain rate) (20) and pressure (diastolic and systolic dimensions) (164). Chinali et al. (2006) found that traditional indexes of LV filling that are altered in adults, might appear normal in obese adolescents but the abnormality appears in left atrial performance reflecting the late phase of LV filling (171), highlighting the progression in dysfunction.

Messerli et al. (1983) confirmed increases in intravascular volume in obese subjects and demonstrated that this elevation of CO was related primarily to augmented stroke volume (SV) rather than in heart rate (HR) (172). The observed changes in total blood volume and CO were again assumed to be secondary to metabolic demands of excess adipose tissue (172). CO was most strongly related to fat-free mass (FFM) which is also known to be higher in children and adolescents with Ob (173,174). In young adolescent females with an average BMI of 34 ± 13 kg·m², Rowland and Dunbar (2007) found a significant direct association of
BMI and resting cardiac output ($r=0.46$) and SV ($r=0.36$) (175). Giordano et al. (2003) reported resting values for cardiac output of 7.3 ± 1.9 and 5.7 ± 1.2 L·min⁻¹ ($p < 0.05$) in obese and normal weight children, respectively (176). Chinali et al. (2006) found a direct relationship between severity of obesity and both CO and SV in 14-20 year old subjects (BMI range 16 to 57kg·m⁻²) using Doppler echocardiography (171). Normal weight, overweight (BMI 85-95th percentile), and obese subjects (>95th percentile) had mean resting CO of 4.82±0.91, 5.14±0.96, and 5.31±1.12 L·min⁻¹, respectively. Average values for SV were 73±10, 77+11, and 80±13 ml (171).

Despite an indication of augmented heart size and CO, obese children and youth often demonstrate evidence of diminished myocardial function (171,177), impacting diastolic or the passive filling properties of the ventricle (174). Gutin et al. (1998) reported that among 62 children ages 7 to 13 years, percent body fat correlated negatively with lower midwall ventricular shortening fraction ($r = -0.37$) (177). Chinali et al. (2006) found a significantly lower left ventricular ejection fraction in 14-20 year old obese subjects (BMI >95th percentile) compared to a non-obese group (171). Rowland and Dunbar (2007) found a progressive decline in LV shortening fraction with increasing BMI in 39 young adolescent females ($r=-0.47$) (175). Between a BMI of 20 and 60 kg·m⁻², mean shortening fraction fell from 40 to 33 percent (but still not below lower limit of normal). The increased resting LV end diastolic volume in Ob has been interpreted as evidence of enhanced recruitment of preload reserve (Frank-Starling mechanism) but failing to increase ejection fraction (178) and may be directly related to the severity and duration of adiposity (174).
Vascular stiffening occurs as a consequence of a complex interplay between several independent, as well, as inter-dependent factors. Hemodynamic forces associated with Ob may be secondary to arterial stiffness (136) but endothelial dysfunction could aggravate structural stiffening because it interacts with impaired muscle tone by releasing vasoactive substances (such as NO) in the progression of elasticity alteration (140). Arterial stiffness, consequently, depends on cyclic strain of the arterial wall, mainly the cyclic change of BP. At a low BP level, the elastin controls the composite behaviour and the vessel wall is relatively extensible, while at a high BP level, the collagen with stiffer property is increasingly important and then the vessel wall becomes inextensible (140). Therefore, arterial stiffness increases at a higher BP even without structural change, leaving a systemically hypertensive individual with potentially serious complications. As the properties of the endothelium become altered, such as the aorta becoming stiff, the physical forces that oppose the aortic valve opening increase and can contribute to the elevation of sBP, increasing afterload and potentially contributing to target organ changes including LV hypertrophy, aortic root dilation, valvular dysfunction, and increasing overall risk of CV event (140). In the Muscatine Study, Juonala et al. (2010) first related pediatric BP levels to vascular damage and found that BP measured as young as 9 years of age predicted higher cIMT as a young adult (179). Sanchez and colleagues (2000) directly measured IMT in healthy adolescents and BP was found to be an important correlate of thicker IMT (180). A similar study in healthy German Caucasian children found thicker carotid and femoral IMT in young people with pre-hypertension who had sBP at the 90th percentile of BP (181). Unfortunately, even thicker IMT is found in young people with
clusters of CV risk factors (hypertension, Ob, and dyslipidemia) compared with patients with isolated hypertension without other risk factors (182).

The structure and function of the large arteries can now be assessed by non-invasive, high-resolution ultrasound, and endothelial dysfunction has been confirmed as an early marker of atherosclerosis that comes before plaque formation (123,138). This is impacted by the degree and duration of Ob (140) exerting further ill effects through structural and functional modifications of the arterial wall. Thus, evaluating arterial stiffness provides important information about about future risk.

1.2.2. Aortic Arterial Stiffness

The aorta functions not only as a conduit delivering blood to the tissues but also as an important modulator of the entire CV system, buffering the intermittent pulsatile output from the heart (dampening the fluctuation over the cardiac cycle, or “Windkessel Effect”; the shape of the arterial blood pressure waveform in terms of the interaction between the SV and the compliance of the aorta and large elastic arteries) (183) to provide a pulsatile flow of blood and oxygen to peripheral tissues and organs. The recurring flow is provided by the pressure created by mean BP, and a pulsatile component (pulse pressure). This pulsatile component is the consequence of intermittent ventricular ejection from the heart (the difference between sBP and dBP) and is influenced mainly by the aorta acting to minimize pulsatility (184). Therefore, by virtue of its elastic properties, the aorta influences LV function based on two properties (185): the cushioning capacity of the aorta, usually expressed in quantitative terms of compliance and distensibility, as well as, the timing and intensity of wave reflections (first, a high-pressure wave from the LV that ejects blood into the proximal
aorta propagating forward at a given speed, and, a second, reflective pressure wave rebounding after each ejection) (184). The timing of the two component pressure waves depends on aortic pulse wave velocity (AoPWV), the traveling distance of the pressure waves, and the duration of ventricular ejection. Arterial compliance, the amount of arterial expansion and recoil that occurs with the cardiac pulsation and relaxation, disturbs the pressure cycle (timing, amplitude), so when the aorta is stiff, it impairs the aortic buffering function. Alterations in arterial stiffness are therefore measured as changes in AoPWV or the arterial pulse waveform (186); the stiffer the aorta, the faster the propagation of the pulsatile flow wave (154). Indices of arterial compliance such as AoPWV and central systolic augmentation index are associated strongly with CV disease in adults and, in fact, stiffer arteries determined by AoPWV are associated with increased risk for a first CV event (187). As well, unlike PWV, which is the measurement of regional arterial stiffness in a certain segment, in this case the aorta, the measurement of changes in arterial diameter and volume can help evaluate the elasticity of the local artery known to be compromised in children and youth with Ob. An increase in arterial stiffness should be prevented to mitigate the progression of CV disease. Because the aorta is not an ideally accessible vessel, more indirect avenues and techniques have evolved to assess aortic stiffness in the pediatric population and the impact of health status and lifestyle factors such as exercise intervention can be studied. This is useful to determine if arterial stiffness cannot just be halted but rather reversed in the at-risk, obese youngster. Because PWV is a validated method, easy to perform, highly reproducible, and low cost, the demonstration of its usefulness for evaluating endothelial dysfunction should be of major interest.
1.2.3. Adiposity and Respiratory Health

Pulmonary function abnormalities such as reductions in lung volumes (189), and expiratory flow rates (190) including such mechanical constraints as decreased chest wall compliance, increased respiratory resistance, increased work of breathing (191) and hypoventilation (190) are reported complications of Ob in adults (189,190,192). However, studies investigating pulmonary function in obese children and adolescents are scant. A few studies have confirmed various abnormal lung functions in obese pediatric populations such as significant decreases in maximum voluntary ventilation (MVV), expiratory reserve volume (ERV), flow rates, and functional residual capacity (FRC) (193,194,195), however, many studies evaluated lung function by spirometry alone and indirect methods, such as anthropometric and skinfold measurement for evaluating volume and distribution of body fat (196,197,198,199) making it difficult to characterize pediatric response and weight status.

The predominant pulmonary function abnormality detected by Paralikar (2012) in a cross-sectional study of 30 obese adolescent South Asian boys (BMI=29.4±4.12 kg/m² compared to the control group's 19.51±1.23 kg/m², and age 15.8±1.37 and 15.9±1.4 years, respectively) was a reduction in the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FEV₁/FVC) and MVV (199). A decrease in FEV₁/FVC was also observed by Inselman et al. (195) and Mallory et al (200). Airflow obstruction refers primarily to a finding, by spirometry, of a reduced expiratory airflow compared to the total amount of air exhaled or a reduction in FEV₁/FVC (190). However, no significant reduction was detected by Bossisio et al (201) for FEV₁/FVC, which may be indicative of airflow limitation without
significant obstruction, suggesting the relationship requires further study in the Ob pediatric population.

Li et al. (2003) used dual energy x-ray absorptiometry (DEXA) scan to quantify adiposity to study 64 obese children (16 girls and 48 boys with median age and BMI of 12 years (interquartile range (IQR): 10–14) and 30.1 kg/m² (IQR: 27.2–32.8) (193). Standardized pulmonary function tests (spirometry, lung volumes, and single breath diffusion capacity for carbon monoxide) showed reduction in FRC and diffusion impairment were the most common abnormalities found. Reduction in static lung volume was correlated with the degree of obesity (193). Davidson et al. (2013) confirmed that increasing weight status in male (n = 168) and female (n = 159) children and adolescents is associated with a general reduction in lung volume measurement in a review of medical records. Percent predicted ERV was lowest in the obese group (BMI>95th percentile; P < 0.001) while residual volume (RV) was lowest in the overweight (BMI 85th-95th percentile) and obese groups (P < 0.001) (202).

Additionally, dyspnea or exertional breathlessness is a common symptom often reported by obese adults (190,191,192). Sjöström et al. (1992) found that 80% of obese, middle aged subjects reported shortness of breath after climbing two flights of stairs compared with only 16% of similarly-aged, non-obese controls (203). More recently, Sin et al. (2002) found that obese adults were 2.6 times more likely to complain of dyspnea when walking up a hill compared to healthy controls (204), however, this finding is not confirmed in children (205,206,207). Originally defined as “pathologic breathlessness” or an uncomfortable awareness of breathing or an increased respiratory effort that is unpleasant and regarded as inappropriate (208), dyspnea is difficult to evaluate because it is a subjective
sensation and its apparent severity may or may not correlate with physiologic measurements in Ob (209,210). This definition is even less clearly defined as a limitation in obese children, especially the very young that may have difficulty accurately perceiving and reporting symptoms (211,212,213). Castro-Rodriguez et al. (2007) (214) have identified five possible biological mechanisms which can explain the relationship between asthma report and Ob: mechanical effects of Ob on respiratory function, altered immune response and inflammatory activation of specific gene regions, hormonal influences related to gender (an elevated BMI between age 6 and 11 is associated with an increased risk of asthma in girls) (215), and influence of diet and PA (214).

1.2.3.1. Obesity as a Restrictive Disorder

Ob places mechanical limitations on the chest, reducing chest wall compliance (the chest wall becomes stiffer, reducing its elasticity), possibly due to the increased weight of the fat mass directly impeding thoracic expansion (216). To compensate, overweight adults typically breathe at high frequencies (F_b) with shallow tidal volumes (V_T) to minimize work against elastic forces (217); the higher f_b and lower V_T, alters V_o/V_T, potentially decreasing gas exchange as they hyperventilate (218). Dempsey et al (1966) suggests, in some obese, PaCO_2 is allowed to increase because the work to move the chest wall becomes very large with some studies reporting differences in responsiveness to CO_2 (218). These differences in the ventilatory dynamics result in obese individuals working harder to ventilate (218). It has also been suggested that obese adults have altered inspiratory drive (V_T/T_i) increasing each breath spent in inhalation (T_i) suggesting some impairment of respiratory muscle function (216,217,218). However, Rowland (2005) notes that children have their own unique
physiology and do not respond similarly to adults in many ways (219); compared to adults, normal children (not specifically trained) have smaller airways relative to lung size (220) and ventilation at rest is higher in children than in adults (221). During exercise the ventilatory equivalent to oxygen is also higher in children (222,223) and they ventilate out of proportion to the metabolic demands of performing work (224,225,226). Moreover, at rest and during exercise, mean inspiratory flow and mouth occlusion pressure, both indices of the inspiratory neural drive, are higher in the younger subjects (223,227,228). Arterial blood gas tensions, however, do not differ (221) and remain near resting levels during effort (229,230).

Gratas-Delamarche et al. (1993) measured the CO₂ ventilatory response in 9 prepubertal boys (10.3±0.1 years) and in 10 adults (24.9±0.8 years) at rest and during moderate exercise (\(V_{\text{CO}_2}=20 \text{ ml·kg}^{-1}·\text{min}^{-1}\)) using the CO₂-rebreathing method and found significantly lower arterial carbon dioxide pressure (PCO₂) and higher ventilatory equivalent for oxygen (\(V_{E}/V_{O_2}\)) in children compared to adults, which was the result of a higher F\(_b\) in the children (223). They concluded that children have, mainly during exercise, a greater sensitivity of the respiratory centres than adults. This greater CO₂ sensitivity could partly explain their higher ventilation during exercise, though greater CO₂ production probably plays a role at rest (223). A hypothesis to explain the higher ventilation level in children put forward by Gratas-Delamarche et al. (1993) was that children’s relatively rapid and shallow breathing would not allow them to wash out alveolar air as efficiently as adults, but more particularly, could also induce an increase in ventilatory work because of an increase in viscous and turbulent work. Consequently, owing to this specific ventilatory response to
exercise, a specific breathing strategy might be observed in children who ventilate more closely to their mechanical limit at high exercise intensity than normal adults (223).

Because there is conflicting evidence on the effect of Ob associated with changes in lung function in children and adolescents with and without asthma, Forno et al. (2018) completed a meta-analysis of 62 studies to elucidate the relationship between overweight or Ob and lung function, and whether such relationship differs by age group or by asthma status (231). The results showed all measures of lung function were decreased among obese subjects. Obese adults showed a pattern (lower FEV₁, FVC, TLC, and RV) different from obese children (more pronounced FEV₁/FVC deficit with unchanged FEV₁ or FVC). There were also seemingly different patterns by asthma status, in that participants without asthma had more marked decreases in FEV₁, TLC, RV, and FRC than those with asthma (231). Compared with overweight participants, the obese also had more marked decrements in FEV₁, FVC, TLC, RV, and FRC. McMurray et al. (2011) considered the ventilatory responses of 73 overweight youth (BMI>85th percentile) compared to 73 age-, sex- and height-matched normal weight youth (BMI<85th percentile), during 15 minutes of rest and steady-state exercise at 4, 5.6 and 8 kph (232). Overweight youth had higher oxygen uptakes (VO₂, mL/min), minute ventilation (Vₑ), V₉, Fₚ, physiological dead air space (V₀) and V₀/V₉ ratios than normal weight youth (P<0.02); however, end-tidal CO₂ (Pₑ₉CO₂), Vₑ/VO₂ and Vₑ/VCO₂ were similar (232). Inspiratory drive (V₉/ti) were greater for overweight youth at rest and during exercise. The correlation between Pₑ₉CO₂ and inspiratory drive was significant for the overweight group at 5.6 and 8 kph (r=0.23-0.44), but not significant for the normal weight youth (r=-0.04 to 0.10). The authors concluded that the greater drive, respiratory frequency and physiologic dead air
space of overweight youth suggest that their adiposity modifies ventilation dynamics during exercise (232). However, the modifications appeared to have met the metabolic demands of the exercise.

The energy expenditure of the breathing muscles to achieve $V_E$ is influenced by both the compliance (distensibility) of the lung and chest wall and the resistance to flow offered by the conducting airways (219,225). These aspects of lung mechanics and flow dynamics change as children grow with the compliance of the lung improving during childhood and the airway resistance progressively diminishing (219). The complication of mass loading on the chest wall in the obese child constrains the improvement noted in early development (231,232,233). This restrictive-type disorder impairs the ability of the child to expand their chest but also increases the elastic work of breathing to overcome the elastic recoil of the chest wall resulting in air hunger or dyspnea (193,194,195) explaining the significant decreases in FRC, ERV, flow rates and MVV noted in obese children and adolescents (193).

The reduction in $FEV_{1.0}/FVC$ ratio indicates airway narrowing without obstructive impairment (199) results indicative of airflow limitation typical of a restrictive not obstructive lung disorder. A decrease in maximum voluntary ventilation in Ob indicates a limit to the movement of air into and out of the lungs during continued maximal effort (199). It is hypothesized that some obese subjects manifest peripheral airway abnormalities, suggested by reduced maximum expiratory flow rates at low lung volumes and air trapping (193,199). As a result of air trapping, inspiratory muscles are placed at a mechanical disadvantage leading to lower inspiratory pressure and flow, and reduced respiratory muscle strength, causing lower MVV (199). In addition, decreased MVV may reflect extrinsic mechanical compression
on the lung and the thorax reducing room for lung expansion during inflation (216). Most studies indicate an inverse relationship with waist circumference and hip circumference, and values of pulmonary function (192,198,235). In the study by Paralikar et al. (2012), waist-to-hip ratio was indeed negatively correlated with MVV and FEV\textsubscript{25-75\%} in obese adolescent boys (199). One possible mechanism is that there is a mechanical limitation of chest expansion during the FVC manoeuvre and that increased abdominal mass may impede the descent of the diaphragm and increase the thoracic pressure (189,199). Also, abdominal adiposity is likely to reduce ERV again by compressing the lungs and diaphragm (192).

1.2.3.2. Obesity as an Obstructive Disorder

The above outlines Ob as primarily a restrictive disease in terms of pulmonary function but there may also be an obstructive component for some: in other words, these categories are not mutually exclusive; many obese adults with a restrictive disease may have an obstructive component (192,204,235). Diseases such as asthma are reported at greater rates in the obese; in Canada and the United States, 8.8%–9.2% of obese adults reported having received a diagnosis of asthma from a physician, as compared with 4%–5% of non-obese adults (236,237,238), but in children there is controversy in the literature interpreting the rates. Part of the increase in prevalence may be attributable to changes in diagnostic labelling. Asthma defined by parental reports, physician diagnoses or pulmonary function testing (PFT) are varied and contribute to the trouble distinguishing actual cases (239). Asthma is characterized by airways that are abnormally responsive to a variety of stimuli or triggers (240); linked to Ob, the pathophysiology may include psychological factors, mechanical factors and hormonal factors (241). The airway obstruction may be caused by
chronic inflammation of the Ob condition itself that stimulates increases in mucous production and thickening of the airway walls (242, 243). In children, it is possible that as their airways grow in size, the obstruction may become less noticeable (241) or may even improve (242). In a Dutch birth cohort study (244), children had an increased risk of bronchial hyper-responsiveness (dyspnea) at age 8 years if they had high BMI at 6 to 7 years of age with or without increased BMI at an earlier age. When BMI normalized, over a longitudinal follow-up, increased bronchial hyper-responsiveness was reduced (244). This might suggest that asthma is over-diagnosed in those that carry extra weight around their chest due to complaints of “breathing heavy”, “gasping” and “breathing more” (245), however, obese individuals may instead experience dyspnea due to reduced compliance of chest wall, increased airway resistance from narrowing of airways due to pressure-load, or by hypoxemia cause by ventilation-perfusion mismatch resulting from atelectasis at the lung (213). Garfinkel et al. (1992) even demonstrated that individuals who thought they were limited by exercise-induced asthma were, in fact, experiencing dyspnea from poor cardiorespiratory fitness (246). The consequence of the asthma over-diagnosis is that there might be an inappropriate prescription of short-acting bronchodilators or corticosteroids for Ob-related dyspnea that does not represent reversible airway obstruction. Dyspnea, or breathing discomfort, is a complex symptom comprising multiple qualitatively distinct sensations (247) which might provide insight in the underlying physical abnormalities producing the sensation. Marinov (2002) performed incremental cardiopulmonary exercise testing and found that obese children rated perceived exertion (RPE) and had awareness of fatigue significantly higher than controls despite standard workload (Borg score 6.2±1.2 versus 5.2±1.1; p<0.001)
They confirmed that absolute metabolic cost of exercise was higher in the obese group (shorter duration on treadmill and higher absolute VO$_2$) compared with healthy weighted controls but both groups had similar ventilatory efficiency ($V_E$, $V_T$ adjusted for body mass) (248). A child who comes with an inhaler or attitudes towards their ability to participate in PA, may limit their movement experience especially as exercise and increasing intensity might trigger breathlessness symptoms and they perceive it to be unsafe. As these conceptions may discourage children from having an active healthy lifestyle, or limit their adherence to an exercise intervention, it is important to determine an effective preventive treatment and counsel these children to not avoid PA.

1.2.4. Role of Physical Activity in Obesity Management

1.2.4.1. General Role of Physical Activity

Regular PA has been considered an effective strategy for improving health and quality of life in both adults and youth (249). This view has been reinforced by the negative association between physical fitness and the development of chronic diseases (88,250). However, increasing sedentary rates (251) and the associated increasing prevalence of Ob severity (66,67,68,69,70,71), highlights that there still is a need for identifying effective methods of prescribing PA. Many studies are focused on multiple lifestyle interventions, for example, diet and PA, in the prevention and treatment of overweight and Ob in children and adolescents (252), and most studies use BMI as the most common method to assess overweight and Ob in children and adolescents reporting a modest to non-significant change in BMI following the intervention (253,254). Consequently, the independent effects of an intervention involving PA on health outcomes is needed to be clarified including dose-
response, optimal modality of engaging in PA, and long term sustainability. In a systematic review of supervised exercise interventions, Atlantis (2006) confirmed that treatment efficacy utilizing exercise alone remains unclear for children and adolescents; 14 studies qualified for their meta-analysis, of which they cited none having a robust design (255). Based on the small number of short-term, randomized trials of different intensities, durations and types of activities, an aerobic exercise prescription of 155-180 minutes/week at moderate to high intensity seemed effective for reducing body fat in overweight children and adolescents, but effects on body weight and central Ob were inconclusive (255). With so few PA intervention studies available and with many focused on non-representative samples of obese and overweight youth who may be more susceptible to change in comparison with the general population (256), information obtained from intervention samples to date have major limitations.

Evidence linking MVPA and CV health outcomes among youth is only just emerging as most data to date has been derived from cross-sectional studies (257,258,259). However, there is limited clinical evidence pertaining to the quantity of MVPA necessary to prevent or reduce CV disease risk (260). It may be that the inverse association between objectively measured MVPA and cardiometabolic risk factors is driven by the time spent in vigorous-intensity PA (261,262). Carson et al. (2014) recently demonstrated that vigourous PA has a significant influence over moderate intensity in terms of reducing cardiometabolic risk in 9-15 year olds when followed up 2 years later (263). Deciding on the correct method of getting obese children to be physically active, in particular, remains a challenge. The lack of success of many interventions illustrates just how difficult it is to create an intervention strategy that
is of sustained interest to the pediatric population (264). Much of the previous intervention work with obese youngsters has relied on an adult evidence-base (264,265) and although short-term success is regularly apparent (266,267), methodological issues abound such as consistency with which the interventions were delivered and the quantity of PA to which children are exposed (264,265,268,269). Therefore, it is unclear if there is a problem with the PA intervention itself or the delivery of it. Also, longer-term adherence has been limited (268,269,270) as very few studies provided any follow-up data to determine if the changes found post-intervention were maintained (271). Younger children may prefer play activities over formal training programs (272), whereas adolescents consistently correlate feeling confident in doing the activity as important (273) and, therefore, types of activities included is an important consideration in intervention design where low motivation and perseverance might be an intrinsic problem in influencing obese children or inactive youth. Successful interventions require sustained interest by the child and youth to participate and remain physically active with the proper intensity design for physiological adaptation (269,270).

The main characteristics of PA designed to derive health benefits that have been widely adopted include intensity, duration, frequency and mode of exercises and activities (274). Exercise prescription generally characterizes the dose and objective physiological markers (such as HR) are often used for prescriptive purposes during exercise training programs. Intensity has been given particular attention in the literature because of its relative efficacy in improving cardiorespiratory fitness (275,276) and weight management programs (277), the latter being due to higher rates of energy expenditure during (277,278) and after (279) exercise. Intensity can be prescribed according to the American College of Sports
Medicine (ACSM) guidelines based upon ratings of perceived exertion, metabolic equivalents (METs), estimated or measured maximal heart rate (HRmax), and maximal oxygen uptake (VO2max) (274). The method based on the relationship between different percentages of HRmax and VO2max has been the most commonly used strategy for intensity prescription and has traditionally been favoured by the ACSM and, more recently, the percentage of the HR reserve (%HRR) (280) and percentage of the VO2 reserve (%VO2R) (281). For children, a VO2max plateau is rarely obtained so peak VO2 is considered a surrogate (282). In either case, this has implications for requiring a true maximum in order to establish VO2max and reserve, which key investigators (282,283,284) argue cannot be established without the use of some additional criteria (such as supramaximal VO2) beyond the usual secondary targets such as maximum HR, Respiratory Exchange Ratio (RER), and volitional fatigue to satisfy maximal effort in young people. Testing obese children and youth for this specific prescription is problematic due to limitations such as improperly scaled lab equipment, lack of appropriate testing protocols, or deconditioned individuals not unaccustomed to hard exercise, as examples, potentially underestimating a maximal response.

Information on the effect of exercise interventions of different intensities and durations on CV risk factors in youth is limited. It seems that each exercise program design has its own distinct cardio-protective effects on adolescent youth. Both brief, high-intensity interval training (HIIT) and moderate-intensity training (MIIT) have been shown to be effective in eliciting favourable changes in physical endurance capacity, anaerobic threshold, total cholesterol, LDL-c, serum TG, waist circumference, insulin sensitivity, and glucose control (285). Buchan et al (2011) studied a cohort of non-obese adolescents (47 boys, 10
girls, 16.4±0.7 years of age) randomized to HIIT (n=17) or MIIT (n=16) exercise training or a control group (no training) over 7 weeks (286). Each session consisted of either four to six repeats of maximal sprint running within a 20 meter area with 20-30 seconds of recovery (HIIT) or 20 minute continuous running within a 20 meter area at 70% VO$_2$max (MIIT) (286). Each exercise protocol elicited positive training results showing improvements in aerobic capacity post-intervention even though total exercise commitment was 15% lower in the HIIT group (420 minutes for MIIT versus 63 minutes for HIIT). Total estimated energy expenditure was lower in the HIIT group (907.2 kcals versus 4410 kcals for MIIT). The MIIT group further significantly improved risk factors related to insulin insensitivity whereas the HIIT group improved in sBP ($p<0.05$). Although there were no changes in body weight under either protocol, % body fat improved in the MIIT group (286).

Effective exercise prescription should not only ensure a sufficient training stimulus to yield relevant health benefits (226) but should do so without over-exertion, unnecessary discomfort, or risk of injury, thereby promoting exercise adherence. The optimal type and amount of intentional PA has not been established for those that carry extra weight, and there is a need to consider the potential of non-traditional exercise interventions as a means to improve CV risk profile and overall fitness. Thus, the door is open to the possibility of designing specific training protocols depending on the disease.

1.2.4.2. Specific Role of Exercise for Weight Control

The few studies on exercise intervention and Ob tend to report weak to modest relationships between exercise and weight control but programs combining diet with PA and behavioural change can have a small, short term effect in reducing weight among children
and adolescents who are overweight or obese (253,254). Two Cochrane reviews that analyzed all available studies in these age groups found that interventions combining diet, PA, and behaviour change had a small, short term effect in reducing children’s body weight, with a mean weight loss of 1.45 kg (95% confidence interval –1.88 to –1.02; P<0.001) in 6-11 year olds (253) and a mean of 3.67 kg (–5.21 to –2.13) in the adolescents 12-17 years (254). This type of intervention also reduced BMI (mean difference –0.53 g/m$^2$ (–0.82 to –0.24); P<0.001) and the BMI z-score. Variations in the effects of age, sex and exercise dose on changes in Ob measures in response to exercise training, however, have not been systematically addressed in the literature. Thus, no conclusions can be drawn on the potential moderating effects of these variables.

Health outcomes discussed in literature are often independent of changes in BMI although actual adiposity may be reduced (287,288). At the present time, evidence is limited to explain whether other factors of the energy balance equation, including compensatory changes in non-exercise PA, resting metabolic rate, movement efficiency, or changes in lean mass, are responsible for limited weight change with exercise training. Stoner et al. (2016) analyzed exercise interventions aimed at improving cardiometabolic health specifically and found reduced BMI (mean 2.0 kg/m$^2$, 95% CI 1.5–2.5; ES moderate), body weight (mean 3.7 kg, 95% CI 1.7–5.8; ES small), body fat percentage (3.1%, 95% CI 2.2–4.1; ES small), waist circumference (3.0 cm, 95% CI 1.3–4.8; ES small) in 13 trials analyzed, but the increase (improvement) in lean mass was trivial (mean 1.6 kg, 95% CI 0.5–2.6) (289). The mean age of participants ranged from 12.2 years (range 10–16 years) to 17.0 years (SD 0.6) and the duration of the interventions varied in length from 8 to 36 weeks, with a median of 12 weeks.
The trials included aerobic exercise only \( (n=5) \), aerobic plus strength training \( (n=1) \), aerobic exercise plus nutrition/behaviour co-intervention \( (n=6) \), strength training plus nutrition co-intervention \( (n=2) \), and aerobic plus strength training and nutrition/behaviour co-intervention \( (n=1) \) (289). Exercise programs alone can have positive effects on BMI and measures of adiposity over short-term (i.e. 10 weeks) (290) and moderate (4 months) time-frames (261,291) in children. However, for the obese population, exercise prescription alone may not affect weight loss at all and that diet modification may be a primary driver. The obese child may not experience weight loss with exercise but there is potentially weight redistribution in patterning and type and must be considered when evaluating exercise effects. It is evident that focus should therefore be shifted away from BMI as a marker of intervention success, and attention paid to health-related outcomes.

Despite evidence that weight loss may be minimal with exercise training, under the traditional biomedical model of medical training, however, physicians prescribe weight loss to manage Ob. While not trained in weight loss practices necessarily, this simple advice seems to have unintended consequences, and serve as a consequence to health care as rates of Ob go up. In response, Exercise is Medicine Canada\(^\text{®} \) (EIMC) initiatives (292), hosted by Canadian Society for Exercise Physiology (CSEP), designed to promote PA, health promotion and wellness, have argued that PA is an integral part of prevention and treatment of chronic disease in the Canadian Health Care System and should be prescribed as a weight control alternate. The goals of Exercise is Medicine Canada are to: increase the number of health care professionals who are assessing, prescribing and counseling patients in PA and facilitate the collaboration between health care professionals. Although some argue that physicians
are no more trained in exercise prescription than they are weight loss methodology (293), the EIMC provides evidence-based, 24-hour movement guidelines (294) for both children and adults, integrating PA, sedentary behaviour, and sleep to support consultation. Long term embracement of this posit has yet to be established so it cannot be determined if exercise prescription from the clinician is a solution. As well, exercise may alter body composition although body mass remains constant, thus, BMI as a primary outcome measure may underestimate the effectiveness of the intervention, particularly with respect its role in modifying CV risk in Ob children and adolescents.

1.2.4.3. Specific Role of Exercise for Vascular Health

Although exercise may not serve to control weight for the morbidly obese, it has been shown to provide cardio-protection such as improving the endothelium and overall function of conductance (aorta and brachial) and resistance (coronary) arteries (295). The potential of exercise to reverse endothelial dysfunction and arterial remodeling and stiffness is described in animal models (296) and adults (191,204,248,249,250) but much less is known about the reversibility of cardiac abnormalities in obese children and adolescents. In most studies, brachial artery FMD has been used as a standard approach in clinical studies for the non-invasive assessment of endothelial function in large vessels, and has been shown to be useful for paediatric CV evaluation (131,132,133,146,297). Shear stress-mediated upregulation of NO synthase expression, resulting from increased blood flow across the endothelium, is explained as a physiologic mechanism for improvement in adults (298). Acute changes in flow and shear stress stimulate the release of NO during exercise in animals (296) and adults (298) and thereby increases blood flow through conduit arteries further stressing arteries. This
same mechanism, vessel wall shear stress-related improvement in NO availability, as well as, possible changes in free radical degradation of NO and fibrinolytic process have been hypothesized for children and adolescents (146,148,299), however, a clear picture is yet to emerge, and conflicted regarding changes to oxidative markers (300,301). Few studies have considered endothelial dysfunction and effects of exercise alone and no studies have considered whether exercise reverses endothelial dysfunction of the aorta in children.

Kelly et al. (2007) studied 19 overweight children randomly assigned to an aerobic exercise training or sedentary control group for 8 weeks (300). Measurements included peak oxygen uptake (\(\dot{V}O_2\)peak), body weight and composition, adipokines (C-reactive protein, interleukin 6, TNF-\(\alpha\), adiponectin, leptin, and resistin), and oxidative stress (8-isoprostane). There were no differences between groups for change in body weight or composition over the 8 weeks. Exercise training improved \(\dot{V}O_2\)peak (exercise group, 1.64 ± 0.13 to 1.85 ± 0.17L/min vs control group, 1.83 ± 0.12 to 1.60 ± 0.13 L/min, \(P<.05\)) but did not change any of the measured adipokines or the marker of systemic oxidative stress (300). Therefore, exercise training, despite improving fitness level, did not improve the adipokine profile or levels of systemic oxidative stress in overweight children. It is important to note that exercise training did not change body weight or composition as measured by body mass, BMI, body fat percentage, and percent trunk fat. From this, it seems that without concomitant weight loss or changes in body composition, exercise may have little to no effect on adipokines and oxidative stress.

Exercise may serve to lower the elevated BP and arterial stiffness associated with endothelial and smooth muscle cell dysfunction seen in children and adolescents by
improving endothelial-dependent vasodilator response and enhancing vasoconstrictor response (302). Farpour-Lambert et al. (301) performed a 3-month randomized controlled trial on obese pre-pubescent children (age 8.9±1.5 years) to investigate the effects of a training intervention on blood pressure and early markers of atherosclerosis (endothelial and smooth muscle cell functions, IMT and arterial stiffness) (301). To measure endothelial function, they used non-invasive measurement of the IMT at the common carotid artery and endothelial and smooth muscle cell functions (measured by brachial FMD) using real-time B-mode Ultrasound. After the 3 month exercise intervention they were able to show a decrease in BP (-7 to -12 mmHg for sBP and from -2 to -7 mmHg for dBP), BMI z-score, and total and abdominal adiposity and an increase in cardiorespiratory fitness. The continuation of the exercise intervention for a sub-group for an additional 3 months lead to a further decrease in blood pressure, a reduction of arterial stiffness and a stabilization of the intimal media thickness (301). Their changes were independent of body weight or fat reduction and had greater magnitude in hypertensive participants. Although their changes to BP were not associated with improved endothelial or smooth muscle cell function or arterial stiffness in the first 3 months, they were able to demonstrate a delayed improvement in arterial stiffness and stabilizing of IMT in the exercise group compared to the control over a longer period of intervention (301).

Watts et al. (2004) demonstrated that conduit vessel function could be normalized with exercise: after an 8-week circuit training intervention (three 60 minute sessions per week comprised of resistance and cycle ergometry exercises) (146); in a randomized cross-over protocol they showed that, compared to lean controls, n=19 obese youth (14±1.5 years)
who all had impaired FMD before exercise, had significantly improved brachial-artery FMD post-intervention (p<0.5) (146). This is consistent with adult literature where evidence has shown that HIIT results had greatest improvement in endothelial function possibly because of greater shear stress-induced by high intensity (204). Regarding training cessation, exercise-induced improvement in FMD in the Watts et al. protocol did not persist after only 6 weeks of inactivity during washout period in those obese children trained first (146).

The appropriate exercise intensity required to obtain beneficial effect on endothelial function remains understudied, but it seems continued exercise training is important. Meyer et al. (2006) assessed the effect of a 6-month exercise program in obese children on cIMT using FMD and cardiovascular risk factors (159). Sixty-seven obese subjects (age 14.7±2.2 years) were randomly assigned to a 6 month exercise or non-exercise protocol. The exercise group was required attend 1 hour sessions, 3 times per week and activities included swimming and aqua aerobic training, sports games, and walking (159). The CV risk profile included BMI, body fat mass, BP, laboratory parameters (insulin, insulin resistance, triglycerides, HDL-c, low-density lipoprotein [LDL]/HDL ratio, fibrinogen, and CRP, echocardiographic measurements, and physical fitness at baseline. Significant improvements were observed in the exercise group for cIMT (0.44 ± 0.08 mm, P= 0.012, −6.3%) and FMD (7.71 ± 2.53%, P<0.001, +127%). This improvement correlated with reduced CV risk factors, such as BMI SDS, body fat mass, waist/hip ratio, ambulatory sBP, fasting insulin, triglycerides, LDL/HDL ratio, and low-degree inflammation (CRP, fibrinogen) (159), showing that regular exercise over 6 months restores endothelial function and improves cIMT associated with an improved CV risk profile in obese adolescents.
These studies showed improved endothelium-dependent vasodilation even in the absence of change in body mass and composition. Furthermore, in the absence of change in body weight, body fat and trunk fat, exercise training alone did not diminish oxidative stress or adipocytokines levels (300). These results suggest that fat reduction (especially visceral fat) is a key mechanism underlying inflammation and oxidative status. However, the benefits of exercise in the vascular system involve more than the amount of fat and linking other parameters of arterial stiffness to endothelial dysfunction in obese children and adolescents, may contribute to better characterize CV risk in its early stages. As well, further study is required to see if exercise has these same effects on central artery function. Prospective studies have not been conducted to determine if exercise can reverse changes in aortic function. Given that AoPWV, an indirect measure of arterial stiffness, is increased in obese children and adolescents (154), further research considering the exercise effects on AoPWV and other aortic indices, might be useful in helping to risk stratify obese youth and guide exercise prescription.

1.2.4.4. Specific Role of Exercise for Respiratory Health

Children are receptive to exercise training that significantly increases their peak oxygen consumption (peak VO₂) (284,303,304,305). During such training, respiratory muscles are stimulated increasing their strength and/or endurance permitting changes to the structural properties of the respiratory system including enhanced development of FVC and or expiratory flow (306). Unfortunately, the training effects of running on these pulmonary function parameters are not well documented in children and certainly not well described in children with Ob. Running better reflects the weight bearing activities of daily life and are
important to consider when evaluating functional exercise capacity so these activities can be prescribed to better reflect the highly sporadic, high-intensity natural play patterns of children. For healthy children, much of the literature has focused on aquatic activities (307,308) particularly related to the pressure load resulting from immersion. Koch and Eriksson (1973) examined running in children longitudinally and found no training effect on vital capacity and FEV$_{1.0}$ after 4 months of endurance training in 11-13 year old children despite improvement in aerobic capability (305). A possible interaction between training effects and the stages of maturation were not considered. Nourry et al. (2005) investigated short duration running training on resting and exercise lung function in healthy pre-pubescent children (306). After an 8-week period of HIIT running, they showed enhanced resting pulmonary function (increased FVC, FEV$_{1.0}$ and peak expiratory flow) and deeper $V_T$ reflecting a better exercise ventilation in prepubescent children compared to controls (306).

Because of the respiratory factors that accompanying Ob in pediatric populations such as significant decreases in thoracic compliance, increased airway resistance, and breathing at low pulmonary volumes contributing to ventilatory constraint (increased expiratory flow limitation) (190,193,194,195,309,310), the ventilatory response to exercise has been described as excessive relative to metabolic demand in obese children (224,225,226). The type of work is important to consider as it has been shown that the increased metabolic cost of weight-bearing exercise (e.g. walking) in obese women (311) and adolescent girls (312) is amplified for a given external work rate when compared with non-weight bearing exercise (e.g. cycling).
The characteristic work of the respiratory system in obese children (decreased $V_T$ and the increased frequency of breathing), may provide the reason for the lowered effort abilities and the higher metabolic cost of work. However, this characterization may not be true at all intensities and is not clearly established in children. Exertional breathlessness has been reported in obese children (248) and can be a barrier to the achievement of recommended levels of PA in this population (26,313). However, it remains unclear whether this breathlessness is due to the increased metabolic cost of locomotion associated with obesity, altered perception of effort, altered breathing strategy or ventilatory constraint resulting from increased thoracic fat mass (314). Ventilatory constraint refers to the extent of expiratory flow limitation, alterations in the regulation of end-expiratory lung volume (EELV) relative to total lung capacity, and a proposed estimate of ventilatory capacity based on the shape of the maximal flow volume loop and the breathing strategy (regulation of EELV and inspiratory lung volumes, EILV) adopted during exercise (315,316).

To measure ventilatory exercise response, submaximal compensation points have been considered (317). The respiratory compensation point marks the onset of hyperventilation during incremental exercise, that is, a loss of linearity in a plot between pulmonary ventilation and production of carbon dioxide ($VCO_2$) (317). Maciejczyk et al. (2014) did not show worse breathing efficiency in overweight children (318). Instead, they showed that when incrementally tested on a cycle ergometer, the respiratory compensation point (detected by power output, point at lower intensity where $V_E/VO_2$ ratio and $FE\text{O}_2$ reach a minimum) occurred earlier in overweight boys than normal-weighted boys and at a significantly ($p<0.05$) lower rate relative to body mass power output but when workloads
were adjusted relative to a secondary ventilatory threshold (higher threshold detected by the power output at which the $V_e/V\text{CO}_{2}$ ratio reached a minimum and the $F_e\text{CO}_2$ reached a maximum), physiological response (absolute and relative to fat-free mass, $O_2$ uptake, HR, $V_e$, $V_T$, and $F_b$) was similar (318). As the boys were followed longitudinally (from age of 9–10 years, until age at peak height velocity (APHV) of 13–14 years), pulmonary efficiency improved with age in both groups (although puberty marking decreases in performance); similarly, breathing pattern including $F_b$ and $V_T$, at the respiratory compensation point was similar in both groups observed with age (318). It may mean that this unfavourable breathing pattern occurs only at the maximum intensity of work and does not occur at the sub-maximal efforts, and therefore may not be a limitation for overweight children to exercise at moderate intensities.

Mendelson et al. (2012) found that after 12-weeks of exercise training, obese adolescents showed improved pulmonary function at rest (static inspiratory muscle strength) and exercise (greater operating lung volumes and delayed expiratory flow limitation) despite lack of decrease in trunk fat and body weight (319). Furthermore, they found that EELV and EILV were greater during submaximal exercise and that the expiratory flow limitation was delayed by not accompanied by an increase in $V_T$. They reported that their obese youth breathed at higher lung volumes and increased the $V_T$ by encroaching on inspiratory reserve volume following the training period (319). Although Mendelson’s group could show an improvement in resting pulmonary function, the modifications did not entirely account for improved dyspnea and exercise performance in obese adolescents. In more recent work, after exercise training, Mendelson et al. (2014) found that Ob adolescents breathed at higher
lung volumes, as indicated by increased EELV and EILV (314). These findings are consistent with previous studies in obese adults, where the authors suggested that this breathing strategy places the exercise flow-volume loop in a more advantageous position within the maximal flow-volume loop, thus minimizing the risk for developing expiratory flow limitation during exercise (315,316). They suggested one potential mechanism to explain the improved breathing strategy and exertional dyspnea observed in Ob is greater inspiratory muscle strength, as evidenced by increased maximal inspiratory pressure (315). Reduced exertional dyspnea is consistent with increased maximal inspiratory pressure because less central drive is required for a given force generated by the muscle (217). Kaufman et al. (2006) also demonstrated improved ventilatory efficiency after 8 weeks of cycle training in n=20 overweight children (BMI>85th % percentile) compared to a non-exercising control group despite no changes to body fatness (320). This may suggest that some of the limitations of Ob on ventilatory efficiency might not be solely attributable to the additional body weight but could be a manifestation of the untrained state that is typically associated with Ob. However, when taking into account body weight, there have been conflicting data on the effects of overweight on levels of cardiorespiratory fitness (321,322,323). Sandercock et al. (2010) studied 10 year old English children (n=303; 158 boys and 145 girls) longitudinally (from 1998-2008) measuring secular changes in BMI and cardiorespiratory fitness based on 20 m shuttle-run test performance (324). They found that girls’ BMI did not change over the 10 year period but there was a significant increase in boys’ BMI (p<0.02) and cardiorespiratory fitness declined significantly (p<0.001) for both (boys 7% and girls 9%) (324). In this case, the decline in cardiorespiratory fitness could not be accounted for by an increase in BMI (324).
1.2.4.5. **Other Considerations**

Studying children and adolescents is complex. Its most essential feature is the change that occurs to cognitive, psychosocial, and biological aspects that can affect the physiologic process of locomotion during the course of childhood (106). Chronological age is usually used to define childhood stage of development. Health Canada recommends the definition of 6-9 years of age for children or pre-adolescence or pre-puberty, and 10-14 years of age designated as youth or pubertal, and 15-18 years as adolescence (325). However, the physiology of children and youth is dynamic, and all assessments of physiologic responses to exercise in children and adolescents must be regarded in the context of change. Additionally, different children do not follow the same rates of change (tempo) as they progress through growth (106). Sexual maturation is a process that extends from the early embryonic differentiation of the sexual organs to full maturity of these organs and fertility (326). Puberty is a transitional period between childhood and adulthood during which the sex organs and the reproductive system mature and the growth spurt takes place (326). Because biological maturation is closely related to growth, it is important to include indicators of biological maturation in pediatric studies. Therefore, Malina (2004) recommends overlapping categories of late childhood and early adolescence (9-12 years), or transition to adolescence, and 13+ (to 18) years as adolescence, to characterize sex differences (expected height, weight and body composition changes for girls begin around 9-10 years, reaches maximum around 12 years, rate slows after 12 years, but growth continues to about 16-18 years; boys begin around 11-12 years, reaches maximum around 14 years, rate slows after 14 years, but growth continues to about 18-20 years) (106).
Superimposed on these variations in rate of maturation, and related to PA and exercise, are inherent (genetically-derived) inter-individual differences, in which case one child to be more fit than another, even when body size and level of biological development are equivalent (327). As is the case with the obese child, the complexity created by these various physiologic patterns during growth can be compounded by the influence of extrinsic variables such as exercise programs (328) and what is happening on the energy intake and storage side of the equation (329). Excess adiposity may also influence various aspects of pubertal development, such as the timing of pubertal initiation and hormonal parameters during puberty (326), potentially impacting trainability and adaptation. As well, there are different psychosocial determinants that will impact PA (330,331) and effect of an intervention (332): examples include motivation and commitment (333), influence of family and peers (334), access to facility (335), confidence in ability and knowledge of how to be physical active (333,335), injury (332), allometric scaling for measurement (336), and complications from the condition itself (337).

Reinforcing the idea that individual variation is an important consideration in interpreting and translating research, is the idea that Ob is not a homogeneous condition. Multiple studies (338,339,340) have started to identify an emerging phenotype within the obese that do not display the typical metabolic disorders associated with Ob and are hypothesized to have lower risk of CV complications. This “metabolically healthy obese (MHO)” phenotype is reported to have a risk somewhere intermediate between healthy normal weight and unhealthy Ob and represents potentially 10-25% of the obese adult population (338). Prince and associates (2014) conducted a cross-sectional study including
8-17 year olds with a BMI≥85th percentile who were enrolled in a pediatric weight management clinic and measured insulin resistance and CV risk factors (BP, serum lipids, glucose) and determined that up to one in three children and youth with Ob can be classified as MHO (339). In the North West Adelaide Health Study on healthy obese adults, Appleton et al. (2013) found that persistence of a MHO phenotype, was associated with favorable outcomes, was related to younger age and a more peripheral fat distribution indicating that maybe MHO phenotype may be sustained by promoting lower waist circumferences (340). While much needs to be learned about this subset of Ob, it is a reminder that caution must be used when interpreting biomarkers with respect to CV risk and exercise effects.

1.2.4.5.1. Maturation

From a clinical standpoint, puberty refers to the period of life spanning 3–5 years characterized by the development of secondary sexual characteristics and the progressive acquisition of the reproductive capacity (106). The physical changes of puberty progress in a predictable sequence within an expected time related to hormone stimulation dependent on specific hypothalamic–pituitary–end organ axes and their direct influences and feedback interactions among their components (326,341). The interactions among these hormonal axes should be considered and not just their main effects (341), and that alterations in body composition and the regional distribution of body fat actually are signals to alter the neuroendocrine and peripheral hormone axes (341,342). Changing hormonal levels provide direct evidence of the maturation of specific structures and tissues that underlie the overt manifestations of biological maturation that are commonly assessed in growth studies, i.e., skeletal age (343), secondary sex characteristics i.e. Tanner Staging (344),
and adolescent growth spurt i.e. peak height velocity (345). Biochemical and hormonal maturation, as steering mechanisms for the other systems, may also be considered (342).

Along the gonadal axis, gonadotropin-releasing hormone is the master hormone of the reproductive endocrine system, largely controlling the secretion of luteinizing hormone and follicle-stimulating hormone from pituitary gonadotrope cells, which, in turn, regulate sex hormones from the gonads, culminating in secondary sexual features’ development and fertility (432). In the male, the clinical landmark of pubertal onset is gonadarche, i.e. rise in intra-testicular androgens for spermatogenesis (testicular volume attains 4 mL) (303), before serum testosterone increases (346). In girls, the clinical onset of puberty, or gonadarche, is marked by breast development (thelarche) and high follicular activity which is followed by a cyclic recruitment of the follicle that will be ovulated during each menstrual cycle (346). The first menstrual bleeding, known as menarche, occurs between 1.5 and 3 years after thelarche with the gonadotropins, estrogens, and progesterone eventually showing a typical, cyclic variation (346).

The growth axis is characterized by the release of growth hormone and its stimulation of insulin-like growth factor I production, responsible for the relatively constant linear growth rate (342). The characteristics of the adolescent growth spurt can provide two indicators of somatic maturity: age at the onset of the growth spurt in height (first inflection point of the adolescent growth curve, takeoff) and age at maximum velocity (second inflection point of the adolescent growth curve, or peak height velocity) (326). The pubertal growth spurt is accompanied by an increased bone mineralization, as well as, a significant weight gain (326). Boys accumulate greater amounts of fat intra-abdominally, and their intra-abdominal to
subcutaneous ratio increases during puberty leading to the sex-specific android distribution of fat tissue (342). As well, testosterone augments muscle protein synthesis, and, with this, a proliferation of mitochondria and contractile protein, allowing for an increase in muscle size and strength (347). For girls, intra-abdominal and subcutaneous fat areas increase during puberty, while their intra-abdominal to subcutaneous ratio decreases leading to gynoid distribution in body composition (348,349). Beyond fat tissue distribution, different musculoskeletal changes in laxity, flexibility and strength of lower limbs during the female adolescent growth spurt have been observed (346,350).

While the Hypothalamic–pituitary–thyroid axis is not responsible for the pubertal growth spurt or sexual maturation (326), it is thought to be permissive for these processes. Adequate thyroxin is necessary for normal growth in infancy and childhood and also for growth hormone gene expression (326). Thyroid dysfunction and its known role in energy metabolism and thermogenesis, has a critical role in glucose and lipid metabolism, food intake and fatty acid oxidation (351). Even slight variations in thyroid function contribute to variations in BMI and weight gain predisposing to Ob (351). In obese children, the most frequent hormonal abnormalities is related to thyroid concentrations characterized by high serum thyroid stimulating hormone and serum thyroxine (T3 and T4) (351,352). Those abnormalities are usually considered a cause of Ob that is normalized when weight is reduced (351), however, a recent review by Witkowska-Sedek et al. (2017) suggests it is really an adaptation process related to energy expenditure (353). In other words, weight or nutrition-related factors may affect the thyroid-axis and the activity of the axis may adapt to changes in the state of energy balance. Marras et al. (2010) suggest that in the state of overfeeding,
the high caloric intake, as well as the amount and composition of ingested food increase thermogenesis, which, if not counteracted by increased PA, result in weight gain and Ob (354). Weight gain, or loss, is therefore associated with compensatory changes in energy expenditure which are mediated by catecholamines and thyroid hormones (355,356,357). Since thyroid hormones regulate both the resting energy expenditure and thermogenesis, changes in thyroid hormone concentrations may represent an adaptation process in weight change (357).

With the serum thyroid stimulating hormone levels frequently elevated in obese children and youth, insulin resistance is also a known link (348,358,359,360). Insulin sensitivity refers to the ability of insulin to stimulate glucose metabolism, while insulin resistance denotes a situation in which an excess of insulin is required to maintain adequate homeostasis of glucose metabolism (346). During puberty, there is a physiological transient drop in insulin sensitivity of approximately 30% (346), with recovery by late puberty and basal insulin increasing throughout puberty (346,348). Insulin is an important nutritional signal from the periphery that may regulate the reproductive axis by direct effects on the gonadotropin-releasing hormone neurons and specifically by stimulating gonadotropin-releasing hormone gene expression (348). The higher levels of insulin during this period may have more pronounced stimulatory effect on the reproductive axis. It may also increase the bioavailability of insulin-like growth factor I, which is positively correlated to the level of obesity (346,359,360). Clearly, there is an inverse relationship between fat mass and insulin sensitivity which might contribute to the physiological insulin resistance of puberty. If fat
mass accumulation is accelerated through youth, the insulin resistance is more pronounced, which is metabolic risk factor for future atherosclerotic vascular disease.

Both growth and reproduction consume high levels of energy, requiring suitable energy stores to face these physiological functions (342). The state of body energy reserves is a key determinant for the onset of puberty and over-nutrition could possibly disrupt the timing and progression (347,360). During the last two decades, knowledge concerning how peptides produced in the digestive tract (in charge of energy intake) and in adipose tissue (in charge of energy storage) provide information regarding metabolic status to the CNS has increased dramatically (348). Moreover, these peptides have been shown to play an important role in modulating the gonadotropic axis with their absence or an imbalance in their secretion being able to disturb pubertal onset or progression (348,360,361).

The adipokine and leptin connection seems to be the most promising link between obesity and regulation of the growth axis (342,360,361). For the initiation of puberty, it is theorized that there requires the attainment of a certain minimum weight or body fat percentage as a requisite for pubertal development and menstrual function (the ‘critical weight hypothesis’) (362). The probable messenger between adipose tissue and the nervous system seems to be the adipocyte-derived hormone leptin (349,350,363). Leptin serves as a signal to the hypothalamus regarding energy stores in the adipose tissue compartment and its physiological effects include appetite reduction and increased thermogenesis (360,363,364). Presumably, an adequate concentration of leptin communicates to the central nervous system (CNS) that energy stores are adequate for the energy-intensive process of pubertal development; this permits central activation of gonadotropin secretion (360,363).
In that regard, leptin may be a factor which allows the start of puberty. This idea is supported by the fact that leptin is increased years before any other hormone associated with pubertal development (363). However, because leptin concentrations are directly correlated with fat mass, early adiposity could trigger early development (361,365). Although leptin is clearly important as a permissive factor, leptin alone may not be sufficient to initiate puberty and there are other factors relevant to obesity may contribute to the metabolic regulation of reproductive function.

In addition to leptin and insulin’s stimulatory effects, another hormone, ghrelin, has inhibitory effects on gonadotropin-releasing hormone secretion form the hypothalamus (366,367). Ghrelin is a gut-derived hormone, whose function as a growth hormone secretagogue is well described (368). It has been shown that ghrelin modulates energy homeostasis by stimulating adipogenesis, stimulating neuropeptide Y in the stomach (through hypothalamic mediation) (369), and increasing growth hormone secretion from hypothalamus (368,369). This results in a net orexigenic (or appetite stimulating effect), functionally opposite to that produced by leptin. Thus, it is currently thought that ghrelin plays a role in reporting information regarding the fuel availability in the body to the CNS and that there is an inverse relationship between activation of the hypothalamic-pituitary gonadal axis and ghrelin levels (361).

The hormonal regulation of growth becomes increasingly complex with the onset of puberty but of greater importance is the interaction between them, which sub-serves the dramatic alterations in linear growth and body composition during puberty. During the quiescent period between the neonatal–early infancy surge and pubertal development, the
full complement of structures and pathways for androgen synthesis, secretion, and action are present but are active at a very low level (a juvenile pause) (341,360). In children with Ob, puberty has been shown to begin and progress earlier in comparison with the normal-weight individuals, particularly girls (360,370,371). It should be noted that adiposity might reduce the reliability of using Tanner staging for determining maturation in Ob; adiposity can directly influence the appearance of external characteristics of puberty more so for overweight than normal weight children due to confounding effects of body fat (372). In girls, for example, excess adiposity could confound the distinction between breast tissue and adipomastia (fat tissue covering glandular tissue) (373,374). Furthermore, excess central adiposity in boys with high skinfold thickness, may impede assessment of gonadal development making subjective estimation of the Tanner genital stage less precise (372,374).

Early onset of puberty could have serious consequences such as increased rates of CV risk later in life. In a cross-sectional study, Werneck et al. (2016), studied n=1034 adolescents aged 10-16 years, and found central Ob as a mediating factor in the relationship between somatic maturation and metabolic risk during adolescence (375). APHV was used to evaluate somatic maturity and central adiposity was estimated through waist circumference measurements. Fasting glucose, triglycerides, HDL-c, and BP were measured as metabolic risk indicators. PA and cardiorespiratory fitness (20-m shuttle run test) were used as covariates (375). Except for fasting glucose, waist circumference showed partial or full mediation of the relationship between maturity and the metabolic risk factors with their z-score values for triglycerides (boys = −3.554 vs. girls = −5.031), HDL-c (boys = +5.300 vs. girls = +5.905), sBP (boys = −3.540 vs. girls = −3.763), dBP (boys = −2.967 vs. girls = −3.264), and metabolic risk.
score (boys = −5.339 vs. girls = −6.362) (375). Tryggestad and Short (2014) reported that in children with Type 2 Diabetes Mellitus associated with their Ob, there was a paradoxical increase in arterial compliance without an increase in endothelial function (376). This finding was attributed to, in part, the earlier maturation and increased body size that occurs in obese children suggesting that maybe obese children may reach peak arterial maturation earlier in life and therefore experience an earlier decline in compliance (376). It is unclear if this is true throughout the arterial tree, peripheral vessels maybe more compliant but not the central ones.

The process of puberty and complication of sex hormones on fat accumulation, bone growth, linear growth and muscle mass must be considered carefully when interpreting the impact on physical fitness and how changes might be affected by sex and pubertal progression. Body size by itself is not a valid indicator of biological maturity, since the adult state is not the same for all individuals. As such, a surrogate measure must be used as an indicator of biological maturation to understand effects of physical training. Corresponding parameters of the growth spurt can also be derived for other linear measurements, e.g., sitting height and leg length (345,377). The assessment of somatic maturity based on the parameters of the growth curve (age at onset and age at maximum velocity) is limited to the adolescent period (345), and only one or two biological events are considered. Percentage of adult height is calculated from present height and adult height (345). True adult height can only be measured if children are followed until adult stature is attained or can be estimated. If chronological age is used as comparison, and not maturational age, conclusions could be
spurious. In contrast, Malina (2004) recommends matching children by stage of sexual development may be useful to know what is not known about pubertal influences (106).

Environmental factors affecting maturation and physical development can involve a large variety of exposures, including modifiable lifestyle choices (nutrition and PA) (331). Starting to be appreciated is the energy expenditure side of the equation which reflects how food is used by the body, and what environmental agents may affect metabolism. One example is investigations into brown adipose tissue, present in large amounts in infants, but more difficult to ascertain in humans as they age (378,379). Brown adipose tissue acts as the body’s thermogenic control, significantly contributing to the control of body temperature and energy expenditure (378,379). Activating brown adipose tissue has been shown to reverse Ob, but the ability to turn on brown adipose in individuals with Ob or Type 2 diabetes mellitus, is reduced (380). Low activation or absence of brown adipose may represent another obstacle to the success of weight-loss strategies. Because puberty is also accompanied by significant changes in insulin production and sensitivity (346,348), in a healthy-weighted child, an acute bout of exercise is accompanied by increased sensitivity to insulin, and, therefore, increased glucose uptake by muscle cells (284,381). Normal puberty is characterized by an increase in cellular resistance to insulin action that is not accompanied by alterations in other insulin actions, such as lipolysis (critical for substrate utilization in aerobic exercise by increasing fatty acid oxidation) (284). For the obese child or adolescent, this mechanism may be impaired by virtue of the altered substrate use.

When examining the trainability of a child or adolescent, or the association between physical activity and health outcomes, shape maturity should be considered including body
size and composition, as well as biological maturity. The greater accumulation of fat and mass in Ob children or youth, for example, may limit the performance in weight bearing activities (i.e. running, pull-ups) (382). That is, the added weight accumulation represents an additional inert load that must be transported (382). Up to moderate levels of Ob, at least, Rowland (2003) showed body fat does not have any detrimental effect on cardiac functional reserve during cycle testing in adolescents (383) and that cycling was a recommended, non-weight bearing activity. Another example of body shape and composition interacting with exercise effects relates to muscle strength potential; muscle strength is a multifaceted, performance-related fitness component which is underpinned by muscular, neural and mechanical factors (384). The complex interaction of these components makes assessing body composition changes challenging. In normal growth and development, the pubertal male is increasing muscle bulk and strength from the time they hit puberty (about age 14 years), and their increase in strength per body mass is still increasing by age 18 years (342,346,347). Muscle protein synthesis, therefore, may explain changes to body weight, and a shift in proportion of fat free mass, so a training intervention may not accompany weight loss, but may actually contribute to weight gain in boys (341).

Anthropometry including girth measures to evaluate weight distribution must therefore be considered in conclusions about exercise response. In fact, Janz et al. (1997) suggested that even peak VO₂ changes seen across the pubertal years (males double from 6-12 years whereas females decline by 200 mL) is accounted for by changes in body composition independent of increases in body mass (385). Also, as with adults, there appears to be a continuum of high responders to non-responders to endurance training in children.
Early studies (386,387) suggested that there is a maturational threshold below which the effects of physical conditioning will be minimal. Katch (1983) defined a conditioning hypothesis, “the trigger hypothesis”, indicating that there is one critical time period in a child’s life for organic adaptation, “the trigger point”, which coincides with hormonal influences at puberty in most children, but may occur earlier in some, below which the effect of physical conditioning will be minimal or will not occur at all (387). More recent research has demonstrated this may not be the case; Armstrong and Barker (2011) suggested that early research has been confounded by training programs using less than optimum intensities and were able to demonstrate following a 12-week training program consisting of 3-4 sessions per week, for 40 minutes per session, an increase in peak VO$_2$ of ~8-9% would be expected in healthy children and adolescents (284). There are too few rigorously determined studies to specifically analyze dose-response to endurance training but literature generally recognizes because of non-responders to moderate intensity work, skill-based work with progressive workloads incorporating adequate rest and incremental increases will yield change over time (250,253,254,267,269,270,272).

The other factors to consider when evaluating maturation and impact of exercise would be related to the growth of the heart and lungs themselves. Animal studies indicate a strong anabolic effect of testosterone on the myocardium (388,389). As well, pubertal growth in boys is associated with blood and metabolic alterations, such as increased haemoglobin and haematocrit values (346). These changes can affect plasma volume that, in turn, can affect CO (346). LV size in males increases at a faster rate during puberty than it does in females (390). This has implications for exercise capacity. Improvements in VO$_2$max as
children grow are mediated by increases in maximal SV, which is turn is a reflection of progressive LV diastolic enlargement (391,392,393). Increases in heart size should occur in concert with increases in other volume measures, such as lung size, but Lanteri and Sly (1993) reported that lung compliance and airway resistance do not necessarily evolve at the same rate during growth, despite the fact balance between these two factors is strongly implicated in expiratory flow and consequently in exercise ventilation (394). Aortic compliance and LV size may also not be matched (43).

Based on this broad spectrum of effects, it is reasonable to think that any expected changes in exercise training in obese children would be different between girls and boys and that individual measures of exercise capacity should be expected to accelerate or spurt at some point in puberty, and that changes in physiologic factors should correlate closely with markers of pubertal development.

1.2.4.5.2. Quantifying Physical Activity

PA is a highly multidimensional construct (395), traditionally conceptualized as `any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level' (396). For children and youth, PA is likely to encompass numerous behaviours such as play, chores or daily activities, organized sports, and exercise (397). Thus, exercise is defined as behaviour that is planned, structured and repetitive, and undertaken for the purpose of improving or maintaining physical fitness (397), and, is therefore, only one form of PA. While PA is considered a behaviour, physical fitness is considered an attribute (397). Although fitness includes several attributes such as muscular strength, flexibility, balance, agility, power, speed and coordination (29,30,32), it is typically
conceptualized as cardiorespiratory endurance. Subsequently, physical fitness is usually measured through maximal exercise tests (282,284), while PA is often assessed by subjective methods such as self-report (typically through diaries and questionnaires) (397,398), objective methods such as motion sensors (399,400,401,402) or heart rate monitors (403,404,405,406,407), and criterion methods such as behavioural observations (408), the use of doubly labeled water (409,410) or indirect calorimetry (411,412) for assessing PA-related energy expenditure over extended periods, under daily, free-living activity.

Although it appears that children and youth today are less active overall compared to previous years both globally (413) and in Canada (27,28,414), there has, until recently, been little high-quality evidence to suggest that children’s activity and or fitness levels are so low that it compromises their current or future health. Such discrepant findings may, in part, be related to the difficulties associated with obtaining valid and reliable measures of PA in children (396,415,416,417). However, the increasing use of objective motion sensors—most notably accelerometers—has greatly increased the ability to measure PA levels more accurately and overcome some of the measurement limitations. Strong inverse correlations between accelerometer-determined PA and precise measures of body composition have been documented in children and adolescents (418,419,420) whereas previously this information was drawn from large epidemiological studies of self-reported behaviours (30,420). Because youngsters have difficulty recalling their past activity behaviours (421,422,423), objective measures are considered more reliable for quantifying PA.

Although PA is important in Ob, a clear relationship has not been established in terms of causality (424): does Ob lead to lower PA levels or does physical inactivity lead to Ob?
Obese children and adolescents generally exhibit lower daily accumulations of MVPA compared to non-obese (425), although total activity and PA is lower and total energy expenditure is not always reduced (425,426). Obese children may engage in more low intensity PA acquired from frequent, short-duration, day-to-day activities, rather than sustained organized sport or exercise (426). Triaxial accelerometry is a useful adjunct to understand PA patterns in children although there are a number of issues associated with the validity and reliability in their interpretation (427). Accelerometry detects and records the magnitude of movement on a real-time basis (428); an important general concept for accelerometry is that it measures segment or limb acceleration rather than overall body acceleration (428); during normal locomotor movements, the hips (and other limbs) accelerate and de-accelerate with each stride, and with the repeated pattern, the device can record a constant signal or count to determine a steady-state (428). Obtaining accurate information from accelerometry-based activity monitors requires careful attention to the way the data are collected, processed and analyzed. A challenge for research with activity monitors is screening data for non-compliance with monitoring protocols and deciding what characteristics of the activity are being captured (423). For example, failure to wear the monitor as directed (such as in the social context of Ob) (429), can lead to measures of activity that are artificially low, an error that would significantly bias the results to the intervention or characterization of the activity (429,430). As well, methodological questions might include: how many days or hours are needed in monitoring to characterize behaviour? Should weekday and weekend day differences in activity be considered? Are PA patterns during specific time periods representative of an entire day? (425) Further, accelerometer-derived
activities may not be related to health outcomes that are associated with self-reported activities (431); and, accelerometer cut-points are known to underestimate certain behaviours such as cycling (429,430) and swimming (429).

With a control for cut-points and a qualitative assessment of the types of activities that account for movement experiences, accelerometry, as an adjunct, can provide a valid indicator of overall PA and whether CV changes are due to an intervention or other outside influences. However, because accelerometry provides a less accurate prediction of energy expenditure which, as discussed, may not be reduced for chosen activities in the obese child, care must be taken in how the data is interpreted (427,431). Trost et al. (2000) suggests for monitoring to be acceptable, accelerometry data must include a minimum of three valid days, one of which is a weekend day (425). Further to this, Colley (2013) defined a valid day as having 10 or more hours of wear time (wear time is determined by subtracting non-wear time from 24 hours and non-wear time is defined as at least 60 minutes of zero counts) (432).

Additionally, when interpreting effects of an intervention, it is important to identify the primary influences on PA behaviour which will help design and deliver better exercise programs later (331,332,333,334,433,434,435). Knowledge of seasonal variation in children’s and adolescent’s health behaviour, for example, may facilitate more precise targeting of behaviour change interventions, which can be delivered specifically or with greater intensity during periods of the year (436). Alongside personal, social, and institutional influences, environmental factors, including weather and daylight hours, may have an impact on behaviour (437). Children’s PA and sedentary time fluctuate across the year, with greater seasonal variability seen during the weekend compared with the weekday and among certain
sociodemographic subgroups (436). Seasonality may, in part, account for divergent prevalence estimates derived from studies that conducted assessments within limited (and different) segments of the year (27,413,438,439,440) and should be accounted for in surveillance systems. Accompanied by knowledge of the season-specific determinants of behaviour, this information may contribute to the development of intervention programs that are more efficient and effective when activity levels are lowest (436). Seasonality is also important in the context of assessing population prevalence or secular trends in behaviour because estimates may be biased if data are collected within a restricted period of the year (437,439). These considerations will help understand limits to within- and between-group PA habits over a longitudinal study (437).

1.2.4.5.3. Movement Competency in Children and Adolescents with Obesity

Without a mechanistic explanation of the role of PA in the prevention of Ob, one of the potential mechanisms affecting the weight-gain cycle is movement competency. Motor competence refers to the degree of skilled performance in a wide range of motor tasks as well as the movement coordination and control underlying a particular motor outcome (116,117,441,442). In the early childhood years, children begin to learn a group of foundational motor skills known as fundamental motor skills composed of locomotor (moving body through space such as through running, galloping, skipping, hopping, sliding and leaping) (443) and object control skills (manipulating and projecting objects and include skills such as throwing, catching, bouncing, kicking, striking, and rolling) (443). These fundamental skills form the foundation for future movement and PA (117,444,445). In childhood, Clark and Metcalfe (2002) suggest the overall goal of this period is to build a
sufficiently diverse motor repertoire that will allow for later learning of adaptive, skilled actions that can be flexibly tailored to different and specific movement contexts (444). If children cannot proficiently run, jump, catch, throw, etc., then they will have limited opportunities for engagement in PA later (443,444,445). Therefore, an adequate level of motor skill is not only considered a key factor in children’s general development, it is also a correlate for an active lifestyle (117,441,442). As well, Welk (1999) suggests that the importance of actual competence and skillfulness may be overshadowed by an individual’s perception of competence, and mastering a variety of physical skills helps children to participate in different physical activities (446). Because children who are overweight and obese engage in limited PA, there are less opportunities to practice and improve motor planning thus potentially limiting overall motor skill acquisition.

Lower foundational skills mastery (i.e. qualitative measures related to movement execution) (442), as well as, poorer performances on gross motor skill and coordination tests (i.e. quantitative measures related to motor outcome) (447,448,449) have been consistently linked with a higher body weight in childhood, but the causal direction of this association is not fully understood. For example, differences in walking, postural control, and gross motor skills in obese children have been noted (450); during walking, individuals that are overweight or obese have shorter step lengths, slower walking velocities, wider step widths, shorter single limb support times, shorter swing times, and longer double limb support times compared with the counterparts with normal weight (450,451,452). Adaptive changes to the gait pattern exhibited with Ob have been linked to the attempt of reducing energetic costs (453). Preferred gait variables may be chosen to minimize the mechanical work required to
transfer the excessive body mass and effort required to stabilize. Gait patterns are also different in obese children during functional gross motor tasks; they decrease velocity when walking on a line (454), and land heel-first when crossing obstacles (455). Differences in gait and gross motor skills contribute to compromised balance and postural control (117,448,454). When performing dynamic tasks, stability may be lost with the combination of position and velocity changes as the body center of mass shifts relative to the base of support which ensures the balanced upright body posture (448,454). Because PA tasks may not only involve the use of a linear, self-selected pace of walking, but instead involve changes of direction, differing speeds, and the ability to perform more than one task at a time (i.e. dual tasking) such as picking up a ball on the fly, or catching a moving Frisbee, etc., modifications to the gait spatiotemporal parameters suggest a compromised reaction to maintain dynamic stability and recover balance during activity. Hence, movement organization may be impeded in delayed motor development (441,442). Additionally, postural adjustments require the integration of sensory information from visual, vestibular, and somatosensory inputs, all of which contribute to postural balance (448). Due to the continuous increased loading of the feet as a result of the excess body mass, childhood overweight and Ob causes substantial changes in foot structure (456,457). Even from an early age, overweight and obese children display significantly larger foot dimensions, a more flattened medial longitudinal arch, larger contact areas with the ground, and increased plantar pressure values (457). The structural changes associated with excessive weight-bearing may also affect the functional capacities of the foot, characterized by a decrease in the quality of sensory information from the mechanoreceptors within the plantar surface,
which could contribute to the maintenance of postural stability (458,459). This has implications for obese children and adolescents responding to movement tasks during PA and may suggest compromised adaptation when moving quickly.

Hung et al. (2013) examined the influence of dual-task constraints during walking in children who are overweight and obese (460). They found that overweight children compared to their normal weight peers modified lateral movements by increasing hand and trunk movement and force organization by increasing ground reaction force through wider step width for balance when faced with walking with a box in hand (460). For the obese child or youth, a wider step width may lead to decreased metabolic efficiency, leading to sooner fatigue; it has been shown that obese children may fatigue more quickly than non-obese children as they typically have a reduced cardiorespiratory capacity (461), higher absolute costs of exercise (462,463), and greater relative muscular demands (464,465). Ekelund et al. (2004) compared walking economy in 18 obese adolescents and 18 normal-weight adolescents matched on age and sex (466). \( \dot{V}O_2 \) expressed relative to fat-free mass was higher in the obese group. When absolute \( \dot{V}O_2 \) was expressed as a function of total body mass, however, submaximal \( \dot{V}O_2 \) was similar for the obese and normal weight group, despite group differences of 29 kg in fat mass and more than 40 kg in total mass (466). It was concluded that body mass is a major contributor to difference in absolute walking energy expenditure observed between obese and non-obese youth (466). However, with higher ventilatory effort and uneconomical gait mechanics for the obese child, it is unclear whether this distribution of mass contributes to efficiency. When Volpe and Bar-Or (2003) considered pooled data for lean and obese participants, there was no discernable within or between-group relationship
between percentage of fat in legs (the most active limbs when walking) and net VO₂ (467). Hence, they concluded that the aerobic demand of walking in obese boys is influenced primarily by total body mass and not by total or regional adiposity (467).

There could be other factors contributing to the slow gait speed among children with Ob. Obese individuals generally experience lower muscle strength than their normal-weight counterparts when adjusting for body mass (468). For the child with Ob, the influence of higher weight bearing mass to transport compared to the normal-weight child during daily activities, may contribute to greater bone adaptation, but not necessarily in proportion to the mass they are transporting (469,470). This could contribute to greater joint strain and gait asymmetries (469). Riddiford et al. (1998) investigated the effects of Ob on the strength and power of n=43 obese (BMI: 24.1 ± 2.3 kg·m⁻²) and 43 non-obese (BMI: 16.9 ± 0.4 kg·m⁻²) healthy, pre-pubescent children (8.4 ± 0.5 years) (468). Age-appropriate field tests of a basketball throw for distance, arm push/pull ability, and vertical and standing long jump performance, were used. Although Ob did not negatively impact upper limb strength or power in these activities, it impeded the children’s ability to perform tasks involving lower limb strength and power in which the obese children were required to move their larger mass against gravity (468). That is, the obese children were disadvantaged in both standing long jump and vertical jumping tests by the need to apply a greater force to accelerate their larger mass against gravity over a given distance.

A combination of factors may expedite the onset of fatigue in this population, therefore, prescribing long-duration activities, even at low intensities, may be sufficient to induce significant fatigue and subsequent gait alterations (471). In adults, it is hypothesized
that combining abnormal loading conditions with musculoskeletal fatigue through longer
duration activities may exacerbate the risk of musculoskeletal injuries or further alterations
in joint loading (472). Adding the limited range of motion during the dual-task condition, by
holding some joints rigid while performing a skill, may also put the obese child at risk for injury (460,472,473); increasing lateral movements during walking or running could increase
the risk for falls and sprains, for example. Although not well studied in children or youth,
adults with Ob have demonstrated higher lateral friction force compared with the lean
counterparts, which increases their fall risks in the lateral direction (455,458,459,473,474).
Lerner et al (2009) showed that altered tibiofemoral loading during walking in obese children
may contribute to their increased risk of knee pain and pathology (475).

Cheng et al. (2016) recently studied the temporal ordering between children's motor
skills and weight status at 5 and 10 years (476). According to their study, Ob preceded the
declines in motor skills and not the reverse, suggesting that early childhood Ob intervention
efforts might help prevent declines in motor proficiency that, in turn, may positively impact
children's PA and overall fitness levels (476). Children and youth with better motor abilities
may find it easier to be physically active and may more likely to engage in PA compared with
peers that have poor motor competence (477). Conversely, over-weight children may
become caught in a perpetuating cycle of physical inactivity and unhealthy weight-gain. Self-
efficacy toward PA is also important (477); Trost et al. (2001) conducted a cross-sectional
study of n=133 non-obese and n=54 obese (age-, race- and gender-specific 95th percentile
for BMI from NHANES-1), 6th grade children (mean age of 11.4±0.6 years), and showed that
obese children report lower levels of PA self-efficacy, and are involved in fewer community
organization promoting PA opportunities to develop fundamental movement skills (328). Using objective measure, Trost et al. (2001) also demonstrated these obese children exhibited significantly lower daily accumulations of MVPA and participated in significantly fewer 5, 10 and 20 min bouts of MVPA then their non-obese counterparts (328). Stodden et al. (2008) provided a conceptual model positing that actual competence precedes perceived competence as a predictor of PA (477). Slykerman et al. (2016) showed this in healthy children, where actual physical skill competence predicted MVPA, a crucial variable for improving fitness, especially in older children, where competence perceptions become more in line with actual ability over time (478). They also showed that locomotor skill competence may be more important than object control skill competence for girls specifically, as they may engage in types of PA that do not require object control mastery. Although little research has explored these relationships over time in children with Ob, Morano et al. (2014) conducted a feasibility study of a multi-modal training program promoting changes in PA, fundamental motor skills and real and perceived physical abilities of obese children (479). Forty-one participants (9.2 ± 1.2 years; BMI>97th percentile) were assessed before and after an 8-month intervention with respect to body composition, physical fitness, self-reported PA and perceived physical ability. After treatment, they found real and perceived physical competence correlated with an increasing volume of activity (versus increasing intensity), concluding that a multi-modal program focused on actual and perceived physical competence might be an effective strategy to improve adherence of the participants and to increase the lifelong exercise skills of obese children (479). Morano et al (2014) noted, however, real and perceived competence was correlated in boys but not in
girls, suggested that improving motor competence in obese girls may not influence their perceived physical ability, as much as could happen in boys, and that boys and girls likely perceive PA differently. Thus, perceptions of competence may vary depending on the subjective meaning ascribed to those activities (479) and social development may play a role. However, perceived physical competence should be considered overall during program development in order to promote confidence and enjoyment of activities undertaken.

These are important concepts for exercise planning in obese children and adolescents starting an exercise program who may have delayed fundamental movement development. Cliff et al. (2012) suggest that establishing strong locomotor skills (e.g. run, hop, dribble, and kick) should be included in any exercise plan and specific movement patterns could be used to target improvement including positioning of the body and feet, the control or release of an object at an optimal position, and better use of the arms to maintain effective force production (object control) (442). Additionally, training activities should decrease the challenge of performing multiple tasks at once for this population to reduce the dual-task constraints of movement (442). Caution should also be used in movements requiring dynamic postural shifts such as running direction change or backwards movement where quick postural adjustments and gait initiation may be compromised in the obese child increasing the risk for falling (480). Exercise programs should foster fundamental movement patterns to improve movement quality and allow the child to progressively increase intensity for fitness changes.
1.2.5. Overview Conclusions

With the aforementioned considerations in mind, the remainder of this document will present an exercise intervention aimed at affecting physical conditioning and altering CV and respiratory response in children and adolescents with Ob. The general methods used in these studies are discussed in chapter 2. The first original study (chapter 3) provides a validated, treadmill exercise protocol aimed at establishing aerobic capacity in obese children and adolescents whose peak oxygen consumption values may be underestimated by use of traditional protocols. This study was conducted to be able to accurately prescribe training intensities for the second original study conducted. The second study (chapter 4) presents a novel exercise intervention designed to evaluate CV changes in obese children and youth over its 12-week course. The use of non-invasive echocardiography is used to assess the biophysical properties of the aorta, specifically PWV, and treadmill testing is used to evaluate fitness response. The third original study (chapter 5) conducted incorporates the methodology used in the exercise intervention study and includes pulmonary function testing to describe any changes to the respiratory system following exercise training in these same obese children and adolescents. A discussion regarding the limitations to studying this population and significance of its findings (chapter 6) will conclude this document.
CHAPTER 2: General Methods

2.1. Rationale

Vascular changes to the aorta in obese children and adolescents following an exercise intervention has not been studied. Over the past few years, aortic arterial stiffness has been investigated in children and youth (1), but not specifically following exercise training. With the advent of non-invasive techniques for use in children and adolescents, the phenomenon and significance of arterial stiffening in the central artery in young Ob is beginning to be unveiled (1,2,3). Non-invasive measures for the assessment of arterial elasticity in vivo, fall into three broad groups: measuring pulse wave velocity, relating change in diameter (or area) of an artery to distending pressure, and assessing arterial pressure waveforms (4). A number of technologies can be used for measurement such as dual pressure wave and Doppler ultrasound methods, and magnetic resonance imaging but methodological limitations such as time required, ease of use, acceptability to patients, and reproducibility of measures, for example, have highlighted difficulties for widespread clinical practice (4). With this need for a simple, reliable, non-invasive method of detecting early disturbances in arterial stiffness at a time when therapeutic intervention can be most beneficial, Sandor et al. (2003) developed a novel Echocardiography-Doppler method validated for measuring the biophysical properties of the aorta in pediatric patients (3). Using this method, Harris et al (2012) prospectively recruited a cohort of obese boys and girls (13.8±2.3 years) to determine whether childhood Ob is associated with abnormal biophysical properties of the aorta compared to normal weighted controls (2). All their participants also underwent cardiopulmonary exercise testing. They found the obese cohort were already compromised;
they had greater AoPWV, characteristic impedance (Zc), β-stiffness index (β), pressure-strain elastic modulus (Ep), peak aortic velocity, increased LV mass, altered diastolic properties, and reduced exercise capacity (about 68% of predicted) (2). Their study confirmed that AoPWV is a useful measure in monitoring the progression of arterial disease and could be used to monitor the effects of a therapeutic intervention. The question remains then if these same children and youth were exposed to a supervised exercise intervention would these maladaptive changes still be evident or could they be reversed or returned to normal values?

The Harris et al. (2012) (2) study provides useful comparison data for the primary dissertation study and demonstrates the utility of the Sandor et al. (2003) Echocardiography Doppler method (3) of measurement. A 12-week, supervised, progressively high intensity exercise intervention was employed to modify vascular stiffness in obese children and adolescents, 10-18 years. In chapter 4, the relationship between the exercise intervention and other biophysical properties of the aorta and potential anthropometric factors influencing AoPWV were investigated. The aim of chapter 2 is to describe how the exercise training intervention was derived and discuss how the Sandor et al. (2003) Echocardiography Doppler method (3) was applied, and inter-rater reliability established, for assessment in the studies thereafter.

2.2. Exercise Intervention

Many different exercise interventions have been used in obese children and adolescents, but no consensus has been reached as to the optimal design for training this population. Appropriate exercise prescription may consider the following factors: (i.) frequency of activity; (ii.) intensity of activity; (iii.) time spent in the activity; and (iv.) type of
activity performed (5). Any of these elements can be manipulated when developing an exercise intervention but modifying intensity, by incorporating periods of vigorous activity, may have the greatest effect on CV health and fitness (6,7,8). In adults (9,10), and more recently in children (11), it has been suggested that vigorous high-intensity training (HIT) activity can lead to improved body composition, lipid profiles and greater changes in CV fitness (assessed by peak VO₂). Moreover, Bartlett et al (2011) showed that HIT is perceived to be more enjoyable than continuous, moderate intensity exercise even though perceived exertion is scored higher (12) which has significant, and practical, implication for those that are uninitiated or do not like to exercise. The impact of interval types of training to incorporate these intensities, in order to alter CV structure and function, has also been considered but is limited in depth of research (13): low volume high-intensity intermittent (or interval) training (HIIT) may have an advantage over higher volume, more moderate-intensity intermittent (or interval) training (MIIT) specifically in those who are deconditioned (10,13). The ACSM recommends combinations of moderate- and vigorous-intensity activity and strength training should be performed to meet PA guidelines (5). Strength training should be performed a minimum of 2 days each week, with 8-12 repetition of 8-10 different exercises that target all major muscle groups that can be accomplished by using body weight, resistance bands, free weights, medicine balls (if no access to gym equipment) (5).

HIIT describes physical exercise that is characterized by brief, intermittent bursts of vigorous activity, interspersed by periods of rest (or low intensity exercise) where near maximal efforts are generally performed at an intensity eliciting ≥80% of maximal HR (6,13); the intense work periods may range from 5 seconds to 8 minutes long with the recovery
periods lasting equally long as the work periods, usually at 40-50% of maximal HR (5). The workout continues with the alternating work and relief periods totaling 20 to 60 minutes. The relationship of work to recovery is important: a ratio of 1:1 might be a 3 minute intensity bout followed by a 3-minute recovery, for example (5). Alternately, sprint interval training, another HIIT protocol, might include 30 seconds of sprint at near all-out effort, followed by 4 minutes of recovery, and repeated 3-5 times (5). The ACSM recommends prior to HIIT training, a foundational level of fitness is needed (5). This might include consistent aerobic training delivered by more continuous bouts at lower intensities varying (20-60 minutes per session). A base fitness level with consistent aerobic training, at more steady state, that produces muscle adaptation can improve oxygen transport to the muscles (5,14). As well, establishing appropriate exercise form and muscle strength are important before engaging in regular HIIT to reduce the risk of musculoskeletal injury (5).

Physiological adaptation induced by exercise training is influenced by the precise nature of the stimulus, however, the individual’s response to the exercise training is determined not only by the physiological stress of the exercise bouts but also by the variations in the individual’s geno- and phenotype. In terms of genotype, for example, large inter-individual differences in the response to training, i.e., trainability, for all traits have been modestly investigated, including maximal VO\textsubscript{2}, submaximal exercise capacity, skeletal muscle oxidative potential indicators, and adipose tissue lipid mobilization and storage markers (15,16,17,18,19). Data on the heritability of physical performance phenotypes in children and adolescents is sparse (Canada fitness survey data (20); Leuven Longitudinal twin study (21,22)). The most comprehensive data on the individual differences in trainability come from
the HERITAGE Family Study, in which 742 healthy but sedentary adults from two generation families followed a highly standardized, well-controlled, laboratory-based, endurance-training program for 20 weeks (23,24). Using a model-fitting procedure, they found the most parsimonious model yielded a maximal heritability estimate of 47% for the VO$_2$ max response, which was adjusted for age and sex with a maternal transmission of 28% in one of the models concluding that the trainability of VO$_2$ max is highly familial and includes a significant genetic component (23). Therefore, individual variation following training would need to be demonstrated rather than assumed. A detailed discussion of genomic predictors of trainability is beyond the scope of this discussion, as it is not known how the amount of variance explained by hereditary factors is affected by differences in exercise intensity or exercise mode (25,26). Nevertheless, it is possible that genotype may account for a significant proportion of the variation following training studies, and should be considered in interpreting any intra-group responses to exercise intervention. As well, events occurring during gametogenesis, fertilization, and fetal life have received some attention for their potential contributions to post-natal biological determinants of health and disease, but little is known about the potential effect of the biological programming of the fetus on a child’s ability to make exercise-induced changes in post-natal life (27). Overall, measures of fitness aggregate in families and are affected by additive genetic effects and epigenetic effects (24,27); although genetic effects seen in children seems to remain stable throughout adolescence, it is also evident that non-genetic factors (including lifestyle factors shared among family members such as diet, screen time, obesogenic environments, etc.) contribute to the familial resemblance observed in fitness (24,25,27). Particular attention must be paid
to the sedentary, obese child where the role of genetic differences in the propensity to be sedentary or physically active is important. The role of epigenetic modifications may provide some insight into the variance in performance or the discordance in phenotypes (27).

Considerations for the Ob phenotype may also be related to the effect of the adiposity itself; the rate of fat oxidation during exercise, for example, in obese children is different than for a healthy peer (28). Zunquin (2009) studied thirty pubescent boys (13 lean and 17 obese) who completed a graded, cycle ergometer test linked with a gas analyzer and found at low intensity (0-30% of peak VO\(_2\)) when fat free mass is considered, the fat oxidation rate was identical for the two groups. However, at higher intensities (40%, 50% and 60% of peak VO\(_2\)), the fat oxidation rate was significantly higher in lean boys than obese boys confirming that obese boys have fat free mass-decreased capacities to use fat during moderate exercise (28).

This was also shown by Lazzer et al. (2017) who studied thirty obese adolescents (15-17 years, BMI 37.5 kg/m\(^2\)) randomized to a low intensity group (exercise at 40% peak VO\(_2\)), HIT group (70% VO\(_2\)) or HIIT group (6 repeated 40s efforts at 100% peak VO\(_2\) interspersed with walking at 40% peak VO\(_2\)) and found greater fat oxidation rates in low intensity activity compared to HIT or HIIT (28). Tjonna (2009) considered overweight and obese adolescents (14.0±0.3 years) that participated in HIT exercise (walking/running uphill on treadmill at 4×4 min intervals at 90% of maximal HR, each interval separated by 3 min at 70%, twice a week for 3 months) and concluded that HIT was more favourable in regulating of blood glucose and insulin (CV risk factors) compared to a subgroup randomized to low intensity (11). However, when considering fat metabolism, higher fat oxidation during low intensity exercise does not necessarily mean that total fat metabolism is higher (28,29). Not only is the total energy
expenditure greater in the HIT exercise, but the amount of fat metabolized is also larger per unit of time (29). With even higher intensities (90%), post-exercise oxidation appears to be mainly supplied by fat during the first hours of recovery (30). Therefore, HIT should be considered when designing exercise programs for overweight and obese individuals.

Exercise training that had the best chance to induce changes to vascular properties was important in choosing intensity for the intervention implemented in this dissertation. Endothelial function (assessed using flow mediated dilatation of brachial artery) has been shown to be improved a greater extent following HIT compared with continuous MIT (10,31), as well as, beneficial changes to components of resting BP (32,33,34) and LV morphology (10) have also been demonstrated utilizing high intensity. Ingul et al. (2010) also showed an increase in SV and decrease in HR after a 13 week HIT training program (4 × 4 minutes at 90% of maximal heart rate, 40 minutes of training in total, performed twice per week for 13 weeks) among obese adolescents (35). It appears this type of cardiac remodeling requires a longer duration of training and greater exercise volume than the load required to alter cardiorespiratory fitness or peripheral vascular structure and function (7). Although only tested in healthy adult males, Little et al. (2010) developed a low volume HIT protocol by decreasing the absolute intensity of the work bouts, but increased their duration and shortened rest intervals (10 x 60s cycling work bouts at a constant-load intensity that elicits 90% MHR, interspersed with 60s of recovery, total work time 10 minutes performed over a 20 minute training session) (35). Gibala et al (2012) explains that “short intense bursts of activity with low-volume HIT induce large-magnitude increases in cellular and peripheral vascular stress, while effectively ‘insulating’ the heart from those stresses due the brief
duration of exercise bouts” (7). This central insulation permits the individual to train at a much higher intensity than they would otherwise, but may also result in different timelines and effective stimulus loads between the central and peripheral components of the CV system (7). Furthermore, HIIT may have additional benefits on abdominal Ob and CV health in that it enhances the parasympathetic autonomic modulation of the heart in obese adolescents (7). Farah et al. (2013) compared the effects of HIT (treadmill training at speed of individual ventilatory threshold) versus LIT (treadmill training at speed 20% below individual ventilatory threshold) on BP, HR and HR variability, a marker of cardiac parasympathetic and sympathetic modulation in obese adolescents (13-18 years) (37). They found that after a 6-month intervention, sBP, dBP and mean BP decreased (p<0.05) for individuals in both types of training whereas waist circumference, HR and HR variability showed changes only to the HIT group (37). The additional benefits shown by the HIT group suggests a potential shift towards vagal modulation of the heart, potentially imparting better CV health. Farah et al. (2013) speculated that the magnitude of change in HR variability may be due to an intensity-dependent increase in sympathetic response in obese adolescents (37). Gutin et al. (2005) had previously shown increased vagal tone correlated with higher cardiorespiratory fitness in adolescents (38), also consistent with the work by Tjonna et al. (2009) (11) and Ingul et al. (2010) (35). Although low volume HIT studies in obese children are almost non-existent, there is certainly support in literature to further investigate this type of training as it may not only elicit the desired changes but engage children and adolescents in a shorter time frame.
The other consideration is finding a method to anchor intensity; when doing so, it is recommended to not just focus on the physiological basis of the method but also take into account the practical application of the method (39). Although measurement is an appropriate foundation for prescribing intensity, there are many different protocols designed for determining the anchors and the methods of gathering the data. For example, the traditional approach to assign intensity is to train at some percentage of $\dot{V}O_2^{\text{max}}$ or maximal or peak HR, or to train at or below some metabolic threshold, such as an aerobic threshold relative to oxygen consumption reserve e.g. $V_{O2}$ reserve or HR reserve, or anaerobic threshold such as ventilatory or lactate threshold (5). This can have a large impact on the basis for prescribing relative intensity or to monitor changes in performance. Therefore, verifying the peak measurement value would be an important precaution (40). If participants fail to reach maximal exertion, on cardiopulmonary lab testing for example, it would result in the measure (e.g. peak $\dot{V}O_2$ or maximal HR) being underestimated. Certain checks to evaluate whether the measurement was truly maximal must be made (40,41). Another factor to consider is the reliability of the measure. The measurement on one day must be repeatable and produce the same result on the next day, and then the more likely that exercise bouts, determined relative to the measurement, will have the anticipated physiological effect. It is advantageous to be able to monitor, during a particular exercise bout, whether the measured $\dot{V}O_2$ or HR, is in fact the target response for that bout. With this in mind, both $\dot{V}O_2$ and HR can be monitored continuously and non-invasively during single exercise bouts, although only HR measurements would be practical for use in regular training sessions. The effect of small adjustments in workload can be observed within a short period and as a result it is
comparatively easy to match the measured exercise intensity to the target exercise intensity. While there is strong theoretical basis for using threshold-based exercise prescription (39), the ability to verify both the anchor measurement such as ventilatory or blood lactate threshold, and the target exercise intensity may be impractical. The challenges of determining thresholds in practice may partially explain why many researchers continue to favour the use of %$\dot{V}O_2$max, %maximal HR, %$\dot{V}O_2$ reserve or %HR reserve (5). Additionally, the method of exercise intensity must consider the characteristics of the participants. For example, obese children will likely have a homogeneous, deconditioned level of exercise capacity and exercise designs might favour %$\dot{V}O_2$max or % maximal HR. Furthermore, the time frame for a research study may have practical constraints that may not allow for the most practical method of exercise intensity prescription and must be considered in both design and interpretation (39). Irrespective of relative intensity prescription used, the practical limits of exercise design require activities and intensities the participant can adhere to.

In terms of the mode of exercise, in a systematic review, Escalante (2011) reviewed 8 exercise intervention studies on obese children (< 14 years of age) (42). All study designs improved lipid profiles in the children and were relatively homogenous in terms of the characteristics of the activities: swimming and water games (43,44), machines (treadmills, static cycle ergometry, rowing ergometry) (45), sports activities (soccer, basketball, baseball, hockey) (43,46), and walking (43,47,48). Because the energy expenditure of some of activities is influenced by body position, Goran et al (2000) incorporated swimming or cycling into exercise programs so that obese children could more easily perform these physical tasks with increased energy expenditure (44). Only two studies used programs based on walking (47,48),
even though this is recommended activity for obese children (5). The programs all had very different structures—program durations of 10 to 24 weeks, frequencies of between 2 and 6 sessions per week, and session durations of between 30-90 minutes (47,48). Only four studies detailed the intensity and control for exercise dosage, and the intensity amongst those ranged by 20% (42). While all study designs improved lipid profile, the programs incorporating activities the children could sustain with intensity >75% maximal HR were more effective in achieving improvements in this profile. Too few randomized control trials have been studied to confirm what this correct intensity and combination of activities are.

Bartlett et al (2012) points out the greater enjoyment associated with HIIT running may be relevant for improving exercise adherence, since running is a low-cost exercise intervention requiring no exercise equipment (12). Similar relative intensities have shown to induce health benefits in patient populations (12). Running incorporated into play would also better mimic activities the child might engage in at home, school, or, in the community and would have practical applications for intensities prescribed clinically. It is difficult to relate the intensity of swimming, for example, to a playground-equivalent activity the child would realistically engage in for future exercise.

2.2.1. Exercise Intervention Design

Given these broad considerations for designing and implementing exercise programming, interval training through circuits combining elements of moderate and high intensities for a 12-week duration were selected for this intervention. Each exercise session was approximately 75 minutes and ran twice-weekly for a total of 24 sessions. First, a method of determining peak VO2 in obese children and adolescents (see chapter 3) was validated to
ensure our intensities were reliable when compared to HR followed in the exercise sessions. Then, based on the results of the first lab-based cardiopulmonary exercise test, an individualized training HR zone was calculated for each participant using the Karvonen formula (49): Training HR = [(Peak HR - Resting HR) x intensity + Resting HR] where Peak HR – Resting HR = HR reserve.

For the majority of each session, participants were encouraged to exercise at a moderate intensity (50-70% of HR reserve). HIT activity (>80% of HR reserve) was also incorporated and progressively increased throughout the program. For example, at the onset of the program, two minutes of HIT was included. Every week, thereafter, two additional minutes of HIT activity was added and time spent in MIT was decreased by 2 minutes. See Figure 1 for Schematic of intensity progression. This ensured the necessary base fitness level suggested by ACSM (5) was established, providing more time to practice fundamental movements, mobility, and modify exercise form if necessary, before engaging in regular HIIT, to reduce the risk of musculoskeletal injury and optimize adaptation.

**Figure 2.1:** Schematic of 12-week training intervention illustrating progressions for different phases of the program over time

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<tbody>
<tr>
<td>Warm-Up (&lt;50% HRR)</td>
<td>10’</td>
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<tr>
<td>Conditioning Phase (Moderate Intensity = 50-70% HRR)</td>
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<td>51’</td>
<td>49’</td>
<td>47’</td>
<td>45’</td>
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<td>31’</td>
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<tr>
<td>Conditioning Phase (High Intensity &gt;80% HRR)</td>
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<td>10’</td>
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<td>18’</td>
<td>20’</td>
<td>22’</td>
<td>24’</td>
</tr>
<tr>
<td>Warm-Down (&lt;50% HRR)</td>
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Warm-up consisted of 10 minutes brisk walking/light running around the gym space. The emphasis was on change of direction, change of pace, and change of body height. Walking/running in a clockwise or counter-clockwise direction was discouraged. Signals were added at 4 minutes of warm-up to encourage body movements using own body weight to warm up trunk, arms and legs. Diminishing rest was incorporated. After the warm-up period, training was comprised of both aerobic and anaerobic components with the following principles in mind: anaerobic lactic power and capacity was defined as power = max effort 10s to 2 mins (≥85% peak HR) and capacity as max effort 40s to 2 minutes; work to rest ratios defined as 1:10-12s (total work volume 6-12 minutes); aerobic power and capacity were defined as power=maximal effort 2-5 minutes (70-80% peak HR) and capacity=5 mins plus maximal effort (30 minutes of interval time) at 60-75% HR; work to rest ratio was defined as 2:1 to 1:2 (or 1:1) and total work volume was 15 minutes for power and 30 minutes for capacity) (5).

For the workout session, activities were incorporated into three types of circuits – mobility, aerobic, and strength. Weeks 1-4 emphasized mobility and aerobic fitness to emphasize the moderate intensity conditioning phase; weeks 5-8 emphasized increasing aerobic capacity, number of repetitions in 30 secs for mobility exercises, and adding strength components; weeks 9-12 cycled briskly through all three categories increasing speed/repetitions/holds in each emphasizing the progressively HIIT components (see Appendix B for the training program activities). Finally, a 10-minute cool-down, designed to lower HR slowly and avoid venous pooling, was included incorporating slow walking with change of direction, using full depth and width of training space, and dynamic, controlled
stretching (reach up high, reach down low), progressing to calm recovery with mild, slow, static stretching, off-loading opposing muscle groups and deep recovery breathing and hydration.

2.3. Echocardiography-Doppler Method

2.3.1. Rationale

To investigate the effect of the exercise intervention in modulating vascular health, echocardiography was performed to non-invasively measure properties of the heart before and after the exercise program, as well as, before and after a control period (see chapter 4 for complete study design). Non-invasive methods using formulas involving pulsatile change in aortic dimension and pulse pressure may be used to determine the elastic properties of the aorta; however, they do not provide insights into the mechanism involved in the alteration of the elastic properties of the aorta. Such information is provided with aortic pressure-diameter relationships that must be interpreted. This section discusses how the aortic pressure-diameter relationship was measured, interpreted and quantified for use in this dissertation.

The normal aorta is elastic and acts as a cushion and conduit to buffer the pulsatile blood flow; the stiffer the aorta (decreased capacitance), the faster the propagation of the pulsatile flow wave. Thus, the AoPWV is an indirect measure of aortic stiffness. The Ep and β-index are direct measures of arterial stiffness that assess the relation between pulsatile changes in arterial diameter and pressure. The aortic impedance describes the ratio of pressure to flow in the aortic root. Zc is determined by physical properties such as viscoelasticity and dimension and input impedance (Zi) is determined by reflected
pressure and flow waves generated in the more distal arterial tree producing local oscillations (53). Changes in arterial stiffness affect impedance by altering the physical and wave reflective properties of the aorta and the arterial system (52).

2.3.2. Methodology

The biophysical properties were derived in the ascending aorta non-invasively using an echocardiography-Doppler method first described by Sandor et al. (2003) comparing indices in pediatric patients with arterial disease to control patients (3). This novel, relatively simple method was used in follow up studies at British Columbia Children’s Hospital (BCCH) for other compromised populations such as children with Marfan’s Syndrome (52) and pediatric Ob (2).

2.3.2.1. Procedure

A resting echocardiogram using a Vivid 5TM or Vivid 7TM ultrasound (General Electric Vingmed Ultrasound, Horten, Norway) was performed by a sonographer on each participant at each clinic visit (before and after both the exercise intervention and control phase). Standard M-mode, 2-dimensional echocardiographic dimensions and measures of systolic and diastolic cardiac function were recorded. Images were then transferred from the ultrasound system to a post-processing workstation (General Electric EchoPAC). The raw image set was archived to CD/DVD as part of a regular back-up process. The raw image set was also copied to a DVD for reading by the investigator at the end of the study. Each case was labeled by study-ID and date of visit only.

A period of training on non-study related clinical cases was provided by the senior cardiologist, Dr. George Sandor, to teach the investigator the Echo-Doppler Method (3) and
interpret recordings. All AoPWV and related biophysical properties from the exercise intervention study were then assessed independently by both the senior cardiologist and investigator, once study data collection was complete. Although only the senior cardiologist was blinded to randomization order (control versus intervention order), as the investigator was involved in the intervention, to eliminate biased assessment of outcomes, adjudication was controlled for by blinding the dates of data collection, and by not comparing the level of agreement between the two evaluators until all image data sets had been evaluated. For AoPWV, the curved length around the aortic arch was digitized by the sonographer with electronic calipers providing arch length by summing serial segments (in mm); and transit time was determined from an ascending and descending aortic pulse-wave measured from Doppler tracing. Several consecutive cardiac cycles were captured providing a number of frames to assess for each dimension. For every pulse-wave Doppler tracing recording provided in the ascending and descending aorta, the length between the two sample positions was measured by electronic caliper tools. The ascending and descending readings were averaged and the average then used to determine AoPWV based on the formula stated in Figure 2.2.
For the other biophysical properties of the aorta, \( E_p \), \( \beta \)-index, \( Z_c \), and \( Z_i \) were calculated from pulse pressure (PP), aortic annulus (Ao), aortic root diameter in maximal systole \( (D_s) \) and aortic root diatmeter in end diastole \( (D_d) \). PP was calculated as the difference between systolic and diastolic BP components as recorded by sonographer. The aortic dimensions in end-diastole \( (D_d) \) and peak dimension in systole \( (D_s) \) were measured from the extended aortic image using electronic caliper tools for at least three cardiac cycles and the average value was used for each (see Figure 2.2). Peak aortic flow was calculated as peak aortic velocity x aortic annular cross-section (derived from the radius of the aortic root diameter measured by sonographer); \( E_p \) was calculated as \( \frac{(sBP-dBP)}{[(D_s-D_d)/D_d]} \); \( \beta \)-index was calculated at \( \ln(sBP-dBP)/[(D_s-D_d)/D_d] \); \( Z_c \) was calculated as \( A_o\text{PWV} \times \text{blood density constant (1.06)/aortic annular cross-section} \); and \( Z_i \) was calculated as \( \frac{(sBP-dBP)}{\text{peak flow}} \).
2.3.2.2. Data Analysis

To assess inter-observer variability and investigate the agreement between the two investigators, a Bland-Altman analysis (SigmaPlot software version 13, San Jose, CA: Systat Software Inc., SSI) was performed on means compared for each of the key variables. Plots were generated for showing the bias between mean differences and limits of agreement (LOA).

2.3.3. Results

There was a strong correlation and LOA between the investigators for each of the key variables. The general agreement for AoPWV is reported as \( r=0.863 \); mean bias=5.6054; LOA=-67.122 to 78.332 (see Figure 2.3 below). The plots for \( D_s \) and \( D_d \) dimensions are shown in Figure 2.4 and Figure 2.5 below: For \( D_s \), \( r=0.961 \); mean bias=0.0688; LOA=-0.108 to 0.246. For \( D_d \), \( r=0.959 \); mean bias=0.1119; LOA=-0.056 to 0.279. \( D_s \) and \( D_d \) were used for calculations of other biophysical properties. For \( E_p \), \( r=0.963 \); mean bias=7.5312; LOA=-7.075 to 22.138. For \( \beta \)-index, \( r=0.823 \); mean bias=0.2004; LOA=-0.851 to 1.252. For \( Z_c \), \( r=0.927 \); mean bias=8.070; LOA=-43.173 to 59.314.
Figure 2.3: Bland-Altman comparison: AoPWV

Comparison: Pulse Wave Velocity
Investigator 1 (GS) versus Investigator 2 (KD)

Bland-Altman Graph: PWV

Bias = 5.6054
Std Dev = 37.1060
Limits of Agreement = -67.1224, 78.3332
Bias CI
95% CI = -88.571 to -45.6737
Lower Limit of Agreement CI
95% CI = 56.8845 to 99.7818
Upper Limit of Agreement CI
95% CI = 56.8845 to 99.7818

Average of Investigator 1 (GS) and Investigator 2 (KD)
Figure 2.4: Bland-Altman comparison: Max systolic dimension ($D_s$)
Figure 2.5: Bland-Altman comparison: End diastolic dimension ($D_d$)

Comparison: End Diastolic Dimension
Investigator 1 (GS) versus Investigator 2 (KD)

Bland-Altman Graph: End Diastolic Dimension

Bias = .1119
Std Dev = .0854
Limits of Agreement = -.0555, .2793
Bias CI
95% CI = 0.081 To 0.1427
Lower Limit of Agreement CI
95% CI = -0.1089 to -0.0021
Upper Limit of Agreement CI
95% CI = 0.2259 to 0.3327
CHAPTER 3: Exercise Testing in Children and Adolescents


3.1.1. Rationale

Cardiopulmonary exercise testing is advised ahead of implementing an exercise intervention in obese children and adolescents to assess medical safety of exercise, simultaneously evaluate both the CV and ventilatory response to exercise, and describe intensities for PA. Optimal validity and reliability of test results are required to identify maximal exercise effort but literature is wrought with limitations for assessing maximal production in children, as most protocols were originally designed for adults and do not consider the scale limitations of children, never mind those with chronic disease. As such, there are few studies involving comparisons of obese versus non-obese children, and those that do make such comparisons show a similar lack of protocol uniformity. This remains an unresolved methodological issue that is attempted to be addressed here. Therefore, the aim of chapter 3 is to analyze aerobic fitness and its relationship with meaningful measurement, for implementing exercise training and PA during youth especially in those with Ob.

Aerobic fitness may be defined as the ability to deliver oxygen to the muscles and to utilize it to generate energy to support muscle activity during exercise (1). Hill and Lupton (1923) introduced the term VO$_2$max as “the oxygen intake during an exercise intensity at which actual oxygen intake reaches a maximum beyond which no increase in effort can raise it” (2); its rigorous determination depends on a particular criterion having been met such as the oxygen being consumed is no longer continuing to rise (despite an increase in work rate) resulting in a plateau when VO$_2$ is plotted as a function of work rate (3). The determination
of \( \dot{V}O_2 \text{max} \) utilizes a series of progressively-increasing work rates that challenge the body to transport and utilize the necessary oxygen. The modalities include some form of leg (e.g. cycling) or arm (e.g. rowing, arm cranking, wheeling) ergometry to involve a large proportion of the muscle mass. Accordingly, a \( \dot{V}O_2 \) plateau achieved for arm exercise would be appreciably less (about 70%) (3) than for leg exercise and would be less using conventional cycle ergometry compared with treadmill ergometry (about 89-95%) (3) where both arm and leg exercise (walking, running) is employed. Thus, the form of ergometry and muscle groups involved must be considered when predicting the highest oxygen consumed.

Studies in children, however, have consistently indicated that a \( \dot{V}O_2 \) plateau is not typical during maximal exercise tests (appearing in less than 30%) (4,5,6). Indeed, \( \dot{V}O_2 \) values in children often show no deviation from linearity even at exhaustive work levels and a non-plateau, so alternate indicators (such as peak HR, peak Respiratory Exchange Ratio (RER) or volitional fatigue) need to be considered to determine if a true maximum has been achieved (7). Therefore, peak \( \dot{V}O_2 \) is considered a surrogate to \( \dot{V}O_2 \text{max} \) in children, and is recognized as the best single measure of young people’s aerobic fitness (4,5).

Peak \( \dot{V}O_2 \), as the highest rate at which oxygen can be consumed during exercise, is characteristic of elite sport performance but it does not describe all aspects of aerobic fitness, certainly not for children with chronic health conditions, such as Ob, where fat oxidation during exercise is disturbed. In everyday life, intermittent exercise and the ability to engage in rapid changes in exercise intensity are at least as important as peak \( \dot{V}O_2 \). Under these conditions, it is the transient kinetics of \( \dot{V}O_2 \) which best describe the relevant component of aerobic fitness (8). Therefore, intensities of peak \( \dot{V}O_2 \) are most useful clinically when
prescribing PA for children and youth, but these intensities can only be described as a proportion of an accurate assessment of some maximum. With the frame of reference for peak \( \dot{V}O_2 \) as the highest value achieved regardless of the participant’s effort, it may not necessarily define the highest value attainable by the participant. The point of terminating a progressive test may be subject to reported endpoints of participant fatigue (pain in legs due to unaccustomed exercise, refusal to exercise further, jumping off the treadmill, or falling back into the spotter). Although subjective indicators of intense effort (e.g. facial flushing, sweating, unsteady gait) supported by secondary objective criteria can verify a maximal response, Barker et al. (2011) suggest abandoning the use of secondary criteria to validate a maximal \( \dot{V}O_2 \) (10). Rather, as supra-maximal testing elicits a peak \( \dot{V}O_2 \), the plateau criteria could be satisfied in healthy children (10). Supra-maximal testing, where the child is immediately (or after a brief rest interval) re-tested at intensities greater than that which had produced an exhaustive effort on the first test (although there is no supra-maximal protocol consensus, approximately a 2 minute bout at a workload producing no more than 3-5% increase beyond the incrementally-derived \( \dot{V}O_2 \) provides a guideline from literature) (11,12,13), would need to be performed to illustrate if a true maximal test was achieved (10). If the testing protocol was not suitable for the scale of an obese child, such as too steep a slope for climbing at last stage, this supramaximal recommendation may not be feasible. If a testing protocol were refined so the last stage were incrementally smaller without slope, then supramaximal testing would be useful adjunct to verify that peak \( \dot{V}O_2 \) criteria have been met. To date, testing protocols for treadmill walking or running are problematic for adding supramaximal loading for compromised individuals.
Treadmill testing has the advantage of extensive clinical use and is a well-established mode of exercise testing in both pediatric (14) and adult cardiac patients (15). In addition, it yields the highest HR and oxygen consumption due to upright posture and larger exercising muscle mass compared with other modalities such as cycle ergometers (3). As such, children who are ambulatory can be effectively tested by treadmill exercise. Much of the existing data on Ob, however, have employed cycle ergometry because investigators have felt the ambulating protocols unsafe or they are uncertain how obese children will respond to the challenge of maximal testing when weight-bearing. However, at least for the levels of Ob described in existing exercise testing literature, there is no evidence that obese children appear any less capable of meeting maximal effort protocol on treadmill as their non-obese peers (7,16). Also, there is little evidence to suggest that obese children are more likely than their non-obese counterparts to terminate a testing session short of maximal effort (17). In fact, Maffeis et al. (1994) reported that a higher percentage of non-obese children stopped the cycle ergometry test due to local muscle fatigue (18). Cycling is a less natural movement for obese children than walking or running and does not involve as large a muscle mass during the test. Conversely, treadmills have the advantage because during daily activities obese children have to move their total body weight and a treadmill protocol allows for more realistic intensities that can be related to in exercise prescription.

There are a variety of treadmill protocols that are used in both children, youth and adults. These protocols differ in their methodological characteristics, such as stage duration, speed increments, and slope increments (e.g. Balke, Astrand, Bruce, Ellestad, Naughton protocols) (3) which can impact test performance. Classic protocols, such as the Bruce
protocol (19), using slope variations to adjust exercise intensity during tests are still commonly used by clinicians and researchers despite having limitations for the practical application of laboratory information. Exercise testing in children presents its own unique challenges largely due to their small body size in relation to the testing equipment and less compliant nature to the exhaustive and monotonous exercise protocol. Especially challenging are very young children and those with chronic illness who are either unfamiliar with exercising to fatigue or unable to keep up with large changes in workload. Although the Bruce protocol has been validated in children (20,21) normative values are limited for submaximal parameters without metabolic data provided (20,22) or extensive data for varied age ranges (21) often providing peak exercise times or HR only (20,21). When functional capacity or aerobic endurance is not able to be assessed due to low fitness or disease state, clinicians and researchers tend to develop prediction models based on submaximal workload (23) or make protocol modifications to achieve peak values (modified Bruce) (24,25) leading to a wide heterogeneity in exercise protocols used. This makes it impossible to determine a reliable set of reference values for children (26) and reflects the overall challenge in using the Bruce protocol for many pediatric clinics performing cardiopulmonary exercise testing. The main criticism of the Bruce protocol, in particular, is that it has biomechanical limitations due to its large step-wise increases between stages. While establishing peak in healthy children is challenging enough, it is compounded with the additional burden of chronic disease. Ob is a physiological derangement which may contribute significantly to exercise intolerance (3). Ob adds to the oxygen cost of exercise by restricting the ventilatory system and increasing the work of breathing. The restriction of ventilatory capacity caused by Ob is more marked
as the $V_e$ requirement increases, possibly leading to hypercapnia (3). On many of the protocols, especially the Bruce protocol, the work increments between successive stages for obese children may be too great, resulting in the tendency for participants to quit prematurely during the first few seconds of a new stage (27), thereby, underestimating their aerobic power. For peak evaluation, Wasserman (2012) recommends that reported peak $\dot{V}O_2$ values should preferably be based on the average of 20 or 30 seconds of data at peak exercise (3). It should not be based on a single breath or less than 10 seconds of data (3). Also, the long 3-minute stages of the Bruce protocol, may lead to boredom and, regardless of fitness of the individual, the steep grade may lead to premature peripheral fatigue, with participants complaining of tired legs and ending the test without achieving maximal performance values. This has implications for subsequent exercise prescription where HR or energy expenditure (METS or peak $\dot{V}O_2$) reserves or RPE might be used to describe intensity (28).

The issue of scaling is also a significant challenge when interpreting the results of the exercise test. A better peak $\dot{V}O_2$ (in mL/min) indicates better fitness. While absolute $\dot{V}O_2$ is closely associated with lean body mass, adipose tissue reduces the value of the $\dot{V}O_2$ max per kg, acting as an inert component that inflates the denominator (hence the differences reported in mass-relative peak $\dot{V}O_2$ in young girls explained by body fat accumulated in pubertal years) (29). Absolute units favour larger children and youth due to their larger mass; therefore, if absolute peak $\dot{V}O_2$ (in mL/min or L/min) is used to assess the aerobic capacity of obese children, they appear to have greater cardiorespiratory fitness than the normal-weight children. However, if relative peak $\dot{V}O_2$ (in mL/kg/min) is used, their fitness appears reduced (percentage of predicted). Rowland (1991) described a close correlation ($r=0.72$) between
\( \dot{V}O_2 \text{max (L/min)} \) during treadmill testing and skinfold sum in \( n=27 \) obese adolescent females (30). When \( \dot{V}O_2 \text{max} \) was expressed relative to body mass the reverse trend was observed \( (r=-0.49) \). Rowland (1991) suggested that low aerobic fitness such as indicated by a lower relative peak \( \dot{V}O_2 \), does not necessarily reflect decreased functional capacity; therefore, indexing peak \( \dot{V}O_2 \) to body mass may lead to a spurious inverse correlation (29,30). This is problematic when assessing CV risk factors related to aerobic power; most studies have reported oxygen consumption scaled in conventional units of \( \text{mL/kg/min} \) is associated with CV risk factors such as BP, insulin resistance and dyslipidemia (31,32,33). This has not regarded body mass inclusive of fat and fat-free mass, supporting an association between CV risk and body fat regardless of peak \( \dot{V}O_2 \) (34,35,36). The use of allometric scaling has been suggested instead, which allows for size-related changes in physiological functioning and the disproportionate increase in muscle mass with increasing body size (37,38); despite acknowledging this, the relationship of allometric-scaled peak \( \dot{V}O_2 \) and CV risk factors has not been widely explored. Part of the reason for the lack of research may be related to controversy about how to express peak \( \dot{V}O_2 \): while it seems clear that peak \( \dot{V}O_2 \) is most closely related to lean body mass and not fat mass, indexing fat-free mass (FFM) \( (\text{mL/kg}_{\text{FFM/min}}) \) may (18,39,40,41) or may not (42,43) eliminate significant differences (when \( \dot{V}O_2 \) is scaled to fat-free mass, there is little association between aerobic fitness and body fat) (44). Another approach of scaling aerobic power is adjusting for size by using \( \text{mL}O_2/\text{m}^2 \) of body surface area (BSA) or \( \text{mL}O_2/\text{cm} \) of height in metres (29,45). Scaling per centimetre of height adjusts for growth and is generally related to age and BP (37). Scaled to BSA could be problematic for healthy children because the BSA-to-mass ratio declines as children age (29) but may be suitable for children
on the Ob trajectory. The appropriateness of scaling also then requires an exercise testing protocol to provide incremental metabolic data to elicit meaningful information. If a participant must adjust to large intermittent workloads during the test, such as with the Bruce protocol, submaximal information may not provide linear response sufficient enough to characterize the participant’s cardiorespiratory response to the exercise. Conversely, a test performed with very small increments, prolonging the time to reach peak capacity, can result in increased metabolic markers and sooner fatigue (at lower work intensities) resulting in lower peak work capacity.

While peak VO₂ assessment is documented in children and youth, other aspects of aerobic fitness are less well-understood such as what threshold levels or cut-points of peak VO₂ are associated with youth health and well-being. The challenge in determining youth thresholds is that they are compromised by being expressed in ratio with body mass, and, when extrapolated from actual data, study participants used to assess peak performance may not reflect population values. Armstrong (2012) suggests there is no compelling evidence that low levels of peak VO₂ are common anymore today than in previous generations by demonstrating that youth peak VO₂ remained stable overall several decades (46). Using a systematic review and meta-analytical strategy, Armstrong identified peak VO₂ data, expressed in ratio with body mass, for >4000, 9-17 year olds from five countries, and determined that over the time period 1962-1994, a very small mean change in peak VO₂ of 0.3% was reported (47). However, the ability to perform maximal aerobic exercise has not kept up with the secular increases in fat mass. Despite the relative stability of peak VO₂, there has been a decline of about 13% over the last 35 years in young people’s ability to transport
their body mass when peak performance was indirectly assessed by 20 m shuttle run testing (46,48). The transport of body mass is important for health and well-being and for successful PA and sport participation. Young children with Ob must transport greater mass and might engage in less habitual PA as their adiposity accumulates. However, the link between aerobic fitness and PA in children has show weak to moderate correlations in literature (47,48,49); either there is truly a weak correlation and the difference is due to some underlying intra-individual factor (e.g. puberty or adiposity), or perhaps there have been methodological issues in studying the relationship (inaccurate assessments of PA). Alternately, it may be that young people rarely experience habitual PA of sufficient intensity and duration to enhance peak \( \dot{V}O_2 \), leaving no meaningful relationship between peak \( \dot{V}O_2 \) and habitual PA (46). At play, rarely will a child perform at peak oxygen power, rather, at intermittent intensities that require the ability to engage in rapid changes in exercise intensity (50,51). In any case, it is important to get a better understanding of this relationship in order to prescribe exercise intensities for aerobic improvement. Sufficient dose-response data are available to design exercise training programs to improve the peak \( \dot{V}O_2 \) of both trained and untrained children and adolescents (52), however, data on the effects of different exercise training programs on \( \dot{V}O_2 \) kinetics is non-existent. Further, the few control trials on obese children have discussed their exercise intervention dose-components (usually intensity) but not provided justification explaining dose choice and do not rely on evidence-based determination (47,52).

In sum, in order to prescribe exercise intensity for training and daily PA and provide information on changes to aerobic power and capacity, exercise testing must provide an accurate assessment of both submaximal and maximal response to exercise, which is scaled
and feasible for use in young children, and describes the VO$_2$ kinetics along the progression of slow walking to running spectrum without prolonging the time to reach volitional fatigue. To resolve these methodological issues, a novel, clinically-useful, scaled institutional protocol (BCCH) has been validated here. The work has been published in *British Medical Journal Open Sport & Exercise Medicine*. The BCCH protocol increases the speed of the treadmill each minute of exercise without an associated increase in ramp slope. This research serves to focus on adjusting intensity with VO$_2$ capacity for clinical and exercise intervention recommendations. This validated protocol will allow the subsequent research presented in chapters 4 and 5 to focus on the mechanisms driving exercise-induced changes in aspects of aerobic fitness that are associated with childhood Ob following an exercise intervention.

3.1.2. Contribution of Authors

*Kathryn Duff* was responsible for recruitment and scheduling the patients and supervising the exercise tests, data analysis and writing of all reports and manuscripts. *Astrid De Souza* was responsible for supervising the exercise tests and assisting with the writing and editing of all reports and manuscripts. *Dr. Kevin Harris* oversaw the project, performed medical exams and provided medical supervision of the exercise sessions. Dr. Harris contributed to editing reports and manuscripts. *Dr. James Potts* was responsible for supervising the exercise tests and providing methodological and statistical support to all aspects of the study. He assisted with writing and editing reports and manuscripts. *Dr. Derek Human* is a Pediatric Cardiologist and was the Head of the Division of Pediatric Cardiology and the Heart Centre at BCCH at the time of the study. He is a Clinical Professor in
the Department of Pediatrics at UBC and Senior Associate Clinician Scientist at the BCCH Research Institute. Dr. Human provided important intellectual input regarding project design and analysis given his knowledge and expertise in the field of clinical testing.

3.1.3. Manuscript Information Page


3.1.4. Methodology

3.1.4.1. Study Design

All testing was completed in the Exercise Physiology Lab in the Heart Centre at British Columbia Children’s Hospital, Vancouver, Canada. Study participants were required to come to our lab on two separate occasions to complete two exercise protocols. There was a minimum of 48 hours and a maximum of 2 weeks between testing sessions. Using the Bruce Protocol, the speed and grade of the treadmill simultaneously increased every 3 minutes until volitional fatigue (20). With the BCCH Protocol, the incline stayed at a constant 1% grade starting at a speed of 2.0 mph, increasing by 0.5 mph every minute until volitional fatigue (See Table 3.1).
### Table 3.1: Methodology BCCH Protocol versus Bruce Protocol

<table>
<thead>
<tr>
<th>Stage</th>
<th>BCCH Protocol</th>
<th></th>
<th>Bruce Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cumulative Time (min)</td>
<td>Grade (%)</td>
<td>Speed (mph)</td>
</tr>
<tr>
<td></td>
<td>Cumulative Time (min)</td>
<td>Grade (%)</td>
<td>Speed (mph)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1</td>
<td>3.5</td>
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<tr>
<td>5</td>
<td>5</td>
<td>1</td>
<td>4.0</td>
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<tr>
<td>6</td>
<td>6</td>
<td>1</td>
<td>4.5</td>
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<td>7</td>
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<td>5.0</td>
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<td>8</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>1</td>
<td>6.0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1</td>
<td>6.5</td>
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<tr>
<td>11</td>
<td>11</td>
<td>1</td>
<td>7.0</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>1</td>
<td>7.5</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>1</td>
<td>8.0</td>
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<tr>
<td>14</td>
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<td>1</td>
<td>8.5</td>
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<tr>
<td>15</td>
<td>15</td>
<td>1</td>
<td>9.0</td>
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<tr>
<td>16</td>
<td>16</td>
<td>1</td>
<td>9.5</td>
</tr>
<tr>
<td>17</td>
<td>17</td>
<td>1</td>
<td>10.0</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>1</td>
<td>10.5</td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>1</td>
<td>11.0</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>1</td>
<td>11.5</td>
</tr>
<tr>
<td>21</td>
<td>21</td>
<td>1</td>
<td>12.0</td>
</tr>
</tbody>
</table>

### 3.1.4.2. Participants

Seventy healthy boys and girls from the local community were recruited for this study divided into three age groups (10-12 years; 13-15 years; 16-18 years). All participants were involved in extra-curricular sports. Ethical approval to conduct this study was received from the University of British Columbia Children’s and Women’s Health Centre of British Columbia Clinical Research Ethics Boards. Once participants were informed of the procedure, written informed consent and assent was obtained from each participant.
3.1.4.3. Measurements

Prior to the first test, participants were randomly assigned a test sequence to control for an order-effect bias. Body mass was measured at each visit to the nearest 0.1 kg. Standing and sitting height were measured to the nearest 0.1 cm at the first visit. Sitting height was used to predict Age at Peak Height Velocity (APHV) to assess biological maturity (53). Body surface area (BSA, m²) and body mass index (BMI, kg/m²) were calculated. BMI was converted to age-specific percentile reference values using Centre for Disease Control and Prevention growth charts (54).

Metabolic gas exchange parameters (minute ventilation, $\dot{V}E$; $\dot{V}O_2$, carbon dioxide production, $\dot{V}CO_2$; and RER) were calculated by open-circuit spirometry using a metabolic cart (Moxus Metabolic Cart, AEI Technologies, Pittsburgh, PA). The metabolic cart was calibrated prior to each test being conducted using two concentrations of calibration gas (20.9% $O_2$, 0.03% $CO_2$, balance $N_2$ and 15.0% $O_2$, 5.0% $CO_2$, balance $N_2$). Calibration of the turbine flow meter of the volume sensor was performed with a standard 3L syringe (5570 Series, Hans Rudolph Inc., Kansas City, MO). Gas-exchange was measured continuously during each test using a breath-by-breath method and averaged over 15-second intervals. $\dot{V}E$, tidal volume ($V_T$), breathing frequency ($F_b$), and ventilatory equivalents for $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) and $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) during the exercise test were recorded. HR was monitored continuously during exercise using an E600 Polar Heart Monitor transmitter/receiver pair (Polar Electro Canada, Lachine, QC). Study participants wore a small flexible rubber mouthpiece in their mouth. The mouthpiece was attached to a one-way, non-rebreathing valve (Style 2700B, Hans Rudolph, Inc., Shawnee, KS) that was connected to the metabolic cart. Peak $\dot{V}O_2$ (L/min, mL/min/kg), $V_T$ (mL/breath), $F_b$
(breaths/minute), $\dot{V}E$ (L/min), $\dot{V}O_2$ (L/min, mL/min/kg), $\dot{V}CO_2$ (L/min, mL/min/kg), and RER were measured, and metabolic equivalents (METs) were calculated by dividing peak $\dot{V}O_2$ by 3.5. The speed and grade of the treadmill were adjusted according to the protocol used (Table 3.1). Participants were provided with verbal encouragement to achieve volitional fatigue and discouraged from holding handrails during the test. Criteria for completion of a valid peak $\dot{V}O_2$ test included two of the following three criteria: (1) a heart rate $\geq$ 195 bpm; (2) an RER $\geq$ 1.0; (3) volitional fatigue. Systolic and diastolic blood pressure (sBP, dBP) was taken at rest and immediately post-exercise. BP was obtained from the right arm by auscultation where diastolic pressure was defined by muffling of the Korotkoff sounds (phase V unless the diastolic BP was heard to zero then phase IV was used).

### 3.1.4.4. Data Analysis

Sample size (Gpower, Version 3.1)[19] was determined $a$ priori, $\alpha=0.05$, $\beta=0.80$, using a correlation coefficient $r=0.84$ (based on our preliminary, unpublished work in 10 year old boys comparing peak $\dot{V}O_2$ using each protocol) yielding a sample size of 9. Since we wanted to develop comparison data for various age groups and sexes, we chose 10 participants for each of three age groups for both males and females; 10-12 years; 13-15 years; 16-18 years, with the goal to recruit 60 study participants in total. The distribution of variables was assessed using visual inspection (histogram) and a Shapiro-Wilk test for normality. Non-parametric data were analyzed and expressed as median (interquartile range, IQR) and Spearman rank correlations ($r_s$) generated for key variables: peak exercise HR, sBP and dBP (at rest and immediately post-exercise), $\dot{V}E$, $\dot{V}O_2$ (absolute, relative and predicted), RER ($\dot{V}CO_2$ L min$^{-1}$/ $\dot{V}O_2$ L min$^{-1}$), total exercise time (s) and estimated energy expenditure (METs). Differences between protocol
medians were compared using a Wilcoxon Matched Pairs Signed-Ranks Test. All tests were two-sided and significance was set at $P<0.05$. Statistical analyses were completed using IBM SPSS statistical software version 23.0 (Armonk, NY: IBM Corp). To investigate the agreement between the two protocols, we performed a Bland-Altman analysis (SigmaPlot software version 13, San Jose, CA: Systat Software Inc., SSI). Plots were generated showing the bias between mean differences and limits of agreement (LOA).

3.1.5. Results

Participant characteristics (n=70, median age 14.4 years) are shown in Table 3.2. We were able to predict maturation from sitting height for n=55 children. Age at Peak Height Velocity (APHV) and time to APHV are shown in Table 3.3. All participants were considered healthy in terms of percentile cut-points for BMI.

<table>
<thead>
<tr>
<th>Table 3.2: Participant Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable (n=70)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>14.4 (12.2-16.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>164.4 (154.7-174.0)</td>
</tr>
<tr>
<td>Body Mass (kg)</td>
</tr>
<tr>
<td>53.8 (44.0-62.6)</td>
</tr>
<tr>
<td>BSA (m²)</td>
</tr>
<tr>
<td>1.57 (1.42-1.76)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>19.4 (18.1-21.5)</td>
</tr>
</tbody>
</table>

BSA = body surface area; BMI = body mass index

<table>
<thead>
<tr>
<th>Table 3.3: Age at Peak Height Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Girls (10-12 yrs)</td>
</tr>
<tr>
<td>10 (Total n=70)</td>
</tr>
<tr>
<td>10 (Observations)</td>
</tr>
<tr>
<td>11.7 (10.7-12.5)</td>
</tr>
<tr>
<td>0.15 (-0.6-0.6)</td>
</tr>
<tr>
<td>Girls (13-15 yrs)</td>
</tr>
<tr>
<td>17 (Observations)</td>
</tr>
<tr>
<td>12.5 (12.0-13.3)</td>
</tr>
<tr>
<td>2.3 (0.9-2.3)</td>
</tr>
<tr>
<td>Girls (16-18 yrs)</td>
</tr>
<tr>
<td>10 (Observations)</td>
</tr>
<tr>
<td>12.8 (12.5-13.8)</td>
</tr>
<tr>
<td>3.7 (3.1-4.0)</td>
</tr>
<tr>
<td>Boys (10-12 yrs)</td>
</tr>
<tr>
<td>12 (Observations)</td>
</tr>
<tr>
<td>- (Observations)</td>
</tr>
<tr>
<td>- (Observations)</td>
</tr>
<tr>
<td>Boys (13-15 yrs)</td>
</tr>
<tr>
<td>12 (Observations)</td>
</tr>
<tr>
<td>13.6 (12.5-14.8)</td>
</tr>
<tr>
<td>0.75 (-0.8-2.5)</td>
</tr>
<tr>
<td>Boys (16-18 yrs)</td>
</tr>
<tr>
<td>9 (Observations)</td>
</tr>
<tr>
<td>14.4 (12.9-15.1)</td>
</tr>
<tr>
<td>3.1 (2.2-3.7)</td>
</tr>
</tbody>
</table>

APHV = Age at Peak Height Velocity
\( \dot{V}_E \), relative and absolute \( \dot{VO}_2 \), and METs were strongly correlated, all \( r_s > 0.80 \) (See Table 3.4). Furthermore, a Bland-Altman analysis showed a high LOA between the two protocols (See Table 3.4 and Figures 3.1a, 3.1b, and 3.1c).

**Table 3.4: Metabolic Data**

<table>
<thead>
<tr>
<th>Variable (n=70)</th>
<th>BCCH Protocol (Median+IQR)</th>
<th>BRUCE Protocol (Median+IQR)</th>
<th>( r_s )</th>
<th>( P )-value</th>
<th>Mean Bias (LOA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{VO}_2 ) (mL\textbullet min(^{-1}))</td>
<td>2897 (2342-3807)</td>
<td>2901 (2427-3654)</td>
<td>0.94</td>
<td>0.022</td>
<td>*34.6 (-269 to 338)</td>
</tr>
<tr>
<td>( \dot{VO}_2 ) (mL\textbullet min(^{-1})\textbullet kg(^{-1}))</td>
<td>56.8 (51.7-61.8)</td>
<td>57.4 (51.3-62.6)</td>
<td>0.99</td>
<td>0.043</td>
<td>0.7 (-5.3 to 6.7)</td>
</tr>
<tr>
<td>( \dot{V}_E ) (L\textbullet min(^{-1}))</td>
<td>96.7 (72.0-110.2)</td>
<td>99.2 (75.6-120.0)</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td>3.0 (-14.1 to 10.0)</td>
</tr>
<tr>
<td>Total Exercise Time (secs)</td>
<td>915 (829-1005)</td>
<td>810 (750-919)</td>
<td>0.67</td>
<td>NS</td>
<td>-63 (-296 to 169)</td>
</tr>
<tr>
<td>Peak Heart Rate (bpm)</td>
<td>196 (191-202)</td>
<td>195 (189-200)</td>
<td>0.78</td>
<td>0.041</td>
<td>*1 (-11 to 9)</td>
</tr>
<tr>
<td>RER</td>
<td>1.00 (0.96-1.02)</td>
<td>1.03 (0.99-1.07)</td>
<td>0.48</td>
<td>&lt;0.001</td>
<td>0.05 (-0.07 to 0.16)</td>
</tr>
<tr>
<td>METs</td>
<td>16.2 (14.8-17.7)</td>
<td>16.4 (14.7-17.9)</td>
<td>0.89</td>
<td>&lt;0.001</td>
<td>*0.2 (-1.3 to 1.6)</td>
</tr>
</tbody>
</table>

*Indicates graphed in Figure 3.1

\( \dot{VO}_2 \)=peak oxygen consumption; \( \dot{V}_E \)=minute ventilation; bpm=beats per minute; RER=Respiratory Exchange Ratio; METs=Metabolic Equivalent Units

The median peak exercise stage achieved on BCCH was 15 (13-16) with a peak speed of 9.0 miles/hour (mph) (8.0-9.5) (or 4.0 (3.6-4.2) meters per second (m/s)). The median peak exercise stage achieved on the Bruce protocol was 4 (4-5) with a peak speed of 4.2 mph (4.2-5.0) (or 1.9 (1.9-2.2) m/s at peak). \( V_T \) (median 1809 mL/breath for BCCH and 1921 mL/breath for Bruce protocol; \( r_s =0.93; P<0.001 \) and \( F_b \) (median 58 breaths per minute on BCCH and 54 breaths per minute for Bruce) (\( r_s =0.78; P<0.001 \) were similar between protocols. Eight participants did not achieve a maximal test during the BCCH and nine did not achieve a maximal test during the Bruce based on the defined criteria. Group Medians for Relative Peak \( \dot{VO}_2 \) for BCCH and Bruce protocols by Age and Sex are shown in Figure 3.2.
Figure 3.1a Bland Altman comparison: Peak VO₂

a. Peak VO₂ (mL/min)

Figure 3.1b Bland Altman comparison: Heart Rate

b. Peak exercise heart rate (bpm)
3.1.6. Discussion

We have shown that our institutional BCCH protocol yields similar peak responses in $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$, RER, METS, and HR when compared to the Bruce protocol. Our Bland-Altman plots show strong limits of agreement and, as such, the BCCH protocol may serve as an alternative clinical exercise testing protocol in children. The goal of peak effort exercise testing in children is to get an objective measure of a child’s fitness. Although peak $\dot{V}O_2$ during childhood and adolescence is well documented (8,9,10), other aspects of aerobic fitness during youth are less well-understood, such as the $\dot{V}O_2$ kinetics at smaller incremental intensities, which inhibits our ability to get a true understanding of a child’s ability to run and transport body mass to provoke adaptation to PA.

The BCCH protocol provides utility for both clinical and non-clinical exercise testing in children. Our protocol requires children to run at an earlier stage and at faster speeds.
Generally, the transition from walking to running occurs at 4.5 to 5.0 mph or six to seven minutes into the BCCH protocol in contrast to the Bruce protocol where a slow run may not occur until nine minutes at Stage 4 (4.2 mph; 16% grade) of the protocol. Running at an earlier stage and at higher speeds allows clinicians to evaluate symptoms such as chest pain, palpitations and/or dyspnea that are often reported with running in school or during other sporting activities. In our experience, children often complain of increased feelings of fatigue and leg discomfort while running uphill which may lead to early test termination during the Bruce protocol. The BCCH protocol may alleviate some of these complaints of peripheral fatigue as the grade is held constant at 1% for the duration of the test. The addition of the 1% grade in our protocol allows us to quantify work (product of weight (mass) of a person and vertical distance achieved by walking or running up an incline).

Sgherza et al. (2002), suggests that peak $\dot{V}O_2$ test termination may be associated with perceived exertion, rather than by any physiological limitation (55). Barker et al. (2011) has shown that using secondary criteria such as RER, HR or effort to verify a maximal effort (peak $\dot{V}O_2$) in young people during ramp cycling exercise may result in undervaluing a true maximum (10). Supra-maximal testing where the child is immediately re-tested at intensities greater than that which had produced an exhaustive effort on the first test (generally, between 5-10% greater intensities are added) would need to have been performed to illustrate if a true maximal test was achieved (4,5). As the focus of this study was to determine if the metabolic responses were similar between the two testing protocols rather than to determine the true maximal value for $\dot{V}O_2$, we did not perform supra-maximal testing.
For the exercise scientist, the BCCH protocol may be useful to evaluate the effects of training and rehabilitation programs and to determine target intensities for exercise prescription. Optimal exercise intensity domains for training prescription should be anchored to the ventilatory threshold, $T_{\text{VENT}}$ (ie. moderate exercise (below $T_{\text{VENT}}$) or heavy exercise (above $T_{\text{VENT}}$)) (10), or alternately, at some percentage of HR reserve or METs (28). The BCCH protocol provides an alternative to treadmill exercise at slow speeds and steep grades and is more complementary to normal PA. It is known that uphill running requires higher energy expenditure than level running (56). It is possible that the Bruce protocol which starts at a steeper grade (10% in Bruce compared to 1% in BCCH) may not characterize $\dot{V}O_2$ kinetics for exercise transitions in regular activity prescription as participants may recruit their Type II muscle fibers earlier resulting in greater anaerobic metabolism (57). The BCCH protocol, with a similar ability to the Bruce protocol to determine peak performance, provides a strong relationship between work rate and gas exchange making it easier to relate intensities for regular activity prescription.

Our findings on age-sex patterns in peak $\dot{V}O_2$ when normalized for body weight are consistent with those described by Armstrong and van Mechelen (58). Armstrong and van Mechelen (2008) state that while boys show an almost linear increase in peak $\dot{V}O_2$ in relation to age, girls’ data demonstrates a similar but less consistent trend, with a progressive rise to age 13 and then a levelling off or slightly decreasing at around 14 years of age (58). Pre-pubertal boys’ peak $\dot{V}O_2$ is higher than those of girls and the sex difference becomes more pronounced as children progress through adolescence (58). The boys in this study had lower peak $\dot{V}O_2$ scores for the age 10-12 year group than our girls of the same age group, likely
because our subset of boys were mostly 10 year olds and our girls were closer to 12 years of age. In the older age groups, the expected gender differences between boys and girls was observed with peak $\dot{V}O_2$ declining through adolescence in girls.

**Figure 3.2 Age-sex patterns in peak $\dot{V}O_2$ per protocol**

Our participants were healthy, physically active children who were involved in sports outside of school and our findings may not be representative of a true “normal” population. Without a change in grade, we found that healthy, physically active children tend to run slightly longer to yield the same peak performance parameters from the BCCH protocol compared to the Bruce protocol. It is unclear if this would hold true in less fit healthy children or in clinical populations (such as children with congenital heart disease). We specifically chose a physically active group to ensure consistency in performance. As such, we did not
test younger age groups (<10 years) due to difficulties in getting consistent performances with metabolic testing on two different occasions.

Our RER values may be slightly lower at peak exercise than those previously reported. We suspect that this may be related to the flow turbine that was used in our metabolic cart system. Given that the same equipment was used for both tests, we believe that our finding that the two protocols produce similar responses is valid. Future investigation using supra-maximal testing would allow us to determine if a true peak \( V\dot{O}_2 \) was achieved during both protocols.

3.1.7. Conclusion

The BCCH and Bruce treadmill exercise protocols yield similar exercise responses in children aged 10-18 years. The BCCH protocol provides an alternative testing protocol for use in children and may have better utility for testing children.

3.1.8. Acknowledgements

Acknowledgements: I would like to thank our study participants for volunteering their time to complete the study. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Funding: This study was supported by funding from the Douglas College Research and Scholarly Activity Fund Research Incentive Grant.

Competing Interests: None declared.

Ethics Approval: This study was approved by the UBC C&W Research Ethics Board.

Provenance and Peer Review: Not commissioned, externally peer reviewed.
CHAPTER 4: Exercise Intervention and Aortic Pulse Wave Velocity

4.1. Second Manuscript – Does a 12-week Supervised Exercise Intervention Reduce Aortic Stiffness in Obese Children and Adolescents?

4.1.1. Rationale and Research Question

Aortic distensibility and AoPWV are two parameters closely related to the elastic function of the aorta (aortic stiffness) and changes in these parameters serve as early pathogenic markers in CV disease (1,2). Quantification of aortic distensibility and AoPWV by Echocardiography-Doppler assessment has been shown to be accurate and reproducible (3,4) and is useful for identifying early CV disease in at-risk obese children and youth (5). As well, potential changes elicited from interventions designed to modulate AoPWV and other biomarkers of aortic stiffness can be non-invasively assessed (3). The impact of exercise on vascular function in obese children and adolescents has not been rigorously evaluated. High intensity exercise has been shown to improve exercise capacity and reverse aortic stiffness in obese adults (6,7). Chapter 4 investigates whether exercise training as an intervention has a similar effect in obese children and adolescents. The central question to be answered is “Does a 12-week supervised exercise program reduce aortic stiffness in obese children and adolescents?”

4.1.2. Outcomes and Hypotheses

Aortic distensibility induced by endurance training may be caused by changes of functional factors such as AoPWV. Therefore, the primary outcome measure for this study is AoPWV. Tanaka et al. (2000) studied n=20 middle-aged and elderly subjects (53 ± 2 years) who performed endurance exercise training at an intensity of about 70% of the maximum HR for 3 months, and showed the aortic compliance increased by about 25%, and β-stiffness
decreased by about 20% \((P < 0.01\), respectively\) (8). Aortic distensibility may be increased even by low or moderate intensity of endurance training. Kakiyama et al (2005) showed AoPWV in young males was decreased by 5\% by short-term \((8\text{-wk})\) cycle ergometry exercise training at 70\% maximum HR (9). This suggests that the central hemodynamic responses to acute aerobic exercise is enhanced by exercise training and, within the framework of our intervention, it would be reasonable to expect a 15\% improvement in 12 weeks. Of interest also, then, is the relationship between exercise intervention and other biophysical properties of the aorta and potential anthropometric factors influencing AoPWV. Therefore, the secondary outcome measures are other indices of aortic stiffness \((Zi, Zc, Ep, \text{ and } \beta\text{-index})\); consistent with Tanaka et al.’s work (8), a 10\% reduction in impedance measures and 10\% improvement in stiffness could be expected. As well, when the body engages in regular exercise training, depending on intensity and duration of training sessions, the force of load used in training and the body's initial level of fitness, it is expected that the cardiorespiratory system undergoes specific adaptations that increase the body’s efficiency and capacity. Gutin et al. (2000) found that the CV fitness of obese 13-16 year old adolescents was significantly improved by physical training and moreso at high intensity (10). Study participants exercised for 4 months randomized to either 55–60\% of peak \(\dot{V}O_2\) (moderate-intensity physical training) or 75–80\% of peak \(\dot{V}O_2\) (high intensity physical training) and with effects of training programs pooled, demonstrated a \(0.230 \pm 0.069 \text{ L/min}\) (or nearly 10\%) improvement (10). Hence, another secondary outcome in the exercise intervention study presented in chapter 4, will be the cardiorespiratory system’s response to training as measured by peak \(\dot{V}O_2\). Based
on Gutin et al. (2000) findings (10), a 10% improvement in fitness could be expected in 12 weeks of training.

*Primary hypothesis:*

1. The 12-week supervised exercise program will result in a 15% reduction in AoPWV.

*Secondary hypotheses:*

1. The 12-week supervised exercise program will result in a 10% reduction in other measures of aortic stiffness including Zi and Zc, and a 10% increase in Ep and β-index.
2. The 12-week supervised exercise program will result in a 10% increase in aerobic capacity (peak VO₂).

4.1.3. *Contribution of Authors*

*Kathryn Duff* was responsible for recruitment and scheduling of the patients, supervising the exercise tests, designing the exercise intervention circuits, and supervising the individual exercise sessions. She was responsible for all data collection and analysis and writing of all reports and manuscripts.

*Dr. Kevin Harris* oversaw the project, performed medical exams, and provided medical supervision of the exercise sessions. He was also involved in designing the echocardiography protocols. Dr. Harris contributed to editing reports and manuscripts.

*Dr. George Sandor* was responsible for designing the echocardiography protocols and provided training for the analysis of the echocardiography results. He helped to develop this unique method of assessing vascular function and has made important observations about vascular function in a number of disease states in children. Dr. Sandor was also involved in the editing of all reports and manuscripts.
Dr. James Potts was responsible for supervising the exercise tests and providing methodological and statistical support to all aspects of the study. He assisted with the editing of reports and manuscripts.

Astrid De Souza was responsible for supervising the exercise tests, designing the exercise intervention intensities, and supervising the individual exercise sessions. She assisted with the editing of all reports and manuscripts.

4.1.4. Collaborator

Dr. Jean-Pierre Chanoine is a Pediatric Endocrinologist and Head of the Division of Endocrinology at BCCH and Clinical Professor in the Department of Pediatrics at UBC. He is a Senior Associate Clinician Scientist at the BCCH Research Institute. Dr. Chanoine's research focus is nutrition and childhood Ob with a specific interest in the physiological role of the hormone, ghrelin, in the development of Ob and glucose intolerance. Dr. Chanoine provided important intellectual input regarding project design and analysis given his knowledge and expertise in the field.

4.1.5. Methodology

4.1.5.1. Study Design

Using a prospective, randomized, crossover design, participants were assigned to either a 12-week, supervised, progressively high intensity, exercise program or a 12-week control phase (Figure 4.1). During the exercise intervention phase, participants attended twice-weekly, 75-minute, periodized, circuit training sessions. During the control phase, participants received no intervention. There was an 8-week wash-out period between study phases. After completing the first randomly assigned phase of the study, and the 8-week wash-out period,
participants then crossed over to the study phase they had not yet completed. A resting echocardiogram and cardiopulmonary exercise test (using BCCH protocol, see Chapter 3) were performed before and after both the exercise intervention and the control arm of the study, requiring participants to attend a total of four clinic visits. Ethical approval to conduct this study was obtained from the UBC C&W Research Ethics Board.

**Figure 4.1: Cross-over design timeline**

The exercise intervention consisted of a 12-week program with two 75-minute exercise sessions per week in a gymnasium at BCCH. The frequency of activity and the total time spent in activity was held constant (2 days per week; 75 minutes per session). Participants needed to attend at least 75% of the sessions in order to have their data considered complete. The exercise program was designed to increase vigorous activity over the course of the 12-week intervention (see Sec. 2.3. Exercise Intervention Design). A variety of movements and games (e.g. spatial movement drills, relay and tag games, and circuit training involving ladder drills, mini-hurdle jumps, step-ups, skipping, etc.) were used to ensure the participant achieved success and enjoyed the program. Each exercise was performed for a short period of time (30 seconds to 120 seconds) and structured rest periods were incorporated. Quantitative
assessment of exercise intensity during the exercise session was performed using individual HR monitors (E600 Polar Heart Monitor transmitter/receiver pair, Polar Electro Canada, Lachine, QC). After each set of exercises within the workout, participants provided their RPE (11) and level of breathing discomfort using the Children’s Omni Scale (12) and Dalhousie Dyspnea Scale (13), respectively.

4.1.5.2. Participants

A comprehensive recruitment strategy was used to identify children and youth: community flyers posted on social media, at Metro Vancouver community and fitness centers, and at community medical centers; physician referrals from prevention clinics held at the Children’s Heart Centre at BCCH, and from counsellor referrals from local school communities. In addition, participants were identified from local pediatricians offices in the lower mainland, the UBC Family Practice Clinic at British Columbia Women’s Hospital (BCWH), local primary care physicians’ offices, and sub-speciality offices at BCCH. Participants referred to the Shapedown Program (a program designed for children and adolescents to achieve healthy weights) at BCCH who were not enrolled in their program were recruited. A recruitment notice was placed in the BC Medical Association newsletter and children were recruited from community pediatricians with the assistance of the BC Pediatric Society.

Inclusion Criteria

Children and youth (male and female) between the ages of 10-18 years with a body mass index (BMI) ≥ 97th percentile for their age (IOTF reference) (14) were included in this study.

Exclusion Criteria
Children and adolescents in whom there was a systemic condition as the primary cause of their Ob (e.g. Prader-Willi syndrome) were excluded from the study. Children and adolescents in whom it was not possible to obtain echocardiographic and Doppler data due to poor image quality were also excluded.

4.1.5.3. Measurements

All testing was completed in the Exercise Physiology Lab in the Heart Centre at BCCH, Vancouver, Canada. A paediatric cardiologist performed a physical examination to rule out any structural heart disease. Participants were measured for height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) and BMI was calculated (kg/m²). BMI was converted to age-specific percentile reference values (IOTF reference) (14) to ensure participant eligibility. Once consent and assent was obtained, qualifying participants were then assigned by block randomization to the control or exercise phase of the study.

4.1.5.3.1. Physical Exam

At each visit, standing height, sitting height and body mass were measured to the nearest 0.1 cm, 0.1 cm, and 0.1 kg, respectively. Sitting height was used to predict APHV to assess biological maturity categorically (15). Waist and hip circumference were measured to the nearest 0.1 cm (16). Waist to hip and hip to height ratios were calculated. BSA (m²) and BMI were calculated. BMI was converted to age-specific percentile reference values using IOTF references (14).

4.1.5.3.2. Resting Echocardiogram

Prior to exercise testing, a resting echocardiogram using a Vivid 5TM or Vivid 7TM ultrasound (GE Vingmed Ultrasound, Horten, Norway) was performed by a sonographer at
each clinic visit. Standard echocardiographic dimensions and measures of systolic and
diastolic cardiac function were recorded. The biophysical properties of the aorta were
derived using the echocardiography-Doppler method (see chapter 2, section 2.2.).

4.1.5.3.3. Exercise Testing

Using a validated, institutional (BCCH) protocol (17) (see chapter 3), where the incline
of the treadmill stayed at a constant 1% grade with a starting speed of 2.0 mph, increasing
by 0.5 mph every minute until volitional fatigue, participants were required to undergo peak
VO$_2$ testing. Metabolic gas exchange parameters (VE, VO$_2$, carbon dioxide production (VCO$_2$
and RER) were measured and calculations made by open-circuit spirometry using a metabolic
cart (Moxus Metabolic Cart, AEI Technologies, Pittsburgh, PA). The metabolic cart was
calibrated (and report generated) prior to each test being conducted using two
concentrations of calibration gas (20.9% O$_2$, 0.03% CO$_2$, balance N$_2$ and 15.0% O$_2$, 5.0% CO$_2$,
balance N$_2$). Calibration of the turbine flow meter of the volume sensor was performed with
a standard 3L syringe (5570 Series, Hans Rudolph Inc., Kansas City, MO).

Study participants wore a small, flexible, rubber mouthpiece in their mouth. The
mouthpiece was attached to a one-way, non-rebreathing valve (Style 2700B, Hans Rudolph,
Inc., Shawnee, KS) that was connected to the metabolic cart. Open circuit spirometry was
used to determine respiratory exchange variables during exercise. Breath-by-breath data
was collected and averaged over 15-second intervals during the test. Absolute and relative
peak VO$_2$, $V_T$ (mL/breath), $f_b$ (breaths/minute), VE (L/min), VCO$_2$ (L/min, mL/min/kg), RER, and
estimated energy expenditure (METS) were measured or calculated. Participants were
provided with verbal encouragement to achieve volitional fatigue and discouraged from
holding handrails during test. However, for safety purposes, participants were permitted to have one hand on the front rail for balance if necessary. Criteria for completion of a valid peak VO₂ test included: (1) a heart rate (HR) ≥ 190 bpm; (2) an RER ≥ 1.0; (3) volitional fatigue. A 12-lead electrocardiogram (ECG) was used to continuously measure the R-to-R interval and determine heart rate (60/R-to-R). sBP and dBP were obtained by cuff in the right arm by auscultation at rest (supine and standing) and immediately post exercise. Diastolic pressure was defined as muffling (Phase IV) of the Korotkoff sounds.

4.1.5.3.4. Accelerometry/PAQ-C/A

PA at home over a 7-day period was quantified using tri-axial accelerometry (GT3X+, ActiGraph Corp., Pensacola, FL) during both control and exercise study phases (18), as well as, by self-report using a PAQ-C/A questionnaire (19,20). For accelerometry data, a minimum of three valid days was required in order for data to be considered, with a valid day defined as having 10 or more hours of wear time (wear time was determined by subtracting non-wear time from 24 hours and non-wear time is defined as at least 60 minutes of zero counts).

4.1.5.4. Data Analysis

The study was powered to detect a significant change in AoPWV. An a priori power calculation (Gpower, Version 3.1) based on pilot data published by Harris et al. (2012) (α=0.05, β=0.8, effect size (δ)=75, and standard deviation=135) yielded a sample size of 27 (5). The distribution of variables was assessed using visual inspection (histogram) and Shapiro-Wilk test for normality. Univariate analysis was performed on all continuous variables to describe baseline values expressed as mean (standard deviation, SD). The association between key variables such as peak VO₂, HR, BP and AoPWV was determined by
Pearson product correlation (r). Paired t-tests were used to assess changes between the two study phases for metabolic and anthropometric data. Non-parametric data was compared using Wilcoxon Signed Rank test and reported as median (interquartile range; IQR, 25-75th percentile). All tests were one-sided and significance was set at $P<0.05$. Statistical analyses were completed using IBM SPSS statistical software v23.0 (Armonk, NY: IBM Corp). Graphs were generated using SigmaPlot software v13 (San Jose, CA: Systat Software Inc., SSI).

Accelerometry data was downloaded to an excel spreadsheet; intensity-related cut-points were applied as follows: 0-100 counts per minute (sedentary), 101-2295 (light activity), 2296-4011 (moderate activity) and 4012 and above (vigorous activity), therefore the minimum count for MVPA was considered 2296 active counts per minutes (21). Results for PAQ-C questionnaire were also entered into an Excel spreadsheet with mean responses generated and overall PAQ score assigned per study phase (22).

4.1.6. Results

In total, n=44 leads were obtained for participant recruitment of which approximately one-third (n=16) agreed and consented to the study; of these, three dropped out before the study started (two moved away; one refused follow up), three dropped out prior to completion of the protocol (two did not return for final clinic visit post-exercise and one dropped out part way through the exercise intervention due to previous injury flaring up). In total, n=10 participants completed the protocol. Of the n=10 participants that completed the protocol, two had incomplete echocardiograms for assessment on at least one of the visits, leaving n=8 with complete echocardiographic data. See Tables 4.1, 4.2 and 4.3 for baseline characteristics prior to each study period.
Table 4.1: Demographic variables (n=10; 3 females, 7 males); Mean±SD (Range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Phase at Baseline</th>
<th>Control Phase at Baseline</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>14.3±3.2 (10.2-19.5)</td>
<td>14.4±3.0 (10.7-19.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.6±15.2 (136.3-183.5)</td>
<td>164.1±14.8 (138.9-183.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>92.2±29.2 (55.6-132.7)</td>
<td>92.7±29.7 (50.6-135.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>110.2±14.8 (89.5-132.0)</td>
<td>112.8±16.9 (93.0-143.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hip Circumference (cm)</td>
<td>111.9±17.0 (87.0-134.0)</td>
<td>115.6±15.2 (88.0-137.0)</td>
<td>NS</td>
</tr>
<tr>
<td>W-Ht Ratio</td>
<td>1.0±0.05 (0.9-1.1)</td>
<td>1.0±0.07 (0.9-1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>W-Ht Ratio</td>
<td>0.7±0.8 (0.6-0.8)</td>
<td>0.7±0.8 (0.6-0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.6±6.4 (25.0-43.1)</td>
<td>33.6±6.7 (23.7-45.1)</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.97±0.39 (1.4-2.4)</td>
<td>1.98±0.39 (1.4-2.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: Waist to Hip Ratio (W-Hip), Waist to Height Ratio (W-Ht), Body Mass Index (BMI); Body Surface Area (BSA)

Table 4.2: Hemodynamic variables (n=10; 3 females, 7 males); Mean±SD (Range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Phase at Baseline</th>
<th>Control Phase at Baseline</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting sBP (mmHg)</td>
<td>118±11 (100-138)</td>
<td>118±13 (90-140)</td>
<td>NS</td>
</tr>
<tr>
<td>Resting dBP (mmHg)</td>
<td>65±5 (58-74)</td>
<td>61±8 (50-75)</td>
<td>NS</td>
</tr>
<tr>
<td>Resting PP (mmHg)</td>
<td>53±10 (41-68)</td>
<td>56±10 (37-70)</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate Post sBP (mmHg)</td>
<td>168±8 (160-188)</td>
<td>162±11 (140-178)</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate Post dBP (mmHg)</td>
<td>66±9 (50-80)</td>
<td>72±10 (60-84)</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate Post PP (mmHg)</td>
<td>100±13 (80-118)</td>
<td>91±14 (64-110)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>88±6 (77-99)</td>
<td>87±11 (68-101)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: systolic Blood Pressure (sBP), diastolic blood pressure (dBP), pulse pressure (PP)

Table 4.3: Cardiorespiratory variables (n=10; 3 females, 7 males); Mean±SD (Range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Phase at Baseline</th>
<th>Control Phase at Baseline</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Heart Rate (bpm)</td>
<td>84.9±14.9 (67-110)</td>
<td>78.1±8.3 (65-90)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak Heart Rate (bpm)</td>
<td>194.5±11.3 (177-212)</td>
<td>192.3±11.8 (175-207)</td>
<td>NS</td>
</tr>
<tr>
<td>Vₑ (L/min)</td>
<td>93.2±30.2 (49-142)</td>
<td>96.1±29.3 (46-132)</td>
<td>NS</td>
</tr>
<tr>
<td>peak VT (L/min)</td>
<td>3.0±0.9 (1.6-4.1)</td>
<td>3.1±0.9 (1.7-4.0)</td>
<td>NS</td>
</tr>
<tr>
<td>peak VO₂ (mL/min/kg)</td>
<td>32.4±4.5 (27.3-39.8)</td>
<td>34.1±4.5 (28.3-41.7)</td>
<td>NS</td>
</tr>
<tr>
<td>%Pred VO₂ (mL/kg)</td>
<td>90.0±14.5 (66-109)</td>
<td>94.0±16.7 (64-125)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Work (METs)</td>
<td>9.3±1.3 (7.8-11.4)</td>
<td>9.7±1.3 (8.1-11.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Exercise Time (s)</td>
<td>517.5±89.9 (390-666)</td>
<td>528.9±76.5 (420-634)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: Heart Rate, beats per minute (BPM); minute ventilation (Vₑ); oxygen consumption (VO₂); Metabolic Equivalents (METs)
Following the exercise intervention, there was a modest reduction in body mass (weight in kgs) \( p=0.0135 \); post-control kgs 95.6\(\pm\)28.7 compared to post-intervention kgs 91.5\(\pm\)27.7. There was no significant change to the distribution of weight; waist and hip circumference did not change. All participants remained >99\(^{th}\) percentile for age and sex-adjusted BMI through all study phases. There was a small, but non-significant improvement in absolute \( \dot{V}O_2 \) (L/min) (post-control peak \( \dot{V}O_2 \) 3.05\(\pm\)0.87; post-intervention peak \( \dot{V}O_2 \) 3.14\(\pm\)0.95). Study period changes in peak \( \dot{V}O_2 \) remained insignificant when indexed to height in metres (mL/min/m) but significant when expressed relatively with body weight (mL/kg/min) (control change in peak \( \dot{V}O_2 \) -1.05\(\pm\)2.50; intervention change peak \( \dot{V}O_2 \) 1.85\(\pm\)2.67; \( p=0.0415 \)). Exercise tolerance was improved following the intervention; both METS \( p=0.003 \) and treadmill time \( p=0.015 \) improved significantly following the intervention (see table 4.4).

Table 4.4: Changes (\( \Delta \)) in physical fitness and biological markers during 12-week study phases, \( n=10 \); 3 females, 7 males; Mean\(\pm\)SD

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \Delta ) Intervention Phase</th>
<th>( \Delta ) Control Phase</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass (kg)</td>
<td>-0.5(\pm)4.3</td>
<td>2.9(\pm)2.7</td>
<td>0.0135</td>
</tr>
<tr>
<td>BMI (kg/ m(^2))</td>
<td>-0.66(\pm)1.3</td>
<td>0.94(\pm)0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Waist Circum (cm)</td>
<td>-1.3(\pm)2.6</td>
<td>2.3(\pm)3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hip Circum (cm)</td>
<td>-1.4(\pm)5.0</td>
<td>0.9(\pm)3.6</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>0.005(\pm)0.06</td>
<td>0.035(\pm)0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Resting sBP (mmHg)</td>
<td>-4.4(\pm)9.5</td>
<td>-1.3(\pm)14.7</td>
<td>NS</td>
</tr>
<tr>
<td>Resting dBP (mmHg)</td>
<td>-4.4(\pm)7.9</td>
<td>1.1(\pm)5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Resting PP (mmHg)</td>
<td>0.00(\pm)10.1</td>
<td>-0.2(\pm)13.4</td>
<td>NS</td>
</tr>
<tr>
<td>Resting MAP (mmHg)</td>
<td>-4.42(\pm)7.0</td>
<td>1.9(\pm)7.8</td>
<td>0.024</td>
</tr>
<tr>
<td>( V_E ) (L/min)</td>
<td>6.51(\pm)6.8</td>
<td>2.17(\pm)8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak ( \dot{V}O_2 ) (mL/min)</td>
<td>183.6(\pm)245.4</td>
<td>-37.1(\pm)203.7</td>
<td>NS</td>
</tr>
<tr>
<td>Total Work (METs)</td>
<td>0.42(\pm)1.1</td>
<td>-0.86(\pm)1.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Total Exercise Time (s)</td>
<td>53.9(\pm)34.5</td>
<td>9.6(\pm)37.9</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: body surface area (BSA); systolic blood pressure (sBP); pulse pressure (PP); mean arterial pressure (MAP); minute ventilation \( (V_E) \); oxygen consumption \( (\dot{V}O_2) \); Metabolic Equivalents (METs)
Echocardiography showed a significant reduction in AoPWV following the intervention (p=0.003) (see Table 4.5 and Figure 4.2). Because two participants had incomplete echocardiography data, statistical tests for normality failed and a non-parametric, Wilcoxon signed-rank test was used to assess for significant change. The median AoPWV (cm/s-1) at baseline prior to the intervention was 484.5 (453.8-608.7) and following the intervention 451.8 (420.6-477.0). There were no significant differences in resting sBP, dBP, or pulse pressure after training. No correlations were found between AoPWV and systolic BP, pulse pressure, nor exercise capacity (peak V̇O₂) during any of the study phases.

**Table 4.5: Changes (Δ) in biophysical properties during 12-week study phases,**
Median (IQR), n=8

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ Intervention Phase</th>
<th>Δ Control Phase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Aortic Flow (cm²/s)</td>
<td>-0.14 (-0.84-0.04)</td>
<td>-0.40 (-1.33-0.32)</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Pulse Wave Velocity (cm/s⁻¹)</td>
<td>-34.35 (-137.9 to -13.2)</td>
<td>62.70 (-22.8-101.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Arterial Pressure Strain (mmHg)</td>
<td>-2.60 (-15.3-12.3)</td>
<td>2.78 (-13.3-19.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial Wall Stiffness (β-index)</td>
<td>0.19 (-0.8-1.2)</td>
<td>-0.08 (-2.0-0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic Input Impedence (dyne s/cm⁵)</td>
<td>-2.67 (-15.4-17.5)</td>
<td>8.02 (-38.1-24.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Character Impedence (dyne s/cm⁵)</td>
<td>-14.29 (-39.2-10.2)</td>
<td>5.13 (-13.1-25.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Accelerometry data is presented in Table 4.6. Only n=7 participants were able to provide data for at least three valid days. There was no difference in wear time between the study phases. Less sedentary time was spent in the exercise phase but more MVPA time was spent in control phase. Only one participant wore the accelerometer during the exercise training sessions. All study participants filled out a PAQ-A/C questionnaire for both study phases. Because there is not enough data to draw any conclusions about PA during the study phases, a qualitative commentary can only be offered.

Table 4.6: Accelerometry (n=7 with 3+d wear time)/PAQ-C (n=10); median (IQR)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Phase</th>
<th>Control Phase</th>
<th>Qualitative Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steps / day</td>
<td>8899 (5507-9682)</td>
<td>9522 (8369-10178)</td>
<td>&lt;12,000+ s/d expected for children</td>
</tr>
<tr>
<td>MVPA (mins/d)</td>
<td>45 (32-60)</td>
<td>57 (43-68)</td>
<td>MVPA below req’d 60 mins</td>
</tr>
<tr>
<td>Sedentary Time</td>
<td>624 (590-900)</td>
<td>663 (601-1006)</td>
<td>&lt;SED time during exercise phase</td>
</tr>
<tr>
<td>(mins/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAQ-C/A SCORE</td>
<td>2.373 (1.8-2.8)</td>
<td>2.550 (2.1-2.9)</td>
<td>Exercise displaced normal activities</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>PAQ-C/A Percentile</td>
<td>17.1 (9.5-71)</td>
<td>38.0 (29.1-62.4)</td>
<td>Inactive sample of children similar to non-obese age-group peers</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: moderate-to-vigorous physical activity (MVPA), Physical Activity Questionnaire for Children and Adolescents (PAQ-C/A)

4.1.7. Discussion

The present study shows that a supervised exercise intervention can improve AoPWV in obese children and adolescents. This was important to determine as a strong association between childhood Ob and measures of aortic stiffness has been documented previously (5). However, before now, it was not known if the observed changes in aortic stiffness were reversible in children. Given the link between aortic stiffness and early CV disease, it was important to determine whether exercise was an effective therapy for reducing aortic stiffness in obese children and whether CV improvements such as alterations to the biophysical properties of the heart could be made following an exercise intervention program. This study indicates that exercise is indeed a potential and viable option for disease management, as exercise training instigated an improvement in endothelial structure by reducing arterial stiffness as measured by a decrease in AoPWV.

The AoPWV data shown here is similar at baseline to Harris et al. (2012) in that it characterizes obese children as having elevated AoPWV compared to non-obese peers (see Figure 4.2.) (5). The clinical relevance of improving endothelial function can be assumed from the Harris study (2012): reducing AoPWV by 140 cm/s\(^{-1}\) ameliorates CV risk profile in obese children (5); the exercise intervention described in this study achieved a 7% improvement (33 cm/s\(^{-1}\)) in AoPWV in 12 weeks. It is not known if a longer intervention period might completely normalize these values to the baseline noted by Harris et al. (2012) in their non-
obese cohort (5). Only one participant in the current study showed a return to normal values following the exercise intervention and this one subject had notably high values at baseline pre-exercise. This may represent phenotypic variability within obese children.

The baseline BP in this study showed no significant effect from the exercise intervention. All participants had elevated resting sBP and pulse pressure compared to the healthy controls in Harris et al. (2012) in both phases of the study (5). Harris et al. (2012) suggested that increased AoPWV may be independent of BP (5). Watts et al. (2005) also demonstrated an improvement in vascular function in the absence of changes in BP in 19 obese youth (14.3±1.5 years) (23). They looked at the influence of 8-weeks of circuit training using a randomized, crossover protocol. Training was associated with significant improvements in flow-mediated dilatation of the brachial artery relative to matched lean controls demonstrating that vascular changes could be normalized despite lack of change to BP (23). Farpour-Lambert et al. (2009) suggested that reducing elevated systemic BP is possible in pre-pubescent children (24). They conducted a 12-week exercise intervention that included three, 60-minute sessions per week (total 180 min/week in addition to regular physical education class activities up to 135 min/week) of aerobic and strengthening exercises. They showed that PA reduced systemic BP and arterial stiffness delaying the early arterial wall remodeling in peripheral arteries (carotid and brachial) in 8.9±1.5 year olds (p<0.0001) (24). Their changes in BP were even greater in the hypertensive participants. Although arterial stiffness improved, they found exercise had no effect on endothelial or smooth muscle cell function (24). Therefore, the differences seen in the studies may relate to the time course of pathological adaptation (increased arterial stiffness) in obese children.
Pubertal status, through changes in vasoactive hormone concentrations and exposure time to hemodynamic variables acting through vessel wall shear stress, are critical factors known to influence arterial wall properties and function (25,26). As such, the influence of age on aortic stiffness indices like BP may be confounded by pubertal status.

Exercise training had little effect on body mass nor distribution. These findings are consistent with literature describing weight loss programs with exercise in general (27,28). It is unknown if an improvement in vascular function may precede weight loss. It is possible that compensation of the vascular structure may occur first in overweight or obese youth. Charakida et al. (2012) suggest that conduit artery adaptation may occur to subdue the hemodynamic effects of adiposity (29). Measures of aortic impedance, Zc and Zi, incorporate changes in aortic structure, likely due to changes in function of the elastic aorta (29). Although the data here did not find a change to these properties after the intervention, it may be that the improvement in vascular function was not restricted to vessels of the exercising musculature. If structural change (artery stiffness) supersedes the functional change, if the exercise intervention had continued, it is possible that weight reduction might follow once the conduit compliance was improved.

Exercise training modifies body composition, however, with initial decreases in fat predominantly occurring from the viscera (10); although body weight and BMI were not decreased in this study, it is possible there was a shift in lean body mass but not in absolute weight. As our intervention intensity increased, so too did the components of resistance training whereby participants were using their own body weight for loading (e.g. planks, squats, bear crawls, etc.). Several studies have reported beneficial countervailing effects
occur through increases in lean body mass and decreases in fat mass that using BMI would not detect (23,30). The lack of change in gross body composition measures (weight, BMI and waist/hip girth), despite possible regional changes in fat and lean body mass, emphasize the importance of comprehensive assessment of body composition in future training studies.

Training improved exercise tolerance and capacity; although absolute peak VO$_2$ only showed a modest, non-significant improvement, it is consistent with other intervention studies. Dias et al. (2015) conducted a meta-analysis of intervention studies pooling data from 219 obese and overweight children and adolescents where the mean difference of 3.64 mL/kg/min (p<0.05) was achieved after exercise training compared with controls (31). Following our exercise intervention, when expressed relative to body weight, our participants demonstrated a 2.03 mL/kg/min improvement (p=0.0193). Despite the small increase in fitness, exercise tolerance improved following training which has implications for overall vascular health. With respect to CV risk, further reduction may be contributed by the nearly 0.5 MET improvement in CV fitness. Myers et al. (2002) demonstrated that in adults, every 1-MET increase in exercise capacity was associated with a 12% improvement in survival (32). In the study performed here in chapter 4, when data from the pre-pubertal children (10-12 year olds) were removed from the sample, exercise capacity was significantly increased for the older children (p<0.0304). However, it is likely that these age-related differences lie in the fact that it is difficult to design one exercise protocol to yield similar results across such a wide age range. The younger children (10-12 years) demonstrated less tolerance to the upper limits of the HIIT design, refusing to complete as many reps in the later stages (weeks 10-12) of the increasing intensity. They worked at high % HR reserve but for less duration.
Despite a limited sample size, this study had a number of strengths. First, a novel, non-invasive technique was used to assess aortic stiffness in children and adolescents. This validated technique was developed at BCCH (3) and has been used extensively in children with congenital and acquired heart disease, as well as, in obese children and youth (4,5). Second, the exercise intervention was designed based on evidence from the literature and was overseen by an exercise physiologist. Third, the study design was robust. The crossover design ensured that each child served as their own control and in so doing limited the effect of covariates which may be difficult to quantify or control. Although the study design required the recruitment of a realistic number of children accounting for significant attrition (as this was recognized to be an issue that complicates studies in childhood Ob that require longitudinal follow-up), recruitment was challenging in this population. The sample size fell short of the desired n=27 participants, however, a post hoc power calculation (Gpower, Version 3.1) based on this new data (effect size=0.6433378; actual power=0.8140635) shows a sample size of n=17 to determine a strong effect.

This study demonstrated that this exercise intervention was effective in reducing AoPWV in obese children and adolescents. With the new sample size calculation, recruitment of n=6 more participants could extend this work to determine the utility of exercise as a therapeutic option for managing Ob and whether the improvements can be maintained over time. This data will help clinicians move forward to further investigate the underlying mechanisms regulating aortic stiffness in obese children. At present, it is not clear whether changes to endothelial structure precede functional changes impeding any weight loss that could be achieved through an exercise program. Additionally, it is not known how quickly the
changes might reverse if the child deconditioned after the program termination. Because the non-trained data did not differ depending on how the participants were sequenced for training first or second, and that 8 weeks seemed to be adequate washout, it does not appear that the effect of exercise training on endothelial function persisted after 12 weeks. It is therefore likely that continued training is necessary to maintain the vascular and anthropometric benefits of exercise. As well, it appears that four participants were the main drivers of the decline in AoPWV during the exercise intervention and that these were the four with the highest AoPWV before the intervention. Further research could help determine if exercise only affects AoPWV in children with advanced aortic stiffness.

4.1.8. Conclusions

A progressively, HIIT program is feasible in obese children and adolescents and may improve CV fitness. Furthermore, a reduction of AoPWV and improvement in other biophysical properties of the aorta can be achieved with exercise. Therefore, it may be confirmed here that exercise is an important strategy to help reduce CV risk, specifically aortic stiffness, for obese children. The findings of this study provide important data to further investigate the underlying mechanisms regulating aortic stiffness in this population.

4.1.9. Acknowledgements

Acknowledgements: I would like to thank our study participants for volunteering their time to complete the study. I would also like to thank the following individuals for their time and expertise: Astrid De Souza, Barb Morrison (exercise physiology support); Christine Voss, Boris Kuzeljevic (statistical analysis support); Raman Gill and Lindsey Williams (sonographers); Dr. William Sheel, Director of UBC Health and Integrated Physiology Lab, (intellectual support);
Dr. George Sandor, Pediatric Cardiologist (Echocardiography); Undergraduate students from UBC Kinesiology and Douglas College Sport Science program (assistance with exercise sessions). The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

**Funding:** This study was supported by a grant from the BCCH Telethon Projects Competition.

**Competing Interests:** None declared.

**Ethics Approval:** This study was approved by the UBC C&W Research Ethics Board.

**Provenance and Peer Review:** Not commissioned, externally peer reviewed.
CHAPTER 5: Exercise Intervention and Respiratory Function

5.1. Third Manuscript – Respiratory Function in Obese Children and Adolescents Before and After a 12-Week Exercise Intervention Program

5.1.1. Rationale and Research Question

Ob impacts a multitude of body systems including the respiratory system, both at rest and during exercise; specifically, Ob can cause changes in respiratory function, exercise tolerance, pulmonary gas exchange, breathing pattern, and strength and endurance of the respiratory muscles (1,2,3). The cardinal symptoms of chronic respiratory complaints that limit exercise in most Ob are dyspnea and/or fatigue (3,4,5) which may result from ventilatory constraints (3), pulmonary gas exchange abnormalities, peripheral muscle dysfunction, cardiac dysfunction, or any combination of the above (3,4,5). In adults, pulmonary function abnormalities are commonly reported complications of Ob, with the most frequently reported irregularities being reduction in lung volumes (6) and forced expiratory flow (7,8). However, the effects of Ob on pulmonary function in children and adolescents remains poorly understood, and the relationship between PA and pulmonary function in obese children hardly studied, and, what is available, is limited and conflicting (8,9); hence, it remains unclear in children as to whether activity-related breathlessness is due to (i.) abnormal respiratory mechanics related to the increased chest wall loading of adiposity, (ii.) the increased metabolic demand of locomotion in Ob, (iii.) altered perception of effort or (iv.) a combination of these factors (1,2,6). Therefore, the primary aim of this chapter is to evaluate the effect of an exercise intervention on respiratory characteristics of children with a high BMI. These findings can contribute to optimal management programs and better clinical
guidelines for obese children reporting breathing concerns. The secondary aim is to identify any respiratory limitation during exercise in these obese adolescents because exercise intensities for the intervention were prescribed from maximal exercise testing and it was therefore important to characterize the response for these individuals to this form of exercise. If respiratory responses of obese adolescents to exercise were disadvantageous then maintaining moderate to high intensity exercise in this group could be compromised. This is important as at least 60 min per day of MVPA is recommended for children and adolescents to achieve health benefits (7). It is hypothesized that obese adolescents are more likely to experience a respiratory limitation at baseline and during exercise that would be unfavourable in maintaining prescribed intensities, but that training would improve exercise tolerance, breathing strategies and functional pulmonary scores.

5.1.1.1. Evidence for Obesity-Related Abnormalities in Resting Lung Function

Respiratory disturbances associated with Ob include impaired respiratory mechanics with low lung volumes and decreased respiratory system compliance (3), increased small airway resistance (8), and alterations in both breathing pattern and respiratory drive (9,10). Reductions in expiratory reserve volume (ERV), functional residual capacity (FRC), respiratory system compliance and impaired respiratory system mechanics produce a restrictive ventilatory defect (11). Low FRC and reductions in ERV increase the risk of expiratory flow limitation and airway closure during quiet breathing (11). Consequently, Ob may cause expiratory flow limitation and the development of intrinsic positive end expiratory pressure (11). This is especially true in the supine position, such as when sleeping, thus, there is a subgroup of Ob that develop chronic daytime hypoventilation (3). Changes in pressure
increase the work of breathing by imposing a threshold load on the respiratory muscles leading to dyspnea (11). If hypoventilated, those with Ob will have resting daytime hypoxemia and hypercarbia, impaired central respiratory drive with decreased ventilatory responsiveness to CO₂, and nocturnal alveolar hypoventilation (3,8,9,11,12).

Several possible mechanisms of altered pulmonary mechanics have been cited related to the mechanical effect of adipose tissue on the lung, such as airway smooth muscle dysfunction from thoracic restriction (8,9), Ob-related circulating inflammation priming the lung (1), and Ob-related co-morbidities mediating asthma-like symptom development in the absence of restriction (13). Steele et al. (2012) showed that Ob was inversely associated with lung function in adults, but described central fat distribution as appearing to have a stronger relationship with respiratory mechanics in men than in women (14). The accumulation of fat in the chest, diaphragm and abdomen can compress the chest structures reducing lung volumes and flow (1). Ob-related chest wall restriction and the resultant breathing at low lung volume leads to airway obstruction, reactivity, and an asthma-like phenotype (14). These physiologic characteristics seen in some obese adults appear less commonly in children (1,2), perhaps due to a reduced duration of Ob in children relative to adults. However, Ob’s effects on airway mechanics and airway reactivity among children and youth require more investigation.

It is also known that Ob is an inflammatory disease, with cytokine expression that can alter pulmonary function (15). Adipose tissue releases pro-inflammatory ‘adipokines’ (e.g., adiponectin, IL-6, TNFα, leptin) that primes the lung for exaggerated responses to environmental triggers (13,16), leading to asthma-like symptoms. In this way, in the absence
of restriction, airway obstruction may be caused by chronic inflammation of the Ob condition itself that stimulates increases in mucous production and thickening of the airway walls (13,17). Therefore, Ob-related inflammation may play a role in the development and severity of actual asthma, or at least in a child being assigned an asthma diagnosis (18). However, as mentioned, a clear picture has not been elucidated in children (19,20,21,22).

The effect of Ob on spirometry and lung volumes is complicated and influenced by the degree of obesity, age, and type of body fat distribution (central or peripheral) (1,3,4,8,23). Full PFT is often necessary to better characterize the spirometric abnormalities seen with Ob. PFT in obese adults has shown abnormalities (3,4,8) but disproportionately with increasing BMI (26,27,28). Childhood Ob on PFT parameters have revealed inconsistent results (1,2,24,30,31). In mild adult Ob, results of spirometry might be normal or might suggest a restrictive process with symmetric reduction in FEV\(_{1.0}\) and FVC (27). In adults with a BMI above 35 kg/m\(^2\), Ob has been associated with reduced total lung capacity (TLC), FRC and expiratory reserve capacity (ERC) (27,28) and greater residual volume (RV) (8) as the most representative findings. Even a moderate elevation in BMI has been associated with a substantial reduction in FRC and ERV in otherwise healthy obese adults (8,23). Lazarus (1997) showed that BMI is significantly associated with the FEV\(_{1.0}\)/FVC ratio \(p<0.01\) (26). This suggests the presence of a restrictive respiratory pattern associated with Ob (26).

In contrast, in severely obese adults (1,28), BMI of 45 or above, can demonstrate airflow limitation on spirometry. Biring et al. (1999) showed in morbidly obese individuals (BMI>62 kg/m\(^2\)), there was a reduction in the FEV\(_{1.0}\)/FVC ratio and mid-expiratory flow rate (28). Therefore, differences in body fat distribution are also important. For example, both
Lazarus et al. (26) and Collins et al. (27) showed that FVC, FEV\textsubscript{1.0}, and TLC were significantly lower in patients with a waist-to-hip ratio of 0.95 or greater compared with values in those with a waist-to-hip ratio of less than 0.95 \((p<0.05)\) (26,27). When considered as a ratio, RV:TLC, and higher TLC by plethysmography (a method which shows greater sensitivity than by helium dilution) (29), shown in morbidly obese may indicate air trapping (28). Further to this, the decrease in maximal voluntary ventilation (MVV) in massively obese individuals observed by Sahebjami et al. (30) led authors to hypothesize that some obese adults manifest peripheral airway abnormalities, suggested by reduced maximum expiratory flow rates at low lung volumes and air trapping (26,27). Because MVV depends on the movement of air into and out of the lungs during continued maximal effort throughout a pre-set interval (31), it provides an assessment of the effort, co-ordination, and flow-resistive properties of the respiratory system. As a result of air trapping, inspiratory muscles are placed at a mechanical disadvantage leading to lower inspiratory pressure and flow, and reduced respiratory muscle strength, causing low MVV (26,27,30,31). This supports the notion that obstructive deficit becomes a problem in the group with severe Ob (30). Ob has been shown to increase ventilation heterogeneity and reduced respiratory conductance and reactance (8,32). It is possible that airway smooth muscle stretch is a potent bronchodilator, and because those with Ob breathe at small VTs at low lung volumes, they might have reduced airway smooth muscle stretch and therefore worsening airway hyper-responsiveness (8).

To date, there is limited understanding of how Ob affects pulmonary function in the pediatric years because, pulmonary mechanics have either not been studied as extensively in children, or, findings have not been consistent. The predominant pulmonary function
abnormalities detected in obese children have been a reduction in the FEV\textsubscript{1.0}/FVC ratio and maximal voluntary ventilation (MVV). Paralikar et al. (2012) has shown significantly decreased FEV\textsubscript{1.0} and FEV\textsubscript{1.0}/FVC ratio in obese adolescent boys measured at rest (31). This decrease in the FEV\textsubscript{1.0}/FVC was also observed by Inselman et al. (2) and Mallory et al. (33) in earlier studies. Inselman et al. (1993) showed RV, RV/TLC, V\textsubscript{E}, and energy expenditure were elevated in 13 children with Ob, but all other lung volumes were normal (2). Thus, they concluded that obese children have altered pulmonary function, which is characterized by reductions in diffusing capacity and ventilatory muscle endurance and airway narrowing (2). These alterations may reflect extrinsic mechanical compression on the lung and thorax, and/or intrinsic changes within the lung. The reduced diffusing capacity may result from decreases in alveolar surface area relative to lung volume (2). A reduction in the FEV\textsubscript{1.0}/FVC ratio indicates airway narrowing, the severity of which is indicated by the absolute value of FEV\textsubscript{1.0} (30). Because no obstructive impairment was detected in any of the obese, results are indicative of airflow limitation without significant obstruction. Li and colleagues (2003) showed that there was a reduction in FRC (median 93% predicted, IQR: 68.5-116.5%) and diffusion impairment (median 83.5% predicted, IQR: 70.0-100.7%) in n=16 girls and n=48 boys with Ob (median age and BMI of 12 years, IQR 10-14; and 30.1 kg/m\textsuperscript{2}, IQR 27.2-32.8) studied by DEXA (1). However, in a study using fat mass indexing, also determined by DEXA, Kongkiattikul et al. (2015) found a high prevalence (73%) of abnormal lung function in obese Thai children and adolescents (34). The mean BMI z-score of the study population was also quite high, suggesting that most of the study cases were moderately to severely obese. As such, they determined that this high prevalence may not be associated with the less obese
Decreased FRC was the most common lung function abnormality found in the index study (64.4% of cases) (34). This finding is comparable to Li et al. (2003) (1), however, a higher frequency of decreased FRC was found, as compared to the Li et al. (2003) study (64.4% vs. 46%) (34). This difference in FRC may be attributable to higher levels of obesity (higher BMI z-score) in the index study (BMI z-scores 3.2 vs. 2.4 in Li et al.). This is consistent with the view that the mechanism of decreased FRC results from a decrease in ERV due to restrictive fat deposition in the chest wall and displacement of the diaphragm into the thorax by the obese abdomen (26,35). In a large cohort study of n=657 children with BMI>85th percentile (357 overweight, 300 obese) and a group of n=196 normal weight children, Spathopoulos et al. (2009) studied 6-11 year old children and found pulmonary function in children with Ob was characterized by a reduction in most spirometric indices such as FEV_{1.0}, FVC, FEF_{25–75}, and FEV_{1.0}/FVC, varying from normal by 2.5% to 7.5% (36). Clearly, more investigation is required in order to fully understand childhood respiratory response.

5.1.1.2. Factors Contributing to Ventilatory Response to Exercise in Obesity

Ob may lead to a reduced capacity for functional exercise as it may be compromised by ventilatory limitations, gas exchange limitations, cardiac dysfunction, skeletal or respiratory muscle dysfunction, or simply by deconditioning (3,35). The respiratory factors that accompany Ob, such as decreased thoracic compliance, increased airway resistance and breathing at low pulmonary volumes (9,37,38) contribute to ventilatory constraint (increased risk of expiratory flow limitation) (39), inspiratory muscle fatigue (40) and ultimately, exertional dyspnea (41). Because ventilatory response to exercise in children is excessive
relative to metabolic demand (42,43), this may increase the ventilatory constraint in children and adolescents with severe Ob. In addition, since children have small airways relative to lung size (44), the risk of expiratory flow limitation is also increased.

There is certainly enough evidence that Ob represents an important burden on the respiratory system, causing alterations in pulmonary volumes, pattern of breathing, and airway smooth muscle (35), but there have been conflicting findings when assessing pulmonary function results in obese children and adolescents. Many studies have been limited by small sample sizes (41,45,46), the inclusion of children who may or may not have clinically-defined asthma, but asthma-like symptoms instead (46,47), and variability in the definition used for what constitutes Ob particularly where actual fat mass is not measured and distribution not considered (45,46,47). As a consequence, the effects of Ob on pulmonary function in children remains poorly understood, and the relationship between PA and pulmonary function in obese children hardly studied. Symptomatically, among school-aged children, Ob has been associated with increased breathlessness (dyspnea) and cough (48) and increased exercise-induced bronchospasm (45) but it is likely that the relationship between Ob and lung outcomes vary based on other factors such as age, gender, activity level, and age-of-onset of Ob. In adolescents, the relationship between Ob and lung function is more similar to that observed in adults (1,2,6). Otherwise healthy, obese adolescents have variably reduced RV and FRC (accounted for by chest restriction) and impaired diffusion capacity (1). However, airflow obstruction is shown less commonly in obese adolescents compared to younger children (49) suggesting that asthma remits after puberty in Ob. Alternately, like younger children, obese adolescents are more likely to display exercise-
induced bronchospasm (50,51). The exact mechanism causing this reported Ob-related bronchospasm requires further exploration.

It has been shown that body fat stored in different depots (visceral, organ, subcutaneous, peri-cardial, etc.) may confer different health risks in adults (52,53). Further to this, fat distribution in children and adolescents can differ from that in adults, especially as they progress through puberty (54). However, the degree to which there are differences in both the storage and health consequences of adipose tissue stored in different locations, is not well understood in children and adolescents (55). In other words, the inverse association between cardiometabolic risk and peripheral fat has been predominantly demonstrated in adults, and it is unclear whether or not cardiometabolic risk is associated with fat distribution earlier in life, during childhood, and adolescence. Early life Ob, for example, particularly in boys, may reduce lung growth (56), suggesting that lipid deposition in obese lungs may indicate alterations in pulmonary composition occurring with Ob.

There is some evidence in young boys that Ob associates with greater airflow obstruction (measured by FEV1.0/FVC) (35,57). Lang (2013) found airflow impairment among young boys with asthma (58) but admitted the interaction between Ob and gender in children requires further study. Most studies associating lung function with Ob and exercise are performed in children and adolescents with asthma (45,51,58), as children reporting asthma or breathing complaints associated with their Ob are becoming more common in the clinical setting (59). However, it is unclear if these are true asthma-diagnoses and non-asthmatic obese are often not included. As a potential confounder, sedentary behaviour is a risk factor for Ob and is a plausible factor leading to breathing difficulties during exercise (60,61).
Children who are overweight often sustain less routine physical exertion than their lean counterparts (62) and are simply deconditioned. The pulmonary dysfunction caused by Ob can become a cyclical problem. Overweight children who easily get short of breath tend to avoid exercise, remain sedentary, and thus enhance their need for medication during asthma flare-ups (59,63). Children with Ob are found to have similar cardiorespiratory function compared with non-obese children in a few studies (64,65,66); however, in these studies, PA was expressed as absolute energy expenditure and no correction was made for the large body mass of the obese subjects. Based on weight relative scores, however, it is understood that obese children and adolescents are less fit than their normal-weight counterparts (67,68,69) and that the increased metabolic demand of exercising with adiposity decreases functional performance and mechanical efficiency (70,71). Hence, children with Ob may avoid moderate or strenuous exercise, because of the higher degree of effort needed (71,72). This may contribute to the maintenance of overweight (68,69).

Exercise training contributes to decreasing ventilatory demand (73,74) and possibly limits the effects of ventilatory constraint on exercise capacity. Repeated exercise promotes hyperventilation, cyclic airway smooth muscle stretch, and bronchodilation (75,75,77). In this way, it may constitute a way to increase inspiratory muscle function (40). As such, lung function has been observed to be the highest in physically active children compared with their less active peers (72). Accordingly, exercise training and exhaustive play should protect against the development of pulmonary dysfunction (78).

In adults, weight reduction has resulted in improved lung function, better asthma control, and less need for asthma medication (79). In children, again, this is hardly studied.
Although Jensen (2013) reported that weight loss through diet restriction among obese, asthmatic children may improve asthma-related outcomes, relatively little data exist on the effects of exercise and exercise capacity in children with asthma or Ob (80). Ob may impact the relationship between PA and airway responsiveness, including those who have not been diagnosed with asthma (81). The mechanisms underlying this relationship could include a lack of airway stretch attributable to low PA levels (81) and also altered breathing patterns in Ob that result in airway remodeling (inflammation from adipocytes may play a role that is closely linked to airway remodeling) (82) or chronic desaturation may play a role (3). Similar to asthma, Ob may increase the severity of the airway narrowing seen in children not getting adequate PA (3). So, the question remains, in the absence of weight reduction, can the effects of exercise improve respiratory function in children and youth with Ob?

Peak VO₂ improvements have been demonstrated in non-obese children undergoing HIIT (83,84). During such training, children reach high levels of oxygen consumption associated with high levels of ventilation (83). Nourry et al. (2005) demonstrated enhanced resting pulmonary function and deeper exercise ventilation in pre-pubescent children compared to controls following an 8-week HIIT running training program (85). The repetitive bouts of HIIT may stimulate the respiratory muscles leading to increased strength and/or endurance or changes in the structural properties of the respiratory system (85). This could bring about enhanced development in ventilation, and, therefore, in breathing pattern during exercise. In contrast, in continuous, endurance, training studies, where the stimulus on respiratory muscles was not as high, Ericksson and Koch (1973) showed improved aerobic
capability in 11-13 year old children after four months, but did not report changes to lung volumes (86). A control group was not used to compare for effects of maturation.

Overall, ventilatory adaptations to exercise training in adolescent Ob and its effects on ventilation, operational lung volumes, dyspnea and their interactions have hardly been studied. Mendelson et al. (2012) studied n= 16 obese adolescents (13.8 ± 1.7 years; BMI 34.1 ± 4.9 kg/m²) before and after 12 weeks of exercise training and n=16 normal-weight volunteers (14.3 ± 1.3 years; BMI 19.1 ± 1.2 kg/m²) (78). They found obese children presented lower end expiratory (EELV) and end inspiratory lung volumes (EILV) at rest and during submaximal cycling exercise, and modest expiratory flow limitation (78). After training, the obese children increased maximal aerobic performance (+19%) and maximal inspiratory pressure (93.7 ± 31.4 vs 81.9 ± 28.2 cm H₂O, +14%) despite lack of decrease in trunk fat and body weight. Furthermore, EELV and EILV were greater during submaximal exercise (+11% and +9% in EELV and EILV, respectively), expiratory flow limitation delayed but was not accompanied by increased VE. Overall, higher oxygen uptake was noted but similar ventilation in obese adolescents before exercise training (78). In contrast, in previous studies in children and adults (47,73,74,87,88), higher VO₂ and V̇E in obese individuals at the same work rate during cycle ergometer exercise was found. Mendelson (2012) attributed this difference to a possible blunted ventilatory response as evidenced by V̇E/ V̇CO₂ at rest and during submaximal exercise in their obese children compared to the non-obese. EELV (at rest and during submaximal exercise) and EILV (during submaximal exercise and at peak exercise) was significantly reduced in the obese children in Mendelson’s study (2012) (78) when compared with healthy weight peers, illustrating the impact of excess trunk adiposity on dynamic lung
volumes (9). Their obese participants experienced increased exertional symptoms during submaximal exercise when compared to non-obese peers, despite identical ventilation. At peak exercise, the same pattern was observed despite lack of significance: in the obese compared to non-obese, exertional symptoms reached the same level for lower peak \( \dot{V}O_2 \), power output and ventilation (78).

In a follow up study, Mendelson’s group (2014) found that exercise training could improve breathing strategies and 6-minute walk performance in n=20 obese adolescents (age 14.5 ± 1.7 years; BMI 34.0 ± 4.7 kg·m\(^{-2}\)) compared to non-obese peers (89). After exercise training, mean increase in the distance achieved during the 6 minutes walking test was 64.5 meters (95%CI: 28.1–100.9, \( p = 0.014 \)) and mean decrease in exertional breathlessness was 1.62 (95%CI: 0.47–2.71, \( p = 0.05 \)). Obese adolescents breathed at higher lung volumes, as evidenced by the increase in EILV from rest to 6-min exercise (9.9 ± 13.4 vs 20.0 ± 13.6%, TLC \( p < 0.05 \)) (89). Improved performance was associated with improved change in EILV from rest to 6-min exercise (\( r = 0.65, p = 0.025 \)).

Although Mendelson’s exercise training studies are promising, showing decreased exertional dyspnea and improved inspiratory muscle strength, operating lung volumes, breathing pattern and cardiorespiratory fitness in obese adolescents, the response to exercise at maximal intensities have not been described.

5.1.1.3. Research Question

The aim of this study was to examine ventilatory responses to training in obese children and adolescents to see whether the respiratory system limits their exercise. To answer this, ventilatory differences at rest needed to be considered, as well as, in response
to maximal exercise and in both conditions following training. Spirometry is a procedure that measures the rate of changing lung volumes during forced breathing (90). Children have a dynamic developmental phase during which lung volume size and airway size change with increasing age (43). Spirometry parameters are influenced by weight, height, age, sex, environmental factors, ethnicity, prematurity, participant cooperation and effort (90), and technical factors including technician experience. Ventilation patterns are generally identified as: normal, obstructive, restrictive or mixed pattern. FEV\textsubscript{1.0} (>80% of predicted or above the lower limits of normal), and FEV\textsubscript{1.0}/FVC are suggestive of normal spirometry (86). The obstructive pattern is usually characterized by decreased FEV\textsubscript{1.0} (<80% of predicted or below the lower limits of normal), decreased FEV\textsubscript{1.0}/FVC and normal FVC (FVC may be decreased in severe obstruction) (90). A value of mid expiratory flow (FEF\textsubscript{25-75}) below 60% of predicted is also suggests an obstructive pattern (90). FEF\textsubscript{25-75} is thought to be less effort-dependent than FEV\textsubscript{1.0} as it does not include high flows in the lung volume and is considered a measurement of small airway patency (90). The restrictive pattern is suggested by predominantly decreased FVC, normal or decreased FEV\textsubscript{1.0} and normal or increased FEV\textsubscript{1.0}/FVC. The proportionate reduction in both FEV\textsubscript{1.0} and FVC is suggestive of a restrictive pattern or poor participant effort (90).

Ventilatory efficiency can also be examined in progressive exercise testing: ventilatory equivalents for CO\textsubscript{2} (V\textsubscript{E}/CO\textsubscript{2}) defines ventilatory efficiency because it reflects the matching of ventilation and lung perfusion (91). Ventilatory efficiency can be examined at certain points of exercise, like the anaerobic threshold, or expressed as slope of the relationship between V\textsubscript{E} and carbon dioxide output (V\textsubscript{CO\textsubscript{2}}) throughout the test (91). Here, anaerobic threshold is
defined as the level of exercise above which oxygen supply to the working muscles and/or oxygen utilization are inadequate for energy requirements and so aerobic energy production is supplemented by anaerobic mechanisms (92). Elevated values of this parameter indicate ineffective ventilation and are present in the functional profile in a number of lung and heart diseases, but is generally only assessed in healthy pediatric groups (47). Marinov et al. (2002) showed that absolute metabolic cost of exercise was higher in 6-17 year old overweight children and youth compared with controls, but both groups showed similar ventilatory efficiency (47). They found, however, an increased awareness of fatigue that furthermore limits the physical capacity in the children that carried extra weight (47). For prescriptive reasons, ventilatory efficiency and RPE in obese children performing standardized exercise should also be compared. The question of whether a progressively HIIT exercise program can improve lung function and ventilatory efficiency in obese children the same way it is demonstrated in healthy-weight children has not been clearly established.

5.1.2. Outcomes and Hypotheses

The primary outcome measures for this study include respiratory values acquired from resting PFT including: forced expiratory volume in 1 s (FEV\textsubscript{1.0}), forced vital capacity (FVC), and forced expiratory flow at 25–75% of vital capacity (VC) (FEF\textsubscript{25–75}). Of interest, also, is the relationship between exercise intervention and gas exchange influencing breathing. Therefore, the secondary outcome measures are the other indices of breathing adaptation that increase ventilatory efficiency and capacity. Hence, secondary outcomes will be the cardiorespiratory system’s response to training as measured by gas exchange including peak exercise gas exchange, V\textsubscript{T}, V\textsubscript{E} and f\textsubscript{b}. 
Primary Hypothesis:

1. The 12-week, progressively HIIT exercise program will improve FEV\textsubscript{1.0}, FVC, and FEF\textsubscript{25–75}.

Secondary Hypothesis:

2. The 12-week, progressively HIIT exercise program will improve $V_e$, $f_b$ and $V_T-f_b$ relationship at peak exercise and sub-maximal intervals.

5.1.3. Contribution of Authors

*Kathryn Duff* was responsible for recruitment and scheduling of the patients, supervising the exercise tests, designing the exercise intervention, and supervising the individual exercise sessions. She was responsible for all data collection and analysis and writing of all reports and manuscripts.

*Dr. Kevin Harris* oversaw the project, performed medical exams, and provided medical supervision of the exercise sessions. He was also involved in designing the echocardiography protocols. Dr. Harris contributed to editing reports and manuscripts.

*Dr. George Sandor* was responsible for designing the echocardiography protocols and provided training for the analysis of the echocardiography results. He helped to develop this unique method of assessing vascular function and has made important observations about vascular function in a number of disease states in children. Dr. Sandor was also involved in the editing of all reports and manuscripts.

*Dr. James Potts* was responsible for supervising the exercise tests and providing methodological and statistical support to all aspects of the study. He assisted with the editing of reports and manuscripts.
Astrid De Souza was responsible for supervising the exercise tests, designing the exercise intensities, and supervising the individual exercise sessions. She assisted with the editing of all reports and manuscripts.

5.1.4. Collaborator

Dr. Jean-Pierre Chanoine is a Pediatric Endocrinologist, Head of the Division of Endocrinology at BCCH, and Clinical Professor in the Department of Pediatrics at UBC. He is a Senior Associate Clinician Scientist at the BCCH Research Institute. Dr. Chanoine's research focus is nutrition and childhood Ob with a specific interest in the physiological role of the hormone, Ghrelin, in the development of Ob and glucose intolerance. Dr. Chanoine provided important intellectual input regarding project design and analysis given his knowledge and expertise in the field.

5.1.5. Methodology

5.1.5.1. Study Design

Using the prospective, randomized, crossover design, described in Chapter 4 of this thesis, participants were first assigned to either a 12-week, supervised, progressively HIT, exercise program or a 12-week control phase (Figure 2.1). Once the 12-week assigned phase was complete and after an 8-week washout period, participants crossed-over and completed the phase of the study they had not previously done. Prior to and following the 12 weeks of training (or no training), participants completed a resting PFT. Following the PFT, each participant underwent exercise testing using the method described in chapter 3 of this thesis. Open circuit spirometry was used to determine respiratory exchange variables during exercise. Breath-by-breath data was collected and averaged over 15-second intervals during
the test. Full ventilatory values were reported for peak testing: \( \dot{V}O_2 \) (L/min, mL/min/kg), \( V_T \) (mL/breath), \( f_b \) (breaths/minute), \( \dot{V}E \) (L/min), \( \dot{V}O_2 \) (L/min, mL/min/kg), \( \dot{V}CO_2 \) (L/min, mL/min/kg), RER, and estimated energy expenditure (METs) were measured or calculated. Additionally, during the 12-week exercise training program, participants rated their breathing discomfort and perceived exertion using the Dalhousie Dyspnea Scale (93) and Children’s OMNI Scale (94), respectively, after each set of exercises within the workout. Two dyspnea constructs were used from the Dalhousie Scale consisting of two sets of seven pictures depicting chest tightness and throat closure. The researcher gave participants an explanation of the pictorial scales at the outset with instruction as follows: “this test is to see how your breathing feels during exercise. There is no right or wrong answer. The pictures in front of you show how your breathing might feel from no difficulty at all (scored as 0), to the most difficulty you can imagine (scored as 6). You might feel this difficulty breathing in your chest or in your throat. Another scale simply asks you to tell us how hard it is to breathe—from nothing at all, to the hardest breathing imaginable. With the final set of pictures, tell us how your legs feel—from nothing at all, to the hardest imaginable. We will ask you the same using this other scale (pointing to the Borg CR-10)”. Ratings after each exercise set were prompted by the questions: “how does your breathing feel?” and ratings using the OMNI scale were prompted by the questions: “How tired are your legs?”

5.1.5.2. Pulmonary Function Testing

Prior to exercise testing, a standardized, portable spirometry system (MIR Minispir, portable USB spirometre, Medical International Research, Waukesha, WI) with FlowMir disposable turbine and cardboard mouthpiece was used to assess pulmonary mechanics. FVC
was measured and flow volume curves plotted. In addition, FEV\textsubscript{1.0}, FVC, FEV\textsubscript{1.0}/FVC (ratio of FEV\textsubscript{1.0} and FVC), PEF, FEF\textsubscript{25-75\%} were measured. The best score on three trials was recorded. Predictions were based on Global Lung Function Initiative 2012 multi-ethnic reference standards (91).

5.1.5.3. Data Analysis

SigmaPlot statistical software v13 (San Jose, CA: Systat Software Inc., SSI) was used for data analysis. All parametric statistical assumptions were checked and the appropriate statistics were chosen. Data are expressed as mean±SD. Paired t-tests were used to assess changes between the two study phases for FVC, FEV\textsubscript{1.0}, FEV\textsubscript{1.0}/FVC, PEF, and FEF\textsubscript{25-75} and gas exchange including V\textsubscript{T}, V\textsubscript{E} and f\textsubscript{b}. V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} was plotted and visually inspected for breakaway point to determine submaximal thresholds. Significance was set at $P < 0.05$ for all analyses.

5.1.6. Results

Of the n=10 participants that completed the protocol, four had incomplete PFTs for assessment on at least one of their four clinic visits, leaving n=6 full cases for analysis. For these, the results showed that 12 weeks of progressively HIIT did not significantly improve PFT values. However, the training led to increases in peak exercise values of $\dot{V}_{E}$ and $V_{T}$ and conversely to decreases in $V_{E}/V_{CO_{2}}$ for 9 cases included (1 female participant did not achieve peak exercise values on two occasions).

5.1.6.1. Participant Characteristics

Participant characteristics are described in Chapter 4 (see Table 4.1). There were no significant differences in anthropometric data at the start of each study period.
5.1.6.2. Resting Pulmonary Function

Resting PFT values and % of predicted at baseline prior to training and prior to control phase are shown in Table 5.1. There were no differences between baseline values starting each study phase. Except for one child that maintained a classification of mild obstruction during each study phase (see Table 5.2), all participants had normal spirometry at each clinic visit and all were close to or exceeded 100% of their predicted for FVC each time.

Table 5.1: Pulmonary function testing baseline values (n=6; Mean±SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Exercise</th>
<th>Pre-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Predicted</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.00±1.27</td>
<td>108±7.8</td>
</tr>
<tr>
<td>FEV₁₀ (L)</td>
<td>3.14±0.96</td>
<td>98±7.6</td>
</tr>
<tr>
<td>FEV₁₀ / FVC (%)</td>
<td>78.9±3.4</td>
<td>91±3.7</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>5.7±1.8</td>
<td>85±9.5</td>
</tr>
<tr>
<td>FEF₂₅-₇₅% (l/s)</td>
<td>2.9±0.9</td>
<td>81±13.2</td>
</tr>
</tbody>
</table>

Predicted values from (NHANES III). Definition of Abbreviations: forced vital capacity (FVC); forced expiratory volume in 1 second (FEV₁₀); peak expiratory flow (PEF); forced expiratory flow between 25-75% (FEF₂₅-₇₅%)

Table 5.2: Individual spirometry classification (category) per study phase

<table>
<thead>
<tr>
<th>Participant</th>
<th>Pre-Exercise</th>
<th>Post-Exercise</th>
<th>Pre-Control</th>
<th>Post-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIS-003</td>
<td>Mild obstruction</td>
<td>Mild obstruction</td>
<td>Mild obstruction</td>
<td>Mild obstruction</td>
</tr>
<tr>
<td>EIS-004</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>EIS-009</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal*</td>
</tr>
<tr>
<td>EIS-011</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>EIS-015</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>EIS-016</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*FEF₂₅-₇₅% (l/s) <53% Predicted

Effect of Training on Pulmonary Function Test

Table 5.3 shows mean change (Δ) in FVC and FEV₁₀ between study periods, from pre- to post- exercise to pre- to post- control, indicating that there was a decreased FEV₁₀% following training for all six of the measured participants. Those who showed the least change
in post-exercise FEV₁% were the participants with the smallest decreases in post-exercise FEV₁% at baseline. These were not significant improvements. The ΔFEF₂₅₋₇₅ pre-post exercise also modestly improved with training, although not significantly.

Table 5.3: Change (Δ) in pulmonary function testing values (n=6; Mean±SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Δ Intervention Phase</th>
<th>Δ Control Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Predicted (%)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>0.131±1.07</td>
<td>4.8±22.8</td>
</tr>
<tr>
<td>FEV₁.₀ (L)</td>
<td>0.160±0.48</td>
<td>1.8±12.0</td>
</tr>
<tr>
<td>FEV₁.₀ / FVC (%)</td>
<td>-0.833±5.42</td>
<td>0.8±6.1</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>-0.083±0.35</td>
<td>-4.7±8.5</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅% (l/s)</td>
<td>0.117±0.56</td>
<td>1.0±11.7</td>
</tr>
</tbody>
</table>

Predicted values from (NHANES III). Definition of Abbreviations: forced vital capacity (FVC); forced expiratory volume in 1 second (FEV₁.₀); peak expiratory flow (PEF); forced expiratory flow between 25-75% (FEF₂₅₋₇₅%)

5.1.6.3. Ventilation During Exercise Testing

Exercise tolerance was improved following the intervention (see table 5.4 for outcome variables by study phase and table 5.5 for change between study phases). METS improved significantly 0.42±1.1 following exercise intervention versus 0.86±1.1 decline following control phase (p=0.003) as did treadmill time (sec) 53.9±34.5 increase (exercise phase) versus 9.6±37.9 (control phase) (p=0.015). There was a modest change (Δ) in \( \dot{V}_{T} \) (mL/br) and \( f_{b} \) (br/min) with exercise training: \( \dot{V}_{T}=40.6±178.0 \) mL/breath following exercise training and \( \dot{V}_{T}=107.3±165.8 \) mL in the control phase and \( f_{b}=2.0±6.4 \) (exercise intervention) versus \( f_{b}=−1.89±6.6 \) (control phase), although neither of these variables were significant. There were no intolerable reports of dyspnea during any of the exercise sessions (see table 5.6).
Table 5.4: Outcome Variables by study phase (n=9; 2 females, 7 males; Mean+SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Phase</th>
<th>Control Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-</td>
<td>Post-</td>
</tr>
<tr>
<td>$V_E$ (L/min)</td>
<td>103.9±23.8</td>
<td>106.48±23.6</td>
</tr>
<tr>
<td>Breathing frequency ($f_b$)</td>
<td>52.67±7.75</td>
<td>54.67±5.72</td>
</tr>
<tr>
<td>$V_T$ (mL/breath)</td>
<td>1902.3±558.4</td>
<td>1942.9±469.6</td>
</tr>
<tr>
<td>Total Work (METS)</td>
<td>9.34±1.2</td>
<td>9.90±1.3</td>
</tr>
<tr>
<td>Total Exercise Time (s)</td>
<td>526.5±79.7</td>
<td>575.3±90.4</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: minute ventilation ($V_E$); breathing frequency ($f_b$); tidal volume ($V_T$); Metabolic Equivalents (METS)

Table 5.5: Change ($\Delta$) in ventilatory performance (n=9; 2 females, 7 males; Mean+SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\Delta$ Intervention Phase</th>
<th>$\Delta$ Control Phase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_E$ (L/min)</td>
<td>6.51±6.8</td>
<td>2.17±8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Breathing frequency ($f_b$)</td>
<td>2.0±6.4</td>
<td>-1.89±6.6</td>
<td>NS</td>
</tr>
<tr>
<td>$V_T$ (mL/breath)</td>
<td>40.6±178.0</td>
<td>107.3±165.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total Work (METS)</td>
<td>0.42±1.1</td>
<td>-0.86±1.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Total Exercise Time (s)</td>
<td>53.9±34.5</td>
<td>9.6±37.9</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: minute ventilation ($V_E$); breathing frequency ($f_b$); tidal volume ($V_T$); Metabolic Equivalents (METS)

Table 5.6: Characteristics of breathing and perceived exertion during exercise sessions (n=10; Mean±SD)

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>115-130</th>
<th>131-145</th>
<th>146-160</th>
<th>161-175</th>
<th>&gt;175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived Exertion (RPE)</td>
<td>2.38±1.28</td>
<td>2.35±0.98</td>
<td>2.63±1.05</td>
<td>3.30±1.04</td>
<td>4.73±1.88</td>
</tr>
<tr>
<td>Throat Squeezing</td>
<td>0.16±0.25</td>
<td>0.10±0.19</td>
<td>0.21±0.36</td>
<td>0.21±0.33</td>
<td>0.21±0.51</td>
</tr>
<tr>
<td>Chest Tightness</td>
<td>0.10±0.20</td>
<td>0.14±0.23</td>
<td>0.22±0.22</td>
<td>0.29±0.24</td>
<td>0.52±0.54</td>
</tr>
</tbody>
</table>

Definition of Abbreviations: Rating of Perceived Exertion (RPE)

5.1.7. Discussion

This study was conducted to determine whether there were any differences in ventilatory responses at rest and during maximal exercise testing in obese children and adolescents following an exercise intervention in this group. Additionally, exercise intensities for the intervention were prescribed from maximal exercise testing and it was therefore important to characterize the response for these individuals to this form of exercise. Our study participants showed normal spirometry throughout the study phases and no apparent
pulmonary adaptation to exercise training when assessed by PFT. However, although all participants fell within the predictable spirometry limits throughout each study phase, it is remains unknown if exercise training would have no effect on those with a respiratory impairment prior to exercise.

The modest changes observed in breathing pattern at peak exercise potentially allowed a higher \( \dot{V}_E \) to respond to the increase in oxygen demand of the muscular tissues after training. In normal children, as \( \dot{V}_E \) increases during progressive exercise, the initial increase is achieved by increases in \( V_T \), and to a lesser extent, \( f_b \) (96). At heavier intensities of exercise, the increase in \( \dot{V}_E \) is met predominantly by increasing \( f_b \), while the increase in \( V_T \) is attenuated and approaches a plateau (at about 50-60% of vital capacity) and \( f_b \) continues to account for the difference (96). Therefore, the \( V_T - f_b \) relationship in exercise could be altered depending on the intensity. This same response was verified in the obese participants studied here. The increase in \( f_b \) and to meet \( \dot{V}_E \) that occurred as exercise intensity neared maximal efforts is similar to the rapid, shallow breathing expected as muscle fatigues suggesting that the longer the sustained high intensity exercise, the greater the fatigue. The participants in this study increased their \( f_b \) (not significantly) to accommodate the higher speeds at peak \( \dot{V}O_2 \). This negligible change in \( f_b \) may reflect entrainment or coordination of \( f_b \) to exercise rhythm (97). This might be an important consideration when evaluating a participant that has respiratory limitations, as well as, an important consideration for prescriptive exercise.

It is also possible that, in our study, training led to increased \( \dot{V}_E \) perhaps allowing stretch in the airway smooth muscle, but, only modestly, as changes were not significant. In accordance with the hypothesis that adipose tissue acts as an endocrine organ (15), chronic
inflammation is one possible mechanism by which prior unhealthy airway remodeling may have occurred, eventually leading to airway hyper-responsiveness (98), maybe explaining the mild obstruction in one participant. This child had a high mass, so systemic inflammation likely persisted as there was no change in weight following the intervention, thereby not likely allowing improvement in airway narrowing to the extent where it might in leaner children. Lowder and colleagues (2010) indicated that repeated bouts of moderate intensity aerobic exercise training in mice may attenuate airway inflammation within the asthmatic airway via regulatory T-cells (99). This may be true of the cumulative nature of our interval training as well, but, either the intervention was not long enough to realize in the higher weight individuals, or not a factor due to already normal function in the others. As well, ratings of perceived breathlessness were not significant during the exercise sessions in the participants.

Previous studies in obese children and youth were also unable to establish a relation between pulmonary deficit and anthropometric assessments of obesity (2,33,100). Pre-intervention, physical inactivity, as well as, adiposity, may have contributed to the increased $\dot{V}_E$ seen in our higher weight participants following training. Simply being conditioned contributed to a training effect of ventilatory improvement although not affecting weight significantly. Therefore, through training, improvement was seen in one contributing factor, but not the other, diminishing the overall improvement in airway function. This is consistent with Rosenkranz et al. (2012) findings that suggest in non-asthmatic, pre-pubescent children, inactivity negatively impacts airway responsiveness, which can be improved with HIT (77). Excess adiposity, however, may constrain these improvements. Ob and adolescence is characterized by children becoming less active and engaging in inadequate PA (62,69,70), as
well, higher rates of asthma have been shown to be more prevalent (15,16) in Ob, especially in boys (58,101). Whether this data represents accurate assessments of actual asthma or rather asthma-like symptoms is unknown; in any case, breathing difficulty may be foreseen as a barrier to exercise. The sex difference could be explained by the pressure-load and the distribution of adipose in pubertal boys (58). Based on the data found here, none of our Ob participants were compromised in respiratory function and were able to make positive changes to exercise tolerance. We did not have a large enough sample size to stratify for sex differences nor did we have any children nor youth with an asthma diagnosis; further investigations should track children with Ob through adolescence to determine whether PA levels, specifically at higher intensities, provide the same benefit as in pre-adolescence.

5.1.8. Conclusions

These results suggest a progressively HIIT program is feasible in obese children and adolescents and that complaints of breathing discomfort are not a limitation to exercise. Increased body fat, however, may diminish potential improvements in training. There are many factors contributing to the rapid increase in asthma and asthma-like symptoms in children over the past few decades, but early intervention relevant to lifestyle factors may be one potential way to reverse the trend of increasing airway complaints in obese children as potential limits for engaging in exercise. In the obese children and youth studied here, while a progressively HIIT program did not induce changes in resting pulmonary function, it did slightly alter exercise ventilation. During exercise, ventilation became slower and deeper allowing better effectiveness. These beneficial effects were obtained in 12 weeks which could easily be integrated into an endurance cycle of physical education lessons for school children.
5.1.9. **Acknowledgements**

**Acknowledgements:** I would like to thank the study participants for volunteering their time to complete the study. I would also like to thank the following individuals for their time and expertise: Astrid De Souza, Barb Morrison (exercise physiology support); Christine Voss, Boris Kuzeljevic (statistical analysis support); Raman Gill and Lindsey Williams (sonographers); Dr. Bill Sheel, Director of UBC Health and Integrated Physiology (HIP) lab, (intellectual support); Dr. George Sandor, Senior Cardiologist (Echocardiography); Undergraduate students from UBC Kinesiology and Douglas College Sport Science program (assistance with exercise sessions). The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

**Funding:** This study was supported by funding from the Douglas College Centre for Academic and Faculty Development Research and Scholarly Activity Fund.

**Competing interests:** None declared.

**Ethics Approval:** This study was approved by the UBC C&W Research Ethics Board.

**Provenance and peer review:** Not commissioned, externally peer reviewed.
Chapter 6: Challenges and Recommendations for Child and Adolescent Obesity Trials and Concluding Remarks

6.1. Research Considerations

In the context of the research studies prepared for this thesis, the challenge was to describe the patterns of change in the physiological variables over time but also to explain their separate, or maybe mutual, determinant factors. For example, if the goal was to determine the effect of an exercise intervention on Ob, the study was structured to study the physiological variables (using appropriate FITT) but the interpretation had to include growth or disease considerations. Does training simply improve heart response or is HR response due to change in the rate of biological development independent of training? If the obese child has impaired sympathetic tone (due to phenotypic expression), does HR response represent improved neural pathology, improved metabolic profile, or differences due to maturation that would improve performance anyways, or all of the above? As such, care must be taken in interpreting these results as it will have significant implications in terms of exercise training and disease control recommendations for obese youth—a healthist perspective in which “people are held responsible for their health outcomes and commitment to health-promoting behaviours” (1)—and the interpretation must also be made in the context of complicated disease factors such as the sociocultural context within which we are asking these children and youth to exercise—an ecological perspective. Therefore, embedded in this dialogue of reducing or preventing childhood Ob through PA initiatives to improve health outcomes such as CV disease, a more critical pedagogy might challenge the notion that Ob itself is simply inherently eugenic (often deploying biomedical weight categories for its definition) which may not hold true in population-based approaches designed to manage it.
The obese phenotype has emerged from a quagmire of complexity and likely cannot be addressed through a single action. A child’s social context is a strong determinant of their physical, mental, and social health and well-being (2). Applying a social science perspective on health and well-being means the recognition of the importance of influencing structures and pathways on a societal, organizational, and individual level. Moreover, supportive structures for individuals’ health and well-being are to a great extent shaped by the interactive process between these levels where social context, social position, and resources play an important role (3,4). Therefore, problematizing Ob may be an oppressive approach demonstrated by the fact that population Ob rates are increasing (5) despite public health initiatives aimed at reversing them (6,7). Ob is subject to a large variety of exposures operating in the pre-conception period, during fetal development and in post-natal life, and therefore, must be considered in the context of individual variation related to biological, social, and environmental sources when discussing exercise programming and implementing health initiatives. Some of these limitations and concerns will be attempted to be addressed in this chapter. Another challenge for these studies to be addressed, is timely and effective recruitment as this is often cited as an obstacle for achieving sufficient sample size in Ob trials and the experience was no different here. Although a consistent limit for adolescent Ob-related trials, there remains very little evidence regarding effective strategies for quality recruitment in this population. A review of the recruitment strategies used in our exercise intervention will also be discussed to serve as useful commentary for future research planning activities.
6.1.1. Disease Limitations

Ob is associated with increased inflammation and oxidative stress which is a major pathogenic pathway toward higher CV risk. Evidence supports exercise to protect against systemic inflammation and oxidation (8,9), but acute exercise also exerts pro-inflammatory and oxidative effects (9,10), prompting the necessity for better understanding of the biochemical process in order to interpret the effects of an exercise intervention on Ob. As well, exercise training could potentially reduce chronic inflammation without potentially altering adiposity (11,12) so it may be independent of weight loss. It is best speculated that the underlying modulation of immunologic, inflammatory and oxidative molecules is likely involved (9). For example, various weeks of exercise training has been shown to reduce pro-inflammatory markers (e.g. plasma C-reactive protein (13) and IL-6 (14,15)), improve lipid and glycemic profiles (11) and improve oxidative enzymes (reducing free radical harm that targets endothelium and sub-endothelial layers) (16) even specific to the aorta (17). These long term effects occur despite opposite, acute effects of exercise, during which pro-inflammatory and oxidative markers and free radical formation is increasing (18). This dichotomy of acute and chronic exercise effects underscores the complexity of these processes, in which fine synchronization of diverse interactions are responsible for cardio-protective effects. If the equilibrium is altered, as may occur with Ob (a dysmetabolic state), the overall health benefits of exercise may be reduced. Also, of importance, is intensity and duration of exercise, as a higher intensity may be more likely to illicit an inflammatory response compared to a moderate exercise bout (19). The synchrony of the sympathetic and parasympathetic branches of the ANS provide an important explanation linking immunity and
metabolism to explain local inflammation at the heart. In the resting state, ANS influence is characterized by a relative dominance of the PNS over influences of the SNS (fight-or-flight) (20,21,22) – a pattern of adaptive activity that represents ANS balance. In contrast, however, autonomic imbalance (predictive of mortality and morbidity) (23,24), characterized by a hyperactive SNS and a hypoactive PNS, also known as sympathovagal imbalance, is associated with Ob (23) including pediatric Ob (25,26,27). In an observational study of 103 active soccer players (aged 11.1-1.0 years), Lucini et al. (2013) found that in a subset of 11 overweight boys, despite exposure to a relatively heavy training routine (three structured training sessions plus one game per week), there was an altered profile of autonomic regulation compared to normal weight teammates (28). They concluded that overweight is associated with a clear autonomic impairment even in children subjected to intense aerobic training (28).

6.1.1.1. Inflammatory Reflex

The vagus nerve, the main nerve of the PNS division of the ANS, has an important role in regulation of metabolic homeostasis: controls HR, gastrointestinal motility and secretion, pancreatic endocrine and exocrine secretion, hepatic glucose production and other visceral functions (29). While the vagus nerve afferent and efferent signalling has an important role in metabolic homeostasis, its finely tuned regulation is aimed at preserving energy balance and preventing fluctuations in body weight and metabolism that can be detrimental to the individual (29). Importantly, low vagal (or PNS) activity serves as an independent risk factor for hypertension and other CV and health risks (21,22). The efferent vagus is a major constituent of a neural reflex mechanism—the inflammatory reflex—that controls innate immune responses and inflammation during pathogen invasion and tissue injury (29,30).
Because decreased vagus nerve activity in the context of Ob has been reported (31,32), attention has been given to this inflammatory reflex to explain the dysregulation noted in Ob-related disorders (29,33). Expressed at the heart, dysregulation of vagus nerve-mediated signaling at the sino-atrial (SA) node has a direct effect on the heart’s function by altering contractility and contributing to vascular remodelling (34). Changes in HR result in altered cardiac work and oxygen demand which impact arterial pressure. Increasing BP stretches arteries, increases wall stiffness, and reduces the buffering function of the arteries (i.e. their compliance) which may contribute the progression of atherogenic markers (35). Increased aortic stiffness, in particular, has been correlated with PNS dysfunction (36).

6.1.1.2. Parasympathetic Nervous System Variability

Higher PNS activity can be compensatory when facing greater SNS activity and subsequent increases in BP, particularly sBP. Therefore, PNS activity should dominate SNS activity. Thus, PNS activity is of particular importance as lower PNS activity has been independently associated with CV risk factors (25). The pathogenesis is not known; the molecular components of inflammatory and oxidative processes, which are numerous, complex and variably interconnected, are not limited to one organ system. It likely displays distinct alteration patterns in different dysmetabolic states, including how the fat is distributed which may have implication for sex differences. Greater central fat has been associated with reduced cardiac PNS function in girls (37,38). These patterns remain unknown, however, especially in children.
6.1.1.3. Sympathetic Nervous System Variability

There is a complex interaction between overweight, hypertension and SNS which may contribute to sedentary weight gain or lack of changes to adiposity with exercise. It is widely believed that the coordination of energy homeostasis relies on the normal functioning of the sympathoadrenal system, suggesting that reduced SNS activity leads to a lower rate of thermogenesis, and consequently, to a positive energy balance and overweight (39). After overweight evolves, hormones secreted by fat cells further accelerate SNS over-activity, weight gain and blood pressure increases (39). Therefore, it is postulated that in genetically-prone individuals, prolonged SNS stimulation elicits a down regulation of beta-adrenergic receptors, decreasing the ability to dissipate calories and diminishes the beta-adrenoceptor-mediated vasodilation (39). Nagai et al. (2003) demonstrated that decreased SNS activity or its blunted responsiveness, seems to be present in childhood Ob (40). Their work on healthy, sedentary, obese school children indicated that depressed SNS activity may be linked not only with a higher risk of CV malfunction but also weight gain (40). In addition, the degree of these autonomic reductions depends on the duration of Ob independent of a subject’s age (40).

6.1.1.4. Heart Rate Variability

HR is known to be under the opposing influences of sympathetic and vagal outflows to the heart, and fluctuates on a beat-to-beat basis. These fluctuations in HR, termed HR variability, reflects cardiac vagal activity (41). The measurement of HR variability can determine ANS control of HR providing valid and reproducible markers of cardiac vagal tone (41). Although empirical research is limited, physical exercise can exert a protective effect on autonomic and metabolic regulating in children. If training can increase vagal tone, according
to the inflammatory reflex, it could lead to reductions in systemic inflammation (42). Some cross-sectional data on adults have suggested that exercise training beneficially influences HR variability via modulations in SV Index, however, the neural effect of exercise in children with Ob is limited. Gutin et al. (1997) first showed that a 4-month period of physical training (4 months of exercise, 5 days a week, 40 minutes per day) in 7-11 year old obese children could exert a positive influence on SV Index (SVI=SV/BSA) by reducing the ratio of SNS and PNS activity (p<0.01) and improve vagal tone (p<0.05) (43). Ob was not defined in the study, however, BMI was over 30 kg/m$^2$ in their baseline. Specific to endurance training on HR variability and cardiac adaptations, Mandigout et al. (2002) studied n=19, pre-pubertal (10-11 years), healthy children to determine the relationships between HR variability components and training-induced cardiac adaptations and found that after a 13-week, intensive, endurance training program (>80% HR$_{max}$), there were improved HR variability parameters (measured by ECG recordings) but cardiac morphological and functional adaptations (including increased LV internal diameter and mass, enhanced early diastolic passive LV filling and reduced late diastolic active LV filling) were achieved without inducing SNS or PNS modifications (44). This is important for understanding the relationship between pediatric HR variability and training-induced cardiac adaptations. The training in obese children in Gutin’s work (43) decreased sympathetic tone and might have increased overall vagal tone, thereby leading to a positive effect on autonomic balance, and it is likely the effect of Ob on autonomic activities that explained the marked effect of training (compared to non-obese healthy controls). It is also possible that exposure to repeated exercises over a longer period is required to induce cardiac ANS adaptations in children as evidenced by Mandigout
et al.’s (2002) shorter timeline not eliciting change (44). Nagai et al. (2004) studied the possible effect of moderate and long-term physical exercise on cardiac ANS activity in healthy children (aged 6-11 who participated in a 12-month school based exercise training program) (45). They found that a 1-year exercise training program, even of short duration (20 min/day) and mild intensity (130-140 bpm, 5 days per week), could augment cardiac ANS activity but only in children who initially possessed low HR variability (subset of 100 children) (45). Further research is required but raises important considerations for the exercise intervention study presented in this thesis. As well, it should be noted that using HR as threshold for training may have some limitations if there is individual HR variability at baseline. It is unknown how to modify HR targets in obese subjects as training proceeds given the wider variability and less adaptation to effects.

6.1.1.5. Respiratory Function

We found no increase asthma or obstruction in our participants. However, our sample was drawn from healthy obese and may not represent all children with Ob.

6.1.2. Individual Limitations

6.1.2.1. Sociocultural Concerns

Inactivity and a sedentary lifestyle have become major challenges for health and well-being among young, obese children. The child’s lived experience can be the starting point for identifying and influencing physical, mental, or logistical barriers to exercise (46). The accomplishment of changes can be facilitated or obstructed by these experiences. The more barriers toward implementing and adhering to PA that exist, the poorer the maintenance of the change accomplished (47). Lifestyle interventions may lead to long-term changes in
activity level if facilitators and barriers are approached in a holistic way by professionals. Within the context of a hospital setting, it seems important that health professionals do not miss the central importance of the child’s lifeworld (48). In a qualitative, systematic review, Toft and Uhrenfeldt (2015) identified a number of themes essential to consider when developing lifestyle interventions for adults that incorporate the perspective and experiences of those with Ob: a main theme of ‘Identity’ with sub-themes of ‘considering weight’, ‘being able to’, ‘belonging with others’ (49). They concluded that experience of suffering or well-being during PA affected those with Ob by challenging or motivating them. To be successful, a change in identity may be needed (49). Interventions in adolescence have great potential to alter life trajectories. We have determined that exercise training is important to reduce aortic stiffness in obese children and adolescents. However, clinicians must appropriately prescribe exercise, thereafter, to properly translate this knowledge. Although these factors were not formally measured, our study participants usually had obese parents, one working caregiver at home, had low PA and health knowledge, low self-efficacy, and limited exposure to training. These are important life-world factors to consider in order for the prescription of exercise to be sustainable.

A relationship between BMI and the number of barriers to PA has been identified (50), which could result in particularly difficult challenges for the obese (51). The perceived Ob stigma becomes more acute at higher weights (52), and the feeling of being "too fat to exercise" is found to cause avoidance (53,54) as well as a negative attitude toward PA (55). Motivation to participate in exercise in youth is influenced by perceptions that the activity is fun and enjoyable or unpleasant and boring (56,57,58). Therefore, facilitating positive
experiences of PA is important when aiming for increased activity level. A central concern, however, is that the experiences of youth with large bodies might differ from youth of smaller body sizes (53). Incorporating activities into the fitness circuit that provided variety and that were perceived as ‘fun’ likely contributed to our protocol adherence and provided confidence for the participants’ in their abilities to be physically active. However, enjoyment following exercise was not quantified in this study and serves as a limitation to knowing whether the participant would adhere to similar activities in the long run or if enjoyment was truly a factor for adherence any moreso than the acute fitness benefits received or if the reasons for adherence were any different between boys or girls.

Malik et al. (2017) examined adolescents’ acute cardiorespiratory and perceptual responses during HIIT exercise and enjoyment responses following HIIT and work-matched continuous MI exercise in 54, healthy, 12-15 year old boys (n=27) and girls (59). Enjoyment was measured using the Physical Activity Enjoyment Scale (PACES) following training and found that boys had higher absolute VO₂peak responses during the work and recovery HIIT intervals but elicited lower %VO₂peak during the HIIT recovery intervals compared to girls, no differences in HR during work or recovery, higher HR_max could be achieved in both through HIIT, and that boys elicited greater RPE during the later stages of the HIIT protocol compared to girls (59). In both sexes, HIIT was perceived to be more enjoyable compared to continuous moderate intensity, with individual items on the PACES scale indicating elevated ratings of excitement, success and reward after HIIT. Ropes training, for example, was incorporated into our fitness circuit. Use of body weight for strength exercises is often used in youth strength and conditioning programs (60), however, the ability to repeatedly move one’s own
body weight, if excessive, may lead to premature fatigue and increase injury risk. Upper body performance when expressed in absolute values have been shown to be higher in obese (61) and underlines the need to consider body dimensions when designing training programs and expressing performance, especially in those that carry extra weight. By incorporating upper body repetition through ropes training (through pulling, slamming and wave training), the participants could successfully achieve HIIT to contribute to the cardiometabolic effect. There is no literature that provides a protocol for ropes training in obese children and therefore this study may serve as useful guideline. Recently, Faigenbaum et al. (2018) demonstrated a useful ropes training protocol for healthy boys (2 sets of 30 repetitions of 5 exercises with 30 second rest interval between sets) (62) but it is unclear whether this would generalize to those with Ob or those less physically active. It is also unknown from our study whether upper body training, lower body, or abdominal training were any different in terms of muscle fitness performance gains as this was not measured as an overall variable of interest. It seems that well-being during PA can be developed among inactive persons, when small increases are made (63,64) but it is extremely important to consider how illness, vulnerability, and disability might be intertwined into a person’s health and well-being, and how the person despite these factors can achieve a healthy life (48).

6.1.3. Study Limitations

6.1.3.1. Recruitment Bias, Retention, Adherence

The main limitation of our exercise intervention study was the relatively wide age range of the children and youth (10.2-19.1 years at the start of the trial) and small sample size (n=10). Although failure to retain the targeted number of participants prolongs the time
required for the study, threatens internal and external validity, reduces statistical power and drains study resources, it must be recognized that recruitment in this population is challenging and requires significant effort. Specific populations such as obese children may require targeted efforts to ensure adequate representation. In one of the few studies to detail their recruitment process for community-based adolescent health trials, Nguyen et al. (2012) reported their success utilizing a number of recruitment strategies for the Loozit RCT (a two-armed, community-based, lifestyle intervention program for weight management in overweight and obese 13-16 year olds) and found in using over 20 different recruitment strategies, where they received 474 enquiries, 32% resulted in an enrolment to the trial (65). This was an average of 14 adolescents recruited per cohort. In our exercise intervention study, 44 enquiries were obtained for participant recruitment of which, 16, or 36%, consented to the study originally, with 10 children and youth completing the protocol (65). In the Loozit RCT design, referrals from general practitioners and other health professionals resulted in the fewest enquiries and strategies with the most successful enrolments being newspapers and school newsletters. Recruitment strategies such as radio, television, school counsellors and community-focused strategies resulted in lower enrolment yields (65). These results are consistent with those found in our study with commentary as follows:

6.1.3.1.1. Recruitment Strategies

1. Flyers-Mailouts—flyers were posted on every bulletin board at BCCH/C&W site (used tear-offs with contact on advertisement poster), mail-outs to previous study participants that had consented for follow up, flyers posted at every local community centre (required permissions); flyers posted with paediatric groups (e.g. City Square pediatrics,
Cross roads clinics, etc.) in Vancouver, Burnaby, Richmond and Surrey, etc. Flyers posted in non-active communities such as Vancouver School of Music, etc.

2. Program Contacts (face-to-face meetings)—YMCA (Langara) program leaders, counsellors at various organizations such as Britannia Youth Outreach, Musqueam community nurse/program coordinator, etc. were contacted and delivered study material.

3. Presentations—study methodology was presented to BCCH medical residents at several academic half-day events, as well as presented to Shapedown program graduates at discharge, etc.

4. Media—recruitment notices with study details was posted electronically on sites such as obesity network, SCOPE, Child Obesity Foundation, allied health groups such as Heart and Stroke Foundation, etc.

5. Targeted Health Care Professionals—BCCH Heart Centre Prevention Clinic and Family Practice at BC Women’s Hospital

6. Personal Contacts—Surrey School District Activity Coordinator (required application to advertise through Surrey School Board Research and Education); counsellors and PE teachers notified of study; Vancouver School board PE teachers also notified through personal contacts.

6.1.3.1.2. Recruitment Outcomes

1. From each strategy, 44 enquiries were followed up with by phone or email where possible (n=35 came from prevention clinic referral; n=3 Surrey School Counsellors; n=3 from BCCH flyers; n=1 from medical resident; n=1 friend referral; n=1 previous study).
2. Of the 44 enquiries, n=16 consented to participate with n=10 completing entire protocol (n=1 moved away before program started, n=2 withdrew before study started but after baseline testing; n=3 withdrew partway through protocol). Of the three that got partway through the protocol, two completed the whole program including all the exercise sessions but failed to return for final follow up test (fourth clinic visit) (both from Surrey satellite group) and one went through half the exercise protocol and all the previous control period but pulled out due to previous musculoskeletal injury flare-up. Two of the 44 enquiries consented to study but did not qualify for inclusion at screening (BMI<97th). During recruitment, we obtained two working phone numbers from each participant (usually parent’s cell phone number and home land line), as well as, an email address. Also, they were asked to provide the best time to reach them. Exercise supervisor provided cell phone number for ease of access.

3. For the two that completed the whole program including all the exercise sessions but failed to return for final follow up testing (fourth clinic visit), no monetary or bonus incentives were offered which may have helped retention. We also could have provided incentives that reimbursed participants for their time and costs, e.g., $10 for parking at each clinic visit as these were during daytime hours. At the final data collection, a bonus incentive could have been provided: $10 for attending the final data collection and $20 if tests were complete for all four time points of data collection. Additionally, incentives could have been provided to the younger children for HR targets during exercise sessions: minute-by-minute HR data was downloaded into a computer after each session, this could have been displayed mid-training with points earned for maintenance
of target HR and prizes given after accumulation of specified number of points. However, none of these incentives were provided and could be considered as part of future research budget applications.

4. Of the n=16 that consented, n=3 were from the Surrey blast (3 of 3 targeted), n=1 BCCH flyer, n=12 from Prevention clinic referral (targeting, most successful route); none of the other avenues yielded any consenting interest including physician referrals. This is consistent with other studies that report barriers for referral as: primary care physicians’ unwillingness to raise weight issue with parents, lack of time or reimbursement for time spent in recruitment, and adolescents usually less often seen in medical offices or when they do attend medical office they have conditions in the first place rendering them ineligible for study criteria (66). In our study, physician referral was made to secondary care instead, the Prevention clinic, by community physician and our recruitment was received from there.

6.1.3.1.3. Recruitment Recommendations

We were able to recruit young, obese adolescents that were able to successfully commit to exercising twice a week for 12 weeks and be followed up for an additional 20 weeks for total study involvement of 32 weeks. Parents and participants completing the protocol all reported a positive interaction between the researchers and the children. The participants reported that they enjoyed the program and felt invigorated to continue to exercise afterwards. For example, many reported intentions to sign up for community activities after follow up such as exercise classes (yoga and Zumba), organized sports (two for football), or be more active with their families (walking program, biking to school, active
living, active charity fund-raisers). Some of the participants requested continued personal training sessions. Clark-Jones and Broome (2001) found that adolescents regardless of health status cite similar reasons for participation and continued engagement in research projects: increased knowledge about health conditions, expectations about research interventions, incentives, and logistical considerations (e.g. transportation, time, location, and setting) (67). Reasons for continued engagement in the project included the content of the intervention, characteristics of the instructor or clinician, having control or choices during intervention, and their relationships with peers in the project (67). Supportive relationships and parental involvement have also been reported as important considerations in the retention of adolescent research participants (68). Activities that establish an environment supportive of health behaviours through teacher and parent involvement in the intervention and enhancing peer support for positive change have been identified as effective recruitment and retention approaches for adolescent intervention research (66). In a study with chronically ill adolescents, Broome and Richards (2003) found that parents had a strong influence in adolescents’ decisions to engage in research (69), in fact, Prado et al. (2005) focused solely on the initial recruitment of parents as a way to engage their adolescent children (70). From this and research by Villarruel et al. (2006) who conducted a randomized control trial designed to reduce sexual risk behaviour among Latino youth, four main facilitator patterns are consistent: peer/family support is important, as well as program incentives, commitment, and participant’s desire to help (66). Participation barriers include conflicts with other commitments, embarrassment and lack of peer support (66). Successful recruitment strategies should be tiered including community-based efforts and broad mass media
outreach (71) and important values should be considered such as familialism (family obligations), respectful interaction, support and trust of community (72).

Therefore, to improve recruitment and retention in obese child and adolescent populations with respect to an exercise intervention, the following field notes from this study are offered to serve as recommendations to inform future research recruitment infrastructure:

1. Make sure all materials are culturally and linguistically appropriate; because weight stigmatization is a potential barrier for recruitment methodologies, training for cultural sensitivity can help overcome some potential recruitment problems. This will allow flyers, targeted recruitment and consent to ensure respectful interaction. As well, with a diverse population from the local community, many of the children and adolescents serve as first generation immigrants from the recruitment pool and parents and grandparents are not fluent in English. Materials should be produced in languages suitable for recruited families.

2. The role of the family is essentially important in children getting to exercise sessions and clinic visits, and adhering to study protocol (compliant to wearing accelerometry equipment, etc). Have adjunct training and support for parents to keep children engaged including education at follow up such as emphasizing positive shared goals like "healthy and happy family." It may also include exercise sessions for parents (while children are engaged in training) and follow up exercise so children are not dropped from supervised care following study completion.
3. Consider training peers to serve as recruiters. Using peers to successfully recruit and retain minority participants has been reviewed (68). In the study presented in this document, one participant invited a friend to participate but was too far into the protocol for the friend to join with them and that friend was not willing to participate alone and the randomization protocol may not have assigned them to same study arm anyways. Harnessing peer networks, however, may have value: if recruited in groups, it is likely participants would have at least one or more friend randomized to their group. It is noted that the use of peer-driven recruitment has the potential to both enhance and undermine scientific and ethical integrity; with this in mind, important conceptual and procedural lessons can be ascertained.

4. Offer interventions at times and locations that are convenient for study participants. A second satellite training centre for Surrey participants was offered in this study and this was useful for cutting down travel time and study feasibility. However, interestingly, the two participants that failed to return for the final clinic visit were from this satellite cohort and additional follow up infrastructure may need to support retention.

5. Recruit cultural insiders: two study participants were from aboriginal communities; the Musqueam and Coast Salish Squamish First Nations. One family had suggested that the study would be of interest and needed in their community, they also offered facility for satellite training. The community program leader was contacted to facilitate recruitment but failed to follow up after initial contact. For future training studies, timely implementation of Tri-Council policy on ethical research involving indigenous people in Canada (TCPS2) recommendations would be useful prior to study initiation (73): for
example, it may be useful for the researcher to embed in the community to network and establish trust, perhaps offering promotional training days for the children to experience the activities and provide education for families.

6. One of the participants from this study asked for a letter of completion verifying their attendance which could serve as a school credit. The British Columbia high school curriculum requires that students must graduate with 30+ hours of work and community service and must justify 150 minutes of PA per week. Participation in the program could contribute to fulfilling this graduation requirement and could serve as an important incentive for adolescents, in particular those who may not otherwise be active outside school hours.

The recruitment methodology used in this exercise intervention study resulted in a population made up primarily of boys, with only three girls participating. It was not anticipated that this would happen, as it was not the intention to recruit one sex over the other. Having adequate representation, however, is important as the negative impact of insufficient activity at higher intensities may be of particular importance to young girls, as PA literature indicates that girls tend to be less active than boys and, perhaps more importantly, less active at MVPA (74). It is also known that adolescent girls drop out of PA at a greater rate than adolescent boys (75).

6.1.3.2. Interpretation, Allometric Scale, Maturation

Maturity and sex are important covariates exerting a size independent influence on peak aerobic fitness. It was planned to recruit children during adolescence, therefore the participants were at different pubertal stages and hormonal changes during the study, which
may have influenced outcomes. However, as published in the literature and discussed previously, PWV, the key metric, does not change significantly across this age range. There is a gradual increase in PWV with aging, but the anticipated background change over the study period was negligible. Tanner staging to assess pubertal status on study participants was not performed as this would be too invasive for this project, and be an impediment to recruitment and retention. As well, Tanner staging is difficult to ascertain in a population with excess adiposity (e.g. breast development may be due to adiposity influencing appearance of the external characteristic; abdominal fat may make it difficult to differentiate testicular volume, etc.); however, sitting height was used in an attempt to predict APHV (76) and maturational status was ascertained. All girls reported whether they were post-menarche with one girl achieving menarche mid-protocol.

6.1.3.3. Measurement Limitations

No blood work nor direct assessment for adiposity was completed as part of the study. As such, it could not be determined whether or not this intervention influenced the lipid profile or markers of inflammation which may be important in the pathophysiology of CV changes. They were not included in these studies because of budgetary constraints and the goal of the study was to measure cardiac dimensions not discuss changes to blood lipid. As well, no nutritional information was gathered as this was not the goal of the study.

Specific to measuring cardiac dimensions, another consideration is that in some obese individuals acquiring echocardiography data can be challenging. This was addressed by using two experienced sonographers to obtain the imaging data to reduce any variability in data acquisition. As well, with the obese population, echocardiography information may be
technically difficult to assess due to visceral adiposity contributing to poor image quality (posing a problem for lifting the sound from the noise). This was addressed by conducting an inter-rater reliability test between the researcher and senior cardiologist to confirm agreement and check for consistency (see general methods, chapter 2.2).

Finally, with respect to any observed changes, another potential consideration was the possibility that the washout was incomplete. It is possible that participants who received the intervention first had a higher level of PA after completing the supervised exercise program. However, this was monitored using accelerometers and activity questionnaires (PAQ-C/A) during the control phase. Based on the accelerometry data, it appears that these obese children did not sustain a high level of PA beyond the completion of the supervised intervention and confirmed that this was an inactive cohort of children (below 12,000 steps per day expectation). It is possible the children once engaged in an exercise routine, limited other active pursuits they might normally engage in. In other words, it is possible that a structured exercise routine may displace daily activities they might do. Whether this is because the exercise intervention was high intensity activity and the level of fatigue was unfamiliar to them, rendering them too tired to do anything else or whether they were satisfied they were getting enough exercise due to the intervention and therefore disengaged from regular activity, can only be speculated. Only one participant wore their accelerometer on the days of the exercise training so it is not clear whether the exercise intervention would have significantly increased exercise on those days. Ensuring accelerometry wear compliance is challenging. Better compliance gives greater confidence that PA data are representative of actual daily PA because of the association between duration of monitoring and reliability of
PA data (77). Traditionally, accelerometers have been worn on the hip because this location is thought to provide most accurate estimations of energy expenditure and activity intensity (78), however, Fairclough et al. (2016) suggests that using the wrist as the accelerometer placement site may promote better device compliance (79). Since the initiation of our exercise intervention study, there has been increased use of wrist-worn devices, which was argued to promote better compliance to device wear. In the NHANES 2011–2012 data collection cycle using wrist-worn accelerometers, median wear time duration was 21–22 hours per day, which was up to 100% longer than that in previous cycles using hip-worn devices (80). However, for our exercise intervention, when using our limited accelerometer data coupled with the PAQ-C/A activity questionnaires, it seemed unlikely that these obese children and youth sustained a high level of PA beyond the completion of the supervised intervention.

6.1.3.4. Prescription Limitations

Developing, understanding and adhering to proper exercise prescription guidelines can reduce exercise risk, help prevent injury, increase benefits, enhance enjoyment, and foster success. Children who are not exposed to opportunities to develop and enhance their motor-skill proficiency tend to be less active, which in turn, may lead to sedentary habits later in life (81,82,83). The effects and benefits are measurable but goals can only be achieved with regular exercise sessions. Individuals will vary from workout to workout but adherence to the prescription is one of the most important variables. With challenges such as poor motor competence, acute cardiorespiratory limitations or low fitness at baseline, low self-efficacy
to exercise, prescription needs to be tailored to the individual needs in these at-risk children and adolescents.

With an increase in fitness, ideally the HR targets should be modified to provoke adaptation. Without serial measurements partway through the exercise intervention, it is difficult to know whether sufficient adaptation was occurring to warrant a revision to HR targets. A strength of our exercise intervention study was that quantification of HR was provided to demonstrate participant compliance with the progressively HIIT protocol and using a predefined threshold in relation to percentage HR maximum. Therefore, as the intensity and duration of the work and recovery intervals during the progressively HIIT session was assessed, adjustments could be made to not exceed threshold. However, because factors such as HR, RPE can influence VO\textsubscript{2} and vary between males and females, it is important the perceptual response of boys and girls to higher intensity components are characterized and understood.

While progressively HIIT was feasible in this study, the current review cannot provide specific recommendations regarding potential mediators of HIIT on health outcomes in obese children and adolescents. Therefore, it is unclear how factors such as age, sex, and biological maturation may interact with health-related adaptations to HIIT nor optimal prescription of HIIT. The children and youth in this study showed a modest weight reduction overall but some of the adolescent boys showed a weight gain. It is difficult to know if improved strength through growth played a role. Future studies should formally compare different HIIT protocols in order to optimize the dose-response relationship for different health outcomes. As well, it is not known if the lack of beneficial change in body size may be due to the short
duration of the progressive HIIT (12 weeks); a longer study or follow up of a sub-group may be beneficial to determine longer term changes or if changes persisted over time if children stopped. Finally, no attempt was made to contrast the beneficial effects of performing this HIIT protocol compared to a non-obese comparison or control group. Although literature indicates that HIIT has a beneficial effect on a myriad of CV risk factors in obese children (84), for most health outcomes the benefits appear similar to performing traditional aerobic training that is either continuous or interval in nature.

6.1.4. Population Limitations

6.1.4.1. Exercise Response and Health Care Costs

The health benefit of regular PA is well established but how much total health care costs are impacted is less well known. A modest fitness change in these obese children, where healthy children may have received a greater expected gain, may actually result in greater long term savings to health care. This is underestimated by downplaying any improvement to CV health. It is also unknown if they remained on the same ill-health trajectory, if this would have impacted their future health as an adult more. Non-pecuniary costs must be considered. Even if there is a modest reduction in weight, self-doubt or depression or increased follow-up engagement of activity, this will have substantial long term impact on health care. Although this returns the discussion to the healthist perspective, the focus has shifted from cultural engagement which results in improved health as a by-product.

6.2. Concluding Remarks

6.2.1. Overall Summary
Current evidence relating childhood Ob to worsening CV health, both immediate and long term, is convincing. The contribution of this pathological state in early life to future CV morbidity and mortality is of immediate concern. Finding effective therapy early on is needed to contain this growing ill-health trend. In adults, exercise training has been shown to improve most of the vascular alterations associated with CV disease, specifically endothelial dysfunction, altered vascular structure, and increased vascular stiffness associated in Ob. Importantly, these beneficial effects are observed not only in arteries from exercised-tissues, but also in other vascular territories, such as the large vessel leaving the heart (aorta), thus providing a plausible explanation of its effects on parametres such as BP. However, whether exercise can alter the biophysical properties of the aorta in obese children and adolescents has previously been unknown. Therefore, it has been critically important to ascertain the role of exercise as an effective therapy for this at-risk group.

Technological advances have significantly improved the ability to study cardiac function in children non-invasively. There are few prospective studies that use echocardiography to provide insight regarding the aortic changes associated with Ob in children. The results from this doctoral work answered one central question, whether CV improvements such as alterations to the biophysical properties of the heart can be made in obese adolescents following an exercise intervention program, demonstrating that exercise is indeed a potential and viable option for disease management. This knowledge can have an important impact on the management of obese children and youth in British Columbia, in particular those who have adverse CV changes. Furthermore, the insight gained may better inform pediatricians and general practitioners caring for obese children. Raising awareness
that these children warrant CV evaluation and informing caregivers regarding evidence-based management strategies may improve the long-term health outcomes for obese children and youth. Demonstrating the benefits of exercise in this population may influence community and school-based programs and ultimately inform policy development. For regular exercise to induce beneficial effects in CV disease, however, questions arise about the frequency, intensity, duration and mode of exercise that would be most favourable. This highlights the need for identifying effective and scientifically-derived methods of prescribing exercise. Future research is needed to clarify dose-response effects, long term sustainability, relationship to health outcomes, and optimal modality of exercise for the treatment of obese children and adolescents, and specifically as it relates to metabolically-important visceral fat depot.

The current chronic diseases associated with Ob present unprecedented public health challenges that have been underestimated and inadequately addressed by policy makers. The rising rates of childhood Ob and associated co-morbidities will significantly accentuate this burden of ill-health unless sufficient strategies are adopted in a timely manner, especially since the risk of chronic disease starts in childhood and increases with age. However, it appears widespread Ob is not so much a failure of personal biology but a social and economic phenomenon and its solution must be considered in a multi-faceted perspective. Therefore, an important strategy to reversing these trends may be to return to a more physically active society. Blair and colleagues (2010) have argued that it is preferable to encourage people to become more physically active rather than to become physically fit, since, as they stated, sedentary people will likely achieve the latter if they do the former (85). Warbuton et al.
(2006) further elaborated on the resultant cycle of decline—with further worsening of fitness, an individual may lose the capacity to perform daily activities (such as getting out of a chair or climbing stairs) and reduced fitness leads to inactivity and further dependence (86). Improvements in function have an enormous potential for delaying or eliminating the onset of disability, dependence and chronic disease.

The PA guidelines in Canada suggest children and youth get 60 minutes of daily MVPA a week, however, these targets are sorely under-achieved, even in healthy children. This has prompted investigators to postulate that even lower levels of weekly energy expenditure may be enough to associate health benefits, especially in those that are extremely deconditioned (87,88,89). While the Canadian PA Guidelines for children and youth are evidence-informed and their development was systematic in nature (90), it is possible that a volume of exercise that is about half of what is currently recommended may be sufficient (89), and should be considered when prescribing exercise to children and youth with Ob.

In general, PA habit formation in children and adolescents must be achieved through multi-literacies including health (91) and physical dimensions; multifaceted programs must target behavioural change through implementation in multiple settings. The inclusion of health care professionals and outreach to families and their communities as key stakeholders are additionally important. Even though there is a lack of scientific evidence on the efficacy of these integrated initiatives, the World Health Organization encourages that this should not postpone their adoption (92). WHO recommends that member groups should take advantage of existing opportunities to introduce these programs in their current context and level of resource (93). Ultimately, this applies the concept of the social determinants of health, or the
“conditions in which people are born, grow, work, live, and age, and the set of forces and systems shaping the conditions of daily life” (93) to address the causal link with chronic diseases (94), in this case, childhood Ob risk (95). WHO finds that these determinants of health influence the extent to which individuals and communities possess the physical, social and personal resources to identify and achieve personal aspirations, satisfy needs, and cope with the environment (96); the burden of Ob is not distributed randomly within and across populations, instead, it is disproportionately located within those individuals and communities that are economically, politically and socially disadvantaged (97). With this in mind, frameworks have been proposed to identify key issues concerning the monitoring and evaluation of policies (2006 WHO document “Global Strategy on Diet, Physical Activity and Health: A Framework to Monitor and Evaluate Implementation”) (92) and intervention points for specific health determinants for Ob prevention (97).

Childhood activity is often intermittent and sporadic. Thus, children likely will not participate in prolonged exercise without rest periods; however, young children will perform relatively large volumes of intermittent, non-structured PA. Given a free choice, most young children will play or invent active ways of passing time which involve jumping, dancing, skipping, hopping, chasing, running, climbing, and cycling. Older children might play more organized sports—either formally, in clubs and teams, or informally, in parks and playgrounds. Generally speaking, these forms of play provide a large volume of activity incorporating a wide variety of movements using many muscle groups, and promoting cardiorespiratory development, muscular strength, muscular endurance, speed, power and flexibility and overall improved motor literacy. These activities also afford opportunity for
children to develop other social, mental, and emotional literacies. Making children fit and active for life by equipping them with the skills and confidence to do so has wide-reaching implications. If childhood activity is already too low, and declines with age, adult activity is undoubtedly too low constituting a problem in the making. The emerging body of evidence suggests associations between childhood PA and childhood health, reflected by more favourable overweight or Ob status or a healthier CV disease risk profile.

In contrast, the focus on PA for Ob prevention especially with a motivation to control weight, may not be the right focus to achieve a more favourable health status; such an approach to health, which promotes fear of ill-health and individual responsibility for health, can be thought of as a form of health fascism, what Fitzpatrick and Tinning (2014) describe as a “highly charged, emotive concept” (98), is a result of the “disembodying and dehumanizing of the person by health providers” (98). If the body is treated as separate from the self, such as in the case of health problems like Ob, the body is then prescribed remedies (such as exercise) without recourse (or sensitivity) to the emotionally and socially-located, embodied person, and the intervention fails (98). Ob prevention has been largely about regulating the body (through weight loss) and so far unsuccessful to date, as evidenced by increasing rates globally. This may be partly due to the medicalization of Ob, which is the focus of most Ob research. Crawford (1980) postulates that weight-focus, contributes to moral panic: a situation where a marginalized group is seen as a threat to societal issues. From this perspective, Ob viewed as a problem contributes to its own exacerbation (1). Engaging in strategies that encourage a culture of healthy behaviour for everyone may prove more successful. Moreover, current data depicts that there have been greater increases in
the prevalence of children with severe Ob (>99th percentile for weight) compared to those with mild overweight status (85th to 99th percentile) during the past 40 years (99,100,101,102). Given this trend, targeted weight reduction approaches aimed at mildly overweight instead of severely obese children is unlikely to have a substantial impact on the overall burden of Ob, as the risk for comorbidities rises steeply at the extremes of BMI (103). However, reductions in Ob at the lower end of the spectrum (between 85th and 90th percentiles) through meaningful active lifestyle may reduce the trend towards the extreme as a positive outcome.

Motivating young, non-obese, physically active children to maintain activity patterns may be less challenging, however, than increasing habits in already obese older children (104). Monitoring free play alone does not seem to encourage participation of heavier children; heavier children may be ignored and ridiculed and often choose indoor, sedentary activities to escape negative activity situations (104). As well, activity levels decrease as child enters adolescence, and moreso for obese children (105). Therefore, encouraging sedentary, obese children to participate in PA is difficult. Structured and vigorous, aerobic-type activities when prescribed to overweight children, regardless of the individual's cognitive, physical, and emotional stage of development, may result in non-compliance or physical injury (104). Prior failure to motivate and maintain increased PA in overweight or obese children may be attributed to inappropriate exercise recommendations and a lack of physical opportunities for overweight children in the traditional school or community environment.

Better public health outcomes might be achieved by tackling the obesogenic environment and viewing health from a social and cultural perspective. Exercise
recommendations should take into consideration the extent of Ob, motivation for activity, the available of resources and support, and must be incrementally applied (106). Glenny et al. (1997) determined that family therapy and lifestyle modification seem to be effective in the prevention and treatment of childhood but not necessarily adult Ob (107). Based on the limited research in the treatment of Ob in children, approaches should include family interventions with nutrition and PA education, structured exercise, and behaviour modification (106). These interventions should be delivered by a team of health care experts in a nurturing, non-intimidating environment; however, it must be recognized that obese children may respond differently physiologically and emotionally to exercise than do healthy-weight children. Obese children and adolescents may experience negative consequences to participation in activities considered appropriate for healthy-weight children and adolescents.

6.2.2. Overall Conclusions

The purpose of this thesis was to understand the role exercise plays in modulating physical properties of vascular and respiratory function in obese children and adolescents. It was observed that exercise training decreased AoPWV, an indirect indication of improved arterial stiffness. As well, training modestly improved exercise tolerance and capacity which may contribute to increased future PA. From this, it is recommended that increasing PA is useful therapy to alter the biophysical properties of the aorta which may have profound effects on the cardiorespiratory system in the management of pediatric Ob. However, it is cautioned that if clinicians simply prescribe exercise they may not be successful and significant social and environmental modifications encouraging PA for everyone should be
implemented instead. Supporting positive lifelong habits, as well as, implementing scientifically designed exercise plans that encourage CV improvement must be provided through broad-based, multi-faceted, multi-literate programs that include the participation of families. This provision may be accomplished only through policy changes, environmental planning, medical training, and school and community educational efforts.
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Chapter 1


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Chapter 2


Chapter 3


Chapter 4


Chapter 5


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Journal


Abstracts


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Appendix B – Training Activities for Exercise Intervention

Warm Up (10 minutes total)
- Brisk Walking/light running in space (8 minutes total plus 2 mins signals/rest)
  o emphasize change of direction, change of pace, change of height
  o De-emphasize running clockwise in a circle or counter-clockwise, use full depth/width of boundaries, cuts, mobility
  o Include stretch up high, reach down low (sweep the ground, low fives when you pass, high fives)
- Add Signals (at 4 mins, add first signal for 30 sec rest, at 6 mins, second signal for 20 sec rest, at 8 mins add 3rd signal diminishing rest)
  o Hit the deck (pronation: push up)
  o Iceberg (stop/start signal: change of direction)
  o Deadbugs (supination: ab crunch)
- Subjects will monitor heart rate, adjust equipment, evaluate perceived exertion

Cool Down (10 minutes total)
- Walking in space (4 minutes)
  o emphasize change of direction, change of pace, change of height
  o Not running clockwise in a circle or counter-clockwise, use full depth/width of boundaries
  o Include stretch up high, reach down low (sweep the ground)
- Static Stretching (move to ground) (4 minutes)
  o Slow static stretching; off-load opposing muscle groups (micro-stretch principles)
- Deep recovery breathing (2 minutes)
- Nutrition/Water
Transition to conditioning phase (55 minutes total) based on:

- **Anaerobic Lactic Power/Capacity**
  - Power: Max effort 10 s to 2 mins (>85% maxVO2)
  - Capacity: Max effort 40 s to 2 mins
  - Work:Recovery 1:10-12 (total work volume 6-12 minutes)

- **Aerobic Power/Capacity**
  - Power: Max effort 2-5 minutes; 70-80% maxVO2
  - Capacity: 5 mins plus max effort (30 mins of interval time+); 60-75% maxVO2
  - Work:Recovery 2:1 to 1:2 (**or 1:1) (total work volume 15 minutes power; total work volume 30 minutes capacity)

Training will be comprised of **Circuit training**: each week trainer will choose activities from three types of circuits – mobility, strength, aerobic. Weeks 1-4 will emphasize mobility and aerobic fitness; weeks 5-8 will emphasize increasing aerobic capacity, number of reps in 30 secs for mobility exercises and adding more strength criteria; Weeks 9-12 will cycle briskly through three categories increasing speed/reps/holds in each.

- **Stations** (generally 3 stations of 6 exercises; 2-3 sets @ 30 secs for mobility and strength; 1-2 sets @ 2-5 mins for aerobic)
- **Participant** will be given 3 minutes to transition between stations; RPE and HR checks will be made between stations

<table>
<thead>
<tr>
<th>MOBILITY CIRCUIT</th>
<th>STRENGTH CIRCUIT</th>
<th>AEROBIC CIRCUIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloured Poly Dots Call out</td>
<td>Ropes</td>
<td>Skipping</td>
</tr>
<tr>
<td>Coloured Poly Dot Tag</td>
<td>Broomstick resistance</td>
<td>Modified Burpee</td>
</tr>
<tr>
<td>Coloured Poly Dot Move</td>
<td>Abdominal Crunches</td>
<td>2 line drills: modified skip</td>
</tr>
<tr>
<td>Ladder – stepping</td>
<td>Elastic Running resistance</td>
<td>2 line drills: side shuffle</td>
</tr>
<tr>
<td>Ladder – typing</td>
<td>Front Plank</td>
<td>2 line drills: mini hurdles</td>
</tr>
<tr>
<td>Ladder – zig zag</td>
<td>Front Plank with leg extension</td>
<td>2 line drills: partner turns</td>
</tr>
<tr>
<td>Ladder – skip</td>
<td>Side Plank</td>
<td>Line tag</td>
</tr>
<tr>
<td>Ladder – karaoke</td>
<td>Side Plank with leg extension</td>
<td>One foot partner tag</td>
</tr>
<tr>
<td>Pylon – 5 m shuffle</td>
<td>Bear crawls forward</td>
<td>Cone drill: knock down</td>
</tr>
<tr>
<td>Pylon – direction change</td>
<td>Bear crawls toward arms</td>
<td>Cooperative ball tag</td>
</tr>
<tr>
<td>Pylon - clock</td>
<td>Knee Push ups</td>
<td>Chain tag/ Snake tag</td>
</tr>
<tr>
<td>Pylon – zig zag runs</td>
<td>Bird Dog</td>
<td>Relay: over/under ball</td>
</tr>
<tr>
<td>Running – Upright poles</td>
<td>Squat with Front kick</td>
<td>Relay: left/right ball</td>
</tr>
<tr>
<td>Running – Upright pole tag</td>
<td>Walking Lunge</td>
<td>Relay: touch floor with forehead, back, top head, hands behind back touch belly</td>
</tr>
<tr>
<td>Boxing Footwork</td>
<td>Isometric Push-up</td>
<td>Relay: shuttle run</td>
</tr>
</tbody>
</table>
Week 1-2

- Moderate Intensity (53 minutes – Week 1; 51 minutes – Week 2)
- 3 sets of each activity x 2 circuits (mobility and aerobic); rest between circuits 3 minutes

### Day 1

<table>
<thead>
<tr>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly Dot – Call</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Modified Skip</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Poly Dot – Tag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Side Shuffle</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Poly Dot – Move</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Mini Hurdles</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Partner turns</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Touch</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
</tr>
<tr>
<td>Ladder – Zig zag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Cones – Knockdown</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
</tr>
</tbody>
</table>

4:30 rest 9:00 work 8:00 rest 34:00 work

- High intensity (2 minutes – Week 1; 4 minutes – Week 2): Continuous direction changes

### Day 2

<table>
<thead>
<tr>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pylon – 5 m Shuffle</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Over/Under</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Pylon – Dir. change</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Left/Right</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Pylon – Clock</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Side shuffle</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Mini hurdles</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Partner turns</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
</tr>
<tr>
<td>Ladder – Zig zag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Modified Burpee</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
</tr>
</tbody>
</table>

4:30 rest 9:00 work 8:00 rest 34:00 work

- High intensity (2 minutes – Week 1; 4 minutes – Week 2): Continuous direction changes
Week 3-4
- Moderate Intensity (49 minutes – Week 3; 47 minutes – Week 4):
- 3 sets of mobility circuit; 2 sets of aerobic circuit; rest between circuits 3 mins

### Day 1

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
<th>Circuit: Aerobic</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Running – Poles</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Over/Under</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
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<tr>
<td></td>
<td>Pylon – Zig zag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Left/Right</td>
<td>3 x 2 min:30s</td>
<td>6:00</td>
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</tr>
<tr>
<td></td>
<td>Pylon – Clock</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Side shuffle</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
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</tr>
<tr>
<td></td>
<td>Ladder – Stepping</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Mini hurdles</td>
<td>2 x 2 min:30s</td>
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</tr>
<tr>
<td></td>
<td>Ladder – Typing</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Partner turns</td>
<td>2 x 2 min:30s</td>
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</tr>
<tr>
<td></td>
<td>Ladder – Zig zag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Modified Burpee</td>
<td>2 x 2 min:30s</td>
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<td></td>
<td>4:30 rest</td>
<td>9:00 work</td>
<td></td>
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<td></td>
<td>7:00 rest</td>
<td>28:00 work</td>
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</table>

- High intensity (6 minutes – Week 3; 8 minutes – Week 4): Continuous direction changes modify with signals

### Day 2

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
<th>Circuit: Aerobic</th>
<th>Activity</th>
<th>Work:Rest</th>
<th>Tot Work Time (min:s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poly Dots – Call</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Line Tag</td>
<td>3 x 2 min:30s</td>
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<tr>
<td></td>
<td>Poly Dots – Tag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Cone Drill – Knockdown</td>
<td>3 x 2 min:30s</td>
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<tr>
<td></td>
<td>Poly Dots – Move</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Shuttle</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
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</tr>
<tr>
<td></td>
<td>Ladder – Stepping</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>Relay – Touch</td>
<td>2 x 2 min:30s</td>
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<tr>
<td></td>
<td>Ladder – Typing</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Partner turns</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ladder – Zig zag</td>
<td>3 x 30s:15s</td>
<td>1:30</td>
<td>2 line – Side Shuffle</td>
<td>2 x 2 min:30s</td>
<td>4:00</td>
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<td></td>
<td></td>
<td></td>
<td>4:30 rest</td>
<td>9:00 work</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7:00 rest</td>
<td>28:00 work</td>
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</tbody>
</table>

- High intensity (6 minutes – Week 3; 8 minutes – Week 4): Continuous direction changes modify with signals
Week 5-6

- Moderate Intensity (45 minutes – Week 5; 43 minutes – Week 6):
- 3 sets ea. activity x 2 circuits (mobil. and strength); 1 set aerobic circuit; rest between sets 3 min

Day 1

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work:</td>
</tr>
<tr>
<td>Boxing Footwork</td>
<td>Chain tag</td>
<td>4-5 min:</td>
</tr>
<tr>
<td>Pylon – 5 m shuffle</td>
<td>Ball hockey</td>
<td>4-5 min:</td>
</tr>
<tr>
<td>Pylon – Clock</td>
<td>Relay – Shuttle</td>
<td>2 min:</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladder – Zig Zag</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:30 rest 9:00 work (as week 3-4)</td>
<td>2:30 rest</td>
<td>10-12 work</td>
</tr>
</tbody>
</table>

- High intensity (10 minutes – Week 5; 12 minutes – Week 6): Aerobic Circuit

Day 2

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work:</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>Cooperative Ball Tag</td>
<td>5 min:1 min</td>
</tr>
<tr>
<td>Poly Dot – Tag</td>
<td>Snake Tag</td>
<td>5 min:1 min</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td>Relay – Shuttle</td>
<td>2 min:30s</td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladder – Zig Zag</td>
<td></td>
<td></td>
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<tr>
<td>Ladder – Karaoke</td>
<td></td>
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</tr>
<tr>
<td>4:30 rest 9:00 work (as week 3-4)</td>
<td>2:30 rest</td>
<td>10-12 work</td>
</tr>
</tbody>
</table>

- High intensity (10 minutes – Week 5; 12 minutes – Week 6): Aerobic Circuit
Week 7-8
- Moderate Intensity (41 minutes – Week 7; 39 minutes – Week 8)
- 2 sets ea. activity x 2 circuits (mobil., strength); 1 set of aerobic circuit; rest between sets 3 mins

**Day 1**

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>Cooperative Ball Tag</td>
<td>5-6 min: 1:30 min</td>
</tr>
<tr>
<td>Poly Dot – Tag</td>
<td>Snake Tag</td>
<td>5-6 min: 1:30 min</td>
</tr>
<tr>
<td>Poly Dot – Move</td>
<td>Relay – Shuttle</td>
<td>2 min:30s</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td>Relay – Over/Under</td>
<td>2 min:30s</td>
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<tr>
<td>Ladder – Typing</td>
<td>Relay – Left/Right</td>
<td>2 min:30s</td>
</tr>
<tr>
<td>Ladder – Zig Zag</td>
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</tbody>
</table>

1:30 rest 6:00 work 2 x 30s:15s (W:R) 4:30 rest 16-18 work 1:30 rest 6:00 work

- High intensity (14 minutes – Week 7; 16 minutes – Week 8): 14-16 minutes indoor soccer (multiple balls)

**Day 2**

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Pylon – Dir. Change</td>
<td>Cooperative Ball Tag</td>
<td>5-6 min: 1:30 min</td>
</tr>
<tr>
<td>Pylon – Clock</td>
<td>Snake Tag</td>
<td>5-6 min: 1:30 min</td>
</tr>
<tr>
<td>Pylon – Zig Zag</td>
<td>Relay – Shuttle</td>
<td>2 min:30s</td>
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<tr>
<td>Ladder – Stepping</td>
<td>Relay – Over/Under</td>
<td>2 min:30s</td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td>Relay – Left/Right</td>
<td>2 min:30s</td>
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<tr>
<td>Ladder – Zig Zag</td>
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</table>

1:30 rest 6:00 work 2 x 30s:15s (W:R) 4:30 rest 16-18 work 1:30 rest 6:00 work

- High intensity (14 minutes – Week 7; 16 minutes – Week 8): 14-16 minutes indoor soccer (multiple balls)
Week 9-10

- Moderate Intensity (37 minutes – Week 9; 35 minutes – Week 10)
- 3 sets strength circuit; 2 sets mobility circuit; 1 set aerobic circuit; rest between sets 3 mins

Day 1

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>2 line drills – Side shuffle</td>
<td>3-4 min: 1 min</td>
</tr>
<tr>
<td>Poly Dot – Tag</td>
<td>2 line drills – Modify skip</td>
<td>3-4 min: 1 min</td>
</tr>
<tr>
<td>Poly Dot – Move</td>
<td>2 line drills – Mini hurdle</td>
<td>3 min: 1 min</td>
</tr>
<tr>
<td>Ladder – Stepping</td>
<td>2 line drills – Partner turns</td>
<td>3 min: 1 min</td>
</tr>
<tr>
<td>Ladder – Typing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladder – Zig Zag</td>
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<td></td>
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<tr>
<td>1:30 rest 6:00 work</td>
<td>4:00 rest</td>
<td>12-14 work</td>
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<tr>
<td>2 x 30s:15s (W:R)</td>
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- High intensity (18 minutes – Week 9; 20 minutes – Week 10): Aerobic Circuit plus 4-6 minutes continuous direction change

Day 2

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
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</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>2 line drills – Side shuffle</td>
<td>3-4 min: 1 min</td>
</tr>
<tr>
<td>Poly Dot – Tag</td>
<td>2 line drills – Modify skip</td>
<td>3-4 min: 1 min</td>
</tr>
<tr>
<td>Boxing Footwork</td>
<td>2 line drills – Mini hurdle</td>
<td>3 min: 1 min</td>
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<tr>
<td>Ladder – Stepping</td>
<td>2 line drills – Partner turns</td>
<td>3 min: 1 min</td>
</tr>
<tr>
<td>Ladder – Typing</td>
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<td></td>
</tr>
<tr>
<td>Ladder – Zig Zag</td>
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<tr>
<td>1:30 rest 6:00 work</td>
<td>4:00 rest</td>
<td>12-14 work</td>
</tr>
<tr>
<td>2 x 30s:15s (W:R)</td>
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</table>

- High intensity (18 minutes – Week 9; 20 minutes – Week 10): Aerobic Circuit plus 4-6 minutes Rope Hopping
Week 11-12

- Moderate Intensity (33 minutes – Week 11; 31 minutes – Week 12):
  - 3 sets strength circuit; 2 sets mobility circuit; 1 set aerobic circuit; rest between sets 3 mins

**Day 1**

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>Cooperative</td>
<td>5-6 min: 1:30 min</td>
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<tr>
<td></td>
<td>Ball Tag</td>
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<tr>
<td>Poly Dot – Tag</td>
<td>Snake Tag</td>
<td>5-6 min: 1:30 min</td>
</tr>
<tr>
<td>Boxing Footwork</td>
<td>Relay – Shuttle</td>
<td>2 min: 30 s</td>
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<tr>
<td>Ladder – Stepping</td>
<td>Stepping</td>
<td>2 min: 30 s</td>
</tr>
<tr>
<td>Ladder – Typing</td>
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<td></td>
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<tr>
<td>Ladder – Zig Zag</td>
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<tr>
<td><strong>1:30 rest 6:00 work</strong></td>
<td><strong>3:00 rest</strong></td>
<td><strong>12-14 work</strong></td>
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<tr>
<td><strong>2 x 30s:15s (W:R)</strong></td>
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</table>

- High intensity (22 minutes – Week 11; 24 minutes – Week 12): 12-14 minutes ball hockey plus aerobic circuit

**Day 2**

<table>
<thead>
<tr>
<th>Circuit: Mobility</th>
<th>Circuit: Aerobic</th>
<th>Circuit: Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Activity</td>
<td>Work: Rest</td>
</tr>
<tr>
<td>Poly Dot – Call</td>
<td>Cooperative</td>
<td>5-6 min: 1:30 min</td>
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<td>Ball Tag</td>
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<tr>
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<td>Snake Tag</td>
<td>5-6 min: 1:30 min</td>
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<tr>
<td>Boxing Footwork</td>
<td>Relay – Shuttle</td>
<td>2 min: 30 s</td>
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<tr>
<td>Ladder – Stepping</td>
<td>Stepping</td>
<td>2 min: 30 s</td>
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<tr>
<td>Ladder – Typing</td>
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<td>Ladder – Zig Zag</td>
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<tr>
<td><strong>1:30 rest 6:00 work</strong></td>
<td><strong>3:00 rest</strong></td>
<td><strong>12-14 work</strong></td>
</tr>
<tr>
<td><strong>2 x 30s:15s (W:R)</strong></td>
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- High intensity (22 minutes – Week 11; 24 minutes – Week 12): 12-14 minutes ball hockey plus aerobic circuit