PHYSICAL ACTIVITY AND AORTIC STIFFNESS IN CHILDREN WITH CONGENITAL HEART DISEASE

by

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Physical activity and aortic stiffness in children with congenital heart disease

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Abstract

**Background** – As the survival rates of children with congenital heart disease (CHD) increase, they are at increased risk for secondary cardiovascular events. Aortic stiffening, an indicator of vascular dysfunction, is predictive of premature cardiovascular events and mortality. It has been demonstrated that children with moderate-to-severe CHD have elevated aortic stiffness compared to healthy age-matched controls. Physical activity (PA) is an important determinant of optimal vascular health. Cross-sectional studies have demonstrated the beneficial associations between PA and vascular function in children with CHD. To date, it is not known how aortic stiffness and levels of PA change over time. The longitudinal relationship between the two parameters has also not been evaluated.

In order to facilitate effective PA counselling in a clinical setting for children with CHD, physicians need to be aware of the effects of seasonal variation on this heterogeneous behaviour. While seasonal variation has been extensively documented in the healthy pediatric population, there are no known data on the longitudinal PA patterns for children with CHD.

**Methods** – Children (9 – 16 years old) with moderate or complex CHDs were recruited at BC Children’s Hospital as part of a prospective cohort study.

Longitudinal changes for aortic stiffness and PA were assessed over 3 time-points over a ~24-months period during routine clinical care. Aortic stiffness was assessed using standard echocardiography and Doppler equipment, while PA was assessed using an accelerometer.
Daily step counts were assessed continuously for 12-months via a commercial activity tracker (Fitbit Charge 2™). PA levels were also assessed conventionally at one time-point via accelerometers and/or physical activity questionnaires (PAQ).

**Conclusions** – We observed that aortic stiffness increases and PA decreases over time. Our longitudinal analysis suggested that there may be an inverse relationship between PA levels and aortic stiffness in children with CHD.

We also demonstrated that PA levels change across seasons in children with CHD. It is important to be aware of this natural fluctuation when assessing and interpreting PA levels when using conventional methods and/or administering physical activity counselling.
Lay Summary

Congenital heart disease (CHD) is a condition at birth where the heart or the blood vessels near the heart do not develop normally. Children with CHD have an increased risk of heart attack, stroke, and death. Physical activity is important to optimize cardiovascular health. There are two goals to this thesis. First, to study the pattern of physical activity and the heart health of children with CHD over a 2-year period and to see if physical activity is beneficial for their heart over time. Second, to look at how levels of physical activity vary across seasons. The findings of the study will help doctors talk to children with CHD and their families about being more active throughout the year to improve their heart health.
Preface

I was principally responsible for the data analysis and interpretation of the results with the assistance of Drs. Kevin C. Harris, and Christine Voss. I performed all statistical analyses and generated all data and figures (Chapter 2 and 3) with the help of Dr. Mike Irvine.

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This study was conducted at the Children’s Heart Centre, BC Children’s Hospital in Vancouver, BC Canada and at pediatric cardiology partnership clinics across British Columbia and the Yukon. The study was approved by UBC Children’s & Women’s Research Ethics Board (H17-01233), and we obtained parent/guardian consent and participant assent prior to the study commencement.
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List of Abbreviations

BMI – body mass index
CHD – congenital heart disease
CI – confidence interval
COA – coarctation of the aorta
CVD – cardiovascular disease
DBP – diastolic blood pressure
FON – Fontan circulation
IQR – interquartile range
MRI – magnetic resonance imaging
MVPA – moderate-to-vigorous physical activity
PA – physical activity
PAQ – physical activity questionnaire
PWV – pulse wave velocity
SBP – systolic blood pressure
SD – standard deviation
TET – tetralogy of Fallot
TGA – transposition of the great arteries
TT – transit time
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Dedication

To all children with congenital heart disease and their families.
Chapter 1: Introduction

1.1 Congenital Heart Disease

Congenital heart disease (CHD) is a condition present at birth where the heart or the blood vessels near the heart do not develop normally. It is the most frequent congenital malformation occurring in one out of 100 live births and is also the leading cause of infant mortality.\(^2\) CHD is a highly heterogeneous disease that can be classified as simple, moderate, or complex. A simple lesion, such as ventricular septal defect, requires only a single intervention to correct the defect and typically has an excellent functional outcome.\(^3\) On the other hand, moderate and complex forms of CHD, such as tetralogy of Fallot and hypoplastic left heart syndrome, respectively, require multiple surgeries during childhood and are associated with long-term morbidity and reduced functional capacity.\(^3\)

In the past, patients with CHD exhibited the highest mortality peak during infancy but over the past decades, the distribution of age at death approximates that of the general population (Figure 1.1).\(^4\) It has been shown that the overall survival rate of children with all types of CHD have significantly increased due to improved preoperative care and surgical interventions.\(^3,5\) The survival curve of individuals with simple lesions mirrors that of the general population and individuals with moderate and severe defects have a median survival of 75 and 53 years, respectively (Figure 1.2).\(^6\) Consequently, the prevalence of CHD in children and adults across all ages has increased (Figure 1.3).\(^7\)
Figure 1.1 Distribution of Age at Death with Patients with Congenital Heart Disease in 1987 to 1988 and 2004 to 2005

Histogram bars depict the proportion of all deaths (x-axis) according to age at death (y-axis). Bold black curves with diamonds represent the corresponding age at death distribution in the general Quebec population. Reprinted from Khairy et al. with permission of the publisher. Copyright ©2010, Elsevier Inc.
Figure 1.2 Kaplan-Meier analysis for adults with congenital heart disease stratified by severity

Dashed line represents survival of the general population, and shaded areas represent the 95% confidence interval (CI) of the survival curves. Reprinted from van der Bom et al.⁵ with permission of the publisher.

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Figure 1.3 The numbers and proportions of adults and children in Quebec, Canada, with all (A) and severe (B) congenital heart disease over time in 2000, 2005, and 2010

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As patients with moderate or complex CHD live to an older age, they are at an increased risk of cardiovascular morbidity and mortality\(^1\) due to a combination of anatomic abnormalities, clinical interventions, and increased cardiovascular disease risk factors.\(^5\) One modifiable cardiovascular disease risk factor is physical activity. It has been shown that children with CHD are not meeting physical activity guidelines\(^9\) and physical inactivity has been shown to be a leading risk factor for morbidity worldwide.\(^10\) Considering both traditional risk factors and environmental factors, children with CHD are at an increased cardiovascular risk compared to the general population.\(^11\) We previously demonstrated that children diagnosed with moderate-to-complex CHD have signs of vascular dysfunction compared to their age-matched healthy controls.\(^12\)-\(^14\) Therefore, this work will focus on the following forms of moderate-to-complex CHD: Coarctation of the Aorta, Tetralogy of Fallot, Transposition of the Great Arteries, and Fontan circulation.

### 1.1.1 Coarctation of the Aorta

Coarctation of the Aorta (COA), a moderate CHD, is characterized by a narrowing (coarctation) of the aorta, which may be focal or associated with varying degrees of aortic arch hypoplasia.\(^3\) The narrowing of the aorta obstructs the blood flow from the heart to the rest of the body. COA occurs in approximately 409 per 1 million (0.0409\%) live births.\(^15\) This condition is more prevalent in males than in females.\(^16\)
1.1.2 Tetralogy of Fallot

Tetralogy of Fallot (TET), a moderate CHD described in 1888 by French physician Etienne-Louis Arthur Fallot, is characterized by four defects: (1) ventricular septal defect, (2) pulmonary stenosis, (3) right ventricular hypertrophy, and (4) overriding aorta. Infants and children with unrepaired TET are often cyanotic due to desaturated blood being pumped through the ventricular septal defect in the setting of severe right ventricular outflow tract obstruction. TET occurs in approximately 421 per 1 million (0.0421%) live births. This condition affects males and females equally.

1.1.3 Transposition of the Great Arteries

In Transposition of the Great Arteries (TGA), a complex CHD, the two main arteries (aorta and pulmonary artery) carrying blood away from the heart are reversed. Specifically, the aorta is connected to the right ventricle and takes deoxygenated-blood to the body, while the pulmonary artery is connected to the left ventricle and takes oxygenated-blood to the lungs. TGA occurs in approximately 315 per 1 million (0.0315%) live births. This condition is more prevalent in males than females affecting 3 boys to every 1 girl.

1.1.4 Fontan Circulation

Fontan circulation (FON) is a palliative surgical intervention first performed by French physician Francis Fontan in 1971. This procedure is devised to help separate the systemic and pulmonary circulations of patients with single ventricle defects. Single ventricle defects refer to a group of CHDs in which one of the ventricles of the heart may be underdeveloped. This means
that there is only one functional ventricle to pump the blood through both the systemic and the pulmonary circulations. Some examples of Single Ventricle Defects include Tricuspid Atresia, Hypoplastic Left Heart Syndrome, Double Inlet Left Ventricle, and Double Outlet Right Ventricle, all of which are complex CHDs. In a Fontan circulation, deoxygenated blood returning from the body flows passively to the pulmonary arteries and into the lungs. Oxygen-rich blood from the lung flows through the pulmonary veins and travels to the functional single ventricle. This single ventricle pumps the blood through the aorta to the rest of the body. There are anatomic and surgical variations amongst patients with a Fontan circulation related to the specific form of CHD they have.18
1.2 Aortic Stiffness

While the field of CHD has advanced to address the structural abnormalities of the heart, the effect of corrective procedure on the vascular bed is not addressed. Children with moderate-to-complex CHD are at increased cardiovascular risk compared to the general population and routine monitoring of their cardiovascular health from a specialist is required. One method of evaluating the cardiovascular health of children with CHD is through assessing their aortic stiffness. Aortic stiffness is a marker of vascular dysfunction and is one of the strongest predictors of cardiovascular events, cardiovascular mortality, and all-cause mortality. The aorta is the main blood vessel that serves as a conduit for oxygenated blood from the heart to the body. It also functions as a cushion for pulsatile flow of the blood from the heart to the rest of the body similar to that of the Windkessel in fire engines (Figure 1.4). During systole, the elastic aortic

![Figure 1.4 The concept of the Windkessel](image)

The air reservoir is the actual Windkessel, and the large arteries act as the Windkessel. The combination of compliance, together with aortic valves and peripheral resistance, results in a rather constant peripheral flow. Reprinted from Westerhof et al. with permission of the publisher. Copyright ©2008, Springer Nature
wall stretches and dampens the large volume of blood ejected by the left ventricle. This dampens the increase in systolic arterial pressure and transforms the pulsatile flow into a steady flow for supplying oxygen to the organs. During diastole, the elastic recoil of the aortic wall enables continuous blood flow and reduces the diastolic drop in arterial pressure. An elastic vascular system reduces cardiac demand, increases coronary artery perfusion, and is associated with reduced atherosclerotic progression. In the Framingham Heart Study, individuals with elevated aortic stiffness had a higher chance of experiencing a cardiovascular event after adjusting for age, sex, and standard risk factors (Figure 1.5).

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**Figure 1.5** Kaplan-Meier plot of cumulative probability of a first major CVD event when participants were grouped according to quartiles of carotid-femoral (aortic) pulse wave velocity

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1.2.1 Underlying Mechanisms of Arterial Stiffening

The arteries are conduits comprised of three key layers: intima, media, and adventitia (Figure 1.6).\textsuperscript{24} The intima is the innermost layer made up of a single layer of endothelial cells on the luminal side of the vessel. The media is made up of connective layers of elastin, fibrillar collagen, and vascular smooth muscle cells. The ratio of elastin and collagen determines the elastic properties of the blood vessels and the vascular smooth muscle cells aid in the contraction and dilation of the blood vessels. The adventitia, the outer most layer of the vascular wall, is made up of fibroblasts and collagen which give the blood vessel most of its tensile strength.\textsuperscript{21} The composition of the arterial vessels is not uniform throughout the body. The proximal aorta is the most compliant since it is rich in elastin to accommodate the stroke volume, whereas the distal vessels become progressively stiffer given the predominance of collagen fibers\textsuperscript{25} In other words, the aorta becomes stiffer the further away from the heart.

![Figure 1.6 Composition of the Artery](image)

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Arterial stiffening is a cumulative effect of changes in the extracellular matrix, vascular calcification, and increased oxidative stress resulting in vessel remodelling.\(^2\)\(^1\)

The extracellular matrix within the media is comprised of collagen, elastin, glycoproteins, and proteoglycans. The structural integrity and elasticity of the blood vessel are dependent on the ratio of elastin to collagen. This ratio is achieved through the actions of lysyl oxidase and matrix metalloproteases. Lysyl oxidase facilitates the intra- and intermolecular covalent cross-linking of elastin and collagen and matrix metalloproteases degrade the extracellular matrix by uncoiling collagen and breaking elastin. Lysyl oxidase-deficient mice are presented with structural alterations in the arterial walls and cardiovascular dysfunction, which suggest that lysyl oxidase activity is important in maintaining the elasticity of the aorta.\(^2\)\(^6\) Whereas elevated levels of matrix metalloproteases (matrix metalloprotease-2 and matrix metalloprotease-9) in the blood serum of healthy individuals were associated with increased arterial stiffness.\(^2\)\(^7\) Therefore, an appropriate balance of lysyl oxidase, matrix metalloproteases, and the resulting elastin/collagen ratio in the extracellular matrix are important in maintaining vascular compliance.\(^2\)\(^1\)

The deposition of glycoproteins to the extracellular matrix has also been shown to contribute to arterial stiffening.\(^2\)\(^8\) This modification may further contribute to vascular calcification which reduces the aorta’s elasticity and increases stiffness.\(^2\)\(^9\) In addition to alterations in the extracellular matrix composition and arterial calcification, arterial stiffening is strongly associated with increased production of reactive oxygen species.\(^2\)\(^1\) The increased production of reactive oxygen species reduces the bioavailability of nitric oxide, a vasodilator, and in turn, contributes to arterial stiffening by promoting abnormal vascular tone.\(^2\)\(^1\)
1.2.2 Natural Progression of Aortic Stiffening

Aging is the dominant process leading to arterial stiffening (Figure 1.7). Changes related to arterial aging include luminal enlargement with wall thickening (remodeling) and a reduction of elastic properties (stiffening). This natural progression of arterial stiffness is referred to as arteriosclerosis and should be distinguished from atherosclerosis, which is a disease of the intima. Age-related arterial stiffening is mainly due to alterations of the extracellular matrix composition. In the extracellular matrix, increased matrix metalloproteases-mediated proteolysis leads to elastin fragmentation and collagen formation. This decrease in elastin content combined with an increase in collagen deposition leads to an imbalance between elastin and collagen ratio, resulting in a decrease in arterial distensibility and systemic compliance. There is also an accumulation of advanced glycation end-products, increased calcium deposition with age after the 5th decade, and an increased adhesion molecule expression in vascular smooth muscle cells of the tunica media. Age-related arterial stiffening may be associated with and further potentiated by the development of chronic, low-grade inflammation, which induces matrix metalloproteases expression, calcification, and fibrosis of the arterial bed. Aging vessels also exhibit chronic oxidative stress due to increased reactive oxygen species production which may further increase vascular collagen production and elastin fragmentation through matrix metalloproteases expression.
Figure 1.7 A, Predicted longitudinal changes in pulse wave velocity (PWV) in men and in women. B, Predicted rate of change in PWV per decade in men and in women.

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1.2.3 Pathological conditions linked to accelerated arterial stiffening

Hypertension is both a consequence and pathogenic contributor to aortic stiffening.\textsuperscript{20} Patients with isolated systolic hypertension have increased aortic stiffness compared to age-matched controls.\textsuperscript{36} Arterial hypertension is a major determinant of arteriosclerosis and aortic stiffening through structural and functional changes in the vascular walls.\textsuperscript{37} The increase in pulse pressure has been shown to stimulate the production of collagen and is also associated with aortic wall calcification and endothelial dysfunction, all contributing to an increase in arterial stiffness.\textsuperscript{36}

Metabolic disorders, such as diabetes mellitus and obesity, are also associated with accelerated arterial stiffening.\textsuperscript{21} The process of diabetes-accelerated arterial stiffening includes matrix metalloproteases-induced elastin degradation, increased calcification of the arterial wall, and enhanced levels of reactive oxygen species production.\textsuperscript{21} The elevated arterial stiffness is also observed in healthy obese children\textsuperscript{38,39} and adults\textsuperscript{40}. In the extracellular matrix, there is a down-regulation of lysyl oxidase activity leading to a decrease in elastin content. Rider et al. also suggested that there exists a liver fat–triglycerides–arterial stiffening pathway, where the distribution and deposition of liver fat content is a powerful predictor of aortic stiffness.\textsuperscript{41}

Aortic stiffness is shown to be elevated in patients with Marfan syndrome, a connective tissue disorder.\textsuperscript{42} In Marfan syndrome, the elevation of transforming growth factor-beta level is associated with an increase in collagen secretion, resulting in increased arterial stiffness.\textsuperscript{43} This predisposes Marfan patients to progressive aortic dilatation and elevated risk to aortic aneurysm and dissection, mandating early surgical treatment to manage this risk.\textsuperscript{44}

A prospective community-based study demonstrated that ideal cardiovascular health was associated with less arterial stiffness.\textsuperscript{45} Ideal cardiovascular health, as proposed by the American
Heart Association in 2010, is based on seven health factors and behaviours: smoking, body mass index, diet, physical activity, blood glucose, total cholesterol, and blood pressure.\(^46\) Thus, having poor cardiovascular health significantly increases arterial stiffness.\(^45\)

Adults with CHD have increased arterial stiffness compared to healthy controls despite no significant difference in systolic pressure.\(^47\) This elevation in arterial stiffness can also be observed in children with CHD as measured by central systolic blood pressure.\(^48\) Similarly, our group at the British Columbia Children’s Hospital has demonstrated that children with moderate-to-complex CHD have significantly elevated aortic stiffness as measured by aortic pulse wave velocity compared with age-matched controls.\(^12\)\(^13\)

### 1.2.4 Increased arterial stiffness: a risk factor for cardiovascular events

Stiffening of the artery, especially the aorta, indicates vascular dysfunction and acts as a risk factor for cardiovascular events via the following mechanisms: increased cardiac afterload, impaired coronary blood flow, arterial remodelling and atherogenic progression, and end-organ damage.\(^49\)

1. Blood ejected into the stiffened aorta increases the end-systolic pressure. This will cause the heart to work harder to overcome arterial resistance, resulting in cardiac hypertrophy and increased cardiac afterload.\(^49\)

2. Coronary arteries are mostly perfused during diastole. The aorta cushions the blood ejected from the heart during systole and the elastic property of the aorta allows it to store the blood for delivery during diastole. Without the elastic property of the arteries, the amount of stored blood is compromised thus impairing coronary blood flow during diastole.\(^49\)
3. Increased arterial stiffness is associated with increased mechanical stress in the luminal side of the vascular wall due to increased pressure and speed of blood flow. This triggers signalling cascades in the arterial wall which leads to vascular growth and remodelling.\textsuperscript{49}

4. Arterial stiffening attenuates the cushioning effect of elastic arteries. This amplifies the pulse pressure and increases the blood flow to peripheral microcirculation. This means that high-blood-flow organs, such as the brain and kidney, can sustain damage due to the increased blood flow within their intricate capillary networks.\textsuperscript{49}

1.2.5 **Non-invasive measurement tools for pulse wave velocity (PWV) in a clinical setting**

PWV is the most validated non-invasive method to measure arterial stiffness.\textsuperscript{31} PWV is determined by measuring the distance traveled by the pulse wave (produced by rapid ejection of blood from the left ventricle during systole) divided by the time taken to travel the distance.

Magnetic resonance imaging (MRI) allows for the detection of subtle changes in stiffness in different regions of the aorta.\textsuperscript{50} However, the use of MRI requires long examination time and is resource-intensive which makes it not suitable for large epidemiology studies. The long examination time is further compounded when used in the pediatric population, where children who are unable to stay still for a prolonged period must be sedated to perform an MRI examination. Furthermore, its use in the clinical setting is limited in patients with metal medical devices, such as pacemakers which preclude the use of MRI.

Carotid-femoral PWV is widely used for assessing central arterial stiffness in clinical practice and research studies. The PWV is calculated by dividing the distance between the carotid and the femoral artery by the time of delay of the arterial pulse between these two arterial
sites.\textsuperscript{49}\textsuperscript{51} However, the use of carotid-femoral PWV requires highly trained technicians and exposure of the groin for its measurements.\textsuperscript{49} To combat this limitation, a group of Japanese researchers advocates the use of brachial-ankle PWV.\textsuperscript{52} This method is simple to use in clinical practice and suitable for large population-based studies. However, due to the peripheral site of the brachial and ankle arteries, the PWV is a reflection of both central arterial stiffness and muscular arterial stiffness.\textsuperscript{49}

Central PWV can be assessed using transthoracic echocardiography with pulse wave Doppler. Our group has developed a novel non-invasive technique for assessing aortic stiffness using transthoracic echocardiography and Doppler equipment (Figure 1.8).\textsuperscript{42} By using echocardiography, measurement of the aortic stiffness could be easily incorporated into routine clinical care for the pediatric CHD population. Aortic stiffness of children diagnosed with COA, TET, TGA, and FON were significantly elevated compared to age-matched healthy controls but were not significantly different from each other despite the different severities of their conditions.\textsuperscript{12,13}

Figure 1.8 Echocardiography and Doppler equipment to measure PWV

Transit Time (TT)(s) = T2(s) \(\text{–}\) T1(s) Pulse Doppler of aorta taken at valve leaflets demonstrating method used in measure time to onset of A) ascending (T1) and B) descending (T2) aortic flow. C) Aortic Arch Length Standard echocardiography of aortic arch length (cm) calculated by the sum of each individual measure
1.3 Physical Activity

Physical activity (PA) is defined as “any bodily movement produced by skeletal muscles that requires energy expenditure”. This behaviour has been studied extensively due to its well-known positive effects on metabolic syndrome, insulin sensitivity, cardiovascular risks, and all-cause mortality. It has been shown that in the USA, physical inactivity is one of the leading cause of death followed by tobacco (18.1%) and poor diet (16.6%). Physical activity is essential for optimal physical, emotional, and psychosocial development for all children, including children with CHD. Thus, it is recommended that children and youth should accumulate an average of 60 minutes of moderate-to-vigorous physical activity (MVPA) per day for health promotion and disease prevention. Furthermore, regular participation in PA by children with CHD leads to an adoption of a healthy lifestyle which is beneficial in preventing atherosclerotic cardiovascular disease, dyslipidemia, obesity, hypertension, osteoporosis, and type II diabetes later in life.

1.3.1 Benefits of Physical Activity to the Cardiovascular System

It has been widely recognized that regular PA reduces the risk of cardiovascular events by inducing changes in the heart and vasculature. The cardioprotective mechanisms of physical activity on the cardiovascular system have been widely studied at the molecular level to determine the specific cardiac and vascular benefits. While increased oxidative stress contributes to arterial stiffening, PA attenuate the progression of arterial stiffening is by altering the cell’s response to oxidative stress. PA enhances the level of myocardial antioxidants which delays the accumulation of reactive oxygen species-mediated cell damage in the myocardium. There is also an increased expression of cardiac heat shock proteins, which are associated with increased
cell survival and protection against ischemic injury under cell stress. Furthermore, mitochondrial adaptations in the cardiomyocytes lead to a further decrease in reactive oxygen species production and reactive oxygen species-mediated cell damage. On the vascular level, PA enhances endothelial function by increasing nitrox oxide production, thus improving the vasodilatory capacity of the artery. PA has also been shown to induce vascular remodelling through two mechanisms: angiogenesis and arteriogenesis. Angiogenesis is an expansion of capillary networks by the formation of new blood vessels and arteriogenesis is the enlargement of blood vessels. These structural changes in the vasculatures lead to improved blood flow throughout the body. By altering the cell’s response to better adapt to oxidative stress, PA attenuates the progression of arterial stiffening. Moderate levels of PA are said to provide the most benefits because it is suggested that there exists a bell shape oxidative stress response to exercise where none and excessive amounts are considered harmful.

1.3.1.1 Modifiable Risk Factor of Aortic Stiffness

Physical activity is a modifiable risk factor of arterial stiffness. It has been demonstrated that in middle-aged and older men, those who are recreationally active or participate in regular aerobic-endurance exercise, can attenuate age-related increase in arterial stiffening compared with age-matched sedentary control subjects. The increased levels of PA are correlated with improved aortic PWV. Furthermore, 3-months of regular aerobic-endurance exercise was able to partially restore the loss of central arterial compliance. The effect of PA on arterial stiffness can also be observed in the pediatric population. In healthy children aged 6 – 8 years old, lower levels of PA were associated with higher arterial stiffness. Children with prematurely elevated arterial stiffness may also benefit from physical activity participation. It has been shown that 6
months of exercise intervention program was able to reduce the arterial stiffness of obese children and this effect may be mediated by a significant reduction in systole blood pressure.\textsuperscript{65}

Our group at the BC Children’s Hospital (Vancouver, BC) has also demonstrated that high levels of PA during adolescence is inversely related to aortic stiffness in our cohort of children with CHD.\textsuperscript{14}

\textbf{1.3.2 Assessment Tools in the Clinical Setting}

There is an increased emphasis on promoting PA to optimize physical, emotional, psychosocial developments, and the long-term cardiovascular health for all children, including children with CHD.\textsuperscript{57} Routine PA assessment during clinical care has been highly recommended for individuals with CHD in order to properly facilitate PA counselling and/or exercise prescription.\textsuperscript{57, 66} However, the evaluation of PA in a clinical setting can be challenging. PA is a complex and heterogeneous behaviour that can be conceptualized to comprise of ‘dimensions’ (frequency, intensity, time, and type) and ‘domains’ (occupational, transport, domestic, and leisure).\textsuperscript{67} Different PA measurement tools capture varying degrees of these constructs. Therefore, it is important for researchers, clinicians, and exercise physiologists of children with CHD to understand the spectrum and roles of different types of PA measurement tools. In this section, we summarized some PA measurement tools that have potential utility in the clinical setting for capturing PA levels in children with CHD.
1.3.2.1 Physical Activity Questionnaires (PAQ)

The PAQ is a self-administered, 7-day recall questionnaire that assesses general levels of physical activity participation on a scale of 1 being the lowest and 5 being the highest.\textsuperscript{68} Physical Activity Questionnaires for Older Children (PAQ-C) is administered for students in elementary school and/or middle school (approximately 8 to 14 years of age) whereas the Physical Activity Questionnaires for Adolescents (PAQ-A), a modified version of PAQ-C with “recess” removed, is administered for students in high school (approximately 14 to 20 years of age).\textsuperscript{68} PAQ is a time-efficient and cost-effective tool to measure levels of PA subjectively. The self-report method can capture sustained activities (e.g. PE classes, team sports) but children have difficulty quantifying the duration, frequency, or intensity of activities that occurs in numerous short spontaneous bursts (e.g. running for the bus, walking to classes).\textsuperscript{69} It also does not discriminate against the intensities between specific activity and is only appropriate to use during the school year.\textsuperscript{68} Despite its limitations, the PAQ-C and PAQ-A have acceptable validity, reliability, and practicality for use in the general children and adolescents\textsuperscript{70} as well as those with CHD.\textsuperscript{71}

1.3.2.2 Accelerometers

Accelerometers are small, lightweight devices, and usually worn around the waist for several days. Accelerometers record time-stamped acceleration signals which are converted to time spent in PA intensities using thresholds calibrated specifically for the device and population/age range. Accelerometers can capture detailed information on the duration, intensity, and frequency of PA. They are widely used to provide an objective measure of physical activity in free-living conditions and can inform whether PA guidelines are met. However, there are some limitations in using accelerometers to capture levels of PA. One of the limitations is the
short wear-time protocol, which means that an individual’s overall levels of PA are quantified from a small window.\textsuperscript{67} Secondly, the device is not able to capture the intensities of fluid-motion activities (e.g. cycling, skating) and water-based activities (e.g. swimming). Furthermore, while it can quantify the intensity of activities, it cannot differentiate different types of PA.

1.3.2.3 Pedometers

The pedometers, devices that count steps taken, are simpler and more cost-effective alternatives to accelerometers. The measurements protocols are similar to that of accelerometers where the device is worn around the waist during waking hours for several consecutive days. The output is in steps per day and is simple to interpret and does not require extensive technical expertise. However, pedometers do not give insight into the intensity or differentiate the types of activity. Furthermore, since there are currently no step-based PA guidelines, we do not know if the individual meets PA guidelines or not.

1.3.2.4 Commercial Activity Trackers

Recently, a large number of commercial activity trackers have appeared on the market that allows users to track their daily PA levels. These devices use a triaxial accelerometer and proprietary algorithms to estimate different activity parameters such as steps taken, stairs climbed, distance travelled, calorie consumed, and types of PA. Depending on the models, some may contain heart rate monitors and global positioning systems. Due to its popularity, affordability, and user-friendliness, commercial activity trackers provide an exciting opportunity to estimate activity over a long period in biomedical research. It is shown that they provide a
valid estimate of activity level compared to accelerometers and demonstrate good wear-time compliance.\textsuperscript{72} Commercial activity trackers can also be used in the clinical setting to enable remote monitoring of a patient’s physical activity levels which may better the facilitation of activity counselling and promotion. However, similar to that of a pedometer, it does not give any insight into the intensity of the activity.

### 1.3.3 Physical Activity in Children with CHD

In our cohort of pediatric CHD patients, the physical activity questionnaire demonstrated that the most commonly self-reported activities are running, walking, soccer, and basketball.\textsuperscript{14} From their accelerometry data, the mean MVPA was 46.7 minutes per day with 25\% of the children meeting PA guidelines.\textsuperscript{14} Their activity levels were comparable to that of the Canadian national data of 49.7 minutes per day and 23.1\% met PA guidelines.\textsuperscript{73} The data demonstrated that the majority of children with CHD are not reaping the beneficial effects of PA and strategies on effective PA promotion should be implemented during clinical visits. However, assessing PA in a clinical setting can be challenging since PA behaviours are highly heterogeneous between individuals, likely to vary over time, and may be impacted by their medical history\textsuperscript{74} and other sociocultural factors.\textsuperscript{75, 76} Furthermore, PA participation may be influenced by natural environmental factors such as weather, temperature, and precipitation within a season. Seasonal variation of PA is the idea of how the fluctuation in weather and daylight hours with each season impact levels of PA. Understanding the determinants of PA among children with CHD is necessary to facilitate effective PA counselling.
1.4 Rationale

Individuals with moderate-to-complex CHD are at an increased risk to cardiovascular disease and cerebrovascular insults compared to the general population due to postoperative cardiac residua and sequelae. With the life expectancy of children with moderate-to-complex CHD extending well into adulthood, healthcare needs to prioritize on the quality of life and long-term health outcome for this high-risk population. One method of assessing their vascular health is through measuring aortic stiffness, a marker of vascular dysfunction and a strong predictor of early cardiovascular events and death. It has been demonstrated that children diagnosed with moderate-to-complex forms of CHD have higher PWV compared to their healthy age-matched controls. However, longitudinal evaluation of aortic stiffness over time in children with CHD are needed to optimize the clinical management for this cohort.

Physical activity is a modifiable risk factor of vascular dysfunction. However, assessing PA can be challenging because the behaviour is highly heterogeneous between individuals and likely to vary over time. No study has assessed and compared the usability of conventional periodic tools (accelerometers and questionnaires) and commercial activity trackers (Fitbit) in a pediatric cohort in a clinical setting. Our group has previously demonstrated that objectively-measured moderate-to-vigorous physical activity in our pediatric CHD cohort did not differ according to CHD severity. We have also demonstrated that, cross-sectionally, aortic stiffness is negatively associated with physical activity in our patient cohort. Currently, there are no studies investigating the longitudinal association between levels of physical activity and aortic stiffness in children with CHD.
1.5 **Hypothesis and Objectives**

**H1:** We hypothesize that physical activity varies across seasons in children with CHD.

**Aim 1:** To determine whether seasonal variation in physical activity exists in children with CHD by measuring physical activity longitudinally (commercial activity trackers) and via conventional periodic measures (accelerometers and questionnaires)

**H2:** We hypothesize that there is an inverse association between physical activity and aortic stiffness over time in children with CHD. In other words, higher levels of physical activity over time will attenuation the progression of aortic stiffness.

**Aim 2a:** To determine if there are changes in aortic stiffness and physical activity over time in children with CHD

**Aim 2b:** To determine whether there is an association between levels of physical activity and aortic stiffness over time in children with CHD.
Chapter 2: Children with congenital heart disease exhibit seasonal variation in physical activity

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2.1 Abstract

**Objective** – We sought to identify seasonal variation in physical activity that different physical activity measurement tools can capture in children with congenital heart disease.

**Methods** – Data were collected as part of a prospective cohort study at BC Children’s Hospital, Vancouver, Canada. Daily step counts of children aged 9–16 years with moderate-to-severe CHD were assessed continuously for 1-year via a commercial activity tracker (Fitbit Charge 2™). Physical activity levels were also assessed conventionally at one time-point via accelerometers (ActiGraph) and physical activity questionnaires.

**Results** – 156 children (mean age 12.7±2.4 years; 42% female) participated in the study. Fitbit data (n=96) over a 1-year period clearly illustrated seasonal peaks (late spring and autumn) and dips (winter and summer school holidays) in physical activity levels, with group mean values being below 12,000 steps per day throughout the year. According to conventional accelerometry data (n=142), 26% met guidelines, which tended to differ according to season of measurement (spring: 39%, summer: 11%, fall: 20%, winter: 39%; p-value = 0.053). Questionnaire data (n=134) identified that the most widely reported activities were walking (81%) and running (78%) with walking being the highest in summer and fall and running in winter and spring. Furthermore, regardless of overall activity levels the children exhibit similar seasonal variation.

**Conclusions** – We demonstrated that physical activity level changes across seasons in children with CHD. It is important to be aware of these fluctuations when assessing and interpreting physical activity levels. Season specific counselling for physical activity may be beneficial in a clinical setting.
2.2 Introduction

Congenital heart disease (CHD) is the most common congenital defect in new-borns occurring in approximately 1 in 100 live births.\textsuperscript{79} Survival rates of children with moderate-to-complex forms of CHD have significantly increased and most of these individuals have a life expectancy that extends well into adulthood.\textsuperscript{5} Consequently, the prevalence of CHD across all age ranges has increased.\textsuperscript{4,7} It is well established that the CHD populations are at an increased risk for cardiovascular events compared to the general population.\textsuperscript{80} Physical activity, defined as “any bodily movement produced by skeletal muscle that results in energy expenditure”,\textsuperscript{53} is a modifiable risk factor and higher levels of physical activity are associated with better long-term cardiovascular risk in population-based studies.\textsuperscript{81} Physical activity is an important determinant in optimizing the long-term cardiovascular health and quality of life in the CHD population.\textsuperscript{66}

Despite the beneficial effect of physical activity, levels of physical activity decline with age in children with CHD.\textsuperscript{9} Adolescent declines in physical activity are particularly concerning given the increased cardiovascular risk of the CHD population.\textsuperscript{80} Physical activity research in children with CHD is an emerging field of study; however, assessing physical activity can be challenging. Physical activity behaviours are highly heterogeneous between individuals, likely to vary over time, and may be impacted by their medical history\textsuperscript{74} and other sociocultural factors.\textsuperscript{75} While seasonal variations have been extensively documented in the healthy pediatric population,\textsuperscript{82} there are no data on longitudinal physical activity patterns for children with CHD.

The aim of this study was to determine whether physical activity varies across seasons in children with CHD by measuring physical activity longitudinally (commercial activity trackers) and via conventional periodic measures (accelerometers and questionnaires).
2.3 Materials and methods

2.3.1 Sample

Data were collected as part of a prospective cohort study of children and adolescents aged 9–16 years old with Tetralogy of Fallot, Coarctation of the Aorta, Transposition of the Great Arteries, or Fontan circulation. Participants were recruited through the Children’s Heart Centre at BC Children’s Hospital in Vancouver, Canada, or at pediatric cardiology partnership clinics across British Columbia and the Yukon, Canada, between April 2017 and May 2019. Accelerometry and physical activity questionnaires were administered during their clinical visit. Physical activity was assessed longitudinally using commercial activity trackers. Data from May 1, 2018 – April 30, 2019 were analysed to evaluate seasonal variation. The study was approved by UBC Children’s & Women’s Research Ethics Board (H17-01233), and we obtained parent/guardian consent and participant assent prior to study commencement.

2.3.2 Participant Characteristics

We obtained participants sex, birth date, and cardiac diagnosis from patient medical charts. Trained clinical staff measured height (0.1 cm) and weight (0.1 kg). Body mass index (BMI; kg/m²) was calculated and expressed as age- and sex-specific percentiles based on World Health Organization International growth charts.③ BMI was categorized based on World Health Organization cut-offs.

2.3.3 Commercial Activity Tracker

We chose the Fitbit Charge 2™ (Fitbit Inc, San Francisco, CA) for our study. Wristband size and placement were in accordance with manufacturer’s guidelines. We asked participants to wear the Fitbit continuously for 12 months and sync the device on a regular basis. We created anonymous user profiles and used the ‘Data Export’ function from the online ‘dashboard’ to
export daily step count data. In the absence of any consensus on wear time validation for commercial trackers in children, we considered a day to be valid if they had \( \geq 1000 \) steps/d, and a month to be valid if they had \( \geq 14 \) valid days. Monthly step counts were calculated by averaging the step counts from all the valid days of each month. We defined meeting physical activity guidelines as having \( \geq 12,000 \) steps per day.\(^8^4\)\(^8^5\)

### 2.3.4 Accelerometry

We fitted participants with an ActiGraph accelerometer (GT3X+, GT9X; ActiGraph LLC, Pensacola, FL) to be worn over the right hip for 7 days during waking hours and only to be removed for water-based activities. The ActiGraph is a commonly used tri-axial accelerometer to objectively measure physical activity levels in children under free-living condition. We used ActiLife v.6.13.2 (ActiGraph LLC, Pensacola, FL) for accelerometer initialization (sampling set at 30Hz) and file download, processing, and analysis. We generated 15s epoch .agd files from the raw .gt3x files and used the wear time function in ActiLife to identify valid accelerometry files. We considered a day to be valid if the device was worn for \( \geq 600 \) mins/day. We previously demonstrated that a minimum of 3 valid days are sufficient to estimate mean physical activity values in children and adolescents with CHD.\(^9\)

For valid accelerometry files, we used Evenson cut-points\(^8^6\) to estimate mean daily minutes spent in moderate-to-vigorous physical activity (MVPA) intensity. We defined meeting physical activity guidelines as \( \geq 60 \) minutes of MVPA per day, on average. We categorized participants’ physical activity levels based on the distribution of MVPA in our sample as follows: ‘low’=\(<30\) mins MVPA/day (\(<25^{th}\) percentile); ‘medium’=30–59 mins MVPA/day (\(25^{th}–75^{th}\) percentile); ‘high’= \( \geq 60 \) mins MVPA/day (\(>75^{th}\) percentile).
2.3.5 Physical Activity Questionnaire (PAQ)

The PAQ is a self-administered, 7-day recall questionnaire that assesses participation in different activities, as well as providing general estimates of physical activity levels. We previously demonstrated that the PAQ is valid for use in children with CHD. The questionnaire was self-administered in a quiet room during clinic visit or at home. The overall PAQ-score is derived from the mean scores of all questionnaire items. We identified the most common activities from the PAQ by calculating the proportion of children who self-reported to have participated in the activity during the previous 7 days. We identified the most commonly participated activities by season by counting the number of days the activity was performed in the past 7 days. We categorized participants’ activity levels based on the distribution of questionnaire scores in our sample as follows: ‘low’ = <2.7 PAQ-score (~<50th percentile); ‘high’ = ≥2.7 PAQ-score (~≥50th percentile).

2.3.6 Statistical Analysis

Descriptive statistics (frequencies [%], mean±SD, or median [IQR]) were calculated for applicable variables. Distributions of continuous variables were assessed visually. The ‘lowess’ function in R was used to generate a physical activity line of best fit for commercial activity tracker over a 1-year period. Between-season differences were assessed via one-way ANOVA (post hoc Bonferroni correction) for continuous variables or chi-square tests for categorical variables. All analyses were performed in R (version 3.6.0) using R Studio (version 1.1.442) and significance was set at $p < 0.05$. Seasons were defined as spring (March–May), summer (June–August), autumn (September–November), and winter (December–February).
2.4 Results

2.4.1 Sample

One hundred and fifty-six children were recruited to the study (mean age 12.7±2.4 years, 42% females) with at least one complete and valid commercial activity tracker, accelerometry, or physical activity questionnaire data. Overall participant characteristics are shown in Table 2.1. Sample characteristics of accelerometer and PAQ are not significantly different between seasons (Appendix Table 1 and 2).

2.4.2 Longitudinal physical activity patterns: commercial activity trackers

Fitbit data were taken over a 1-year period from May 1, 2018 – April 30, 2019 (n=96) and the physical activity line-of-best-fit is shown in Figure 2.1. This clearly illustrated seasonal peaks and dips in physical activity. The peaks occurred in late spring and autumn. There was a severe dip in July and August which corresponds to local school holidays. There was a long trough during the colder winter months. The entire fitted line rests below 12,000 steps per day. Overall, 23% of the children met the recommended step goal and 36%, 19%, 30%, and 12% of the children met the step goal in spring, summer, autumn, and winter respectively (Table 2.2, p<0.001).

2.4.3 Periodic physical activity levels: accelerometry

The mean moderate-to-vigorous physical activity (MVPA) was 45.5±20.6 minutes per day (Table 2.2, n=142). There were no significance between season-differences (p=0.183). Overall, 26% of the children with CHD met physical activity guidelines and 33%, 11%, 20%, and 39% met guidelines in the spring, summer, autumn, and winter respectively.
Table 2.1 Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Fitbit</th>
<th>Accelerometer</th>
<th>Physical Activity Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>156 (100)</td>
<td>104 (66.7)</td>
<td>142 (91.0)</td>
<td>139 (89.1)</td>
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<tr>
<td>Female, n (%)</td>
<td>66 (42.3)</td>
<td>42 (40.4)</td>
<td>58 (40.8)</td>
<td>55 (40.0)</td>
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<td>Age, years (mean, SD)</td>
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<td>12.4 (2.3)</td>
<td>12.7 (2.4)</td>
<td>12.8 (2.4)</td>
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<tr>
<td>Height, cm (mean, SD)</td>
<td>152.2 (15.7)</td>
<td>151.2 (15.6)</td>
<td>152.2 (15.8)</td>
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</tr>
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<td>Weight, kg (mean, SD)</td>
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<td>46.1 (17.0)</td>
<td>47.0 (16.9)</td>
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<td>BMI, percentile (mean, SD)</td>
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<td>56.0 (34.0)</td>
<td>54.4 (33.5)</td>
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<td><strong>BMI Weight Category</strong></td>
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<td>Thinnest, n (%)</td>
<td>6 (3.9)</td>
<td>3 (2.9)</td>
<td>4 (2.8)</td>
<td>5 (3.6)</td>
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<tr>
<td>Normal, n (%)</td>
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<td>71 (68.9)</td>
<td>101 (71.6)</td>
<td>101 (73.2)</td>
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<td>Overweight, n (%)</td>
<td>21 (13.5)</td>
<td>16 (15.5)</td>
<td>19 (13.5)</td>
<td>18 (13.0)</td>
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<td>Obese, n (%)</td>
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<td>13 (12.6)</td>
<td>17 (12.1)</td>
<td>14 (10.1)</td>
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<td><strong>Cardiac Diagnosis</strong></td>
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<td></td>
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<td>COA, n (%)</td>
<td>47 (30.1)</td>
<td>31 (29.8)</td>
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<td>43 (30.9)</td>
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<td>TET, n (%)</td>
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<td>24 (23.1)</td>
<td>33 (23.2)</td>
<td>33 (23.7)</td>
</tr>
<tr>
<td>TGA, n (%)</td>
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<td>20 (19.2)</td>
<td>27 (19.0)</td>
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<td>FON, n (%)</td>
<td>42 (26.9)</td>
<td>29 (27.9)</td>
<td>40 (28.2)</td>
<td>35 (25.2)</td>
</tr>
</tbody>
</table>

Figure 2.1 Seasonal variation from 1-year of Fitbit step count.

The red dashed line is the target steps per day set for the participants’ Fitbit (12,000 steps). Data points in each month are shown side-by-side for visualization of clusters. Grey area is the standard error.
Table 2.2 Physical activity characteristics by seasons

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>Winter</th>
<th>P-value*</th>
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<tr>
<td>Commercial activity tracker</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meet 12,000 steps, %†</td>
<td></td>
<td>35.7</td>
<td>19.1</td>
<td>29.5</td>
<td>12.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Accelerometer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>142</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA, min/d (mean, SD)</td>
<td>45.5 (20.6)</td>
<td>48.9 (21.7)</td>
<td>39.3 (21.4)</td>
<td>43.5 (19.8)</td>
<td>48.7 (18.7)</td>
<td>0.183</td>
</tr>
<tr>
<td>Meet guidelines, n (%)§</td>
<td>37 (26.1)</td>
<td>14 (32.6)</td>
<td>3 (10.7)</td>
<td>8 (20.0)</td>
<td>12 (38.7)</td>
<td>0.053</td>
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<tr>
<td>Activity levels¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High, n (%)</td>
<td>37 (26.1)</td>
<td>14 (32.6)</td>
<td>3 (10.7)</td>
<td>8 (20.0)</td>
<td>12 (38.7)</td>
<td>0.045†</td>
</tr>
<tr>
<td>Medium, n (%)</td>
<td>71 (50.0)</td>
<td>18 (41.9)</td>
<td>14 (50.0)</td>
<td>26 (65.0)</td>
<td>13 (41.9)</td>
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</tr>
<tr>
<td>Low, n (%)</td>
<td>34 (23.9)</td>
<td>11 (25.6)</td>
<td>11 (39.3)</td>
<td>6 (15.0)</td>
<td>6 (19.4)</td>
<td></td>
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<tr>
<td>Physical activity questionnaire</td>
<td></td>
<td></td>
<td></td>
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<td>N</td>
<td>139</td>
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<tr>
<td>PAQ-score (mean, SD)‡</td>
<td>2.65 (0.71)</td>
<td>2.73 (0.76)</td>
<td>2.68 (0.71)</td>
<td>2.40 (0.65)</td>
<td>2.77 (0.66)</td>
<td>0.14</td>
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<td>Activity levels§</td>
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<tr>
<td>High, n (%)</td>
<td>61 (43.9)</td>
<td>22 (46.8)</td>
<td>15 (53.6)</td>
<td>10 (29.4)</td>
<td>14 (46.7)</td>
<td>0.239</td>
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<tr>
<td>Low, n (%)</td>
<td>78 (56.1)</td>
<td>25 (53.2)</td>
<td>13 (46.4)</td>
<td>24 (70.6)</td>
<td>16 (53.3)</td>
<td></td>
</tr>
</tbody>
</table>

MVPA – Moderate-to-Vigorous Physical Activity (min/day)

* p-value for main effect for season
† Proposed daily step target to determine if children are meeting physical activity guideline
§ Meeting physical activity guidelines is defined as mean daily minutes of moderate-to-vigorous physical activity per day of ≥60 minutes
¶ Accelerometry-derived activity level from our cohort: high (≥60 mins/day), medium (30 – 50 mins/day), low (<30 mins/day)
† No significant Bonferroni-adjusted post hoc comparisons present between groups (p<0.008)
‡ Scored on a scale from 1 (no/low activity) to 5 (very active)
§ PAQ-score-derived activity level from our cohort: high (≥2.7), low (<2.7)
2.4.4 Periodic physical activity levels: physical activity questionnaires

The mean PAQ-score was 2.7±0.7 (Table 2.2, n=139). There were no significant differences between season-differences in PAQ-score ($p=0.14$) or PAQ-score derived activity levels ($p=0.239$). Proportion of physical activities participation can be found in Table 2.3. The five most commonly reported activities are walking (81%), running (78%), tag (48%), basketball (40%), and bicycling (39%). Table 2.4 depicts the six most common activities by season in percentage of days. While walking and running were found to be the most common activities throughout the year, other structured and unstructured activities demonstrated seasonal variation. Unstructured activity (e.g., tag) decreased in frequency when children are on school holidays. Structured activities such as basketball and soccer were more prevalent during the school year.

2.4.5 Seasonal variation in step count stratified by physical activity levels using conventional measures

Plotting of participants’ longitudinal Fitbit data stratified by their accelerometry-derived MVPA activity level (high, medium, and low) produced distinct fitted lines for these three groups across seasons (Appendix Figure 1). The standard errors of the three best fit lines showed minimal overlap amongst the groups. The three groups followed similar physical activity patterns across seasons (i.e., physical activity levels were greatest in late spring). In agreement with our previous study, there was a significant association between accelerometry-derived MVPA minutes per day and Fitbit step counts ($r=0.73; p=0.000$; R-squared: 0.54). However, Fitbits overestimate step counts compared to accelerometers with a mean bias of 1694 steps (95% confidence interval: 590–2798 steps; $p=0.003$).

Plotting of participants’ longitudinal Fitbit data stratified by their PAQ-score derived activity level (high and low) produced distinct fitted lines for these two groups across seasons.
The standard errors of the two best fit lines showed minimal overlap amongst the groups. The two groups followed similar physical activity patterns across seasons (i.e. physical activity levels were greatest in late spring). Associations between PAQ-scores and Fitbit step counts were significant ($r=0.355; p=0.013; R$-squared: 0.13).

**Table 2.3 Activities frequency table**

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>Proportion of children who participated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td>80.6%</td>
</tr>
<tr>
<td>Running</td>
<td>77.7%</td>
</tr>
<tr>
<td>Tag</td>
<td>47.5%</td>
</tr>
<tr>
<td>Basketball</td>
<td>40.3%</td>
</tr>
<tr>
<td>Bicycling</td>
<td>38.8%</td>
</tr>
<tr>
<td>Soccer</td>
<td>36.0%</td>
</tr>
<tr>
<td>Dance</td>
<td>33.8%</td>
</tr>
<tr>
<td>Swimming</td>
<td>30.2%</td>
</tr>
<tr>
<td>Skipping</td>
<td>18.7%</td>
</tr>
<tr>
<td>Volleyball</td>
<td>17.3%</td>
</tr>
<tr>
<td>Badminton</td>
<td>15.1%</td>
</tr>
<tr>
<td>Baseball</td>
<td>12.9%</td>
</tr>
<tr>
<td>Street Hockey</td>
<td>12.9%</td>
</tr>
<tr>
<td>Aerobics</td>
<td>11.5%</td>
</tr>
<tr>
<td>Football</td>
<td>10.1%</td>
</tr>
<tr>
<td>Floor Hockey</td>
<td>9.4%</td>
</tr>
<tr>
<td>Ice Skating</td>
<td>7.9%</td>
</tr>
<tr>
<td>Skateboarding</td>
<td>7.2%</td>
</tr>
<tr>
<td>Ice Hockey</td>
<td>6.5%</td>
</tr>
<tr>
<td>In-line Skating</td>
<td>2.9%</td>
</tr>
<tr>
<td>Activity</td>
<td>% Days</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Running</td>
<td>47.4%</td>
</tr>
<tr>
<td>Walking</td>
<td>44.7%</td>
</tr>
<tr>
<td>Tag</td>
<td>25.7%</td>
</tr>
<tr>
<td>Bicycling</td>
<td>23.3%</td>
</tr>
<tr>
<td>Basketball</td>
<td>18.4%</td>
</tr>
<tr>
<td>Dance</td>
<td>15.0%</td>
</tr>
</tbody>
</table>
2.5 Discussion

Our study demonstrated that physical activity varies across season in children with CHD. A key strength of our study is the use of both longitudinal (commercial activity trackers) and periodic (accelerometers and questionnaires) measurement tools to quantify physical activity levels of children with CHD throughout the year.

2.5.1 Seasonal Variation

We demonstrated that commercial activity trackers, which are able to provide continuous measurement of physical activity level in the form of step count, are able to capture seasonal variation over a 1-year period. In contrast with other studies that made assumptions regarding an increase in activity level throughout the summer months due to warm weather and long daylight hours, our use of a continuous monitor clearly showed that activity levels dip in July and August. This is an important observation given that this drop corresponds directly with local school holidays. This fluctuation was likely due to the widely used conventional techniques of accelerometer and questionnaire where data are typically collected periodically during the school year.

Conventional methods, such as accelerometer, are widely used to objectively measure physical activity in population-based studies (NHANES, CHMS). In our study, seasonal variation of the accelerometry data demonstrated that only 11% of the children were able to meet guidelines during the summer period, which is notably lower than the proportion of children meeting guidelines during the other seasons (20-40%). This demonstrates that for researchers who use accelerometers to measure physical activity levels in children, there is a possibility of miscategorizing children with respect to physical activity guidelines. Seasonal influences on
physical activity may also impact the results seen in short-term physical activity intervention programs if pre- and post-intervention measurements are taken at different times of the year.

In our experience, the PAQ has limited capability in discerning activity levels in children with CHD because children tend to be clustered in a narrow range on the 5-point scale (IQR: 2.2–3.1). However, the PAQ provides useful insight on the types of activities children participate in and how those vary across seasons. We demonstrated that certain activities are more prevalent during different times of the year. For example, cycling is more common in the summer, whereas, basketball is more common in the winter. Therefore, it is important for healthcare providers to recognize this since the promotion of season-specific activities at the correct time of the year may be beneficial in increasing activity levels.

Our data suggest that physical activity participation in children with CHD is impacted by the school-year. There are two mechanisms by which school is known to facilitate physical activity, and these likely impact children with CHD as they do typical children. When school is in session, there is significant school-associated physical activity (i.e. active transportation, play before and after school and during recess and lunch on the school grounds, and physical education) and participation in sport programs orientated around the school calendar (i.e. school or community-based sports teams or clubs). Our data also imply that weather acts as a barrier for physical activity participation. Children’s activity levels are blunted during the winter months due to colder temperature and shorter daylight hours despite being in school and getting the physical activity benefits associated with the school year.

Conventional measurement tools and commercial activity trackers provide different and complementary insight into physical activity patterns. With our combined dataset, we demonstrated that seasonal patterns hold for all children regardless of their baseline activity
levels, with activity peaking in late spring and dropping during summer holidays and the winter months. This underscores the importance of repeated physical activity promotion for all children with CHD, especially during the months when children are known to be less active (summer and winter). Recognizing that these patterns are pervasive amongst children may help clinicians and exercise physiologists counsel children with season-specific advice. We also demonstrated that commercial activity trackers can portray long-term activity patterns and may be the more appropriate tool to use when studying seasonal variation or conducting long-term monitoring of physical activity.

2.5.2 Clinical Implications

We have demonstrated that levels of physical activity vary by season in children with CHD. Therefore, it is important for physicians to discuss these fluctuations with families while promoting physical activity participation. Our results suggest that the promotion of physical activity types should be targeted based on the time of the year. Furthermore, discussing the natural fluctuations in physical activity levels may help families identify opportunities to increase physical activity levels at observed nadirs. Summer holidays are a particularly good opportunity for family-based activity promotion.

Simple tools like the PAQ can easily be administered in a clinical setting and be used to identify activities with high level of participation throughout the year. Such information can be used to help identify targets for promotion and facilitation of physical activity by their primary caretakers (i.e. during the summer time, can you try cycling for 10 minutes every day?).

Given that all children demonstrate seasonal variation regardless of baseline activity levels, the incorporation of information from commercial activity tracker, accelerometer, and PAQ provides a comprehensive picture to optimise season-specific physical activity guidance.
2.5.3 Research Implications

Recognizing and understanding the effect of seasonal variation is important for researchers who use periodic measurement tools (accelerometer and questionnaires). Our results demonstrate that caution is needed when comparing cross-sectional results using these conventional physical activity measurement tools. Our study shows the feasibility of monitoring physical activity in children over the course of an entire year. These data provide depth compared to cross-sectional measurements, which clearly have important limitations given the seasonal variation we have shown. We found that 23% of children with CHD are not meeting physical activity recommendations and thus physical activity interventional studies are needed. Commercial activity trackers can play an important role in interventional studies, as compliance with the intervention can be measured continuously before, during, and after the intervention as opposed to the usual approach of before and after measurements with conventional tools.

2.5.4 Strengths and Limitations

To our knowledge, this is the first study to use commercial activity trackers in children with CHD to assess activity patterns over a 1-year period. There are important limitations to physical activity trackers which must be noted. In agreement with our previous Fitbit validation study in children with CHD, the Fitbit device overestimated step counts in the current study compared to the accelerometer.

A limitation of accelerometers is low adherence (~65%); however, in our cohort, ~90% of the children adhered to wear-time protocol and provided sufficient data compared to other studies. In addition, the Fitbit was well-received with good initial adherence to protocols. Over the 1-year period, data capture rate dropped to ~60% due to loss of interest, technical difficulties, or skin irritations (rashes, eczema). Nevertheless, the adherence for 1-year of
continuous data capture remains very good and was positively impacted by reminders from the study team to the children’s guardians. For the PAQ, it is important to note that it is subjected to recall bias and children tend to over-estimate activity levels. However, in our cohort, PAQ-scores were significantly correlated with Fitbit and accelerometry data.

Although season-differences were not significant with accelerometry-derived MVPA or PAQ-score, the seasonal effects may have been masked by the small number of participants in each season and the wide distribution of physical activity levels amongst children. An additional limitation of the PAQ – one of the few suitable questionnaire tools available for use in children and youths – is that it does not provide valid estimates of physical activity outside of the school year and, therefore, would be of limited accuracy in detecting these seasonal changes. Commercial activity trackers overcome these limitations and are well liked by children resulting in high rates of wear time compliance.

2.6 Conclusions

Recognizing the effect of seasonality in physical activity in children with CHD may help healthcare providers administer effective physical activity counselling at each annual routine care encounter. Our data demonstrated that commercial activity trackers are a powerful tool to capture, assess, and understand variations in activity levels over long periods of time. Researchers should consider the significant confounding role of seasonality on physical activity behaviour in the design, implementation, and evaluation of interventions.
Chapter 3: Longitudinal association of aortic stiffness and physical activity in children with congenital heart disease

3.1 Background

Most children with moderate-to-complex forms of congenital heart disease (CHD) have a life expectancy that extends well into adulthood. However, it is well established that the CHD populations are at an increased risk for cardiovascular events, such as stroke, arrhythmia, and death, compared to the general population. Therefore, optimizing their long-term health outcomes and preventing secondary health complications are healthcare priorities for this high-risk population. One method of assessing the cardiovascular health of patients with CHD is through measuring the elasticity of the aorta. Aortic stiffness is a marker of vascular dysfunction and a strong predictor of early cardiovascular events and death. It has been demonstrated that children diagnosed with moderate-to-complex forms of CHD have significantly elevated aortic stiffness compared to their age-matched healthy controls. Physical activity, defined as “any bodily movement produced by skeletal muscle that results in energy expenditure”, is a modifiable cardiovascular risk factor that tracks from childhood to adulthood. Cross-sectional studies have demonstrated the beneficial associations between physical activity and vascular function in children with CHD. To date, the relationship between longitudinal changes in physical activity and aortic stiffness has not been evaluated. In our prospective cohort study, we aim to (1) examine the longitudinal pattern in aortic stiffness and physical activity, and (2) to investigate the association between aortic stiffness and physical activity over time in children with CHD. Such information will help inform clinically relevant physical activity guidelines for children with CHD and is much needed to optimize evaluation and clinical management of this high-risk population.
3.2 Methods

3.2.1. Sample

Data were collected as part of a 2-year prospective cohort study of children and adolescents aged 9 – 16 years old diagnosed with Coarctation of the Aorta (COA), Tetralogy of Fallot (TET), Transposition of the Great Arteries (TGA), or Fontan circulation (FON) (Figure 3.1). Participants were invited to participate in the study during their clinical visit at Children’s Heart Centre, BC Children’s Hospital in Vancouver, Canada, or at pediatric cardiology partnership clinics across British Columbia and the Yukon, Canada. We serve as the only pediatric tertiary hospital for the province and almost all patients with CHD in British Columbia are followed in one of these two settings. Participants were excluded if they had health conditions that would prevent them from completing the study measures or participating in physical activity. Rolling recruitment started in April 2017 and data up until December 2019 were included in the analysis, thus the number of repeat assessments will vary from 1 to 3 between patients (Figure 3.1b). The data in this chapter represent preliminary analyses and that the study is ongoing. The study was approved by UBC Children’s & Women’s Research Ethics Board (H17-01233), and we obtained parent/guardian consent and participant assent before study commencement.

3.2.2. Participant characteristics

Participant sex, age, and cardiac diagnosis were obtained from medical charts. Trained clinical staff measured height (0.1cm), body weight (0.1kg), and resting blood pressure (mmHg). Body mass index (BMI; kg/m$^2$) was calculated and expressed as age- and sex-specific percentiles based on World Health Organization International growth charts.$^{83}$ BMI was categorized based on World Health Organization cut-offs.
3.2.3. **Aortic stiffness: aortic pulse wave velocity**

Aortic pulse wave velocity (PWV) was obtained using 2-dimensional echocardiography and Doppler ultrasound during routine clinical care. Ascending and descending aortic Doppler tracings were obtained at the proximal and distal aortic arch respectively within 10 seconds of each other.\(^{42}\) The length of the aortic arch was measured between these two points, as previously described.\(^{42}\) EchoPAC v201 (GE Healthcare) software was used to measure the time intervals between the ECG wave to the onset of the ascending (T1) and the descending (T2) Doppler envelopes. The transit time was calculated as the difference between the descending and ascending time (T2-T1). Aortic pulse wave velocity (cm/s) was calculated by dividing the distance of the arch by the transit time. All measurements were averaged over a minimum of 6 cardiac cycles.

3.2.4. **Physical activity: accelerometry**

We fitted participants with an ActiGraph accelerometer (GT3X+, GT9X; ActiGraph LLC, Pensacola, FL) to objectively measure levels of physical activity under free-living conditions.
The device was worn over the right hip for 7 consecutive days during waking hours and only to be removed for water-based activities. We used ActiLife v.6.13.2 (ActiGraph LLC, Pensacola, FL) for accelerometer initialization (sample set at 30Hz) and file download and analysis. We generated 15s epoch .adg files from the raw .gt3x files and used the wear time function in ActiLife to identify valid accelerometry files. We considered a day to be valid if the device was worn for ≥600 mins/day. We previously demonstrated that a minimum of 3 valid days is sufficient to estimate mean physical activity values in children and adolescents with CHD. \(^9\) We used Evenson cut-points \(^8\) to estimate mean daily minutes spent in moderate-to-vigorous physical activity (MVPA) intensity for all valid accelerometry files. We defined meeting physical activity guidelines as ≥60 minutes of MVPA per day, on average.

### 3.2.5. Statistical analysis

Descriptive statistics (frequencies [%], mean ± SD, or median [IQR]) were calculated for applicable variables. Distribution of continuous variables was assessed visually with Q-Q plot. Linear mixed-effect models were used to assess the pattern of longitudinal change in pulse wave velocity and physical activity over 3 time-points (24 ± 6 months). We also incorporated PWV as the response variable with current and lagged physical activity as the primary explanatory variable to explore the association between aortic stiffness and physical activity over time. We incorporated age at baseline, sex, body composition, and systolic blood pressure (SBP) to explore potential mediating and/or moderating effects. The linear mixed-effect model is the ideal model to analyze longitudinal changes in data from an observational study since it can easily accommodate for unequally spaced observations or missing data across time within individuals, assess the association of time-varying explanatory variables, account for baseline values, and model rate of change over time. Sex differences were tested by running the model with sex, sex
and age at baseline, and sex and time interaction terms. Quality of models was tested by the correlation between predicted and observed outcome variables. All analyses were performed in R (version 3.6.0) using R studio (version 1.1.442) and significance was set a p < 0.05.

3.3 Results

3.3.1. Sample

One hundred and ninety-three children (mean age 12.4 ± 2.5 years old; 41% females) consented to the study. Participant characteristics at baseline are shown in Table 3.1. Males and females had similar age distribution, BMI weight category, systolic and diastolic blood pressure, and cardiac diagnosis. Compared to females, males were taller, heavier, and had higher BMI percentile. Males also had higher moderate-to-vigorous physical activity (MVPA) minutes per day and lower pulse wave velocity (PWV). There were no sex differences in the proportion of males and females who met the physical activity guidelines. Participant characteristics at each timepoint are show in Table 3.2.
Table 3.1 Baseline sample characteristics of study cohort by sex

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt; (main effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>193</td>
<td>114 (59.1%)</td>
<td>79 (40.9%)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), yrs</td>
<td>12.4 (2.5)</td>
<td>12.4 (2.5)</td>
<td>12.5 (2.4)</td>
<td>0.724</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>151.1 (16.2)</td>
<td>153.4 (17.1)</td>
<td>147.8 (14.3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>45.7 (16.9)</td>
<td>47.9 (17.5)</td>
<td>42.4 (15.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI, mean (SD), %ile&lt;sup&gt;g&lt;/sup&gt;</td>
<td>53.7 (33.6)</td>
<td>58.1 (33.6)</td>
<td>47.4 (32.9)</td>
<td>0.029</td>
</tr>
<tr>
<td>BMI Weight Category&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinness, n (%)</td>
<td>8 (4.1%)</td>
<td>3 (2.6%)</td>
<td>5 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Normal weight, n (%)</td>
<td>134 (69.4%)</td>
<td>75 (65.8%)</td>
<td>59 (74.7%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Overweight, n (%)</td>
<td>30 (15.5%)</td>
<td>19 (16.7%)</td>
<td>11 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Obese, n (%)</td>
<td>21 (10.9%)</td>
<td>17 (14.9%)</td>
<td>4 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>SBP, median (IQR)</td>
<td>107 (100–114)</td>
<td>106 (98–115)</td>
<td>107.5 (100–112)</td>
<td>0.881</td>
</tr>
<tr>
<td>DBP, median (IQR)</td>
<td>63 (58–70)</td>
<td>64 (60–70)</td>
<td>63 (58–71)</td>
<td>0.414</td>
</tr>
<tr>
<td>Cardiac Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COA, n (%)</td>
<td>58 (30.0%)</td>
<td>34 (29.8%)</td>
<td>24 (30.4%)</td>
<td></td>
</tr>
<tr>
<td>TET, n (%)</td>
<td>49 (25.4%)</td>
<td>30 (26.3%)</td>
<td>19 (24.1%)</td>
<td>0.905</td>
</tr>
<tr>
<td>TGA, n (%)</td>
<td>37 (19.2%)</td>
<td>23 (20.2%)</td>
<td>14 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>FON, n (%)</td>
<td>49 (25.4%)</td>
<td>27 (23.7%)</td>
<td>22 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA, mean (SD), min/d</td>
<td>46.5 (21.5)</td>
<td>49.3 (20.5)</td>
<td>42.5 (22.4)</td>
<td>0.0491</td>
</tr>
<tr>
<td>meet guidelines No. (%)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>44 (27.8%)</td>
<td>27 (23.7%)</td>
<td>17 (21.5%)</td>
<td>0.828</td>
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<tr>
<td>PWV, mean (SD), cm/s</td>
<td>476.1 (147.2)</td>
<td>455.1 (138.8)</td>
<td>506.5 (154.6)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

BMI – Body Mass Index (kg/m²); %ile – Percentile; SBP/DBP – Systolic-/Diastolic Blood Pressure (mmHg); COA – Coarctation of the Aorta; TET – Tetralogy of Fallot; TGA – Transposition of the Great Arteries; FON – Fontan circulation; MVPA – Moderate-to-Vigorous Physical Activity (min/day); PWV – Pulse Wave Velocity.

<sup>b</sup>p-value for main effect for sex
<sup>g</sup>BMIm (kg/m²) percentiles calculated based on age-sex-specific World Health Organization 2007 reference charts
<sup>h</sup>BMI weight category based on World Health Organization cut-offs
<sup>g</sup>Meeting physical activity guidelines is defined as mean daily minutes of moderate-to-vigorous physical activity per day of ≥60 minutes
Table 3.2 Baseline sample characteristics of study cohort by timepoint

<table>
<thead>
<tr>
<th></th>
<th>Baseline (T0)</th>
<th>Time-point 1 (12 ± 6 months)</th>
<th>Time-point 2 (24 ± 6 months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>193</td>
<td>89</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Male/Female, N (%)</td>
<td>114 (59.1%)/48 (53.9%)/22 (57.9%)</td>
<td>79 (40.9%)/41 (46.1%)/16 (42.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), yrs</td>
<td>12.4 (2.4)</td>
<td>13.3 (2.2)</td>
<td>14.3 (2.0)</td>
<td>0.000</td>
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<tr>
<td>Height, mean (SD), cm</td>
<td>151.1 (16.2)</td>
<td>155.9 (14.8)</td>
<td>160.4 (12.7)</td>
<td>0.001</td>
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<td>Weight, mean (SD), kg</td>
<td>45.7 (16.9)</td>
<td>50.7 (17.5)</td>
<td>53.9 (18.8)</td>
<td>0.006</td>
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<td>BMI, mean (SD), %ile</td>
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<td>54.0 (35.6)</td>
<td>47.7 (33.2)</td>
<td>0.603</td>
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<td>BMI Weight Category</td>
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<td>8 (4.1%)</td>
<td>3 (3.4%)</td>
<td>2 (5.3%)</td>
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<tr>
<td>Normal weight, n (%)</td>
<td>134 (69.4%)</td>
<td>60 (67.4%)</td>
<td>29 (76.2%)</td>
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<tr>
<td>Overweight, n (%)</td>
<td>30 (15.5%)</td>
<td>17 (19.1%)</td>
<td>5 (13.2%)</td>
<td>0.882</td>
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<td>Obese, n (%)</td>
<td>21 (10.9%)</td>
<td>9 (10.1%)</td>
<td>2 (5.3%)</td>
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<td>SBP, median (IQR)</td>
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<td>110 (105–116)</td>
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<td>64 (58–70)</td>
<td>64 (58–70)</td>
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<td>Cardiac Diagnosis</td>
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<tr>
<td>COA, n (%)</td>
<td>58 (30.0%)</td>
<td>28 (31.5%)</td>
<td>10 (26.3%)</td>
<td></td>
</tr>
<tr>
<td>TET, n (%)</td>
<td>49 (25.4%)</td>
<td>23 (25.8%)</td>
<td>11 (28.9%)</td>
<td>0.569</td>
</tr>
<tr>
<td>TGA, n (%)</td>
<td>37 (19.2%)</td>
<td>13 (14.6%)</td>
<td>3 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>FON, n (%)</td>
<td>49 (25.4%)</td>
<td>25 (28.1%)</td>
<td>14 (36.9%)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA, mean (SD), min/d</td>
<td>46.5 (21.5)</td>
<td>40.2 (19.3)</td>
<td>41.6 (20.5)</td>
<td>0.119</td>
</tr>
<tr>
<td>meet guidelines No. (%)*</td>
<td>44 (27.8%)</td>
<td>11 (12.4%)</td>
<td>5 (13.2%)</td>
<td>0.073</td>
</tr>
<tr>
<td>PWV, mean (SD), cm/s</td>
<td>476.1 (147.2)</td>
<td>473.0 (123.0)</td>
<td>524.4 (117.8)</td>
<td>0.138</td>
</tr>
</tbody>
</table>

BMI – Body Mass Index (kg/m2), %ile – Percentile; SBP/DBP – Systolic/Diastolic Blood Pressure (mmHg); COA – Coarctation of the Aorta, TET – Tetralogy of Fallot, TGA – Transposition of the Great Arteries, FON – Fontan circulation; MVPA – Moderate-to-Vigorous Physical Activity (min/day); PWV – Pulse Wave Velocity.

BMI (kg/m²) percentiles calculated based on age-sex-specific World Health Organization 2007 reference charts.

BMI weight category based on World Health Organization cut-offs

Meeting physical activity guidelines is defined as mean daily minutes of moderate-to-vigorous physical activity per day of ≥60 minutes.
3.3.2. Pattern of longitudinal changes in aortic stiffness

The unadjusted monthly impact of aortic PWV over time demonstrated a significant increase ($\beta=1.78; p=0.005$). In the adjusted model (Table 3.3), higher SBP was associated with a higher rate of PWV increase ($\beta=1.57; p=0.028$). We found that baseline PWV was higher in females than in males (503.4 cm/s vs. 452.7 cm/s; $p=0.028$). However, there was no significant time×sex interaction ($p=0.475$). To illustrate changes in aortic stiffness over time, PWV was plotted against time since baseline measurement for the cohort, males, and females in Figure 3.2.

![Figure 3.2 Longitudinal changes in aortic stiffness in children with CHD](image)

Measured by echocardiography in children with CHD (gray solid line) over a 2-year period. Male (blue dashed line) and female (orange dashed line).
3.3.3. **Pattern of longitudinal changes in physical activity**

The unadjusted monthly impact of levels of physical activity demonstrated a significant decrease over time (β= –0.3; \( p=0.024 \)). There was no significant difference in levels of physical activity for age at baseline (β= –1.2; \( p=0.079 \)) and body mass index (β= –5.0; \( p=0.279 \)) in this population (Table 3.4). We found that baseline levels of physical activity were higher in males (49.1 mins/d vs. 41.7 mins/d; \( p=0.026 \)). However, there was no significant time×sex interaction (\( p=0.696 \)). To illustrate changes in levels of physical activity over time, MVPA was plotted against month since baseline measurement for the cohort, males, and females in Figure 3.3.

![Graph showing longitudinal changes in physical activity levels in children with CHD](image)

**Figure 3.3 Longitudinal changes in physical activity levels in children with CHD**

Daily moderate-to-vigorous physical activity (MVPA) as measured by accelerometer in children with CHD (gray solid line) over a 2-year period. Male (blue dashed line) and female (orange dashed line).
3.3.4. Longitudinal changes in aortic stiffness in relation to physical activity

The impact of physical activity on the change in aortic PWV over time was not significant for the cohort (β= −0.58; p=0.212) (Table 3.5). We fitted separate models for males and females (Table 3.3) and found that longitudinal changes in aortic PWV were not significant in males (β= −1.07; p=0.084) or females (β= 0.47; p=0.518). Adjusting for age at baseline, SBP, and body mass index, there was no association between longitudinal changes in PWV in relation to physical activity (β= −0.45; p=0.361) and only SBP on aortic PWV was significant (β=1.99; p=0.029).
### Table 3.5 Linear Mixed-Effects Model Examining the Longitudinal Changes in Pulse Wave Velocity in Relation to Physical Activity

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% C.I.)</td>
<td>p-value</td>
<td>β (95% C.I.)</td>
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<tr>
<td>Time (1-month)</td>
<td>1.32 (-0.37 – 2.98)</td>
<td>0.125</td>
<td>1.18 (-0.95 – 3.31)</td>
</tr>
<tr>
<td>MVPA (mins/day)</td>
<td>-0.58 (-1.49 – 0.32)</td>
<td>0.212</td>
<td>-1.07 (-2.26 – 0.13)</td>
</tr>
</tbody>
</table>

MVPA – moderate-to-vigorous physical activity

### 3.4 Discussion

This is the first longitudinal study of aortic PWV and physical activity in the pediatric CHD population. Our study observed a significant increase in aortic stiffness and a significant decrease in levels of physical activity in a cohort of children with moderate-to-complex CHD over 2 years. These observed phenomena are particularly worrisome in this high-risk population since elevated aortic stiffness is an established surrogate marker for cardiovascular events later in life. Furthermore, the decline in levels of physical activity means that these children are not fully reaping the beneficial effect of physical activity on the cardiovascular system. Lastly, as the study is still ongoing, it is still underpowered to detect an association between levels of PA and aortic PWV.

#### 3.4.1. Aortic stiffness increases over time in children with CHD

Children with moderate-to-severe CHD are known to have elevated PWV compared to healthy age-matched controls. Our results suggested that annually, PWV in this cohort is increasing by 21.4 centimeters per second. We observed a significant increase in aortic PWV in children with moderate-to-complex CHD over a 2-years period while the Baltimore population
study in older men and women reported rates of PWV increase per decade.\textsuperscript{30} This means that children with moderate-to-severe CHD have accelerated aortic stiffening thus are at an elevated risk for early cardiovascular events.

We also observed that elevated SBP is associated with higher rates of PWV increase in children with moderate-to-severe CHD. Arterial hypertension is a major determinant of arteriosclerosis and aortic stiffening and it has been shown that patients with isolated systolic hypertension have increased aortic stiffness compared to age-matched controls\textsuperscript{36}. Hacker et al. demonstrated that children with CHD have significantly elevated SBP compared to healthy peers,\textsuperscript{48} thus controlling SBP may be a potential therapeutic target in lowering PWV.

3.4.2. Moderate-to-vigorous physical activity decreases over time

Our study demonstrated that our cohort had comparable levels of MVPA compared to the general Canadian population (47 mins/day vs. 49.7 mins/day) and both are below the recommended guidelines of 60 minutes per day. The lower levels of PA observed was not due to exercise restriction by their cardiologist since only a small subset of patients are instructed to avoid isometric exercise\textsuperscript{14}. We also observed age-sex patterns in physical activity in our patient cohort, as did others.\textsuperscript{9} Physical activity correlated negatively with age and males are more physically active at baseline.

Our results suggested the annually, children with CHD decrease their daily MVPA participation by 3.6 minutes. Over time, this decline leads active children with CHD to become less physically active and not meet the recommended guidelines. Furthermore, for children who are already not meeting the guidelines, this decline may be even more detrimental to their long-term health outcomes. This finding highlights the importance of promoting physical activity at a young age since physical activity is a behaviour that tracks from childhood to adulthood.\textsuperscript{97} If the
decline in levels of physical activity in children as they age is an inevitable reality, having a higher baseline measures in physical activity (meeting well above the PA guidelines) may attenuate the decline and mitigate the consequence. Thus, pediatric cardiologists should consider incorporating physical activity histories and plans into routine patient and family consultations.

3.4.3. Association between PWV and PA over time may also explain sex differences in PWV

To date, the inverse association between aortic stiffness and physical activity in children with CHD has only been studied in cross-sectional studies.\textsuperscript{14,95} Although our longitudinal data did not reach statistical significance due to the lower number of participants by the end of time point 2, there seems to be a trend where children with higher levels of PA may be associated with better vascular outcomes over time. This is an important clinical finding since physical activity, a modifiable marker of cardiovascular health, should be promoted for children with CHD. We also observed that this association is mediated in part by systolic blood pressure in our cohort of children with moderate-to-complex CHD, which is different from what is observed in children with obesity where the association is mediated in part by adiposity.\textsuperscript{98}

A novel finding of this study is that we observed sex differences in baseline PWV. Aortic PWV was higher in females at baseline measurements compared to males (503.4 cm/s vs. 452.7 cm/s; $p=0.020$) while other studies reported no sex differences in carotid-femoral PWV in healthy children aged between 6 – 20 years old.\textsuperscript{99,100} We speculated that the lower baseline PWV measurements in males were offset by levels of physical activity. In our cohort, boys were more physically active at baseline. Over time, the rate of increase in aortic stiffness does not differ between males or females.
3.4.4. Clinical significance

We demonstrated that children with CHD have accelerated PWV increase thus putting them a higher risk for cardiovascular events later in life. The assessment of aortic stiffness as part of routine clinical care for children with CHD may assist pediatric cardiologists to better manage their condition when they appear asymptomatic. Furthermore, aortic PWV can be tracked over time and knowing the pattern of PWV trajectory may be used to assess the efficacy of interventions aimed to reduce or slow down arterial stiffening. We demonstrated that the decline in physical activity over time in this patient cohort highlights the importance of assessing and promoting physical activity participation during patient encounters. This is particularly important since cross-sectional study suggested that higher levels of physical activity is associated with decreased aortic stiffening.\textsuperscript{14}

3.4.5. Strengths and limitations

Our study has a recruitment rate of 85% and an attrition rate of 8% demonstrating that we have a provincially representative cohort of children and adolescents with moderate-to-complex CHD. Our study has some limitations that should be considered while interpreting the results. The heterogeneous nature of PWV and physical activity measurements at baseline together with the relatively smaller sample size at follow-up time-points might have blunted the relationship observed over time in this cohort. However, data are still currently being collected and patients and families continued to express interest and support for the study. As more study participants return for their follow-up visit, the increased observations will help detect the dose-dependent effect physical activity necessary to optimize health outcomes. Lastly, interventional studies are needed to better assess the relationship between body mass index on levels of physical activity and systolic blood pressure on vascular function.
3.5 Conclusion

Age and SBP are the main longitudinal determinants of PWV and only age is the main longitudinal determinants of physical activity in children with CHD. Our study emphasized the importance of measuring aortic stiffness during clinical evaluation of vascular function and incorporating PA promotion and counseling in this high-risk population. As of currently, the study is underpowered to detect a significant association between levels of PA and aortic PWV over time.
Chapter 4: Conclusion

4.1 Summary of key findings

We used longitudinal (commercial activity trackers) and periodic (accelerometers and questionnaire) measurement tools to quantify levels of physical activity in children with CHD throughout the year and demonstrated that levels of physical activity vary across seasons.

In our longitudinal study, we observed an increase in aortic PWV and a decrease in physical activity over the 2 years. The association between cardiovascular risk and physical activity in children with CHD seems to be trending towards an inverse relationship. This means that children with higher levels of PA may have better indices of aortic health over time.

4.2 Seasonal variation

While seasonal variation in physical activity has been reported in the healthy pediatric population using periodic measurement tools like questionnaires and accelerometers, this heterogeneous behaviour has not been tracked continuously with commercial activity trackers. We demonstrated that commercial activity trackers are able to capture seasonal variation while minimizing patient burden since their data can be accessed remotely. Interestingly in contrast with other studies, we observed that activity levels dipped in July and August when the temperature is at its highest and the daylight is at its longest. This happens to correspond to local school holidays and studies using periodic measurement tools are typically collected during the school year. Therefore the peak in June is connected to the relatively high level in September, creating the illusion that activity levels remained high during the summer holidays.
Although season-differences were masked by the small number of participants in each season and the wide distribution of PA levels amongst the children with periodic measurement tools (accelerometers and questionnaires), we extracted other useful information from such tools. Accelerometer demonstrated that a notably lower proportion of children met PA guidelines during the summer (11%) compared to the other seasons (20–40%). This demonstrated the possibility of children being miscategorized with respect to PA guidelines depending on the season of measurement. Furthermore, the results seen in short-term PA intervention programs may be influenced by seasonal variations on physical activity if pre- and post-intervention measurements are taken at different times of the year. On the other hand, the physical activity questionnaire (PAQ) demonstrated that certain activities are more prevalent during different times of the year. From this information, healthcare providers should promote season-specific activities (e.g. cycling in the summer and indoor sports in the winter) when promoting PA participation.

We demonstrated that activity levels, types, and contexts can be captured with the use of commercial activity trackers, accelerometers, and physical activity questionnaires and showed variation throughout the year. This information may be helpful in informing PA guidelines and designing effective PA promotion strategies in children with CHD. We also demonstrated the feasibility of using commercial activity trackers to monitor physical activity levels.

4.3 Aortic stiffness as a marker of cardiovascular risk in clinical care

The aorta has dual functions: first, it acts as a conduit to transport blood throughout the body, and secondly, it acts as a cushion to accommodate ventricular ejection. The aorta can accommodate approximately 50% of blood volume ejected from the left ventricle. This elastic
property of the aorta is important for optimal tissue perfusion and cardiovascular performance. Pulse wave velocity (PVW) has the most extensive pathophysiological and clinical background and is the most validated marker to assess arterial stiffness. We have devised a non-invasive, safe, and inexpensive method using echocardiogram and Doppler equipment to measure aortic PWV during routine clinical visit. Aortic PWV is an independent predictor of future cardiovascular events and all-cause mortality in the general population and it has been shown that in high-risk populations, high aortic stiffness conferred a higher risk than those in low-risk populations. These high-risk populations include children with moderate-to-severe CHD, where they demonstrated elevated aortic stiffness compared to healthy age-matched controls. We have also demonstrated in our study that there is an increase in aortic PWV over a 2-years period in children with CHD. This phenomenon of accelerated aortic stiffness at an early age predisposes children with CHD to premature cardiac damage and vascular remodelling. Our study provided support that measurements of PWV can be easily incorporated as part of routine clinical care to aid in risk stratification. It may help to evaluate the efficacy of therapy over time, optimize the clinical management of children with CHD, and also predict future clinical cardiovascular events. Furthermore, aortic PWV is a more powerful marker compared to traditional variables such as blood pressure, lipid levels, or glucose levels since it reflects a long-term biophysical function of the arterial wall. Interventions that reduce long-term cardiovascular risk are needed for this vulnerable population. Longitudinal measurement of aortic PWV in children with CHD may serve as a good surrogate outcome measure given the changes we have found.
4.4 Physical activity declines over time in children with CHD

Physical activity promotes the healthy development of physical, emotional, and psychosocial health in all children and it is the essential determinant of optimal vascular health.\(^{58}\) PA participation has been shown to be associated with 35% reduction in cardiovascular disease mortality and 33% reduction in all-cause mortality in comparison with a sedentary lifestyle after adjusting for risk factors.\(^{54}\) However, the majority of Canadian children and youths are not meeting the PA guidelines.\(^{89}\) This includes our pediatric CHD cohort where the average daily MVPA measured by accelerometry was 45.5 minutes per day and only 26.1% of the children met the PA guidelines. This is comparable to all Canadian youth where the average daily MVPA was 49.7 minutes per day and 23.1% of youth met the PA guidelines.\(^{73}\) PA recommendations by experts note that the CHD population should comply with public health recommendations of PA guidelines and reduce sedentary time to reap the health benefits accrued from a physically active lifestyle.\(^{66}\) Not only are children with CHD not meeting the PA guidelines, but their levels of PA decline with age independent of PA restrictions imposed by their cardiologists. As there is increasing evidence that PA behaviour is established during childhood,\(^{104}\) this highlights the importance of PA counselling and promotion during routine clinical visits. Furthermore, physicians should also consider the age of the patient when trying to promote PA participation to avoid setting an unrealistic goal.

4.5 Aortic stiffness is related to physical activity

Our study has expanded on the inverse association between aortic stiffness and physical activity in children with CHD from cross-sectional studies.\(^{14,95}\) Our 2-year study seemed to be trending towards a similar association where high levels of PA may mitigate the increase in
aortic stiffness over time. This association is more prominent in our more active male cohort where they demonstrated lower baseline PWV measurement. It has been demonstrated in a longitudinal population study that healthy children and young adults who are physically active are associated with better vascular health independent of other cardiometabolic risk factors. Together with the effect seen in the general population, our result in the pediatric CHD population also provided support for the potentially independent benefits of PA on the vascular health where the elevated aortic PWV is attenuated in those who participated in higher levels of PA. Physical activity is an important modifiable risk factor and we should continue to monitor its effectiveness and dose-response on aortic PWV of children with CHD longitudinally.

4.6 Recommendations for care providers

The association between seasonal variation and children’s physical activity differs between locations. Studies have shown that children’s levels of PA demonstrated seasonal variation in countries like the UK and Australia, while other countries such as the US and Switzerland, children’s levels of PA did not vary significantly across seasons. Furthermore, seasonal variation in PA may also be region-specific within a large country like Canada. For example, the winter in the Prairie Provinces of Canada are characterized by low temperature with severe wind chills, whereas the winter in coastal British Columbia is mild and rainy. Therefore, it is important to note that our result may not be representative of Canada since our pediatric CHD population is recruited from British Columbia and Yukon. Studies also observed an age effect on seasonal variation in levels of PA where seasons had more influence on younger children than adolescents. However, we did not see an age difference on seasonal variation in our 9–16 years old cohort. Season variation is a phenomenon that has been observed in different countries.
with the use of accelerometers\textsuperscript{105} and our study demonstrated the feasibility of using commercial activity trackers to capture variation in levels of PA continuously throughout the study period. Commercial activity tracker can also be used to monitor PA levels in a large geographically dispersed sample. Additional studies are needed to examine other possible confounders, such as sex, age, ethnic group, and geographic location, to seasonal variation in PA participation. This would help with physical activity counselling and the development of public health policy and physical activity programs to increase PA year-round for children with CHD.

Although physical activity participation in children and adolescents is associated with a plethora of health benefits such as better physical (cardiovascular, musculoskeletal), mental (anxiety, depression), and emotional (social connection, self-esteem) health,\textsuperscript{59} \textsuperscript{106} \textsuperscript{107} the levels of PA decline in children with CHD over time. School-aged children and youth with low levels of PA are typically associated with an increased risk of cardiovascular events and metabolic diseases.\textsuperscript{59} Children with CHD exhibited elevated aortic PWV\textsuperscript{14} \textsuperscript{95} compared to healthy peers. Their aortic PWV also increases over time which puts them at an increased risk of cardiovascular events later in life. The American Heart Association has also recognized the importance of physical activity to the health and quality of life of all CHD population.\textsuperscript{66} As the prevalence of the pediatric CHD population shifts towards adulthood, their clinicians need to be aware of the detrimental effects of inactivity during childhood. Physical activity counselling should be implemented as part of clinical consultations to encourage all children with CHD to increase their levels of PA as appropriate for the patient’s clinical status. This is of importance because increasing their levels of PA, a modifiable risk factor of cardiovascular risk, may help avoid associated health risks. Although BMI was not associated with aortic PWV or levels of PA in our cohort, anthropometrical data of the patients should be considered since obesity is a well-known
predictor for the development of early atherosclerosis.\textsuperscript{108} This missing association in our cohort may be due to the small weight range where most of the patients fall under normal-weight.

Aortic PWV has been extensively studied in the general population\textsuperscript{20} and validated through large populations study to establish reference values.\textsuperscript{99, 109} As aortic PWV is relatively stable and reflects long-term changes to the arterial wall structure, it may be a better cardiovascular risk predictor in comparison to blood pressure or cholesterol levels which fluctuate over time within a day or week. Clinical care should incorporate the measure of aortic PWV for the CHD population as a cardiovascular risk predictor.

4.7 Future directions

We demonstrated that seasonal variation in PA exists in our cohort of children with CHD and thus have important implications on the effectiveness of PA counselling, PA monitoring, and the design of PA intervention programs. It is important to increase the levels of PA year-round in this high-risk population because the consequence during times of inactivity will diminish the health outcomes associated with PA.\textsuperscript{64} Primary care providers should modify PA counselling according to season and health policymakers should design PA interventions that involve more accessible opportunities and programs for children at different time of the year. A review study\textsuperscript{82} has demonstrated that other factors contributing to seasonal variation include temperature, daylight hours, geographic areas, and weather. Colder temperature and reduced daylight hours may reduce outdoor play, and this association affects the children living in rural regions more than the urban regions.\textsuperscript{82} Although studies regarding the PA levels for children living in urban and rural areas are inconsistent, most find that children living in rural areas are more active.\textsuperscript{110} During the colder seasons, children living in urban areas are more active and it has been
speculated that it may be due to better access to indoor sporting facilities.\cite{82} Lastly, Belanger et al demonstrated that day-to-day variation in weather mostly impacted unplanned activities (ex. free play on the playground) more than planned activities (ex. club sports) in children.\cite{87} More extensive studies are needed to evaluate the multifactorial effects of seasonal variation on physical activity in children with CHD in order to implement effective PA recommendations and policies. While single measurement tools may not be adequate in characterizing children’s usual PA behaviour,\cite{82} we have demonstrated that in our study commercial activity tracker is feasible in providing a valid measurement of PA levels that can be tracked over time.

We observed a decline in daily minutes of physical activity and an increase in aortic stiffness over time in our cohort of children with CHD. Coupled with the potential inverse association of physical activity and aortic PWV in cross-sectional studies\cite{14,95} and in our longitudinal study, physical activity participation should be encouraged in this high-risk population. As of currently, there are no evidence-based guidelines for PA for children and adolescents with CHD and most are based on limited clinical evidence and expert opinions.\cite{57,66} This called for an urgent need for studies to evaluate the dose-response and physiological effects of PA on children with CHD.

From our observational study, it is difficult to detect the effect of systolic blood pressure and adiposity on arterial stiffness and physical activity thus interventional study may be warranted. The goals of interventional study would include: 1) determine the dose-response relation of PA and aortic PWV, 2) determine the minimal length of PA intervention to see a beneficial effect on aortic PWV, and 3) to discern the effects of SBP and adiposity on aortic PWV and/or PA.
Measurements of aortic PWV should be implemented as part of routine clinical care and serial measurement of aortic PWV can be obtained and be used to monitor abnormal changes to the vasculatures. Aortic PWV also behaves heterogeneously since some children with CHD had higher baseline values and some demonstrated an accelerated rate of increase, therefore aortic PWV can also be used for risk stratification in this high-risk population. Furthermore, it can also be used as a potential biomarker of vascular dysfunction in children with CHD to determine the efficacy of lifestyle changes such as increased PA.

4.8 Conclusion

Healthcare providers can administer effective physical activity counselling by recognizing the effect of seasonality in physical activity in children with CHD. Researchers should consider the confounding role of seasonality on physical activity behaviour in the design, implementation, and evaluation of interventions. We demonstrated that commercial activity tracker is a powerful tool in monitoring and tracking levels of physical activity over long periods of time.

The daily minutes of moderate-to-vigorous physical activity is declining in children with CHD while their aortic stiffness continues to increase over time. These phenomena are very worrisome because this high-risk population is not reaping the multiple health benefits of physical activity on their cardiac function and overall well-being. This study highlights the importance to continuously track the long-term effect of physical activity on the cardiovascular health of children with CHD.
References


110. McCormack LA, Meendering J. Diet and Physical Activity in Rural vs Urban Children and Adolescents in the United States: A Narrative Review. *Journal of the Academy of*
Nutrition and Dietetics 2016;116(3):467-80. doi:

https://doi.org/10.1016/j.jand.2015.10.024
## Appendix

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<th>Table</th>
<th>Error! No text of specified style in document.1 Sample characteristics of accelerometer by seasons</th>
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</tr>
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<td>TGA, n (%)</td>
<td>7 (16.3)</td>
</tr>
<tr>
<td>FON, n (%)</td>
<td>10 (23.3)</td>
</tr>
</tbody>
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BMI – Body Mass Index (kg/m<sup>2</sup>); BMI percentiles calculation based on age-sex-specific World Health Organization 2007 reference charts<sup>43</sup>
BMI weight category based on World Health Organization cut-offs
COA – Coarctation of the Aorta, TET – Tetralogy of Fallot, TGA – Transposition of the Great Arteries, FON – Fontan Circulation
<sup>♣</sup>P-value for main effect for season
<sup>†</sup>No significant Bonferroni-adjusted post hoc comparisons present between groups (p<0.008)
### Table 2 Sample characteristics of physical activity questionnaire

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<th>Physical activity questionnaire</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>Winter</th>
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<tr>
<td>N</td>
<td>47</td>
<td>28</td>
<td>34</td>
<td>30</td>
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<td>Female, n (%)</td>
<td>16 (34.0)</td>
<td>15 (53.6)</td>
<td>13 (38.2)</td>
<td>11 (36.7)</td>
<td>0.388</td>
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<td>Age, years (mean, SD)</td>
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<td>13.8 (2.6)</td>
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<td>150.9 (15.5)</td>
<td>157.1 (17.6)</td>
<td>155.8 (14.4)</td>
<td>147.0 (13.3)</td>
<td>0.040&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>44.8 (14.5)</td>
<td>51.6 (19.5)</td>
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<td>BMI, percentile (mean, SD)</td>
<td>53.1 (35.8)</td>
<td>51.3 (35.1)</td>
<td>49.5 (33.6)</td>
<td>51.4 (29.1)</td>
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<td>Thinness, n (%)</td>
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<td>1 (3.6)</td>
<td>1 (2.9)</td>
<td>1 (3.3)</td>
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<td>Normal, n (%)</td>
<td>30 (65.2)</td>
<td>20 (71.4)</td>
<td>27 (79.4)</td>
<td>24 (80.0)</td>
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<td>Overweight, n (%)</td>
<td>7 (15.2)</td>
<td>4 (14.3)</td>
<td>4 (11.8)</td>
<td>3 (10.0)</td>
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<tr>
<td>Obese, n (%)</td>
<td>7 (15.2)</td>
<td>3 (10.7)</td>
<td>2 (5.9)</td>
<td>2 (6.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COA, n (%)</td>
<td>18 (38.3)</td>
<td>7 (25.0)</td>
<td>9 (26.5)</td>
<td>9 (30.0)</td>
<td></td>
</tr>
<tr>
<td>TET, n (%)</td>
<td>11 (23.4)</td>
<td>10 (35.7)</td>
<td>7 (20.6)</td>
<td>5 (16.7)</td>
<td>0.730</td>
</tr>
<tr>
<td>TGA, n (%)</td>
<td>8 (17.0)</td>
<td>6 (21.4)</td>
<td>7 (20.6)</td>
<td>7 (23.3)</td>
<td></td>
</tr>
<tr>
<td>FON, n (%)</td>
<td>10 (21.3)</td>
<td>5 (17.9)</td>
<td>11 (32.4)</td>
<td>9 (30.0)</td>
<td></td>
</tr>
</tbody>
</table>

BMI – Body Mass Index (kg/m²); BMI percentiles calculation based on age-sex-specific World Health Organization 2007 reference charts<sup>81</sup>
BMI weight category based on World Health Organization cut-offs
COA – Coarctation of the Aorta, TET – Tetralogy of Fallot, TGA – Transposition of the Great Arteries, FON – Fontan Circulation
<sup>Φ</sup>p-value for main effect for season
<sup>†</sup>No significant Bonferroni-adjusted post hoc comparisons present between groups (p<0.008)
Distinct LOWESS trend lines of children’s longitudinal Fitbit data categorized by their activity levels from their accelerometry data. High activity level (green) are children who achieved an average of ≥60 minutes of moderate-to-vigorous physical activity per day (MVPA) from their accelerometry data. Medium activity level (blue) are children who achieved an average of 30–59 minutes of MVPA per day. Low activity level (purple) are children who achieved an average of <30 minutes of MVPA per day. Grey area is the standard error.
Distinct LOWESS trend lines of children’s longitudinal Fitbit data categorized by their activity levels from their PAQ-scores. High activity level (green) are children who achieved $\geq 2.7$ PAQ-score from their questionnaire response. Low activity level (purple) are children who achieved $< 2.7$ PAQ-score. Grey area is the standard error.